Circulation

AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics—2020 Update

A Report From the American Heart Association

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CLINICAL STATEMENTS AND GUIDELINES

BACKGROUND: The American Heart Association, in conjunction with the National Institutes of Health, annually reports on the most up-to-date statistics related to heart disease, stroke, and cardiovascular risk factors, including core health behaviors (smoking, physical activity, diet, and weight) and health factors (cholesterol, blood pressure, and glucose control) that contribute to cardiovascular health. The Statistical Update presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, congenital heart disease, rhythm disorders, subclinical atherosclerosis, coronary heart disease, heart failure, valvular disease, venous disease, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs).

METHODS: The American Heart Association, through its Statistics Committee, continuously monitors and evaluates sources of data on heart disease and stroke in the United States to provide the most current information available in the annual Statistical Update. The 2020 Statistical Update is the product of a full year's worth of effort by dedicated volunteer clinicians and scientists, committed government professionals, and American Heart Association staff members. This year's edition includes data on the monitoring and benefits of cardiovascular health in the population, metrics to assess and monitor healthy diets, an enhanced focus on social determinants of health, a focus on the global burden of cardiovascular disease, and further evidence-based approaches to changing behaviors, implementation strategies, and implications of the American Heart Association's 2020 Impact Goals.

RESULTS: Each of the 26 chapters in the Statistical Update focuses on a different topic related to heart disease and stroke statistics.

CONCLUSIONS: The Statistical Update represents a critical resource for the lay public, policy makers, media professionals, clinicians, healthcare administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions.

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SUMMARY

Each year, the American Heart Association (AHA), in conjunction with the National Institutes of Health and other government agencies, brings together in a single document the most up-to-date statistics related to heart disease, stroke, and the cardiovascular risk factors in the AHA's My Life Check – Life's Simple 7 (Figure),[1] which include core health behaviors (smoking, physical activity [PA], diet, and weight) and health factors (cholesterol, blood pressure [BP], and glucose control) that contribute to cardiovascular health. The Statistical Update represents a critical resource for the lay public, policy makers, media professionals, clinicians,

Figure. AHA's My Life Check – Life's Simple 7. Seven approaches to staying heart healthy: be active, keep a healthy weight, learn about cholesterol, don't smoke or use smokeless tobacco, eat a heart-healthy diet, keep blood pressure healthy, and learn about blood sugar and diabetes mellitus.[1] AHA indicates American Heart Association; HDL, high-density lipoprotein cholesterol; and LDL, low-density lipoprotein cholesterol.

healthcare administrators, researchers, health advocates, and others seeking the best available data on these factors and conditions. Cardiovascular disease (CVD) produces immense health and economic burdens in the United States and globally. The Statistical Update also presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, congenital heart disease, rhythm disorders, subclinical atherosclerosis, coronary heart disease, heart failure [HF], valvular disease, venous disease, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs). Since 2007, the annual versions of the Statistical Update have been cited >20 000 times in the literature.

Each annual version of the Statistical Update undergoes revisions to include the newest nationally representative data, add additional relevant published scientific findings, remove older information, add new sections or chapters, and increase the number of ways to access and use the assembled information. This year-long process, which begins as soon as the previous Statistical Update is published, is performed by the AHA Statistics Committee faculty volunteers and staff and government agency partners. This year's edition includes data on the monitoring and benefits of cardiovascular health in the population, metrics to assess and monitor healthy diets, an enhanced focus on social determinants of health, a focus on the global burden of CVD, and further evidence-based approaches to changing behaviors, implementation strategies, and implications of the AHA's 2020 Impact Goals. Below are a few highlights from this year's Statistical Update. Please see each chapter for references and additional information.

Cardiovascular Health (Chapter 2)

- Between 1999 to 2000 and 2015 to 2016, the prevalence of ideal levels for several cardiovascular health components improved for US children (12–19 years of age), including nonsmoking, total cholesterol, and BP. Although no notable changes were observed in the prevalence of an ideal score for the healthy diet score among children across this time frame, the prevalence of ideal levels of body mass index, PA, and diabetes mellitus (DM) declined.
- Adults (≥20 years of age) also showed improvement in cardiovascular health components, with an increased prevalence of meeting ideal criteria for smoking, total cholesterol, BP, and PA. There were declines in the prevalence of ideal levels for body mass index and DM.

- At all levels of household income–to–poverty ratio between 2003 to 2004 and 2015 to 2016, the highest prevalence of meeting ideal criteria for ≥5 cardiovascular health components was observed in adults with the highest levels of education. Recent research expands the general health benefits of ideal cardiovascular health to include improved psychological and muscle strength benefits.

Smoking/Tobacco Use (Chapter 3)

- The prevalence of cigarette use in the past 30 days among middle and high school students in the United States was 1.8% and 8.1%, respectively, in 2018.
- Although there has been a consistent decline in adult and youth cigarette use in the United States, significant disparities persist. Substantially higher tobacco use prevalence rates are observed in American Indian/Alaska Natives and lesbian, gay, bisexual, and transgender populations, as well as among individuals with low socioeconomic status, those with mental illness, and individuals with HIV who are receiving medical care.
- Over the past 7 years, there has been a sharp increase in electronic cigarette use among adolescents, from 1.5% to 20.8% between 2011 and 2018, and electronic cigarettes are now the most commonly used tobacco product in this demographic.
- Tobacco use is the leading cause of disability-adjusted life-years in the United States. Globally, smoking is the second-leading cause of death, accounting for 8.1 million deaths worldwide in 2017.
- Policy-level interventions such as Tobacco 21 Laws are being adopted and have been associated with reductions in tobacco use incidence and prevalence.

Physical Inactivity (Chapter 4)

- According to the National Health Interview Survey, the prevalence of self-reported physical inactivity has declined sharply among adults, from 40.2% to 25.9% between 2005 and 2017, decreasing below the target for Healthy People 2020, which was 32.6%.
- The prevalence of high school students meeting the aerobic PA recommendations of ≥60 minutes of moderate to vigorous PA on all 7 days of the week was 26.1% nationwide, reported in the 2017 Youth Risk Behavior Survey System. Girls were less likely than boys to achieve these guidelines (17.5% versus 35.3%, respectively). Strikingly, only 14.7% of gay, lesbian, and bisexual students compared with 28.5% of heterosexual students met aerobic PA guidelines.
- Evidence has suggested a role for light-intensity PA in preventing CVD. In a recent study from the Women's Health Initiative, every hour per day more of light-intensity PA was associated with lower coronary heart disease (hazard ratio [HR], 0.86 [95% CI, 0.73–1.00]; *P*=0.05) and lower CVD (HR, 0.92 [95% CI, 0.85–0.99]; *P*=0.03).
- In the Cancer Prevention Study II, among participants with the lowest level of PA, replacing 30 minutes per day of sitting with light-intensity PA or moderate to vigorous PA was associated with 14% (HR, 0.86 [95% CI, 0.81–0.89]) or 45% (HR, 0.55 [95% CI, 0.47–0.62]) lower mortality, respectively. For the individuals with the highest PA levels, substitution (replacing 30 min/day of sitting with light-intensity PA or moderate to vigorous PA) was not associated with differences in mortality risk.

Nutrition (Chapter 5)

- The mean AHA healthy diet score improved between 2003 to 2004 and 2015 to 2016 in US adults, although disparities persisted. The proportion with a poor diet decreased from 64.7% to 58.3% for non-Hispanic blacks, from 66.0% to 57.5% for Mexican Americans, and from 54.0% to 45.9% for non-Hispanic whites. Improvements were largely attributable to increased consumption of whole grains, nuts, seeds, and legumes, as well as decreased consumption of sugar-sweetened beverages.
- A 2-by-2 factorial randomized clinical trial of 25 871 adults (males ≥50 years of age and females ≥55 years of age) found that neither daily supplementation with 2000 IU of vitamin D nor 1 g of marine n-3 fatty acids had an effect on major cardiovascular events (vitamin D: HR, 0.97 [95% CI, 0.85–1.12]; marine n-3 fatty acids: HR, 0.92 [95% CI, 0.80–1.06]), invasive cancer, or any secondary outcomes.
- Using a comparative risk assessment approach, the Global Burden of Disease 2017 Study estimated that 11 million deaths (95% uncertainty interval [UI], 10–12 million; 22% of all deaths) and 255 million disability-adjusted life-years (95% UI, 234–274 million; 15% of all disability-adjusted life-years) were attributable to 15 dietary risks in 2017. The leading dietary risk factors were high sodium intake (3 million deaths; 95% UI, 1–5 million deaths), low whole grain intake (3 million deaths; 95% UI, 2–4 million deaths), and low

fruit intake (2 million deaths; 95% UI, 1–4 million deaths). Age-standardized diet-related death rates decreased between 1990 and 2017 from 406 (95% UI, 381–430) to 275 (95% UI, 258–292) deaths per 100 000 population, although the proportion of deaths attributable to dietary risks was largely stable.

- In a pooled analysis of 30 904 participants from 3 cohort studies, the interactions between a genetic risk score composed of 97 body mass index–associated variants and 3 diet-quality scores were examined. The relationship between genetic predisposition for obesity and body mass index was attenuated by higher diet quality. For example, a 10-U increase in the genetic risk score was associated with a 0.84-U (95% CI, 0.72–0.96) increase in body mass index for those in the highest tertile of Alternate Healthy Eating Index score compared with a 1.14-U (95% CI, 0.99–1.29) increase in body mass index for those in the lowest tertile of Alternate Healthy Eating Index score.

Overweight and Obesity (Chapter 6)

- According to 2015 to 2016 data from NHANES (National Health and Nutrition Examination Survey), the overall prevalence of obesity (≥95th percentile) among youth was 18.5%. By age group, the prevalence of obesity for children 2 to 5 years of age was 13.9%; for children 6 to 11 years of age, the prevalence was 18.4%; and for adolescents 12 to 19 years of age, the prevalence was 20.6%. According to 2013 to 2016 data from NHANES, the prevalence of obesity among adults was 38.3% (36.0% of males and 40.4% of females), including 7.7% with class III obesity or a body mass index ≥40 kg/m^2 (5.5% of males and 9.8% of females).
- Long-term follow-up of the Longitudinal Assessment of Bariatric Surgery-2 study, a multicenter observational cohort study of 1300 participants who underwent bariatric surgery, demonstrated that most participants maintained the majority of their weight loss. However, at 7 years after surgery, lower prevalence rates of DM and hypertension were achieved only among those who underwent Roux-en-Y gastric bypass and not among those who underwent laparoscopic gastric banding.
- In 10 large population cohorts in the United States, individual-level data from adults 20 to 79 years of age with 3.2 million person-years of follow-up (1964–2015) demonstrated that overweight and obesity were associated with earlier development of CVD and reinforced the greater mortality associated with obesity.
- Among older adults in the Multi-Ethnic Study of Atherosclerosis, approximately half of participants with metabolically healthy obesity developed metabolic syndrome (MetS) and had increased odds of CVD compared with those with stable metabolically healthy obesity or healthy normal weight. This suggests that metabolically healthy obesity is not a low-risk state.

High Blood Cholesterol and Other Lipids (Chapter 7)

- From 2007 to 2008 to 2015 to 2016, the proportion of US youths 6 to 19 years of age with all ideal levels of total cholesterol, high-density lipoprotein cholesterol, and non–high-density lipoprotein cholesterol increased significantly, from 42.1% (95% CI, 39.6%–44.7%) to 51.4% (95% CI, 48.5%–54.2%). Conversely, from 2007 to 2010 to 2013 to 2016, the proportion of youths with at least 1 of these lipids at adverse levels decreased, from 23.1% (95% CI, 21.5%–24.7%) to 19.2% (95% CI, 17.6%–20.8%).
- In a recent meta-analysis in which low-density lipoprotein cholesterol levels were lowered from a baseline of 63 mg/dL to an end result of 21 mg/dL, major vascular events were consistently reduced (relative risk per 38.7-mg/dL reduction, 0.79 [95% CI, 0.71–0.87]) without adverse effects.
- In the Health Survey for England and the Scottish Health Survey, a U-shaped association of all-cause mortality was seen with the lowest high-density lipoprotein cholesterol level (<58 mg/dL; HR, 1.23 [95% CI, 1.06–1.44]) and the highest high-density lipoprotein cholesterol level (≥77 mg/dL; HR, 1.25 [95% CI, 0.97–1.62]).

High Blood Pressure (Chapter 8)

- Data from 13 160 participants in cohorts in the Cardiovascular Lifetime Risk Pooling Project (ie, the Framingham Offspring Study, the Coronary Artery Risk Development in Young Adults study, and the ARIC [Atherosclerosis Risk in Communities] study) found that the lifetime risk of hypertension from 20 to 85 years of age using 2017 American College of Cardiology (ACC)/AHA guidelines was 86.1% (95% CI, 84.1%–88.1%) for black males, 85.7% (95% CI, 84.0%–87.5%) for black females, 83.8% (95% CI, 82.5%–85.0%) for white males, and 69.3% (95% CI, 67.8%–70.7%) for white females.
- Among 60 027 participants in the Norwegian Mother and Child Cohort Study who were normotensive before pregnancy, the population attributable fraction for pharmacologically treated

hypertension within 10 years postpartum was 28.6% (95% CI, 25.5%–30.3%) for complications of pregnancy (preeclampsia/eclampsia, gestational hypertension, preterm delivery, and pregestational or gestational DM).
- In the HCHS/SOL (Hispanic Community Health Study/Study of Latinos) Sueño Sleep Ancillary Study of Hispanics (N=2148), a 10% higher sleep fragmentation and frequent napping versus not napping were associated with a 5.2% and 11.6% higher prevalence of hypertension, respectively. A 10% higher sleep efficiency was associated with a 7.2% lower prevalence of hypertension.

Diabetes Mellitus (Chapter 9)

- On the basis of data from NHANES 2013 to 2016, an estimated 26 million adults (9.8%) have diagnosed DM, 9.4 million adults (3.7%) have undiagnosed DM, and 91.8 million adults (37.6%) have prediabetes.
- Among adults without DM in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of 150 min/wk and 58.6% met the weight loss or maintenance goal for DM prevention. Adults with prediabetes were less likely to meet the PA and weight goals than adults with normal glucose levels.
- On the basis of NHANES 2013 to 2016 data for adults with DM, 20.9% had their DM treated and controlled, 45.2% had their DM treated but uncontrolled, 9.2% were aware they had DM but were not treated, and 24.7% were undiagnosed and not treated.
- Among Medicare Advantage patients with DM from 2006 to 2013, use of metformin increased from 47.6% to 53.5%, dipeptidyl peptidase 4 inhibitor use increased from 0.5% to 14.9%, insulin use increased from 17.1% to 23.0%, use of sulfonylureas decreased from 38.8% to 30.8%, and use of thiazolidinediones decreased from 28.5% to 5.6%.

Metabolic Syndrome (Chapter 10)

- On the basis of NHANES 1999 to 2014, the prevalence of MetS in adolescents 12 to 19 years of age in the United States varied by geographic region. MetS prevalence was lower in the Northeast (6.25% [95% CI, 4.14%–8.36%]) and West (6.31% [95% CI, 4.73%–7.89%]) regions and higher in the South (7.57% [95% CI, 5.80%–9.33%]) and Midwest (11.42% [95% CI, 8.11%–14.72%]).
- On the basis of NHANES 2007 to 2014, the overall prevalence of MetS in adults was 34.3% and was similar for males (35.3%) and females (33.3%). The prevalence of MetS increased with age, from 19.3% among people 20 to 39 years of age to 37.7% for people 40 to 59 years of age and 54.9% among people ≥60 years of age.
- Secular trends in MetS differ based on the definition used. Using the harmonized MetS criteria, the prevalence of MetS increased from 25.3% in NHANES 1988 to 1994 to 34.2% in NHANES 2007 to 2012. In contrast, using Adult Treatment Panel III criteria, the prevalence of MetS was stable overall in NHANES 2003 to 2014.
- In the ARIC study (1987–1998), the prevalence of MetS increased from 33% to 50% over the mean 10-year follow-up, with differences by age and sex. The prevalence of MetS was lower in black males than in white males at all time points and for all ages across the study. Black females had higher prevalence of MetS than white females at baseline and subsequent time points for all ages except for those >60 years of age.

Kidney Disease (Chapter 11)

- Using data from NHANES 2013 to 2016, the United States Renal Data System has estimated the prevalence of chronic kidney disease by estimated glomerular filtration rate and albuminuria categories. The overall prevalence of chronic kidney disease (estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ or albumin/creatinine ratio ≥30 mg/g) in 2013 to 2016 was 14.8%.
- Chronic kidney disease is a risk factor for incident and recurrent coronary events, stroke, HF, venous thromboembolism, and atrial fibrillation (AF). The association of reduced estimated glomerular filtration rate with cardiovascular risk is generally similar across age, race, and sex subgroups, although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) versus younger people.
- In a nationwide US cohort that included 4726 participants with chronic kidney disease, only 2366 (50%) self-reported taking statins, whereas an additional 1984 participants (42%) met recommendations for statin treatment according to the 2013 ACC/AHA guideline on treatment of blood cholesterol but did not report using statins.
- In 2015, admissions for CVD accounted for 27% of all inpatient spending for patients with end-stage renal disease.

Sleep (Chapter 12)

- A systematic review estimated the prevalence of obstructive sleep apnea in cerebrovascular disease in 3242 patients who had either cerebral infarction, transient ischemic attack, ischemic stroke, or hemorrhagic stroke and found that the pooled prevalence of obstructive sleep apnea (defined as apnea-hypopnea index >10 events/hour) was 62% (95% CI, 55%–69%), and the pooled prevalence of severe obstructive sleep apnea (apnea-hypopnea index >30) was 30% (95% CI, 23%–37%).
- The deepest stage of non–rapid eye movement sleep, also called slow-wave sleep, is thought to be a restorative stage of sleep. In the Sleep Heart Health Study, which used in-home polysomnography to characterize sleep, it was found that participants with a lower proportion of slow-wave sleep had significantly greater odds of incident hypertension (quartile 1 versus quartile 3: odds ratio [OR], 1.69 [95% CI, 1.21–2.36]).
- A meta-analysis analyzed data from 9 cohort studies with 2755 participants that described the association between obstructive sleep apnea and major adverse cardiovascular events after percutaneous coronary intervention with stenting and found that obstructive sleep apnea was associated with a significant increased risk of major adverse cardiovascular events (pooled relative risk, 1.96; 95% CI, 1.36–2.81).
- Analysis of direct and indirect costs related to inadequate sleep in Australia suggested that the cost for a population the size of the United States would be more than approximately $585 billion for 2016 to 2017.
- A recent analysis of the global prevalence and burden of obstructive sleep apnea estimated that 936 million (95% CI, 903–970 million) males and females 30 to 69 years of age have mild to severe obstructive sleep apnea (apnea-hypopnea index ≥5), and 425 million (95% CI, 399–450 million) have moderate to severe obstructive sleep apnea (apnea-hypopnea index ≥15) globally. The prevalence was highest in China, followed by the United States, Brazil, and India.

Total Cardiovascular Diseases (Chapter 13)

- On the basis of the 2017 National Health Interview Survey, the age-adjusted prevalence of all types of heart disease was 10.6%; the corresponding age-adjusted prevalence of heart disease among whites, blacks, Hispanics, and Asians was 11.0%, 9.7%, 7.4%, and 6.1%, respectively. The age-adjusted prevalence of heart disease, coronary artery disease, hypertension, and stroke was higher in males (11.8%, 7.2%, 26.0%, and 3.3%, respectively) than females (9.5%, 4.2%, 23.1%, and 2.5%, respectively).
- A recent study using the Global Burden of Disease methodology examined the burden of CVD among US states and found that a large proportion of CVD is attributable to (in decreasing order of contribution) dietary risks, high systolic BP, high body mass index, high total cholesterol level, high fasting plasma glucose level, tobacco smoking, and low levels of PA.
- In 2017, 2 813 503 resident deaths were registered in the United States, which exceeds the 2016 figure by 69 255 deaths. Ten leading causes accounted for 74.0% of all registered deaths. The 10 leading causes of death in 2017 were the same as in 2016; these include heart disease (No. 1), cancer (No. 2), unintentional injuries (No. 3), chronic lower respiratory diseases (No. 4), stroke (No. 5), Alzheimer disease (No. 6), DM (No. 7), influenza and pneumonia (No. 8), kidney disease (No. 9), and suicide (No. 10). Seven of the 10 leading causes of death had an increase in age-adjusted death rates. The age-adjusted rate increased 4.2% for unintentional injuries, 2.3% for Alzheimer disease, 3.7 % for suicide, 2.4% for DM, 5.9% for influenza and pneumonia, 0.7% for chronic lower respiratory disease, and 0.8% for stroke. The age-adjusted death rates decreased 2.1% for cancer but did not change appreciably for heart disease or kidney disease.
- In 2017, ≈17.8 million (95% CI, 17.5–18.0 million) deaths were attributed to CVD globally, which amounted to an increase of 21.1% (95% CI, 19.7%–22.6%) from 2007. The age-adjusted death rate per 100 000 population was 233.1 (95% CI, 229.7–236.4), which represents a decrease of 10.3% (95% CI, −11.4% to −9.3%) from 2007. Overall, the crude prevalence of CVD was 485.6 million cases (95% CI, 468.0–505.0 million) in 2017, an increase of 28.5% (95% CI, 27.7%–29.4%) compared with 2007. However, the age-adjusted prevalence rate was 6081.6 (95% CI, 5860.8–6320.8) per 100 000, an increase of 0.2% (95% CI, −0.4% to 0.80%) from 2007.

Stroke (Cerebrovascular Disease) (Chapter 14)

- Despite encouraging data about declining stroke incidence, on a global level the aging population and accumulating risk factors contribute to an increasing lifetime risk of stroke. Per the Global Burden of Disease 2016 Lifetime Risk of Stroke Collaborators, the mean global lifetime risk of

stroke increased from 22.8% in 1990 to 24.9% in 2016, a relative increase of 8.9% (95% CI, 6.2%–11.5%) after accounting for the competing risk of death of any cause other than stroke.
- A mendelian randomization study among almost 500 000 Chinese individuals found that genetic markers predictive of low-density lipoprotein cholesterol levels were directly associated with ischemic stroke and inversely associated with intracerebral hemorrhage, thus providing causal evidence of opposing effects of low-density lipoprotein cholesterol levels on the 2 most common stroke types.
- The largest multiethnic genome-wide association study of stroke conducted to date reported 32 genetic loci, including 22 not previously reported. These novel loci point to a major role of cardiac mechanisms beyond established sources of cardioembolism. Approximately half of the stroke genetic loci share genetic associations with other vascular traits, most notably BP.
- Among 81 714 females in the Women's Health Initiative prospective cohort study, those who consumed ≥2 artificially sweetened beverages daily, on average, had an elevated risk of all stroke (adjusted HR, 1.23 [95% CI, 1.02–1.47]) and ischemic stroke (adjusted HR, 1.31 [95% CI 1.06–1.63]) compared with those who consumed <1 artificially sweetened beverage weekly, after adjustment for demographics, CVD history, risk factors, body mass index, health behaviors, and overall diet quality.
- As the US population ages, the number of people with Alzheimer disease will increase dramatically from 2010 to 2050. According to a modeling study based on estimates in a population of 10 800 participants from the Chicago Health and Aging Project in the United States, in 2010 there were 4.7 million individuals ≥65 years of age with Alzheimer disease (95% CI, 4.0–5.5 million); by 2050, the number of people with Alzheimer disease is projected to be 13.8 million, with 7.0 million ≥85 years of age.

Congenital Cardiovascular Defects and Kawasaki Disease (Chapter 15)

- Increasingly, social determinants are being identified as playing an important role in outcomes from congenital cardiovascular defects. One recent, large review of >15 000 infants demonstrated improved survival among patients with fathers >35 years old (versus younger); survival was also impacted by factors such as maternal education, race/ethnicity, and marital status.
- In 2016, there were 6000 all-listed diagnoses hospital discharges for Kawasaki disease in the United States, and in 2017, US mortality attributable to Kawasaki disease was 5 patients for underlying mortality and 10 patients for all-cause mortality.

Disorders of Heart Rhythm (Chapter 16)

- Higher levels of cardiovascular health are associated with decreased risk of developing AF. An analysis of the ARIC study described that individuals with average and optimal cardiovascular health had a 41% and 62% lower risk of AF, respectively, than those with inadequate cardiovascular health.
- High atrial rate episodes detected by cardiac implantable electronic devices are associated with higher risk of clinical AF (OR, 5.7 [95% CI, 4.0–8.0]) and higher risk of stroke (OR, 2.4 [95% CI, 1.8–3.3]), according to a meta-analysis.
- Racial disparities exist in the treatment of patients with AF. In the ORBIT-AF II registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), black patients were 27% less likely than their white counterparts to receive direct oral anticoagulants if an anticoagulant was prescribed. Black and Hispanic patients were more likely than their white counterparts to receive inappropriate doses of direct oral anticoagulants.
- In a cohort of new patients with AF at the University of Pennsylvania who did not have a history of remote stroke, blacks with new-onset AF were more likely to have an ischemic stroke before or after the diagnosis of AF. The rate of ischemic stroke per year after AF diagnosis was 1.5% in whites and 2.5% in blacks.

Sudden Cardiac Arrest, Ventricular Arrhythmias, and Inherited Channelopathies (Chapter 17)

- In 2017, primary-cause sudden cardiac death (SCD) mortality was 18 835, and any-mention SCD mortality in the United States was 379 133. The any-mention age-adjusted annual SCD rate is 97.1 (95% CI, 96.8–97.4) per 100 000 population.
- SCD appeared among the multiple causes of death on 13.5% of death certificates in 2017 (379 133 of 2 813 503), which suggests that 1 of every 7.4 people in the United States died of SCD.
- Incidence of emergency medical services–treated out-of-hospital cardiac arrest in people of any age is 74.3 individuals per 100 000 population based on the 2018 CARES (Cardiac Arrest Registry to Enhance Survival), with >2-fold variation between states (range, 51.6–128.3 per 100 000 population).
- In the National Emergency Department Sample for 2016, the weighted national estimate of emergency department visits with a principal diagnosis

of either cardiac arrest or ventricular fibrillation/flutter was 183 629 (rate of 56.8 per 100 000 people). Of these, 15.8% (29 096) were admitted to the same hospital or transferred to another hospital.

Subclinical Atherosclerosis (Chapter 18)

- The 2018 Cholesterol Clinical Practice Guideline and the 2019 CVD Primary Prevention Clinical Practice Guideline advise that the use of coronary artery calcium is reasonable in intermediate-risk or selected borderline-risk adults if the decision about statin therapy remains uncertain after calculation of the 10-year atherosclerotic cardiovascular disease risk and after accounting for risk-enhancing factors.
- Compared with individuals who sleep 7 to 8 hours per night, and with adjustment for conventional risk factors, people who sleep <6 hours per night have a 1.27 greater odds of noncoronary atherosclerosis.
- Older adult females who consumed ≥3 servings of vegetables each day had an ≈5.0% lower amount of carotid atherosclerosis than females who consumed <2 servings of vegetables.

Coronary Heart Disease, Acute Coronary Syndrome, and Angina Pectoris (Chapter 19)

- The awareness of 5 common heart attack symptoms (jaw, neck, or back discomfort; weakness or lightheadedness; chest discomfort; arm or shoulder discomfort; and shortness of breath) is higher in females than in males (54.4% versus 45.6%) and in whites (54.8%) than in blacks (43.1%), Asians (33.5%), and Hispanics (38.9%).
- Among patients hospitalized for ST-segment–elevation myocardial infarction, lack of health insurance (OR, 1.77 [95% CI, 1.72–1.82]; $P<0.001$) and below-median income (OR, 1.08 [95% CI, 1.07–1.09]; $P<0.001$) are independent predictors of in-hospital mortality.
- Neighborhood socioeconomic status is associated with outcomes in patients with acute myocardial infarction. Compared with those in the highest quintile of neighborhood socioeconomic status, those residing in the most disadvantaged quintile experience higher rates of in-hospital death (OR, 1.10 [95% CI, 1.02–1.18]) and major bleeding (OR, 1.10 [95% CI, 1.05–1.15]).
- Females experience longer door-to-balloon times and lower rates of guideline-directed medical therapy than males. In-hospital mortality is higher in females than in males with ST-segment–elevation myocardial infarction (7.4% versus 4.6%) and non–ST-segment–elevation myocardial infarction (4.8% versus 3.9%).

Cardiomyopathy and Heart Failure (Chapter 20)

- The prevalence of HF continues to rise over time, with aging of the population. An estimated 6.2 million American adults ≥20 years of age had HF between 2013 and 2016, compared with an estimated 5.7 million between 2009 and 2012.
- Of incident hospitalized HF events, approximately half are characterized by reduced ejection fraction and the other half by preserved ejection fraction. The prevalence of HF with preserved ejection fraction, compared with prevalence of HF with reduced ejection fraction, appears to be increasing over time along with aging of the population.
- The prevalence of HF is highly variable across the world, with the lowest in sub-Saharan Africa. Prevalence of HF risk factors also varies worldwide, with hypertension being most common in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa. Ischemic heart disease is most prevalent in Europe and North America. Valvular heart disease is more common in East Asia and Asia-Pacific countries.

Valvular Diseases (Chapter 21)

- In high-risk patients with severe aortic stenosis, recent studies have shown that transcatheter aortic valve replacement is comparable to surgical aortic valve replacement in terms of mortality at 1 and 5 years. In patients at intermediate surgical risk, transcatheter aortic valve replacement and surgical aortic valve replacement have similar rates of death attributable to any cause or debilitating stroke at 2 years. In subjects at low surgical risk, transcatheter aortic valve replacement has lower rates of death, stroke, or rehospitalization at 2 years than surgical aortic valve replacement.
- Percutaneous mitral valve repair techniques for primary or degenerative mitral regurgitation have become a common treatment option for high-risk patients not deemed candidates for surgical repair. Data from the Society for Thoracic Surgeons/ACC Transcatheter Valve Therapy Registry on patients commercially treated with the MitraClip percutaneous mitral valve repair device showed reduction in the severity of mitral regurgitation and procedural success in >90% of cases, although mitral valve dysfunction at 12 months is more common with percutaneous mitral valve repair than with surgical repair.

- The role of the MitraClip in secondary mitral regurgitation was investigated in 2 recently published randomized clinical trials with divergent results. The MITRA-FR trial (Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) did not show a significant difference in the combined end point of death or rehospitalization for HF at 1 year between the group treated with MitraClip and the group treated with optimal medical therapy and cardiac resynchronization alone. However, the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy) demonstrated a significant reduction in rehospitalization because of HF and mortality at 2 years with the MitraClip. Such divergent results may be related to differences in sample characteristics and size, duration of follow-up, and primary end point.

Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism), Chronic Venous Insufficiency, Pulmonary Hypertension (Chapter 22)

- In 2016, there were an estimated 1 220 000 cases of venous thromboembolism.
- According to combined data from the Emerging Risk Factors Collaboration and the UK Biobank, among traditional atherosclerotic risk factors, age and obesity were associated with increased venous thromboembolism risk; for hypertension and dyslipidemia, there was no association; and for DM, the results were inconsistent.
- In a meta-analysis of patients with deep vein thrombosis who underwent ultrasonography at least 6 weeks after their deep vein thrombosis, those with residual vein thrombosis had 2-fold greater risk of postthrombotic syndrome, whereas those with venous reflux at the popliteal level had 34% greater postthrombotic syndrome risk.
- In a cohort of 23 329 patients with first venous thromboembolism, cumulative incidence of chronic thromboembolic pulmonary hypertension was 1.3% and 3.3% at 2 and 10 years after pulmonary embolism and 0.3% and 1.3% after deep vein thrombosis, respectively.

Peripheral Artery Disease and Aortic Diseases (Chapter 23)

- A recent trial demonstrated that a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab, reduced the risk of major adverse limb events, including acute limb ischemia, major amputation, and urgent revascularization (HR, 0.58 [95% CI, 0.38–0.88]), among patients with a history of myocardial infarction, stroke, or peripheral artery disease.
- A recent study with ≈28 000 patients with a history of CVD demonstrated that patients with symptomatic peripheral artery disease but no prior myocardial infarction or stroke had an ≈2 times higher risk of CVD events than those with prior myocardial infarction or stroke but no symptomatic peripheral artery disease.
- A recent report from the Nationwide Inpatient Sample demonstrated that the rate of nontraumatic lower-extremity amputation had increased by 50% between 2009 and 2015 in adults with DM, despite previously declining trends.

Quality of Care (Chapter 24)

- The 30-day postdischarge mortality rate in acute myocardial infarction has decreased in recent years to ≈12%. The Hospital Readmissions Reduction Program did not change this trend, and the rates of reduction remained constant when comparing time before and after the program's initiation.
- There has been controversy concerning the impact of the Hospital Readmissions Reduction Program for patients hospitalized with HF. Although some studies suggested the program was associated with an increase in mortality (HR, 1.10 [95% CI, 1.06–1.14]), studies using other methods suggested no change in mortality.
- For individuals with stroke, admission to institutions participating in the Get With The Guidelines–Stroke program was associated with several positive changes in management, including higher rates of tissue plasminogen activator use, education on risk factors, evaluation for swallowing, lipid evaluation, and neurology evaluation, as well as more appropriate referral for hospice.

Medical Procedures (Chapter 25)

- Data from the Society of Thoracic Surgeons Congenital Heart Surgery Database indicate that a total of 122 459 congenital heart surgeries were performed from July 2014 to June 2018.
- In 2018, 3408 heart transplantations were performed in the United States, the most ever.

Economic Cost of Cardiovascular Disease (Chapter 26)

- The average annual direct and indirect cost of CVD and stroke in the United States was an estimated $351.3 billion in 2014 to 2015.

- The estimated direct costs of CVD in the United States increased from $103.5 billion in 1996 to 1997 to $213.8 billion in 2014 to 2015.
- Between 2015 and 2035, the projected total (direct and indirect) costs of total CVD are estimated to remain relatively stable for 18- to 44-year-olds, increase slightly for 45- to 64-year-olds, and increase sharply for 65- to 79-year-olds and adults ≥80 years of age.

Conclusions

The AHA, through its Statistics Committee, continuously monitors and evaluates sources of data on heart disease and stroke in the United States to provide the most current information available in the Statistical Update. The 2020 annual Statistical Update is the product of a full year's worth of effort by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members, without whom publication of this valuable resource would be impossible. Their contributions are gratefully acknowledged.

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ARTICLE INFORMATION

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; the US Department of Health and Human Services; or the US Department of Veterans Affairs.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

1. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check–lifes-simple-7. Accessed November 9, 2018.

1. ABOUT THESE STATISTICS

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The AHA works with the NHLBI to derive the annual statistics in this Heart Disease and Stroke Statistics Update. This chapter describes the most important sources and the types of data used from them. For more details, see Chapter 28 of this document, the Glossary.

The surveys and data sources used are the following:

- ACC NCDR's Chest Pain–MI Registry (formerly the ACTION Registry)—quality information for AMI
- ARIC—CHD and HF incidence rates
- BRFSS—ongoing telephone health survey system
- GBD—global disease prevalence and mortality
- GCNKSS—stroke incidence rates and outcomes within a biracial population
- GWTG—quality information for resuscitation, HF, and stroke
- HCUP—hospital inpatient discharges and procedures
- MEPS—data on specific health services that Americans use, how frequently they use them, the cost of these services, and how the costs are paid
- NAMCS—physician office visits
- NHAMCS—hospital outpatient and ED visits
- NHANES—disease and risk factor prevalence and nutrition statistics
- NHIS—disease and risk factor prevalence
- NVSS—mortality for United States
- USRDS—kidney disease prevalence
- WHO—mortality rates by country
- YRBSS—health-risk behaviors in youth and young adults

Abbreviations Used in Chapter 1

ACC	American College of Cardiology
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AHA	American Heart Association
AMI	acute myocardial infarction
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities Study
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
FHS	Framingham Heart Study
GBD	Global Burden of Disease study
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
GWTG	Get With The Guidelines
HBP	high blood pressure
HCUP	Healthcare Cost and Utilization Project
HF	heart failure
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NINDS	National Institute of Neurological Disorders and Stroke
NVSS	National Vital Statistics System
USRDS	United States Renal Data System
WHO	World Health Organization
YRBSS	Youth Risk Behavior Surveillance System

Disease Prevalence

Prevalence is an estimate of how many people have a condition at a given point or period in time. The CDC/NCHS conducts health examination and health interview surveys that provide estimates of the prevalence of diseases and risk factors. In this Statistical Update, the health interview part of the NHANES is used for the prevalence of CVDs. NHANES is used more than the NHIS because in NHANES, AP is based on the Rose Questionnaire; estimates are made regularly for HF; hypertension is based on BP measurements and interviews; and an estimate can be made for total CVD, including MI, AP, HF, stroke, and hypertension.

A major emphasis of this Statistical Update is to present the latest estimates of the number of people in the United States who have specific conditions to provide a realistic estimate of burden. Most estimates based on NHANES prevalence rates are based on data collected from 2013 to 2016. These are applied to census population estimates for 2016. Differences in population estimates cannot be used to evaluate possible trends in prevalence because these estimates are based on extrapolations of rates beyond the data collection period by use of more recent census population estimates. Trends can only be evaluated by comparing prevalence rates estimated from surveys conducted in different years.

In the 2020 Statistical Update, there is an emphasis on social determinants of health that are built across the various chapters, and global estimates are provided where available.

Risk Factor Prevalence

The NHANES 2013 to 2016 data are used in this Statistical Update to present estimates of the percentage

of people with high lipid values, DM, overweight, and obesity. NHANES 2015 to 2016 and BRFSS 2017 data are used for the prevalence of sleep issues. The NHIS 2016 data are used for the prevalence of cigarette smoking and physical inactivity. Data for students in grades 9 through 12 are obtained from the YRBSS.

Incidence and Recurrent Attacks

An incidence rate refers to the number of new cases of a disease that develop in a population per unit of time. The unit of time for incidence is not necessarily 1 year, although incidence is often discussed in terms of 1 year. For some statistics, new and recurrent attacks or cases are combined. Our national incidence estimates for the various types of CVD are extrapolations to the US population from the FHS, the ARIC study, and the CHS, all conducted by the NHLBI, as well as the GCNKSS, which is funded by the NINDS. The rates change only when new data are available; they are not computed annually. Do not compare the incidence or the rates with those in past editions of the Heart Disease and Stroke Statistics Update (also known as the Heart and Stroke Statistical Update for editions before 2005). Doing so can lead to serious misinterpretation of time trends.

Mortality

Mortality data are generally presented according to the underlying cause of death. "Any-mention" mortality means that the condition was nominally selected as the underlying cause or was otherwise mentioned on the death certificate. For many deaths classified as attributable to CVD, selection of the single most likely underlying cause can be difficult when several major comorbidities are present, as is often the case in the elderly population. It is useful, therefore, to know the extent of mortality attributable to a given cause regardless of whether it is the underlying cause or a contributing cause (ie, the "any-mention" status). The number of deaths in 2017 with any mention of specific causes of death was tabulated by the NHLBI from the NCHS public-use electronic files on mortality.

The first set of statistics for each disease in this Statistical Update includes the number of deaths for which the disease is the underlying cause. Two exceptions are Chapter 8 (High Blood Pressure) and Chapter 20 (Cardiomyopathy and Heart Failure). HBP, or hypertension, increases the mortality risks of CVD and other diseases, and HF should be selected as an underlying cause only when the true underlying cause is not known. In this Statistical Update, hypertension and HF death rates are presented in 2 ways: (1) as nominally classified as the underlying cause and (2) as any-mention mortality.

National and state mortality data presented according to the underlying cause of death were obtained from the CDC WONDER website or the CDC NVSS mortality file.[1] Any-mention numbers of deaths were tabulated from the CDC WONDER website or CDC NVSS mortality file.[2]

Population Estimates

In this publication, we have used national population estimates from the US Census Bureau for 2016[3] in the computation of morbidity data. CDC/NCHS population estimates[4] for 2017 were used in the computation of death rate data. The Census Bureau website contains these data, as well as information on the file layout.

Hospital Discharges and Ambulatory Care Visits

Estimates of the numbers of hospital discharges and numbers of procedures performed are for inpatients discharged from short-stay hospitals. Discharges include those discharged alive, dead, or with unknown status. Unless otherwise specified, discharges are listed according to the principal (first-listed) diagnosis, and procedures are listed according to all-listed procedures (principal and secondary). These estimates are from the 2016 HCUP. Ambulatory care visit data include patient visits to primary providers' offices and hospital outpatient departments and EDs. Ambulatory care visit data reflect the primary (first-listed) diagnosis. These estimates are from the 2016 NAMCS and 2016 NHAMCS of the CDC/NCHS. Data for community health centers are included in 2016 NAMCS estimates. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in mind, because coding changes could affect some statistics, especially when comparisons are made across these years.

International Classification of Diseases

Morbidity (illness) and mortality (death) data in the United States have a standard classification system: the *ICD*. Approximately every 10 to 20 years, the *ICD* codes are revised to reflect changes over time in medical technology, diagnosis, or terminology. If necessary for comparability of mortality trends across the 9th and 10th *ICD* revisions, comparability ratios computed by the CDC/NCHS are applied as noted.[5] Effective with mortality data for 1999, *ICD-10* is used.[6] Beginning in 2016, *ICD-10-CM* is used for hospital inpatient stays and ambulatory care visit data.[7]

Age Adjustment

Prevalence and mortality estimates for the United States or individual states comparing demographic groups or estimates over time are either age specific or

age adjusted to the year 2000 standard population by the direct method.[8] International mortality data are age adjusted to the European standard population. Unless otherwise stated, all death rates in this publication are age adjusted and are deaths per 100 000 population.

Data Years for National Estimates

In this Statistical Update, we estimate the annual number of new (incidence) and recurrent cases of a disease in the United States by extrapolating to the US population in 2014 from rates reported in a community- or hospital-based study or multiple studies. Age-adjusted incidence rates by sex and race are also given in this report as observed in the study or studies. For US mortality, most numbers and rates are for 2017. For disease and risk factor prevalence, most rates in this report are calculated from the 2013 to 2016 NHANES. Because NHANES is conducted only in the noninstitutionalized population, we extrapolated the rates to the total US resident population on July 1, 2016, recognizing that this probably underestimates the total prevalence given the relatively high prevalence in the institutionalized population. The numbers and rates of hospital inpatient discharges for the United States are for 2016. Numbers of visits to primary providers' offices and hospital EDs are for 2016, whereas hospital outpatient department visits are for 2011. Except as noted, economic cost estimates are for 2014 to 2015.

Cardiovascular Disease

For data on hospitalizations, primary provider office visits, and mortality, total CVD is defined according to *ICD* codes given in Chapter 13 of the present document. This definition includes all diseases of the circulatory system. Unless otherwise specified, estimates for total CVD do not include congenital CVD. Prevalence of total CVD includes people with hypertension, CHD, stroke, and HF.

Race/Ethnicity

Data published by governmental agencies for some racial groups are considered unreliable because of the small sample size in the studies. Because we try to provide data for as many racial and ethnic groups as possible, we show these data for informational and comparative purposes.

Global Burden of Disease

The GBD Study is an ongoing global effort to measure death and disability attributable to diseases, injuries, and risk factors for all countries, from 1990 to the present day. GBD 2017, the most recent iteration of the study, was produced by the collective efforts of >3600 researchers in >145 countries. Estimates were produced for 350 diseases and injuries and 84 risk factors. Detailed methods and results can be found via the study's online data visualization tools, as well as across a range of peer-reviewed scientific research articles, which can be found cited elsewhere in this publication.

For GBD 2017, estimates were produced for 1990 to 2017 for 195 countries and territories, stratified by age and sex, with subnational estimates made available in an increasing number of countries. Improvements to statistical and geospatial modeling methods, as well as the addition of new data sources, could lead to changes in results across GBD Study cycles for both the most recent and earlier years.

For more information about the GBD, and to access GBD 2017 resources, data visualizations, and most recent publications, please visit the study's website.[9]

Contacts

If you have questions about statistics or any points made in this Statistical Update, please contact the AHA National Center, Office of Science & Medicine. Direct all media inquiries to News Media Relations at http://newsroom.heart.org/connect or 214-706-1173.

The AHA works diligently to ensure that this Statistical Update is error free. If we discover errors after publication, we will provide corrections at http://www.heart.org/statistics and in the journal *Circulation*.

REFERENCES

1. National Center for Health Statistics. Centers for Disease Control and Prevention website. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm Accessed April 1, 2019.
2. Centers for Disease Control and Prevention, National Center for Health Statistics, Multiple Cause of Death, 1999-2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
3. US Census Bureau population estimates: historical data: 2000s. US Census Bureau website. https://www.census.gov/programs-surveys/popest.html. Accessed July 19, 2019.
4. U.S. Census Populations With Bridged Race Categories. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/bridged_race.htm Accessed July 19, 2019.
5. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: National Center for Health Statistics; 2016. http://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed April 1, 2019.
6. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. 2008 ed. Geneva, Switzerland: World Health Organization; 2009.
7. National Center for Health Statistics. ICD-10-CM Official Guidelines for Coding and Reporting, FY 2019. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/icd/data/10cmguidelines-FY2019-final.pdf. Accessed July 19, 2019.
8. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. *Natl Vital Stat Rep*. 1998;47:1–16, 20.
9. *Global Burden of Disease Study 2017 (GBD 2017)*. Seattle, WA: Institute for Health Metrics and Evaluation, University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.

2. CARDIOVASCULAR HEALTH

See Tables 2-1 and 2-2 and Charts 2-1 through 2-15

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In 2010, the AHA created a new set of central Strategic Impact Goals to drive organizational priorities for the decade to come:

> *By 2020, to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVDs and stroke by 20%.*[1]

This impact goal introduced a new concept of CVH, characterized by 7 components (Life's Simple 7),[2] including 4 health behaviors (diet quality, PA, smoking, BMI) and 3 health factors (blood cholesterol, BP, blood glucose). Ideal CVH is defined by the absence of clinically manifest CVD together with the simultaneous presence of optimal levels of all 7 components, including not smoking and having a healthy diet pattern, sufficient PA, normal body weight, and normal levels of TC, BP, and FPG (in the absence of medication treatment for these 3 factors; Table 2-1). Because a wide spectrum exists in potential levels of CVH, and the ideal CVH profile is known to be rare in the US population, the broader spectrum of CVH can also be represented using categorical ranges for *ideal*, *intermediate*, or *poor* for each of the health behaviors and health factors.[1] Table 2-1 provides the specific definitions for ideal, intermediate, and poor categories for each of the 7 components of CVH for both adults and children.

This concept of CVH represented a new focus for the AHA, with 3 central and novel emphases:

- An expanded focus on CVD prevention and promotion of CVH as an active, positive, and achievable pursuit, in addition to the treatment of established CVD.
- Efforts to promote both healthy behaviors (healthy diet pattern, appropriate energy intake, PA, and nonsmoking) and healthy levels of health factors (optimal blood lipids, BP, glucose levels) throughout the lifespan.
- Population-level health-promotion strategies to shift the majority of the public toward greater CVH, in addition to targeting those individuals at greatest CVD risk, because healthy lifestyles in all domains are uncommon throughout the US population.

Beginning in 2011, and recognizing the time lag in the nationally representative US data sets, this chapter in the annual Statistical Update has evaluated and published surveillance estimates for the prevalence of CVH and information to provide insights into both progress toward meeting the 2020 AHA goals and areas that require greater attention to meet these goals. The AHA has advocated for raising the visibility of patient-reported CVH status, which includes symptom burden, functional status, and health-related quality of life, as an indicator of CVH in future organizational goal setting.[3]

Abbreviations Used in Chapter 2

AF	atrial fibrillation
AHA	American Heart Association
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DM	diabetes mellitus
ESRD	end-stage renal disease
F&V	fruits and vegetables
FPG	fasting plasma glucose
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HBP	high blood pressure
HF	heart failure
HR	hazard ratio
IHD	ischemic heart disease
IMT	intima-media thickness
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
PA	physical activity
PAF	population attributable fraction
PE	pulmonary embolism
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SE	standard error
SFat	saturated fat
SSB	sugar-sweetened beverage
svg	servings
TC	total cholesterol
VTE	venous thromboembolism

Relevance of Ideal CVH

- Since the AHA announced its 2020 Impact Goals, multiple independent investigations (summaries of which are provided in this chapter) have confirmed the importance of having ideal levels of these components, along with the overall concept of CVH. Findings include strong inverse, stepwise associations in the United States of the number of CVH components at ideal levels with all-cause mortality, CVD mortality, and HF; with subclinical measures of atherosclerosis such as carotid IMT, arterial stiffness, and CAC prevalence and progression; with physical functional impairment and frailty[4]; and with cognitive decline and depression.[4,5] Similar

relationships have also been seen in non-US populations.[4–10]

- A study in a large Hispanic/Latino cohort study in the United States found that associations between CVD and status of CVH components compared favorably with existing national estimates; however, some of the associations varied by sex and heritage.[10]
- A study in blacks found that risk of incident HF was 61% lower among those with ≥4 ideal CVH components than among those with 0 to 2 ideal components.[11]
- Ideal health behaviors and ideal health factors are each independently associated with lower CVD risk in a stepwise fashion (Chart 2-1). In other words, across any level of health behaviors, health factors are associated with incident CVD; conversely, across any level of health factors, health behaviors are still associated with incident CVD.[12]
- Analyses from the US Burden of Disease Collaborators demonstrated that poor levels of each of the 7 CVH components resulted in substantial mortality and morbidity in the United States in 2010. The top risk factor related to overall disease burden was suboptimal diet, followed by tobacco smoking, high BMI, raised BP, high FPG, and physical inactivity.[13]
- An inverse stepwise association was present between the number of ideal CVH components and risk of death based on NHANES data from 1988 to 2006.[14] The HRs for people with 6 or 7 ideal health metrics compared with 0 ideal health components were 0.49 (95% CI, 0.33–0.74) for all-cause mortality, 0.24 (95% CI, 0.13–0.47) for CVD mortality, and 0.30 (95% CI, 0.13–0.68) for IHD mortality.[14]
- A recent meta-analysis of 9 prospective cohort studies involving 12 878 participants reported that having the highest number of ideal CVH components was associated with a lower risk of all-cause mortality (RR, 0.55 [95% CI, 0.37–0.80]), cardiovascular mortality (RR, 0.25 [95% CI, 0.10–0.63]), CVD (RR, 0.20 [95% CI, 0.11–0.37]), and stroke (RR, 0.31 [95% CI, 0.25–0.38]) compared with individuals with the lowest number of ideal components.[15]
- The adjusted PAFs for CVD mortality for individual components of CVH have been reported as follows[14]:
  - 40.6% (95% CI, 24.5%–54.6%) for HBP
  - 13.7% (95% CI, 4.8%–22.3%) for smoking
  - 13.2% (95% CI, 3.5%–29.2%) for poor diet
  - 11.9% (95% CI, 1.3%–22.3%) for insufficient PA
  - 8.8% (95% CI, 2.1%–15.4%) for abnormal glucose levels
- The adjusted PAFs for IHD mortality for individual components of CVH were as follows[14]:
  - 34.7% (95% CI, 6.6%–57.7%) for HBP
  - 16.7% (95% CI, 6.4%–26.6%) for smoking
  - 20.6% (95% CI, 1.2%–38.6%) for poor diet
  - 7.8% (95% CI, 0%–22.2%) for insufficient PA
  - 7.5% (95% CI, 3.0%–14.7%) for abnormal glucose levels
- Several studies have been published in which investigators have assigned individuals a CVH score ranging from 0 to 14 based on the sum of points assigned to each component of CVH (poor=0, intermediate=1, ideal=2 points). Using this approach, data from the REGARDS cohort were used to demonstrate an inverse stepwise association between a higher CVH score component and lower incidence of stroke. On the basis of this score, every unit increase in CVH was associated with an 8% lower risk of incident stroke (HR, 0.92 [95% CI, 0.88–0.95]), with a similar effect size for white (HR, 0.91 [95% CI, 0.86–0.96]) and black (HR, 0.93 [95% CI, 0.87–0.98]) participants.[16]
- The Cardiovascular Lifetime Risk Pooling Project showed that adults with all-optimal risk factor levels (similar to having ideal CVH factor levels of cholesterol, blood sugar, and BP, as well as not smoking) have substantially longer overall and CVD-free survival than those who have poor levels of ≥1 of these CVH factors. For example, at an index age of 45 years, males with optimal risk factor profiles lived on average 14 years longer free of all CVD events and 12 years longer overall than people with ≥2 risk factors.[17]
- Better CVH as defined by the AHA is associated with lower incidence of HF,[18] less subclinical vascular disease,[19,20] better global cognitive performance and cognitive function,[21,22] lower prevalence[23] and incidence[24] of depressive symptoms, lower loss of physical functional status,[25] longer leukocyte telomere length,[26] less ESRD,[27] less pneumonia, less chronic obstructive pulmonary disease,[28] less VTE/PE,[29] lower prevalence of aortic sclerosis and stenosis,[30] lower risk of calcific aortic valve stenosis,[31] better prognosis after MI,[32] and lower risk of AF.[33] In addition, a study among a sample of Hispanics/Latinos residing in the United States reported that greater positive psychological functioning (dispositional optimism) was associated with higher CVH scores as defined by the AHA.[34] A recent study in college students found that both handgrip strength and muscle mass are positively associated with greater numbers of ideal CVH components, providing further evidence of the general health benefits of ideal CVH.[35]
- On the basis of NHANES 1999 to 2006 data, several social risk factors (low family income, low

education level, minority race, and single-living status) were related to lower likelihood of attaining better CVH as measured by Life's Simple 7 scores.[36] In addition, neighborhood factors and contextual relationships have been found to be related to health disparities in CVH, but more research is needed to better understand these complex relationships.[37] Having more ideal CVH components in middle age is also associated with lower non-CVD and CVD healthcare costs in later life.[38] An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with ≥5 ideal CVH components exhibited 24.9% (95% CI, 11.7%–36.0%) lower median annual non-CVD costs and 74.5% (95% CI, 57.5%–84.7%) lower median CVD costs than those with ≤2 ideal CVH components.[38]

- A more recent report from a large, ethnically diverse insured population[39] found that people with 6 or 7 and those with 3 to 5 of the CVH components in the ideal category had a $2021 and $940 lower annual mean healthcare expenditure, respectively, than those with 0 to 2 ideal health components.

CVH: Prevalence (NHANES 2015–2016) (See Table 2-2 and Charts 2-2 through 2-10)

- The most recent national prevalence estimates for children (12–19 years of age) and adults (20–49 years of age and ≥50 years of age) who meet ideal, intermediate, and poor levels of each of the 7 CVH components are displayed in Charts 2-2 and 2-3, respectively.[40] The most current estimates at time of publication were based on data from NHANES 2015 to 2016.
- For most components of CVH, prevalence of ideal levels is higher in US children (12–19 years of age) than in US adults (≥20 years of age), except for the Healthy Diet Score and PA, for which prevalence of ideal levels in children is lower than in adults.
- Among US children (12–19 years of age; Chart 2-2), the unadjusted prevalence of ideal levels of CVH components currently varies from <1% for the Healthy Diet Score (ie, <1 in 100 US children meets at least 4 of the 5 dietary components) to >85% for smoking, BP, and DM components (unpublished AHA tabulation).
- Among US adults (Chart 2-3), the lowest prevalence of ideal levels for CVH components is <1% for the Healthy Diet Score in adults 20 to 49 years of age and ≥50 years of age. The highest prevalence of ideal levels for a CVH component is for smoking (76.6% of adults 20–49 years of age and 81.6% of adults ≥50 years of age report never having smoked or being a former smoker who has quit for >12 months). In 2015 to 2016, 64.6% of adults 20 to 49 years of age and 27.2% of adults ≥50 years of age had ideal levels of TC (<200 mg/dL).
- Age-standardized and age-specific prevalence estimates for ideal CVH and for ideal levels of individual CVH components for 2013 to 2014 and 2015 to 2016 are displayed in Table 2-2.
- In 2015 to 2016, the prevalence of ideal levels of ≥5 or ≥6 CVH components among adults was highest in the youngest age groups (20–39 years of age) and was lowest in the oldest age group (≥60 years of age). A similar pattern occurred for all individual components of CVH except the Healthy Diet Score, for which prevalence of ideal levels was highest in older adults but still <1%.
- Chart 2-4 displays the prevalence estimates for the population of US children (12–19 years of age) meeting ideal criteria for different numbers of CVH components, with a range of 0 to 7 ideal components.
  - Few US children 12 to 19 years of age (3.8%) meet ideal criteria for 2 or fewer components of ideal CVH.
  - Approximately half of US children (50.4%) meet ideal criteria for 3 or 4 components of CVH, and 45.0% meet ideal criteria for ≥5 components of CVH.
  - <1% of children meet ideal criteria for all 7 components of CVH.
- Charts 2-5 and 2-6 display the age-standardized prevalence estimates of US adults meeting ideal criteria for different numbers of CVH components in 2015 to 2016, overall and stratified by age, sex, and race/ethnicity.
  - 2.5% of US adults (≥20 years of age) meet ideal criteria for 0 of the 7 components of CVH, whereas 15.3% meet only 1 of 7 criteria. Having ≤1 ideal CVH component is much less common among younger adults (20–39 years of age), at 4.5%, compared with older adults (≥60 years of age), for whom having ≤1 ideal metric is more common (28.6%).
  - NH Asians have the highest prevalence of meeting ideal criteria for ≥5 components of CVH compared with other racial/ethnic groups.
- Chart 2-7 displays the age-standardized and age-specific prevalence estimates of meeting ideal criteria for ≥5 components of CVH in US adults (≥20 years of age) and US children (12–19 years of age), stratified by race and ethnicity.
  - In adults, the prevalence of ≥5 metrics at ideal levels is highest for NH Asians (26.0%), followed by NH whites (19.2%), Hispanics (12.4%), and NH blacks (11.8%).

- In children, the differences by race/ethnicity are similar to those of adults: prevalence of ≥5 metrics at ideal levels is highest for NH Asians (63.4%), followed by NH whites (48.8%), Hispanics (40.6%), and NH blacks (35.2%).

- Chart 2-8 displays the age-standardized and age-specific prevalence of meeting criteria for ideal levels of ≥5 components of CVH in US adults (≥20 years of age) and US children (12–19 years of age) in 2015 to 2016, stratified by race and ethnicity.
  - In both males and females and in both adults and children, higher prevalence of meeting ideal criteria for ≥5 components of CVH was observed in 2015 to 2016 than in 2007 to 2008, although differences were not statistically significant.
- Chart 2-9 displays the age-standardized percentages of US adults meeting poor or ideal criteria for different numbers of CVH components in 2015 to 2016. Attaining the AHA 2020 Strategic Impact Goal for CVH is predicated on reducing the relative prevalence of individuals with poor levels of CVH while increasing the relative percentage of those with ideal levels for each of the 7 components.
  - Approximately two-thirds (63.2%) of US adults have ≤2 components at poor levels.
  - Conversely, 40.6% of adults have ≤2 components at ideal levels; approximately half (45.9%) of US adults have between 2 and 3 ideal CVH components.
  - Few US adults (3%) have ≥5 components at poor levels.
- Chart 2-10 displays the age-standardized percentages of US adults meeting ideal criteria for ≥5 components of CVH, stratified by both educational attainment and household income-to-poverty ratio in 2015 to 2016.
  - The lowest prevalence (5.7%) of meeting ideal criteria for ≥5 components of CVH was observed in adults with both the lowest level of education (<high school) and lowest household income (<100%).
  - At all levels of household income-to-poverty ratio, the highest prevalence of meeting ideal criteria for ≥5 ideal CVH components was observed in those with the highest level of educational attainment (college graduate; 24.2%–30.3%).

CVH: Trends Over Time (See Charts 2-11 through 2-14)

- The trends in prevalence of meeting ideal criteria for the individual components of CVH from 1999 to 2000 to 2015 to 2016 (for diet, trends from 2003–2004 through 2015–2016) are shown in Chart 2-11 for children (12–19 years of age) and in Chart 2-12 for adults (≥20 years of age).
  - Among children from 1999 to 2000 to 2015 to 2016, the prevalence of meeting ideal criteria for smoking and BP have consistently improved. For example, the prevalence of nonsmoking among children 12 to 19 years of age increased from 76.4% to 93.6%. For ideal TC, the prevalence increased from 72.0% to 77.7%. However, declines in prevalence of ideal levels were observed for PA (38.4% to 25.4%), BMI (69.8% to 60.1%), and DM (92.4% to 86.2%).
  - From 1999 to 2000 to 2015 to 2016, the prevalence of meeting ideal criteria for smoking, TC, BP, and PA increased among adults. For example, the prevalence of being a never-smoker or having quit ≥1 year prior increased from 72.9% to 78.8%. Over the 18-year period, the prevalence of meeting criteria for ideal TC increased from 45.1% to 49.4%. Similar to trends observed in children, declines in prevalence of ideal levels were observed for BMI (from 36.3% to 28.7%), and DM (from 69.1% to 58.4%) among adults.
- The prevalence trends from 2003 to 2004 to 2015 to 2016 for meeting ideal criteria for ≥5 components of CVH according to categories of household income (ie, household income-to-poverty ratio) among adults (≥20 years of age) are shown in Chart 2-13.
  - Across all time points, the highest prevalence of meeting ideal criteria for ≥5 components of CVH was observed among individuals in the highest category of household income-to-poverty ratio (≥500%); higher household income-to-poverty ratio is consistently associated with a higher prevalence of meeting ideal criteria for ≥5 components of CVH.
  - Between 2003 and 2016, little variation was observed in prevalence of meeting ideal criteria for ≥5 components of CVH across categories of household income-to-poverty ratio; the greatest increases were observed among individuals with 300% to 499% household income-to-poverty ratio (15.3% to 20.3%).
- The prevalence trends from 2003 to 2004 to 2015 to 2016 for meeting ideal criteria for ≥5 components of CVH according to categories of educational attainment among adults (≥20 years of age) are shown in Chart 2-14.
  - Trends in prevalence for meeting ideal criteria for ≥5 components of CVH according to category of educational attainment are similar to those observed for household income: higher educational attainment is consistently associated with a higher prevalence of meeting ideal criteria for ≥5 components of CVH.

— Across all time points, the highest prevalence of meeting ideal criteria for ≥5 components of CVH was observed among individuals in the highest category of educational attainment (college graduate). However, ≤10% of individuals with educational attainment of high school or less exhibit ≥5 ideal CVH components over time.

- If trends in CVH metrics established on the basis of NHANES data from 1988 to 2008 continued forward, the estimated CVH in the United States is projected to improve by 6% by 2020, short of the AHA's goal of 20% improvement.[41] On the basis of these trend estimates among individual metrics, anticipated declines in prevalence of smoking, high cholesterol, and HBP (in males) would be offset by substantial increases in the prevalence of obesity and DM and smaller changes in ideal dietary patterns or PA.[41]
- On the basis of these projections for CVH factors and behaviors, CHD deaths are projected to decrease by 30% between 2010 and 2020 because of projected improvements in TC, SBP, smoking, and PA (≈167 000 fewer deaths), offset by increases in DM and BMI (≈24 000 more deaths).[42]

Achieving the 2020 Impact Goals (See Chart 2-15)

To achieve the AHA's 2020 Impact Goals of reducing deaths attributable to CVD and stroke by 20%,[1] continued emphasis is needed on the treatment of acute CVD events and on secondary prevention through treatment and control of health behaviors and risk factors.

- Taken together, the data continue to demonstrate the tremendous relevance of the AHA's 2020 Impact Goals both for improved CVH and health in general. However, progress in health behavior and risk profiles in the United States is needed to more fully realize these benefits for all Americans (Chart 2-15).
- For each CVH metric, modest shifts in the population distribution toward improved health would produce appreciable increases in the proportion of Americans in both ideal and intermediate categories. For example, small reductions in population BP could result from small health behavior changes at a population level, such as increased PA, increased fruit and vegetable consumption, decreased sodium intake, decreased adiposity, or some combination of these and other lifestyle changes, with resulting substantial projected decreases in CVD rates in US adults.[43–45]
- A range of complementary strategies and approaches can lead to improvements in CVH. These include the following:
  — Individual-focused approaches that target lifestyle and treatments at the individual level.
  — Healthcare systems approaches that encourage, facilitate, and reward efforts by providers to improve health behaviors and health factors.
  — Population approaches that target lifestyle and treatments in schools or workplaces, local communities, and states, as well as throughout the nation.
- The metrics with the greatest potential for improvement in the United States are health behaviors, including diet quality, PA, and body weight. However, each of the 7 CVH metrics can be improved and deserve major focus.

Table 2-1. Definitions of Poor, Intermediate, and Ideal for Each Component of CVH

	Level of CVH for Each Metric		
	Poor	**Intermediate**	**Ideal**
Current smoking			
Adults ≥20 y of age	Yes	Former ≥12 mo	Never or quit >12 mo
Children 12–19 y of age*	Tried during the prior 30 d	…	Never tried; never smoked whole cigarette
BMI†			
Adults ≥20 y of age	≥30 kg/m^2	25–29.9 kg/m^2	<25 kg/m^2
Children 2–19 y of age	>95th percentile	85th–95th percentile	<85th percentile
Physical activity			
Adults ≥20 y of age	None	1–149 min/wk moderate or 1–74 min/wk vigorous or 1–149 min/wk moderate + 2× vigorous	≥150 min/wk moderate or ≥75 min/wk vigorous or ≥150 min/wk moderate + 2× vigorous
Children 12–19 y of age	None	>0 and <60 min of moderate or vigorous every day	≥60 min of moderate or vigorous every day
Healthy diet score, No. of components‡			
Adults ≥20 y of age	<2 (0–39)	2–3 (40–79)	4–5 (80–100)
Children 5–19 y of age	<2 (0–39)	2–3 (40–79)	4–5 (80–100)
TC, mg/dL			
Adults ≥20 y of age	≥240	200–239 or treated to goal	<200
Children 6–19 y of age	≥200	170–199	<170
Blood pressure			
Adults ≥20 y of age	SBP ≥140 mm Hg or DBP ≥90 mm Hg	SBP 120–139 mm Hg or DBP 80–89 mm Hg or treated to goal	<120 mm Hg/<80 mm Hg
Children 8–19 y of age	>95th percentile	90th–95th percentile or SBP ≥120 mm Hg or DBP ≥80 mm Hg	<90th percentile
Diabetes mellitus§			
Adults ≥20 y of age	FPG ≥126 mg/dL or HbA_{1c} ≥6.5%	FPG 100–125 mg/dL or HbA_{1c} 5.7%–6.4% or treated to goal	FPG <100 mg/dL or HbA_{1c} <5.7%
Children 12–19 y of age	FPG ≥126 mg/dL or HbA_{1c} ≥6.5%	FPG 100–125 mg/dL or HbA_{1c} 5.7%–6.4% or treated to goal	FPG <100 mg/dL or HbA_{1c} <5.7%

BMI indicates body mass index; CVH, cardiovascular health; DBP, diastolic blood pressure; ellipses (…), data not available; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin or hemoglobin A_{1c}; SBP, systolic blood pressure; and TC, total cholesterol.

*Age ranges in children for each metric depend on guidelines and data availability.

†Represents appropriate energy balance; that is, appropriate dietary quantity and physical activity to maintain normal body weight.

‡In the context of a healthy dietary pattern that is consistent with a Dietary Approaches to Stop Hypertension (DASH)–type eating pattern, to consume ≥4.5 cups/d of fruits and vegetables, ≥2 servings/wk of fish, and ≥3 servings/d of whole grains and no more than 36 oz/wk of sugar-sweetened beverages and 1500 mg/d of sodium. The consistency of one's diet with these dietary targets can also be described using a continuous American Heart Association diet score, scaled from 0 to 100 (see chapter on Nutrition).

§FPG is solely used to determine poor, intermediate, and ideal status for American Heart Association Strategic Impact Goal monitoring purposes. For population surveillance purposes, use of HbA_{1c} was added to define poor, intermediate, and ideal levels of this component, and the name was changed to "Diabetes mellitus" to reflect this addition.

Source: Modified from Lloyd-Jones et al.[1]

Table 2-2. Prevalence of Ideal CVH and Its Components in the US Population in Selected Age Strata: NHANES 2013 to 2014 and 2015 to 2016

	Age 12–19 y	Age ≥20 y*	Age 20–39 y	Age 40–59 y	Age ≥60 y
Ideal CVH profile (7/7)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
≥6 Ideal	7.2 (1.1)	5.3 (0.5)	11.0 (1.0)	2.2 (0.6)	0.7 (0.4)
≥5 Ideal	45.0 (2.7)	17.4 (0.7)	31.6 (1.3)	10.6 (1.0)	4.1 (0.8)
Ideal health factors (4/4)	54.9 (2.4)	17.0 (0.6)	31.4 (1.3)	10.2 (1.1)	2.5 (0.8)
TC <200 mg/dL	77.7 (1.3)	49.4 (1.1)	72.9 (1.4)	39.0 (1.7)	25.2 (1.2)
SBP <120/DBP <80 mm Hg	85.2 (1.0)	41.0 (1.2)	61.7 (1.7)	34.1 (2.0)	15.6 (2.1)
FPG <100 mg/dL and HbA_{1c} <5.7%	86.2 (1.4)	58.4 (1.4)	79.3 (1.1)	51.2 (2.5)	32.4 (1.6)
Ideal health behaviors (4/4)	0.0 (0.0)	0.1 (0.0)	0.0 (0.0)	0.0 (0.0)	0.2 (0.1)
PA at goal	25.4 (1.6)	41.5 (1.7)	52.4 (1.7)	37.9 (2.3)	28.2 (1.9)
Nonsmoker	93.6 (0.9)	78.8 (1.0)	75.0 (1.4)	77.0 (1.5)	86.5 (1.4)
BMI <25 kg/m^2	60.1 (1.9)	28.7 (1.6)	35.2 (1.8)	25.2 (2.1)	24.0 (2.1)
4 or 5 Diet goals met†	0.0 (0.0)	0.3 (0.1)	0.1 (0.1)	0.1 (0.1)	0.7 (0.3)
F&V ≥4.5 C/d	3.7 (0.9)	10.2 (0.6)	7.8 (0.9)	11.1 (1.4)	13.8 (1.1)
Fish ≥2 svg/wk	7.6 (1.0)	18.0 (1.7)	15.9 (2.5)	19.3 (2.3)	18.7 (1.6)
Sodium <1500 mg/d	0.6 (0.3)	0.7 (0.2)	0.8 (0.3)	0.9 (0.4)	0.2 (0.1)
SSB <36 oz/wk	40.4 (2.6)	53.3 (1.7)	47.7 (2.9)	51.6 (2.3)	66.5 (2.7)
Whole grains ≥3 1-oz/d	6.8 (0.8)	7.1 (0.6)	5.9 (1.2)	6.5 (0.9)	9.5 (1.1)
Secondary diet metrics					
Nuts/legumes/seeds ≥4 svg/wk	36.7 (2.4)	52.4 (1.7)	48.9 (3.0)	54.9 (2.3)	54.1 (1.8)
Processed meats ≤2 svg/wk	39.2 (2.8)	44.0 (0.9)	45.4 (1.1)	44.0 (1.7)	41.9 (2.6)
SFat <7% total kcal	4.5 (1.0)	8.4 (0.5)	8.8 (1.1)	8.9 (0.7)	6.8 (0.9)

Values are % (SE). BMI indicates body mass index; CVH, cardiovascular health; DBP, diastolic blood pressure; F&V, fruits and vegetables; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c} (glycosylated hemoglobin); NHANES, National Health and Nutrition Examination Survey; PA, physical activity; SBP, systolic blood pressure; SFat, saturated fat; SSB, sugar-sweetened beverages; svg, servings; and TC, total cholesterol.

*Standardized to the age distribution of the 2000 US standard population.

†Scaled to 2000 kcal/d and in the context of appropriate energy balance and a DASH (Dietary Approaches to Stop Hypertension)–type eating pattern.

Source: Unpublished American Heart Association tabulation using NHANES 2013 to 2014 and 2015 to 2016.[40]

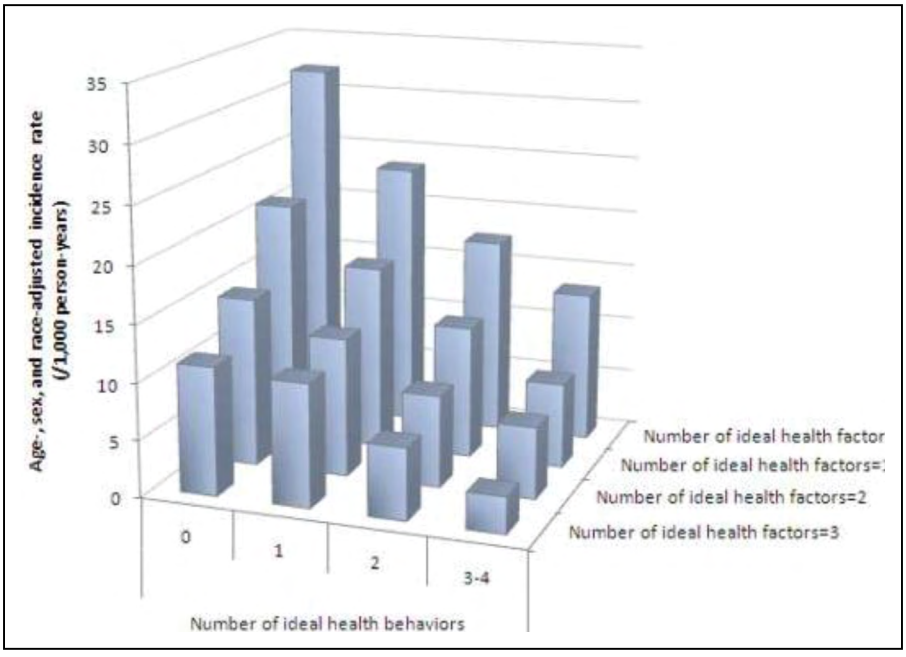

Chart 2-1. Incidence of cardiovascular disease according to the number of ideal health behaviors and health factors.
Source: Reprinted from Folsom et al[12] with permission from the American College of Cardiology Foundation. Copyright © 2011, the American College of Cardiology Foundation.

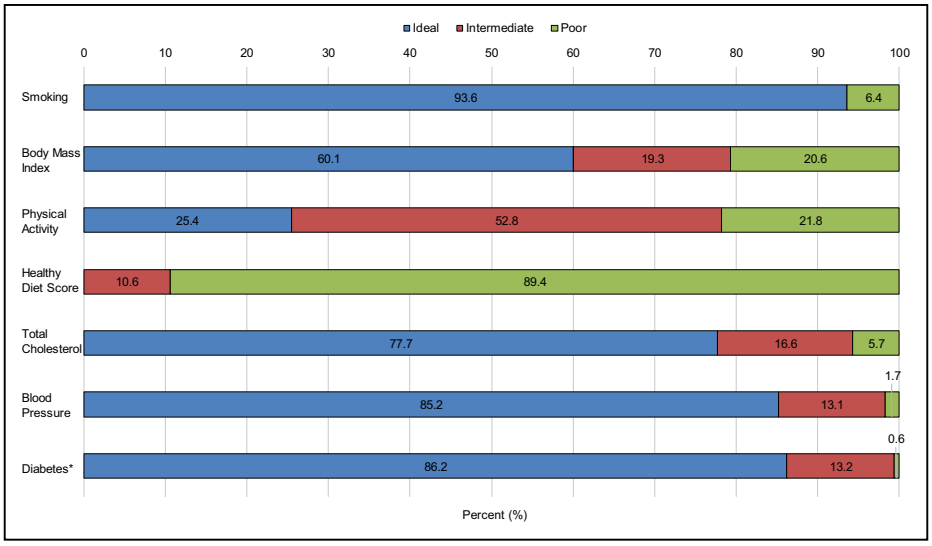

Chart 2-2. Prevalence (unadjusted) estimates of poor, intermediate, and ideal cardiovascular health (CVH) for each component of CVH among US children 12 to 19 years of age, 2015 to 2016.

*Categories defined by either fasting plasma glucose or HbA_{1c} based on data availability.

Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[40]

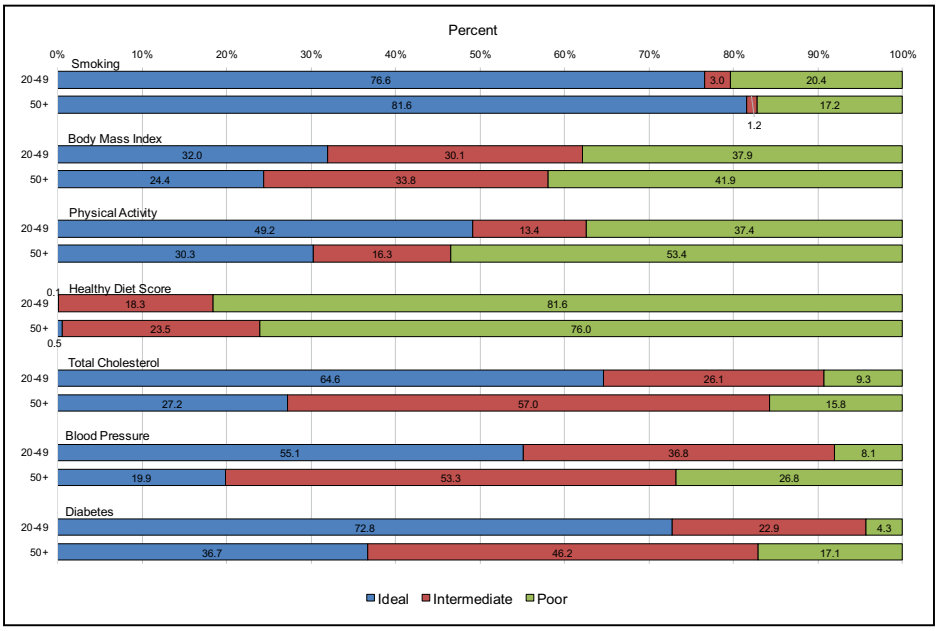

Chart 2-3. Prevalence (unadjusted) estimates of poor, intermediate, and ideal cardiovascular health (CVH) for each component of CVH among US adults 20 to 49 years of age and ≥50 years of age, 2015 to 2016.

Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[40]

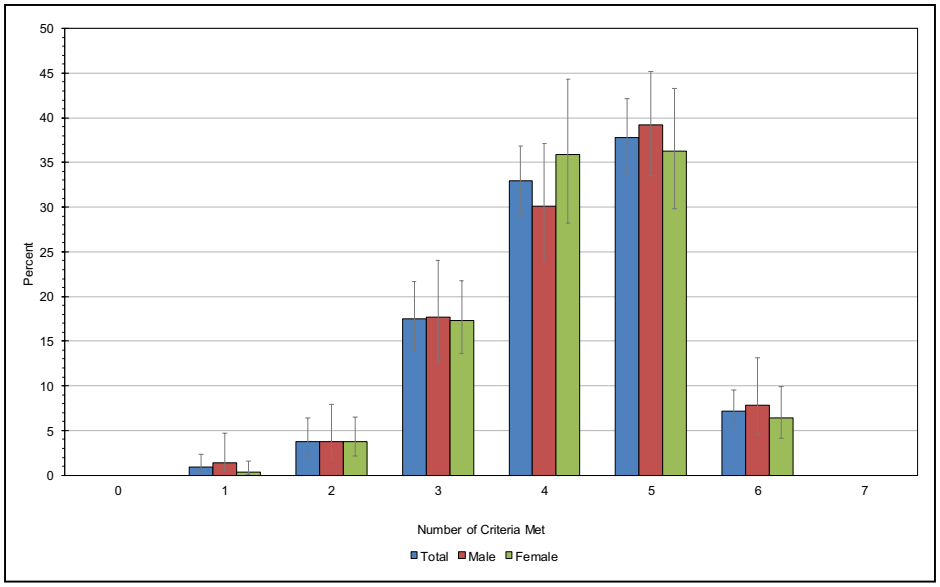

Chart 2-4. Prevalence (unadjusted) of US children 12 to 19 years of age meeting ideal criteria for different numbers of cardiovascular health components, overall and by sex, 2015 to 2016.
Error bars represent 95% CI.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[40]

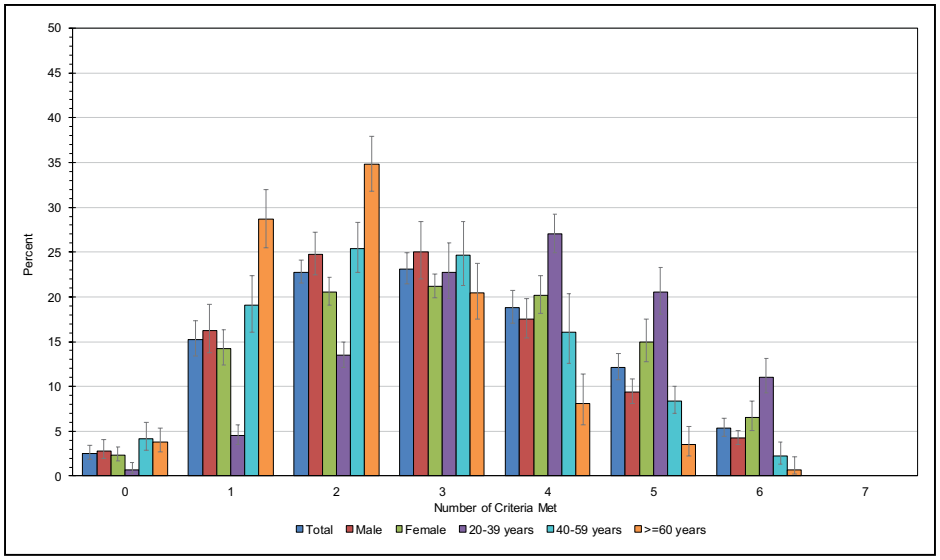

Chart 2-5. Age-standardized prevalence estimates of US adults ≥20 years of age meeting ideal criteria for different numbers of cardiovascular health components, overall and by sex and age groups, 2015 to 2016.
Error bars represent 95% CI.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[40]

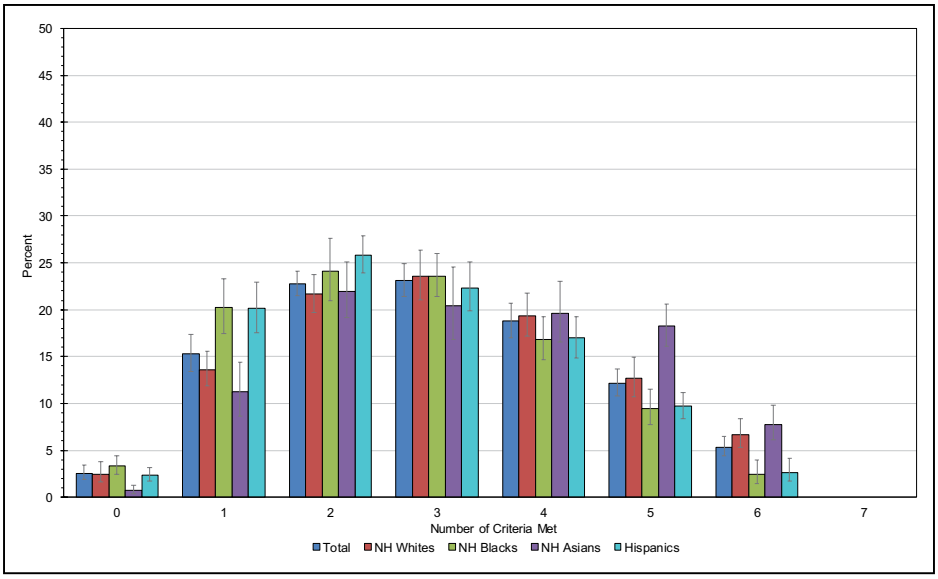

Chart 2-6. Age-standardized prevalence estimates of US adults ≥20 years of age meeting ideal criteria for different numbers of components of cardiovascular health, overall and by race/ethnicity, 2013 to 2014.
Error bars represent 95% CI.
NH indicates non-Hispanic.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2013 to 2014.[40]

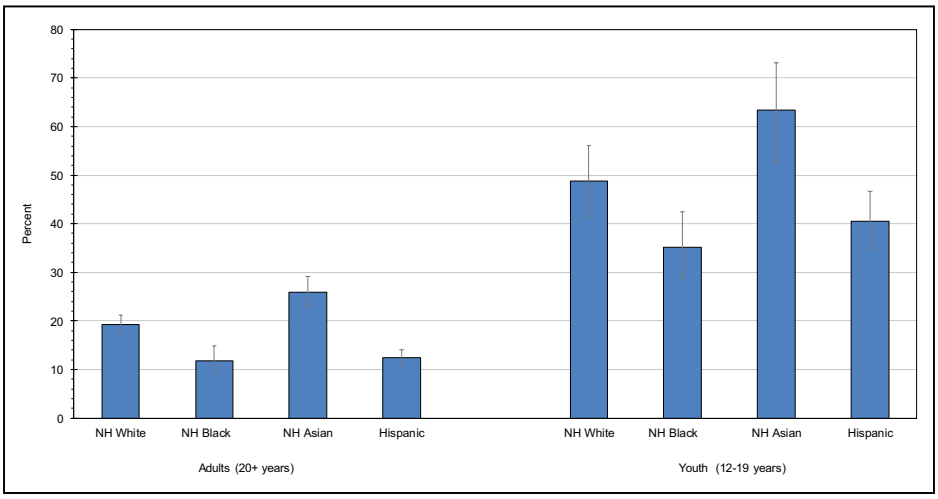

Chart 2-7. Prevalence of meeting ≥5 criteria for ideal cardiovascular health among US adults ≥20 years of age (age-standardized) and US children 12 to 19 years of age by race/ethnicity, 2007 to 2008 and 2015 to 2016.
Error bars represent 95% CI.
NH indicates non-Hispanic.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2007 to 2008 and 2015 to 2016.[40]

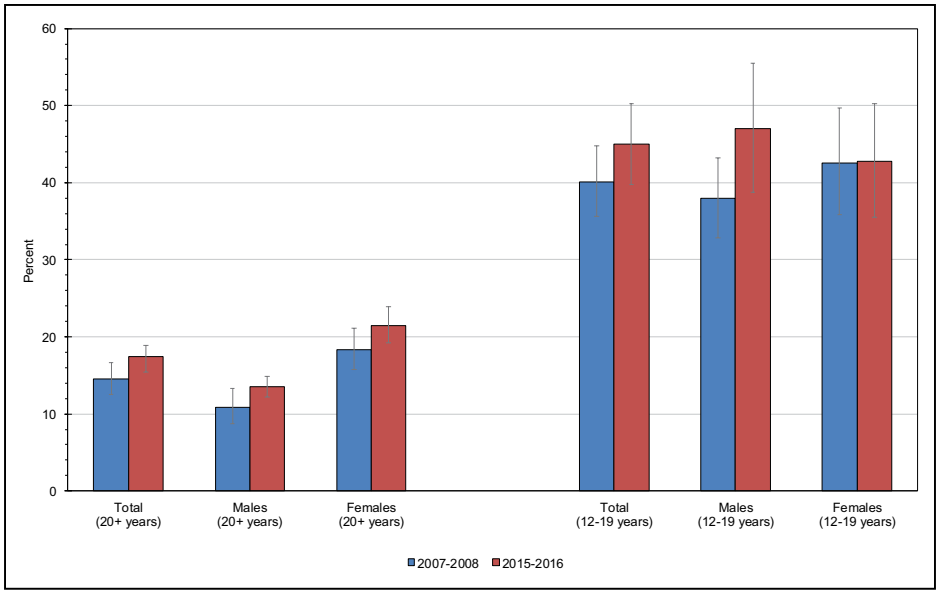

Chart 2-8. Prevalence of meeting idea criteria for ≥5 components of cardiovascular health among US adults ≥20 years of age (age-standardized) and US children 12 to 19 years of age between 2007 to 2008 and 2015 to 2016, overall and by sex.
Error bars represent 95% CI.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2007 to 2008 and 2015 to 2016.[40]

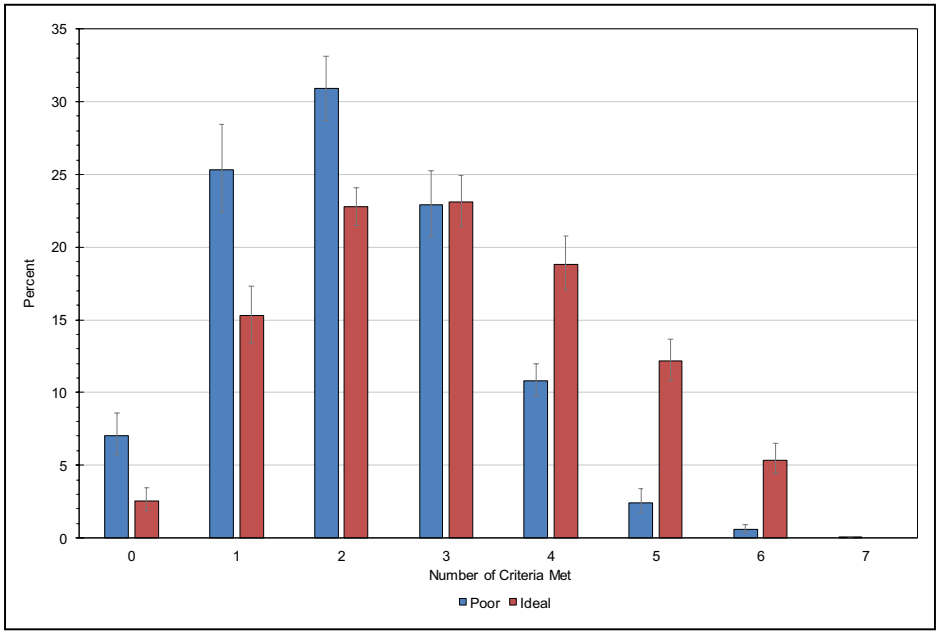

Chart 2-9. Age-standardized prevalence estimates of US adults (≥20 years of age) meeting ideal or poor criteria for different numbers of cardiovascular health components, 2015 to 2016.
Error bars represent 95% CI.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[40]

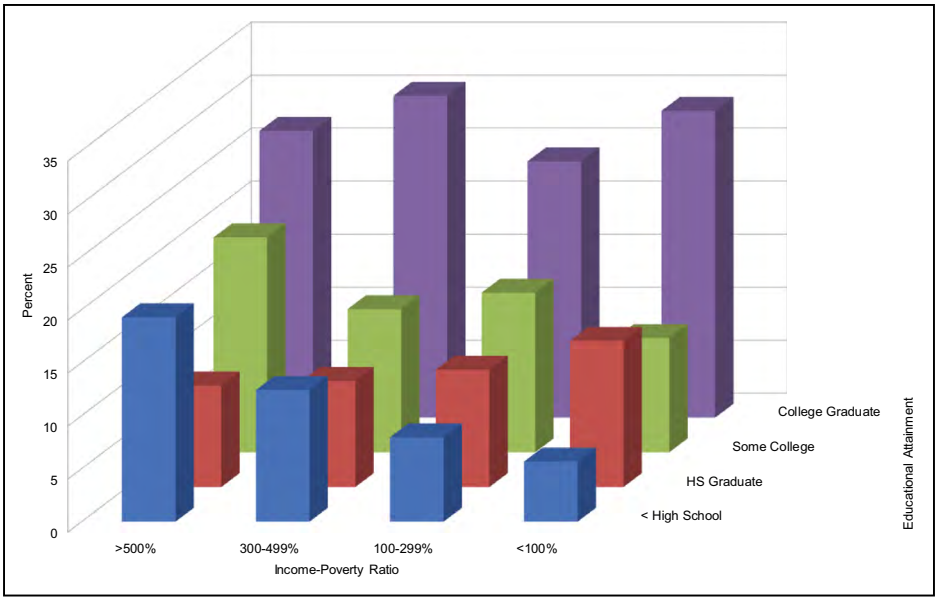

Chart 2-10. Age-standardized prevalence of meeting ideal criteria for ≥5 components of cardiovascular health among US adults ≥20 years of age by educational attainment and household income-to-poverty ratio, 2015 to 2016.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[40]

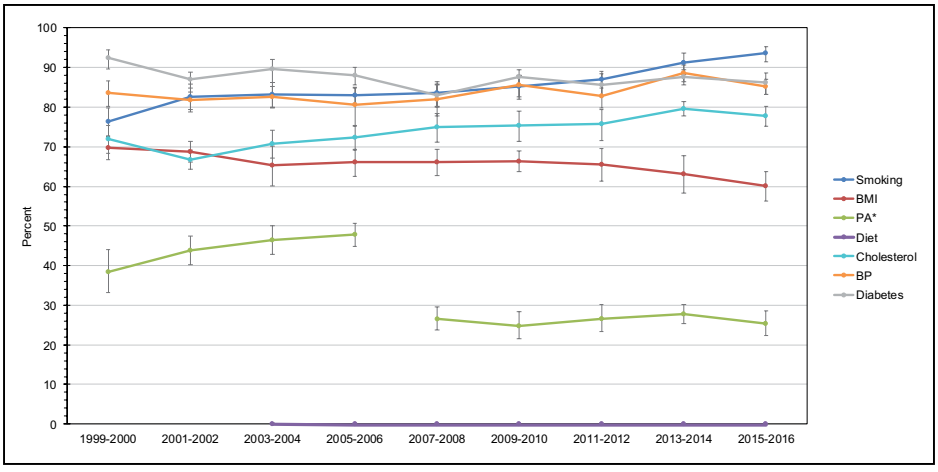

Chart 2-11. Trends in prevalence (unadjusted) of meeting ideal criteria for individual components of cardiovascular health (CVH) among US children (12–19 years of age), 1999 to 2000 through 2015 to 2016.
Error bars represent 95% CI. Data for the Healthy Diet Score, based on a 2-day average intake, were only available for the 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012 NHANES cycles at the time of this analysis.
BMI indicates body mass index; BP, blood pressure; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.
*Because of changes in the physical activity questionnaire between NHANES cycles 1999 to 2006 and 2007 to 2016, prevalence trends over time for this CVH component should be interpreted with caution, and statistical comparisons should not be attempted. Trend lines are absent between these time frames as an indicator of this issue.
Source: Unpublished American Heart Association tabulation using NHANES, 1999 to 2000 through 2015 to 2016.[40]

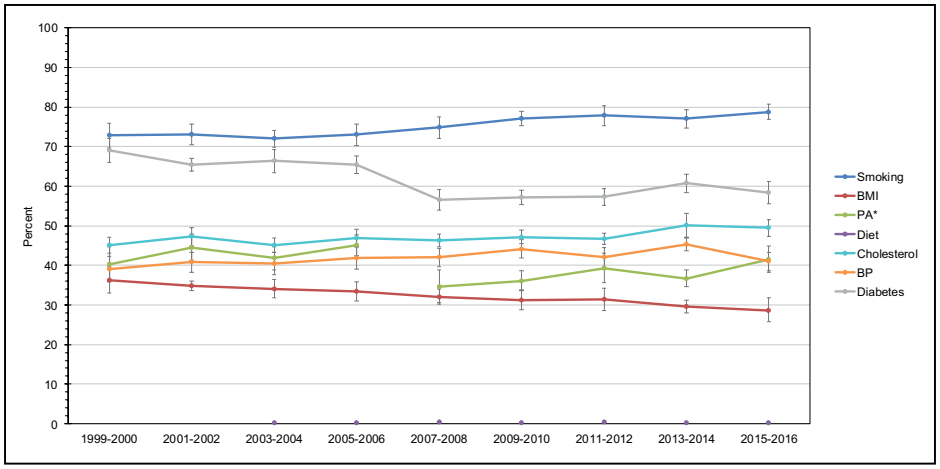

Chart 2-12. Age-standardized trends in prevalence of meeting ideal criteria for individual components of cardiovascular health (CVH) among US adults (≥20 years of age), 1999 to 2000 through 2015 to 2016.

Error bars represent 95% CI. Data for the Healthy Diet Score, based on a 2-day average intake, were only available for the 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012 NHANES cycles at the time of this analysis.

BMI indicates body mass index; BP, blood pressure; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

*Because of changes in the physical activity questionnaire between NHANES cycles 1999 to 2006 and 2007 to 2016, prevalence trends over time for this CVH component should be interpreted with caution, and statistical comparisons should not be attempted. Trend lines are absent between these time frames as an indicator of this issue.

Source: Unpublished American Heart Association tabulation using NHANES, 1999 to 2000 through 2015 to 2016.[40]

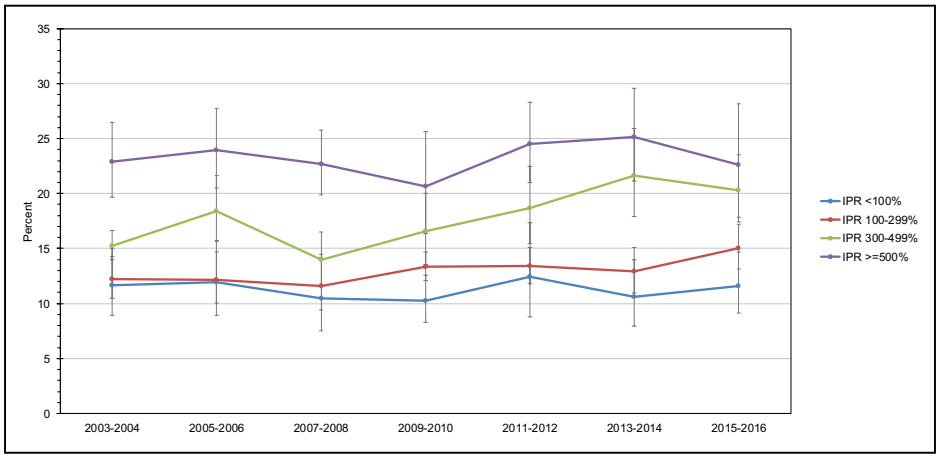

Chart 2-13. Age-standardized trends in prevalence of meeting ideal criteria for ≥5 components of cardiovascular health among US adults (≥20 years of age) by household IPR, 2003 to 2004 through 2015 to 2016.

Error bars represent 95% CI.

IPR indicates income-to-poverty ratio.

Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2003 to 2004 through 2015 to 2016.[40]

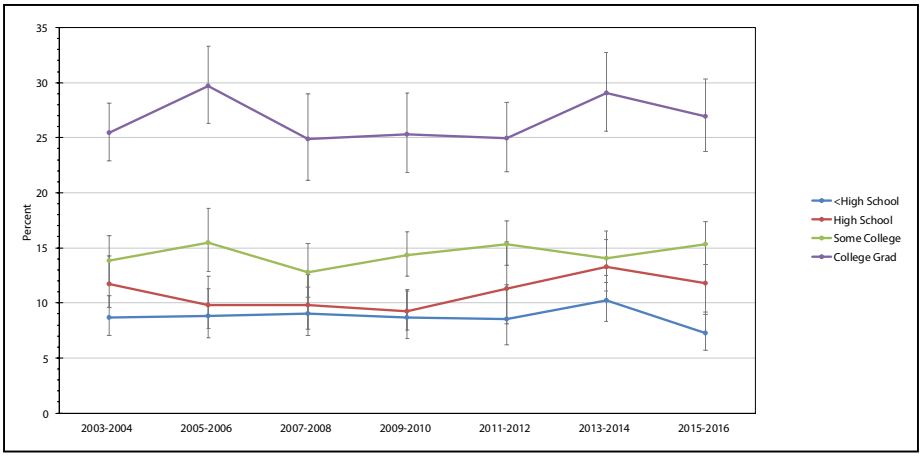

Chart 2-14. Age-standardized trends in prevalence of meeting ideal criteria for ≥5 components of cardiovascular health among US adults (≥20 years of age) by educational attainment, 2003 to 2004 through 2015 to 2016.
Error bars represent 95% CI.
Grad indicates graduate.
Source: Unpublished American Heart Association tabulation using National Health and Nutrition Examination Survey, 2003 to 2004 through 2015 to 2016.[40]

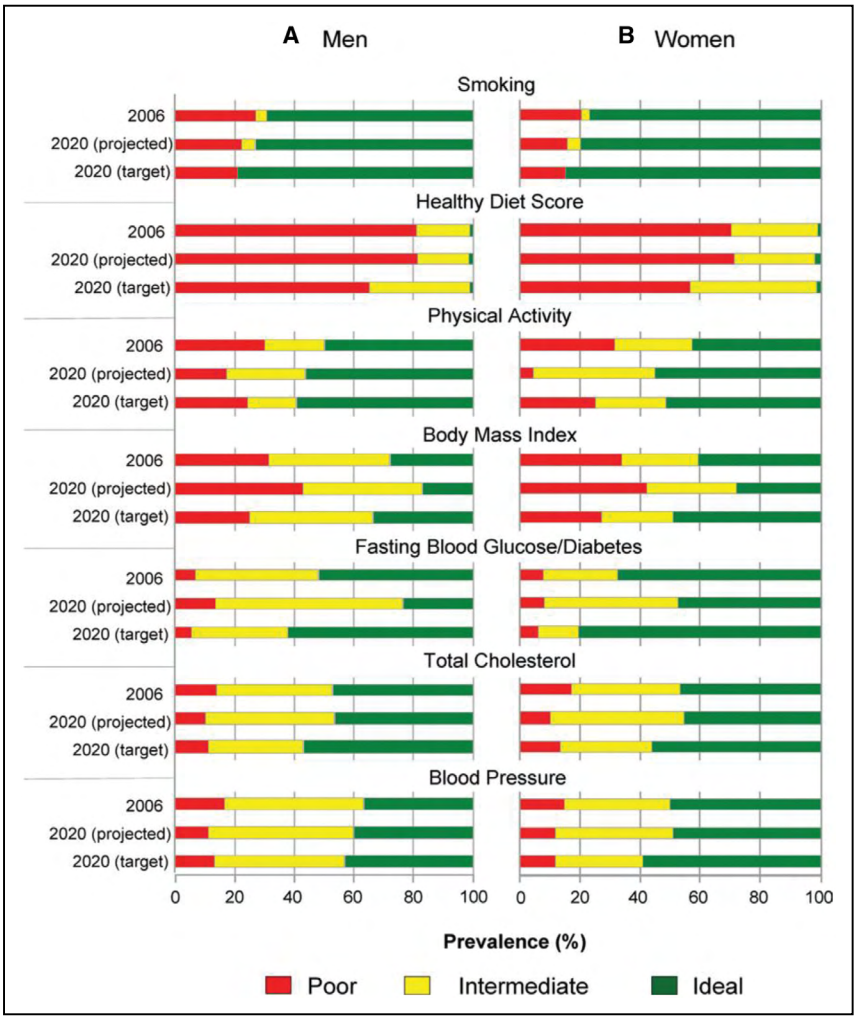

Chart 2-15. Prevalence of ideal, intermediate, and poor cardiovascular health (CVH) metrics in the United States in 2006 (AHA 2020 Strategic Impact Goals baseline year) and 2020 projections assuming current trends continue.
The 2020 targets for each CVH metric assume a 20% relative increase in ideal CVH prevalence metrics and a 20% relative decrease in poor CVH prevalence metrics for males and females.
AHA indicates American Heart Association.
Source: Reprinted from Huffman et al.[41] Copyright © 2012, American Heart Association, Inc.

REFERENCES

1. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
2. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check–lifes-simple-7. Accessed March 11, 2019.
3. Rumsfeld JS, Alexander KP, Goff DC Jr, Graham MM, Ho PM, Masoudi FA, Moser DK, Roger VL, Slaughter MS, Smolderen KG, et al; on behalf of the American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Stroke Council. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation.* 2013;127:2233–2249. doi: 10.1161/CIR.0b013e3182949a2e
4. Shay CM, Gooding HS, Murillo R, Foraker R. Understanding and improving cardiovascular health: an update on the American Heart Association's concept of cardiovascular health. *Prog Cardiovasc Dis.* 2015;58:41–49. doi: 10.1016/j.pcad.2015.05.003
5. Chang Y, Guo X, Chen Y, Guo L, Li Z, Yu S, Yang H, Sun G, Sun Y. Prevalence and metrics distribution of ideal cardiovascular health: a population-based, cross-sectional study in rural China. *Heart Lung Circ.* 2016;25:982–992. doi: 10.1016/j.hlc.2016.02.007
6. Laitinen T. *Cardiovascular health from childhood to adulthood–with special reference to early vascular changes: The Cardiovascular Risk in Young Finns Study [master's thesis].* Helsinki, Finland: University of Turku; 2015.
7. Laitinen TT, Pahkala K, Magnussen CG, Oikonen M, Viikari JS, Sabin MA, Daniels SR, Heinonen OJ, Taittonen L, Hartiala O, et al. Lifetime measures of ideal cardiovascular health and their association with subclinical atherosclerosis: the Cardiovascular Risk in Young Finns Study. *Int J Cardiol.* 2015;185:186–191. doi: 10.1016/j.ijcard.2015.03.051
8. Younus A, Aneni EC, Spatz ES, Osondu CU, Roberson L, Ogunmoroti O, Malik R, Ali SS, Aziz M, Feldman T, et al. A systematic review of the prevalence and outcomes of ideal cardiovascular health in US and non-US populations. *Mayo Clin Proc.* 2016;91:649–670. doi: 10.1016/j.mayocp.2016.01.019
9. Zhou L, Zhao L, Wu Y, Wu Y, Gao X, Li Y, Mai J, Nie Z, Ou Y, Guo M, et al. Ideal cardiovascular health metrics and its association with 20-year cardiovascular morbidity and mortality in a Chinese population. *J Epidemiol Community Health.* 2018;72:752–758. doi: 10.1136/jech-2017-210396
10. González HM, Tarraf W, Rodríguez CJ, Gallo LC, Sacco RL, Talavera GA, Heiss G, Kizer JR, Hernandez R, Davis S, et al. Cardiovascular health among diverse Hispanics/Latinos: Hispanic Community Health Study/Study of Latinos (HCHS/SOL) results. *Am Heart J.* 2016;176:134–144. doi: 10.1016/j.ahj.2016.02.008
11. Spahillari A, Talegawkar S, Correa A, Carr JJ, Terry JG, Lima J, Freedman JE, Das S, Kociol R, de Ferranti S, et al. Ideal cardiovascular health, cardiovascular remodeling, and heart failure in blacks: the Jackson Heart Study. *Circ Heart Fail.* 2017;10:e003682. doi: 10.1161/CIRCHEARTFAILURE.116.003682
12. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol.* 2011;57:1690–1696. doi: 10.1016/j.jacc.2010.11.041
13. Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, Dellavalle R, Danaei G, Ezzati M, Fahimi A,et al; U.S. Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310:591–608. doi: 10.1001/jama.2013.13805
14. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA.* 2012;307:1273–1283. doi: 10.1001/jama.2012.339
15. Fang N, Jiang M, Fan Y. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: a meta-analysis. *Int J Cardiol.* 2016;214:279–283. doi: 10.1016/j.ijcard.2016.03.210
16. Kulshreshtha A, Vaccarino V, Judd SE, Howard VJ, McClellan WM, Muntner P, Hong Y, Safford MM, Goyal A, Cushman M. Life's Simple 7 and risk of incident stroke: the Reasons for Geographic and Racial Differences in Stroke study. *Stroke.* 2013;44:1909–1914. doi: 10.1161/STROKEAHA.111.000352
17. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA.* 2012;308:1795–1801. doi: 10.1001/jama.2012.14312
18. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med.* 2015;128:970–976.e2. doi: 10.1016/j.amjmed.2015.03.027
19. Robbins JM, Petrone AB, Carr JJ, Pankow JS, Hunt SC, Heiss G, Arnett DK, Ellison RC, Gaziano JM, Djoussé L. Association of ideal cardiovascular health and calcified atherosclerotic plaque in the coronary arteries: the National Heart, Lung, and Blood Institute Family Heart Study. *Am Heart J.* 2015;169:371–378.e1. doi: 10.1016/j.ahj.2014.12.017
20. Saleem Y, DeFina LF, Radford NB, Willis BL, Barlow CE, Gibbons LW, Khera A. Association of a favorable cardiovascular health profile with the presence of coronary artery calcification. *Circ Cardiovasc Imaging.* 2015;8:e001851. doi: 10.1161/CIRCIMAGING.114.001851
21. Crichton GE, Elias MF, Davey A, Alkerwi A. Cardiovascular health and cognitive function: the Maine-Syracuse Longitudinal Study. *PLoS One.* 2014;9:e89317. doi: 10.1371/journal.pone.0089317
22. Thacker EL, Gillett SR, Wadley VG, Unverzagt FW, Judd SE, McClure LA, Howard VJ, Cushman M. The American Heart Association Life's Simple 7 and incident cognitive impairment: rhe REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc.* 2014;3:e000635. doi: 10.1161/JAHA.113.000635
23. Kronish IM, Carson AP, Davidson KW, Muntner P, Safford MM. Depressive symptoms and cardiovascular health by the American Heart Association's definition in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *PLoS One.* 2012;7:e52771. doi: 10.1371/journal.pone.0052771
24. España-Romero V, Artero EG, Lee DC, Sui X, Baruth M, Ruiz JR, Pate RR, Blair SN. A prospective study of ideal cardiovascular health and depressive symptoms. *Psychosomatics.* 2013;54:525–535. doi: 10.1016/j.psym.2013.06.016
25. Dhamoon MS, Dong C, Elkind MS, Sacco RL. Ideal cardiovascular health predicts functional status independently of vascular events: the Northern Manhattan Study. *J Am Heart Assoc.* 2015;4:e001322. doi: 10.1161/JAHA.114.001322
26. Gebreab SY, Manna ZG, Khan RJ, Riestra P, Xu R, Davis SK. Less than ideal cardiovascular health is associated with shorter leukocyte telomere length: the National Health and Nutrition Examination Surveys, 1999-2002. *J Am Heart Assoc.* 2017;6:e004105. doi: 10.1161/JAHA.116.004105
27. Han QL, Wu SL, Liu XX, An SS, Wu YT, Gao JS, Chen SH, Liu XK, Zhang Q, Mao RY, et al. Ideal cardiovascular health score and incident end-stage renal disease in a community-based longitudinal cohort study: the Kailuan Study. *BMJ Open.* 2016;6:e012486. doi: 10.1136/bmjopen-2016-012486
28. Fan W, Lee H, Lee A, Kieu C, Wong ND. Association of lung function and chronic obstructive pulmonary disease with American Heart Association's Life's Simple 7 cardiovascular health metrics. *Respir Med.* 2017;131:85–93. doi: 10.1016/j.rmed.2017.08.001
29. Olson NC, Cushman M, Judd SE, McClure LA, Lakoski SG, Folsom AR, Safford MM, Zakai NA. American Heart Association's Life's Simple 7 and risk of venous thromboembolism: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc.* 2015;4:e001494. doi: 10.1161/JAHA.114.001494
30. Sengeløv M, Cheng S, Biering-Sørensen T, Matsushita K, Konety S, Solomon SD, Folsom AR, Shah AM. Ideal cardiovascular health and the prevalence and severity of aortic stenosis in elderly patients. *J Am Heart Assoc.* 2018;7:e007234. doi: 10.1161/JAHA.117.007234
31. Perrot N, Boekholdt SM, Mathieu P, Wareham NJ, Khaw KT, Arsenault BJ. Life's Simple 7 and calcific aortic valve stenosis incidence in apparently healthy men and women. *Int J Cardiol.* 2018;269:226–228. doi: 10.1016/j.ijcard.2018.07.107
32. Mok Y, Sang Y, Ballew SH, Rebholz CM, Rosamond WD, Heiss G, Folsom AR, Coresh J, Matsushita K. American Heart Association's Life's Simple 7 at middle age and prognosis after myocardial infarction in later life. *J Am Heart Assoc.* 2018;7:e007658. doi: 10.1161/JAHA.117.007658
33. Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, Alonso A. American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Heart Assoc.* 2018;7:e008424. doi: 10.1161/JAHA.117.008424

34. Hernandez R, González HM, Tarraf W, Moskowitz JT, Carnethon MR, Gallo LC, Penedo FJ, Isasi CR, Ruiz JM, Arguelles W, et al. Association of dispositional optimism with Life's Simple 7's Cardiovascular Health Index: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Sociocultural Ancillary Study (SCAS). *BMJ Open*. 2018;8:e019434. doi: 10.1136/bmjopen-2017-019434
35. Garcia-Hermoso A, Correa-Bautista JE, Izquierdo M, Tordecilla-Sanders A, Prieto-Benavides D, Sandoval-Cuellar C, González-Ruíz K, Ramírez-Vélez R. Ideal cardiovascular health, handgrip strength, and muscle mass among college students: the FUPRECOL Adults Study. *J Strength Cond Res*. 2019;33:747–754. doi: 10.1519/JSC.0000000000003052
36. Caleyachetty R, Echouffo-Tcheugui JB, Muennig P, Zhu W, Muntner P, Shimbo D. Association between cumulative social risk and ideal cardiovascular health in US adults: NHANES 1999-2006. *Int J Cardiol*. 2015;191:296–300. doi: 10.1016/j.ijcard.2015.05.007
37. Mujahid MS, Moore LV, Petito LC, Kershaw KN, Watson K, Diez Roux AV. Neighborhoods and racial/ethnic differences in ideal cardiovascular health (the Multi-Ethnic Study of Atherosclerosis). *Health Place*. 2017;44:61–69. doi: 10.1016/j.healthplace.2017.01.005
38. Willis BL, DeFina LF, Bachmann JM, Franzini L, Shay CM, Gao A, Leonard D, Berry JD. Association of ideal cardiovascular health and long-term healthcare costs. *Am J Prev Med*. 2015;49:678–685. doi: 10.1016/j.amepre.2015.03.034
39. Osondu CU, Aneni EC, Valero-Elizondo J, Salami JA, Rouseff M, Das S, Guzman H, Younus A, Ogunmoroti O, Feldman T, et al. Favorable cardiovascular health is associated with lower health care expenditures and resource utilization in a large US employee population: the Baptist Health South Florida Employee Study. *Mayo Clin Proc*. 2017;92:512–524. doi: 10.1016/j.mayocp.2016.12.026
40. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
41. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988-2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. *Circulation*. 2012;125:2595–2602. doi: 10.1161/CIRCULATIONAHA.111.070722
42. Huffman MD, Lloyd-Jones DM, Ning H, Labarthe DR, Guzman Castillo M, O'Flaherty M, Ford ES, Capewell S. Quantifying options for reducing coronary heart disease mortality by 2020. *Circulation*. 2013;127:2477–2484. doi: 10.1161/CIRCULATIONAHA.112.000769
43. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362:590–599. doi: 10.1056/NEJMoa0907355
44. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ*. 2013;346:f1325. doi: 10.1136/bmj.f1325
45. Wang M, Moran AE, Liu J, Coxson PG, Penko J, Goldman L, Bibbins-Domingo K, Zhao D. Projected impact of salt restriction on prevention of cardiovascular disease in China: a modeling study. *PLoS One*. 2016;11:e0146820. doi: 10.1371/journal.pone.0146820

3. SMOKING/TOBACCO USE

See Table 3-1 and Charts 3-1 through 3-6

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Tobacco use is one of the leading preventable causes of death in the United States and globally. Tobacco smoking, the most common form of tobacco use, is a major risk factor for CVD and stroke.[1] The AHA has identified never having tried smoking or never having smoked a whole cigarette (for children) and never having smoked or having quit >12 months ago (for adults) as 1 of the 7 components of ideal CVH in Life's Simple 7.[2] Unless otherwise stated, throughout the rest of the chapter we will report tobacco use and smoking estimates from the NYTS[3] for adolescents and from the NHIS[4] for adults (≥18 years of age), because these data sources have more recent data. As a survey of middle and high school students, the NYTS may not be generalizable to youth who are not enrolled in school; however, in 2016, 97% of youth 10 to 17 years of age were enrolled in school, which indicates that the results of the NYTS are likely broadly applicable to US youth.[3]

Other forms of tobacco use are becoming increasingly common. E-cigarette use, which involves inhalation of a vaporized liquid that includes nicotine, solvents, and flavoring ("vaping"), has risen dramatically, particularly among young people. The variety of e-cigarette–related products has increased exponentially, giving rise to the more general term *electronic nicotine delivery systems*.[5] A notable evolution in electronic nicotine delivery systems technology and marketing has occurred recently with the advent of "pod mods," small rechargeable devices that deliver high levels of nicotine derived from nicotine salts in loose-leaf tobacco.[6] Use of cigars, cigarillos, filtered cigars, and hookah also has become increasingly common in recent years. Thus, each section below will address the most recent statistical estimates for combustible cigarettes, electronic nicotine delivery systems, and other forms of tobacco use if such estimates are available.

Abbreviations Used in Chapter 3

ACS	acute coronary syndrome
AHA	American Heart Association
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CVH	cardiovascular health
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DM	diabetes mellitus
EAGLES	Study Evaluating the Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders
e-cigarette	electronic cigarette
EVITA	Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome
GBD	Global Burden of Disease
HD	heart disease
HIV	human immunodeficiency virus
HR	hazard ratio
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NNT	number needed to treat
NSDUH	National Survey on Drug Use and Health
NYTS	National Youth Tobacco Survey
OR	odds ratio
PAF	population attributable fraction
PAR	population attributable risk
PATH	Population Assessment of Tobacco and Health
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SE	standard error
SHS	Strong Heart Study
UI	uncertainty interval
WHO	World Health Organization

Prevalence (See Charts 3-1 through 3-4)

Youth

- Prevalence of cigarette use in the past 30 days for middle and high school students by sex and race/ethnicity in 2018 is shown in Chart 3-1.
- In 2018[3]:
  - 27.1% (95% CI, 25.3%–29.0%) of high school students (corresponding to 4 040 000 users) and 7.2% (95% CI, 6.3%–8.1%) of middle school students (corresponding to 840 000 users) used any tobacco products. Additionally, 8.1% (95% CI, 7.1%–9.3%) of high school students (1 180 000 users) and 1.8% (95% CI, 1.4%–2.2%) of middle school students (200 000 users) smoked cigarettes in the past 30 days.
  - 5.9% (95% CI, 5.0%–7.0%) high school students (870 000 users) and 1.8% (95% CI, 1.5%–2.3%) of middle school students (210 000) used smokeless tobacco in the past 30 days.

— 7.6% (95% CI, 6.7%–8.6%) of high school students (1 100 000 users) and 1.6% (95% CI, 1.3%–2.1%) of middle school students (190 000 users) used cigars in the past 30 days.

- Of youth who smoked cigarettes in the past 30 days in 2015 to 2017, 19.4% (95% CI, 17.1%–22.0%) of high school students (corresponding to 230 000 users) and 12.8% (95% CI, 10.0%–16.3%) of middle school students (corresponding to 30 000 users) reported smoking cigarettes every day in the past 30 days.[7]
- In 2018, tobacco use within the past month for high school students varied by race/ethnicity: the prevalence of past 30-day cigarette use was 9.9% (95% CI, 8.5%–11.6%) in NH white youth compared with 3.2% (95% CI, 2.3%–4.6%) in black and 7.2% (95% CI, 5.8%–8.8%) in Hispanic youth. For cigars, the respective percentages were 7.8% (95% CI, 6.7%–9.1%), 9.2% (6.8%–12.4%), and 7.3% (95% CI, 5.9%–9.1%).[3]
- The percentage of high school students who used e-cigarettes (20.8% or 3 050 000 users) exceeded the proportion using cigarettes (8.1% or 1 180 000 users) in 2018 (Chart 3-2).

Adults

- According to the NHIS 2017 data, among adults ≥18 years of age[4]:
  - 14.0% (95% CI, 13.4%–14.6%) of adults reported cigarette use "every day" or "some days."
  - 15.8% (95% CI, 15.0%–16.7%) of males and 12.2% (95% CI, 11.4%–13.0%) of females reported cigarette use "every day" or "some days."
  - 10.4% of those 18 to 24 years of age, 16.1% of those 25 to 44 years of age, 16.5% of those 45 to 64 years of age, and 8.2% of those ≥65 years old reported cigarette use "every day" or "some days."
  - 24.0% of NH American Indians or Alaska Natives, 14.9% of NH blacks, 7.1% of NH Asians, 9.9% of Hispanics, and 15.2% of NH whites reported cigarette use "every day" or "some days."
  - By annual household income, reported cigarette use "every day" or "some days" was 21.4% of people with <$35 000 income compared with 15.3% of those with income of $35 000 to $74 999, 11.8% with income $75 000 to $99 999, and 7.6% with income ≥$100 000.
  - In adults ≥25 years of age, the percentage reporting current cigarette use was 23.1% for those with <12 years of education and 36.8% in those with a General Educational Development high school equivalency, compared with 4.1% among those with a graduate degree.
  - 20.3% of lesbian/gay/bisexual individuals are current smokers compared with 13.7% of heterosexual/straight individuals.
  - By region, the prevalence of current cigarette smokers was highest in the Midwest (16.9%) and South (15.5%) and lowest in the Northeast (11.2%) and West (11.0%).[4]
- The 2009 NHIS report estimated that 42.4% of adults with HIV receiving medical care were current smokers compared with 20.6% of all US adults.[8]
- Using data from BRFSS 2017, the state with the highest age-adjusted percentage of current cigarette smokers was West Virginia (28.0%). The states with the lowest age-adjusted percentage of current cigarette smokers were Utah (8.8%) and California (11.5%; Chart 3-3).[9]
- In 2017, smoking prevalence was higher among adults ≥18 years of age who reported having a disability or activity limitation (20.7%) than among those reporting no disability or limitation (13.3%).[4]
- Among individuals reporting serious psychological distress, 35.2% were current smokers compared with 13.2% in those without serious psychological distress.[4]
- Among females who gave birth in 2016, 7.2% smoked cigarettes during pregnancy. Smoking prevalence during pregnancy was greatest for females 20 to 24 years of age (10.7%), followed by females 15 to 19 years of age (8.5%) and 25 to 29 years of age (8.2%).[10] Rates were highest among NH American Indian or Alaska Native females (16.7%) and lowest in NH Asian females (0.6%). With respect to differences by education, cigarette smoking prevalence was highest among females who completed high school (12.2%), followed by females with less than high school education (11.7%).
- E-cigarette prevalence in 2017 is shown in Chart 3-4. Comparing e-cigarette prevalence across the 50 states, the average age-adjusted prevalence was 5.3%. The lowest age-adjusted prevalence was observed in California (3.2%), and the highest prevalence was observed in Oklahoma (7.5%). The age-adjusted prevalence was 1.3% in Puerto Rico.

Incidence

- According to the 2017 NSDUH, ≈1.90 million people ≥12 years of age had smoked cigarettes for the first time within the past 12 months, compared with

1.78 million in 2016 (2017 NSDUH Table 4.2B).[11] Of new smokers in 2017, 604 000 (31.8%) were 12 to 17 years of age, 817 000 (43.0%) were 18 to 20 years of age, and 335 000 (17.7%) were 21 to 25 years of age; only 142 000 (7.5%) were ≥26 years of age when they first smoked cigarettes.

- The number of new smokers 12 to 17 years of age in 2017 (604 000) decreased from 2016 (723 000 million); however, new smokers 18 to 25 years of age increased from ≈978 000 million in 2002 to 1.15 million in 2017 (2017 NSDUH Table 4.2B).[11]
- According to data from the PATH Study between 2013 and 2016, in youth 12 to 15 years of age, use of an e-cigarette was independently associated with new ever combustible cigarette use (OR, 4.09 [95% CI, 2.97–5.63]) and past 30-day use (OR, 2.75 [95% CI, 1.60–4.73]) at 2 years of follow-up. For youth who tried another non–e-cigarette tobacco product, a similar strength of association for cigarette use at 2 years was observed.[12] Approximately 45 000 new current smokers may have started smoking cigarettes after initiating e-cigarette use over the 2-year period between 2013 to 2014 and 2015 to 2016.[12]

Lifetime Risk

Youth

- Per NSDUH data for individuals 12 to 17 years of age, overall, the lifetime use of tobacco products declined from 15.3% to 14.9% between 2016 and 2017, with lifetime cigarette use declining from 11.6% to 10.8% during the same time period (2017 NSDUH Tables 2.21B and 2.16B).[11]
  - The lifetime use of tobacco products among adolescents 12 to 17 years old varied by the following:
    - Sex: Lifetime use was higher among boys (17.0%) than girls (12.7%; 2017 NSDUH Table 2.21B).
    - Race/ethnicity: Lifetime use was highest among American Indians and Alaska Natives (26.7%), followed by whites (17.9%), Hispanics or Latinos (12.3%), blacks (11.0%), and Asians (4.7%; 2017 NSDUH Table 2.21B).

Adults

- According to NSDUH data, the lifetime use of tobacco products in individuals ≥18 years of age did not decline significantly between 2016 and 2017, from 67.7% to 67.5%, with lifetime cigarette use declining in the same interval from 62.1% to 61.8% (2017 NSDUH Table 2.6B).[11] Similar to the patterns in youth, lifetime risk of tobacco products varied by demographic factors:
  - Sex: Lifetime use was higher in males (76.2%) than females (59.3%).
  - Race/ethnicity: Lifetime use was highest in American Indians or Alaska Natives (81.2%) and whites (75.2%), followed by Native Hawaiian or Other Pacific Islander (56.4%), Hispanics or Latinos (55.3%), blacks (54.8%), and Asians (39.1%).
- In 2017, the lifetime use of smokeless tobacco for adults ≥18 years of age was 17.3%.

Secular Trends (See Chart 3-5)

Youth

The percentage of adolescents (12–17 years old) who reported smoking cigarettes in the past month declined from 13% in 2002 to 3.4% in 2016 (Chart 3-5). The percentages for daily cigarette use among those with past-month cigarette smoking in 12- to 17-year-olds were 31.8% in 2002 and 15.0% in 2016.[13]

Adults

Since the US Surgeon General's first report on the health dangers of smoking, age-adjusted rates of smoking among adults have declined, from 51% of males smoking in 1965 to 15.8% in 2017 and from 34% of females in 1965 to 12.2% in 2017, according to NHIS data.[4] The decline in smoking, along with other factors (including improved treatment and reductions in the prevalence of risk factors such as uncontrolled hypertension and high cholesterol), is a contributing factor to secular declines in the HD death rate.[14]

- On the basis of weighted NHIS data, the current smoking status among 18- to 24-year-old males declined 46.5%, from 28.0% in 2005 to 15.0% in 2015; for 18- to 24-year-old females, smoking declined 47.0%, from 20.7% to 11.0%, over the same time period.[15] On the basis of age-adjusted estimates in 2015, among people ≥65 years of age, 9.7% of males and 7.3% of females were current smokers.
- From 2005 to 2015, adjusted prevalence rates for tobacco use in individuals with serious psychological distress (according to the Kessler Scale) went from 41.9% to 40.6%, which represents a nonsignificant decline; however, rates for people without serious psychological stress declined significantly, from 20.3% to 14.0%.[15]

CVH Impact

- A 2010 report of the US Surgeon General on how tobacco causes disease summarized an extensive body of literature on smoking and CVD and the

mechanisms through which smoking is thought to cause CVD.[16] There is a sharp increase in CVD risk with low levels of exposure to cigarette smoke, including secondhand smoke, and a less rapid further increase in risk as the number of cigarettes per day increases. Similar health risks for CHD events were reported in a systematic review of regular cigar smoking.[17]

- Smoking is an independent risk factor for CHD and appears to have a multiplicative effect with the other major risk factors for CHD: high serum levels of lipids, untreated hypertension, and DM.[16]
- Cigarette smoking and other traditional CHD risk factors might have a synergistic interaction in HIV-positive individuals.[18]
- A meta-analysis of 75 cohort studies (≈2.4 million individuals) demonstrated a 25% greater risk for CHD in female smokers than in male smokers (RR, 1.25 [95% CI, 1.12–1.39]).[19]
- Cigarette smoking is a risk factor for both ischemic stroke and SAH in adjusted analyses and has a synergistic effect on other stroke risk factors such as oral contraceptive use.[20]
- A meta-analysis comparing pooled data of ≈3.8 million smokers and nonsmokers found a similar risk of stroke associated with current smoking in females and males.[21]
- Current smokers have a 2- to 4-times increased risk of stroke compared with nonsmokers or those who have quit for >10 years.[20,22]
- Short-term exposure to water pipe smoking is associated with a significant increase in SBP and heart rate compared with nonsmoking control subjects,[23] but long-term effects remain unclear. Current use of smokeless tobacco was associated with an adjusted 1.27-fold increased risk of CVD events compared with never-users. Per 1000 person-years, the CVD rate was 11.3 in never-users and 21.4 in current users of smokeless tobacco.[24]
- The CVD risks associated with e-cigarette use are not known.[25,26]

Family History and Genetics

- Genetic factors might contribute to smoking behavior; common and rare variants in several loci have been found to associate with smoking initiation, number of cigarettes smoked per day, and smoking cessation.[27,28]
- Genetics might also modify adverse CVH outcomes among smokers, with variation in *ADAMTS7* associated with loss of cardioprotection in smokers.[29]

Smoking Prevention

Tobacco 21 laws increase the minimum age of sale for tobacco products from 18 to 21 years.

- Such legislation would likely reduce the rates of smoking during adolescence, a time during which the majority of smokers start smoking, by limiting access, because most people who buy cigarettes for adolescents are <21 years of age. For instance, investigators compared smoking rates in Needham, MA, after introduction of an ordinance that raised the minimum purchase age to 21. The 30-day smoking rate in Needham declined from 13% to 7% between 2006 and 2010, compared with a decline from 15% to 12% ($P<0.001$) in 16 surrounding communities.[30]
- In several towns where Tobacco 21 laws have been enacted, 47% reductions in smoking prevalence among high school students have been reported.[31] Furthermore, the National Academy of Medicine estimates that a nationwide Tobacco 21 law would result in 249 000 fewer premature deaths, 45 000 fewer lung cancer deaths, and 4.2 million fewer lost life-years among Americans born between 2010 and 2019.[31]
- As of May 17, 2019, 14 states (Hawaii, California, New Jersey, Oregon, Maine, Massachusetts, Illinois, Virginia, Delaware, Arkansas, Vermont, Maryland, Washington, and Utah) and at least 470 localities (including New York City, New York; Chicago, Illinois; San Antonio, Texas; Boston, Massachusetts; Cleveland, Ohio; and both Kansas Cities [Kansas and Missouri]), have set the minimum age for the purchase of tobacco to 21 years.[32]

Awareness, Treatment, and Control

Smoking Cessation

- According to NHIS 2015 data, 59.1% of adult ever-smokers had stopped smoking.[33]
  - The majority (68.0%) of adult smokers wanted to quit smoking; 55.4% had tried in the past year, 7.4% had stopped recently, and 57.2% had received healthcare provider advice to quit.
  - Receiving advice to quit smoking was lower among uninsured smokers (44.1%) than among those with health insurance coverage through Medicaid or those who were dual eligible for coverage (both Medicaid and Medicare; 59.5%). Receiving advice to quit also varied by race, with a lower prevalence in Asian (34.2%), American Indian/Alaska Native (38.1%), and Hispanic (42.2%) smokers than in white smokers (60.2%).

  - The period from 2000 to 2015 revealed significant increases in the prevalence of smokers who had tried to quit in the past year, had stopped recently, had a health professional recommend quitting, or had used cessation counseling or medication.
  - In 2015, fewer than one-third of smokers attempting to quit used evidence-based therapies: 4.7% used both counseling and medication, 6.8% used counseling, and 29.0% used medication (16.6% nicotine patch, 12.5% gum/lozenges, 2.4% nicotine spray/inhaler, 2.7% bupropion, and 7.9% varenicline).
- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with and without CHD.
  - In several studies, a dose-response relationship has been seen among current smokers between the number of cigarettes smoked per day and CVD incidence.[34,35]
  - Quitting smoking at any age significantly lowers mortality from smoking-related diseases, and the risk declines more the longer the time since quitting smoking.[1] Cessation appears to have both short-term (weeks to months) and long-term (years) benefits for lowering CVD risk.
  - Smokers who quit smoking at 25 to 34 years of age gained 10 years of life compared with those who continued to smoke. Those 35 to 44 years of age gained 9 years, those 45 to 54 years of age gained 6 years, and those 55 to 64 years of age gained 4 years of life, on average, compared with those who continued to smoke.[34]
- Cessation medications (including sustained-release bupropion, varenicline, and nicotine gum, lozenge, nasal spray, and patch) are effective for helping smokers quit.[36,37]
- EVITA was an RCT that examined the efficacy of varenicline versus placebo for smoking cessation among smokers who were hospitalized for ACS. At 24 weeks, rates of smoking abstinence and reduction were significantly higher among patients randomized to varenicline. The abstinence rates at 24 weeks were higher in the varenicline (47.3%) than the placebo (32.5%) group (P=0.012; NNT=6.8). Continuous abstinence rates and reduction rates (≥50% of daily cigarette consumption) were also higher in the varenicline group.[38]
- The EAGLES trial[39] demonstrated the efficacy and safety of 12 weeks of varenicline, bupropion, or nicotine patch in motivated-to-quit smoking patients with major depressive disorder, bipolar disorder, anxiety disorders, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, psychotic disorders including schizophrenia and schizoaffective disorders, and borderline personality disorder. Of note, these participants were all clinically stable from a psychiatric perspective and were believed not to be at high risk for self-injury.[39]
- Extended use of a nicotine patch (24 weeks compared with 8 weeks) has been demonstrated to be safe and efficacious in randomized clinical trials.[40]
- An RCT demonstrated the effectiveness of individual- and group-oriented financial incentives for tobacco abstinence through at least 12 months of follow-up.[41]
- In addition to medications, smoke-free policies, increases in tobacco prices, cessation advice from healthcare professionals, and quit-lines and other counseling have contributed to smoking cessation.[33,42]
- Mass media antismoking campaigns, such as the CDC's Tips campaign (Tips From Former Smokers), have been shown to reduce smoking-attributable morbidity and mortality and are cost-effective. Investigators estimated that the Tips campaign cost about $48 million, saved ≈179 099 QALYs, and prevented ≈17 000 premature deaths in the United States.[43]
- Despite states having collected $25.6 billion in 2012 from the 1998 Tobacco Master Settlement Agreement and tobacco taxes, <2% of those funds are spent on tobacco prevention and cessation programs.[44]
- A randomized trial of e-cigarettes and behavioral support versus nicotine-replacement therapy and behavioral support in adults attending the United Kingdom's National Health Service stop-smoking services found that 1-year cigarette abstinence rates were 18% in the e-cigarette group compared with 9.9% in the nicotine-replacement therapy group (RR, 1.83 [95% CI, 1.30–2.58]; P<0.001). However, among participants abstinent at 1 year, in the nicotine-replacement therapy group only 9% were still using nicotine-replacement therapy, whereas 80% of those in the e-cigarette group were still using e-cigarettes.[45]

Mortality

- Of risk factors evaluated by the US Burden of Disease Collaborators, tobacco use was the second-leading risk factor for death in the United States and the leading cause of DALYs, accounting for 11% of DALYs, in 2016.[46] Overall mortality among US smokers is 3 times higher than that for never-smokers.[34]

- On average, based on 2016 data, male smokers die 12 years earlier than male never-smokers, and female smokers die 11 years earlier than female never-smokers.[14,47]
- Increased CVD mortality risks persist for older (≥60 years old) smokers as well. A meta-analysis of 25 studies comparing CVD risks in 503 905 cohort participants ≥60 years of age reported an HR for cardiovascular mortality of 2.07 (95% CI, 1.82–2.36) compared with never-smokers and 1.37 (95% CI, 1.25–1.49) compared with former smokers.[48]
- In a sample of Native Americans (SHS), among whom the prevalence of tobacco use is highest in the United States, the PAR for total mortality was 18.4% for males and 10.9% for females.[49]
- Since the first report on the dangers of smoking was issued by the US Surgeon General in 1964, tobacco control efforts have contributed to a reduction of 8 million premature smoking-attributable deaths.[50]
- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.[16]

Electronic Cigarettes (See Charts 3-2 and 3-4)

- Electronic nicotine delivery systems, more commonly called electronic cigarettes or e-cigarettes, are battery-operated devices that deliver nicotine, flavors, and other chemicals to the user in an aerosol. Although e-cigarettes were only introduced into the United States around 2007, there are currently >450 e-cigarette brands on the market, and sales in the United States were projected to be $2 billion in 2014. In 2015, Juul came on the market and has rapidly become the most popular e-cigarette product sold in the United States. The popularity of the Juul likely relates to several factors, including its slim and modern design, appealing flavors, and the intensity of nicotine delivery, which approximates the experience of combustible cigarettes.[51]
- Current e-cigarette user prevalence for 2017 in the United States is shown in Chart 3-4.
- According to the NYTS, in 2018, e-cigarettes were the most commonly used tobacco products in youth: in the prior 30 days, 4.9% (570 000) of middle school and 20.8% (3.05 million) of high school students endorsed use (Chart 3-2).[3] A significant nonlinear increase in current e-cigarette use in high school students was observed between 2011 (1.5%) and 2018 (20.8%). A significant increase in current e-cigarette use was also observed for middle school students, where the corresponding values were 0.6% and 4.9% in the 2 periods. Among high school students, rates of use were most pronounced in males (22.6%) and NH whites (26.8%). In middle school students, slightly higher rates were observed in males (5.1%) and in Hispanics (6.6%).
- Between 2017 and 2018, frequent use of e-cigarettes among high school students who were current e-cigarette users increased significantly by 38.5% (from 20.0% to 27.7%). In middle school students, the percentage using frequently among current e-cigarette users increased by 16.2%.[3]
- In 2016, 20.5 million US middle and high school students (80%) were exposed to e-cigarette advertising.[52]
- Among US adults, awareness and use of e-cigarettes has increased considerably.[53] In 2016, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 4.5% according to data from the BRFSS. The prevalence of current e-cigarette use was highest in individuals 18 to 24 years of age (9.2%) and in current combustible cigarette users (14.4%).[54]
- According to BRFSS 2016, current use of e-cigarettes in adults ≥18 years of age was higher in sexual and gender minority individuals. With respect to sexual orientation, 9.0% of bisexual and 7.0% of lesbian/gay individuals were current e-cigarette users compared with 4.6% of heterosexual people. Individuals who were transgender (8.7%) were current e-cigarette users at a higher rate than cisgender individuals (4.7%). Across US states, the highest prevalence of current e-cigarette use was observed in Oklahoma (7.0%) and the lowest in South Dakota (3.1%).[54]
- Effective August 8, 2016, the US Food and Drug Administration's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.[55]

Secondhand Smoke

- Data from the US Surgeon General on the consequences of secondhand smoke indicate the following:
  - Nonsmokers who are exposed to secondhand smoke at home or at work increase their risk of developing CHD by 25% to 30%.[16]
  - Exposure to secondhand smoke increases the risk of stroke by 20% to 30%, and it is associated with increased mortality (adjusted mortality rate ratio, 2.11) after a stroke.[56]
- A meta-analysis of 23 prospective and 17 case-control studies of cardiovascular risks associated with secondhand smoke exposure demonstrated 18%, 23%, 23%, and 29% increased risks for

total mortality, total CVD, CHD, and stroke, respectively, in those exposed to secondhand smoke.[57]
- A meta-analysis of 24 studies demonstrated that secondhand smoke can increase risks for preterm birth by 20%.[58]
- As of April 1, 2018, 11 states (California, Connecticut, Delaware, Hawaii, Maine, New Jersey, New York, North Dakota, Oregon, Utah, and Vermont), the District of Columbia, and Puerto Rico have passed comprehensive smoke-free indoor air laws that include e-cigarettes. These laws prohibit smoking and the use of e-cigarettes in indoor areas of private work sites, restaurants, and bars.[32]
- Pooled data from 17 studies in North America, Europe, and Australia suggest that smoke-free legislation can reduce the incidence of acute coronary events by 10% (RR, 0.90 [95% CI, 0.86–0.94]).[59]
- The percentage of the US nonsmoking population with serum cotinine ≥0.05 ng/mL (which indicates exposure to secondhand smoke) declined from 52.5% in 1999 to 2000 to 25.3% in 2011 to 2012, with declines occurring for both children and adults. During 2011 to 2012, the percentage of nonsmokers with detectable serum cotinine was 40.6% for those 3 to 11 years of age, 33.8% for those 12 to 19 years of age, and 21.3% for those ≥20 years of age. The percentage was higher for NH blacks (46.8%) than for NH whites (21.8%) and Mexican Americans (23.9%). People living below the poverty level (43.2%) and those living in rental housing (36.8%) had higher rates of secondhand smoke exposure than their counterparts (21.1% of those living above the poverty level and 19.0% of those who owned their homes; NHANES).[60]

Cost

- According to the Surgeon General's 50th anniversary report on the health consequences of smoking, the estimated annual cost attributable to smoking from 2009 to 2012 was between $289 and $332.5 billion; direct medical care for adults accounted for $132.5 to $175.9 billion, lost productivity because of premature death accounted for $151 billion (estimated from 2005–2009), and lost productivity from secondhand smoke accounted for $5.6 billion (in 2006).[14]
- In the United States, cigarette smoking was associated with 8.7% of annual aggregated healthcare spending from 2006 to 2010, which represented roughly $170 billion per year, 60% of which was paid by public programs (eg, Medicare and Medicaid).[61]
- In 2016, $9.5 billion was spent on marketing cigarettes and smokeless tobacco in the United States.[62]
- 249 billion cigarettes were sold in the United States in 2017, which is a 3.5% decrease from the number sold in 2016.[63]
- Cigarette prices in the United States increased steeply between the early 1970s and 2016, in large part because of excise taxes on tobacco products. Per pack in 1970, the average cost was $0.38, and tax was $0.18, whereas in 2016 the average cost was $6.43, and average tax $2.85.[63]

Global Burden of Tobacco Use (See Table 3-1 and Chart 3-6)

- Although tobacco use in the United States has been declining, the absolute number of tobacco users worldwide has climbed steeply.[64]
- On the basis of the GBD synthesis of >2800 data sources, the age-standardized global prevalence of daily smoking in 2017 was 8.7% (95% UI, 7.72%–9.79%) in males and 1.76% (95% UI, 1.52%–2.02%) in females. The investigators estimate that since 1990, smoking rates have declined globally by 23% in males and 42% in females.[65]
- The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories. East and Southeast Asia and Eastern Europe have the highest mortality rates attributable to tobacco (Chart 3-6).
- In 2015, there were a total of 933.1 million (95% UI, 831.3–1054.3 million) smokers globally, of whom 82.3% were men. The annualized rate of change in smoking prevalence between 1990 to 2015 was –1.7% in women and –1.3% in men.[66]
- Worldwide, ≈80% of smokers live in low- and middle-income countries.[67]
- Tobacco (including smoking, secondhand smoke, and chewing tobacco) caused an estimated 8.1 million deaths globally in 2017 (6.2 million men and 1.9 million women; Table 3-1). GBD investigators estimated that in 2017, smoking tobacco was the second-leading risk of mortality (high SBP was number 1), and smoking tobacco ranked fourth in DALYs globally.[64,65]
- The WHO estimated that the economic cost of smoking-attributable diseases accounted for US $422 billion in 2012, which represented ≈5.7% of global health expenditures.[68] The total economic costs, including both health expenditures and lost productivity, amounted to approximately US $1436 billion, which was roughly equal to 1.8% of the world's annual gross domestic product. The WHO further estimated that 40% of the expenditures were in developing countries.

- To help combat the global problem of tobacco exposure, in 2003 the WHO adopted the Framework Convention on Tobacco Control treaty. From this emerged a set of evidence-based policies with the goal of reducing the demand for tobacco, entitled MPOWER. MPOWER policies outline the following strategies for nations to reduce tobacco use: (1) monitor tobacco use and prevention policies; (2) protect individuals from tobacco smoke; (3) offer to help with tobacco cessation; (4) warn about tobacco-related dangers; (5) enforce bans on tobacco advertising; (6) raise taxes on tobacco; and (7) reduce the sale of cigarettes. More than half of all nations have implemented at least 1 MPOWER policy.[54,69]

Table 3-1. Deaths Caused by Tobacco Worldwide, by Sex, 2017

	Both Sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions) deaths	8.1 (7.8 to 8.4)	6.2 (6.0 to 6.4)	1.9 (1.8 to 2.1)
Percent change in total number, 2007 to 2017	11.3 (9.1 to 13.4)	12.6 (10.1 to 15.1)	7.3 (4.0 to 10.4)
Percent change in total number, 1990 to 2017	20.8 (17.1 to 24.6)	27.9 (23.9 to 31.9)	2.5 (–2.8 to 8.4)
Mortality rate per 100 000	103.2 (99.0 to 107.3)	173.5 (166.9 to 180.1)	44.7 (41.5 to 48.2)
Percent change rate, 2007 to 2017	–15.9 (–17.6 to –14.4)	–15.6 (–17.5 to –13.8)	–19.1 (–21.5 to –16.8)
Percent change rate, 1990 to 2017	–39.2 (–40.9 to –37.4)	–37.5 (–39.4 to –35.7)	–47.8 (–50.4 to –44.9)
PAF, %	14.5 (13.9 to 15.0)	20.4 (19.7 to 21.1)	7.5 (6.9 to 8.0)
Percent change in PAF, 2007 to 2017	1.9 (0.3 to 3.5)	3.2 (1.6 to 4.9)	–2.0 (–4.5 to 0.4)
Percent change in PAF, 1990 to 2017	0.4 (–2.4 to 3.2)	4.8 (2.1 to 7.5)	–13.5 (–17.8 to –8.9)

PAF indicates population attributable fraction; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[64] Printed with permission. Copyright © 2018, University of Washington.

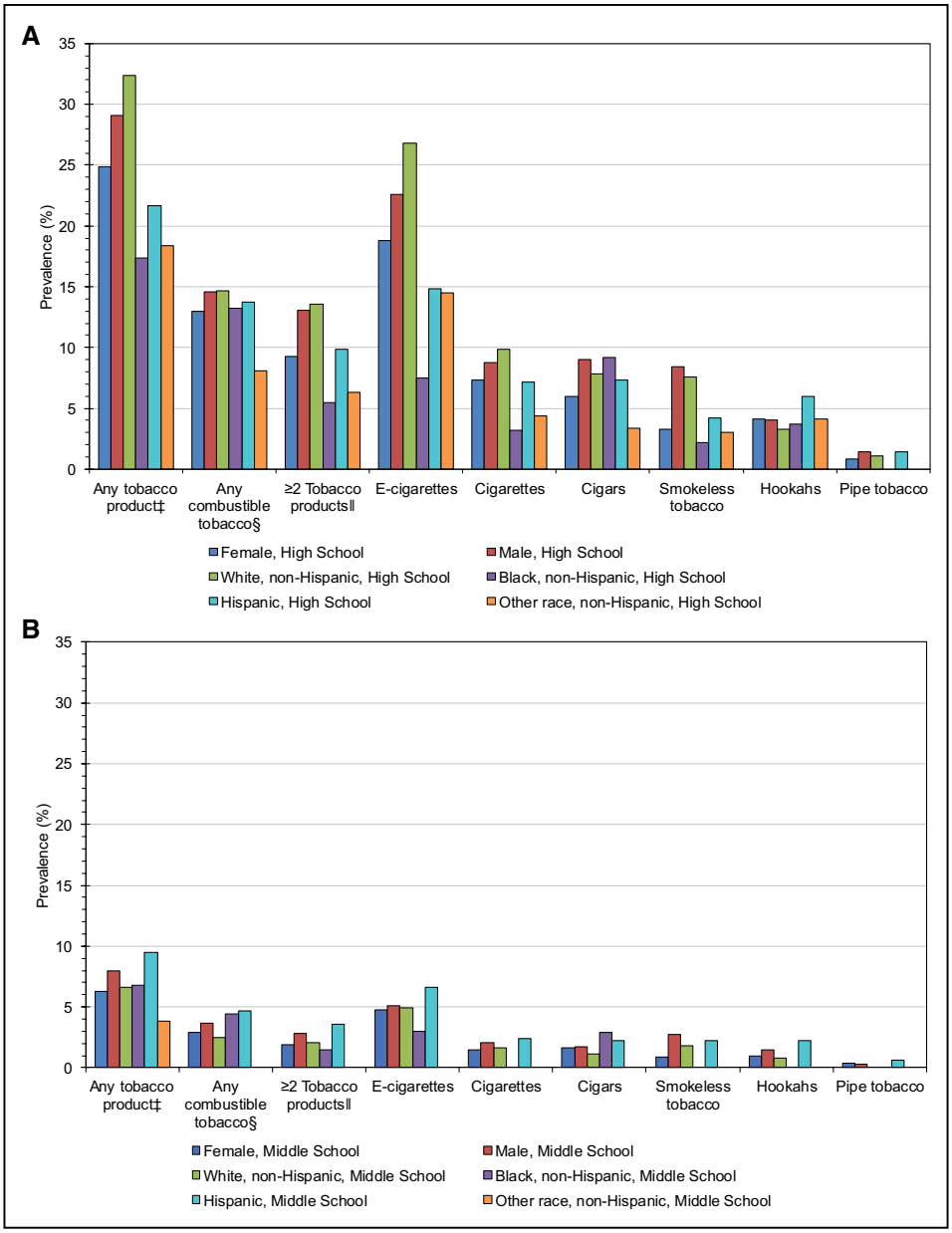

Chart 3-1. Prevalence (%) of cigarette use in the United States in the past 30 days, by product,* school level, sex, and race/ethnicity† (NYTS, 2011–2018).

Data in (**A**) relate to high school students and (**B**) relate to middle school students. Because of methodological differences among the NSDUH, the Youth Risk Behavior Survey, the NYTS, and other surveys, percentages of cigarette smoking measured by these surveys are not directly comparable. Notably, school-based surveys might include students who are 18 years old, who are legally permitted to smoke and have higher rates of smoking.

E-cigarettes indicates electronic cigarettes; NSDUH, National Survey on Drug Use and Health; and NYTS, National Youth Tobacco Survey.

*Past 30-day use of e-cigarettes was determined by asking, "During the past 30 days, on how many days did you use e-cigarettes?" Past 30-day use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?" Past 30-day use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?" Past 30-day use of hookah was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a hookah or waterpipe?" Smokeless tobacco was defined as use of chewing tobacco, snuff, dip, snus, or dissolvable tobacco products. Past 30-day use of smokeless tobacco was determined by asking the following question for use of chewing tobacco, snuff, and dip: "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?" and the following question for use of snus and dissolvable tobacco products: "In the past 30 days, which of the following products did you use on at least one day?" Responses from these questions were combined to derive overall smokeless tobacco use. Past 30-day use of pipe tobacco (not hookahs) was determined by asking, "In the past 30 days, which of the following products have you used on at least one day?"

†Blacks, whites, and others are non-Hispanic; Hispanic people could be of any race.

‡Any tobacco product use was defined as use of any tobacco product (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, or bidis) on ≥1 day in the past 30 days.

§Any combustible tobacco product use was defined as use of cigarettes, cigars, hookahs, pipe tobacco, or bidis on ≥1 day in the past 30 days.

ǁUse of ≥2 tobacco products was defined as use of ≥2 tobacco products (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookahs, pipe tobacco, or bidis) on ≥1 day in the past 30 days.

Source: Data derived from Gentzke et al.[3]

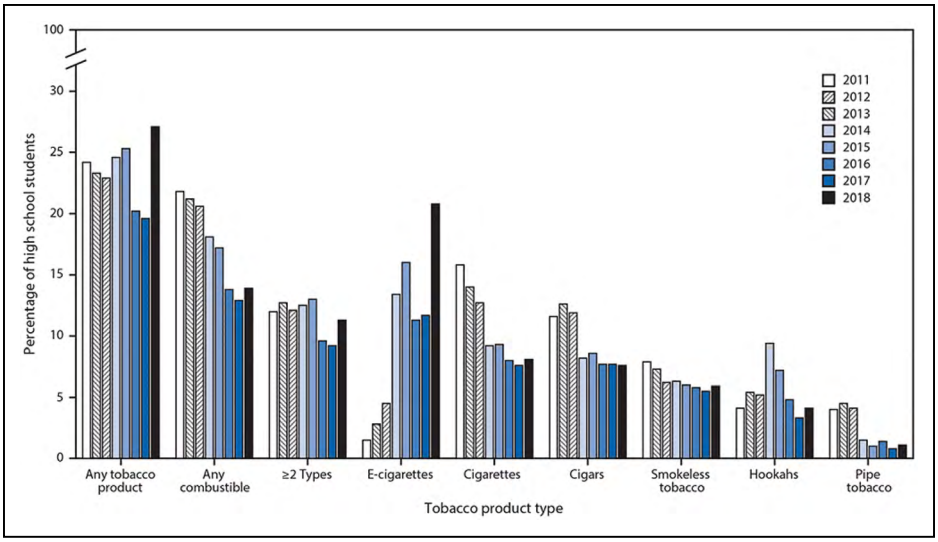

Chart 3-2. Estimated percentage of US high school students who currently use any tobacco product,* any combustible tobacco product,† ≥2 tobacco product types,‡ and selected tobacco products (NYTS, 2011–2018).§‖¶

E-cigarettes indicates electronic cigarettes; and NYTS, National Youth Tobacco Survey.

*Any tobacco product use was defined as use of e-cigarettes, cigarettes, cigars, hookahs, smokeless tobacco, pipe tobacco, or bidis (small brown cigarettes wrapped in a leaf) on ≥1 day in the past 30 days.

†Any combustible tobacco product use was defined as use of cigarettes, cigars, hookahs, pipe tobacco, or bidis on ≥1 day in the past 30 days.

‡Use of ≥2 tobacco product types was defined as use of ≥2 of the following tobacco products: e-cigarettes, cigarettes, cigars, hookahs, smokeless tobacco, pipe tobacco, or bidis on ≥1 day in the past 30 days.

§During 2017 to 2018, current use of any tobacco product, ≥2 types of tobacco products, and e-cigarettes significantly increased ($P<0.05$).

‖During 2011 to 2018, current use of combustible tobacco products, ≥2 types of tobacco products, cigars, smokeless tobacco, and pipe tobacco exhibited linear decreases ($P<0.05$). Current use of cigarettes exhibited a nonlinear decrease ($P<0.05$). Current use of hookahs exhibited a nonlinear change ($P<0.05$). Current use of e-cigarettes exhibited a nonlinear increase ($P<0.05$). No significant trend in use of any tobacco product overall was observed.

¶Beginning in 2015, the definition of smokeless tobacco included chewing tobacco/snuff/dip, snus, and dissolvable tobacco to better reflect this class of tobacco products. Thus, estimates for individual smokeless tobacco products (chewing tobacco/snuff/dip, snus, and dissolvable tobacco) are not reported. This definition was applied across all years (2011–2018) for comparability purposes.

Source: Reprinted from Gentzke et al.[3]

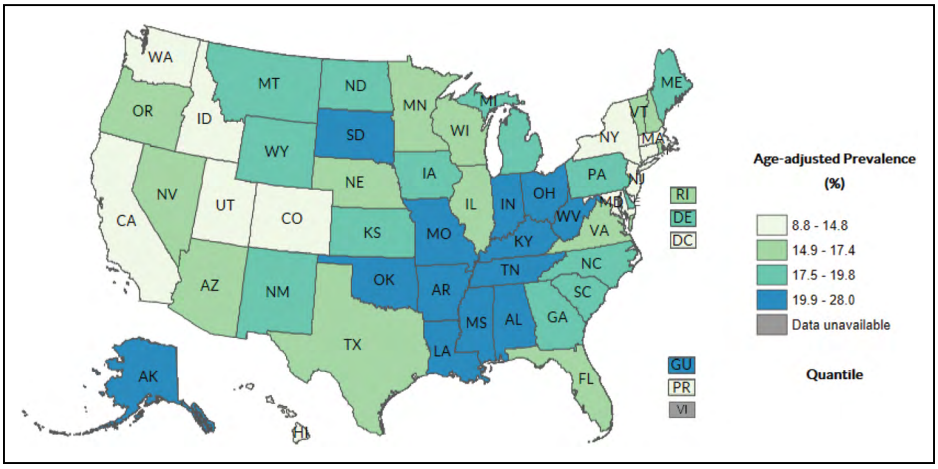

Chart 3-3. Age-adjusted prevalence (%) of current cigarette smoking for US adults, by state (BRFSS, 2017).

White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.

BRFSS indicates Behavior Risk Factor Surveillance System.

Source: BRFSS Prevalence and Trends Data, 2017.[9]

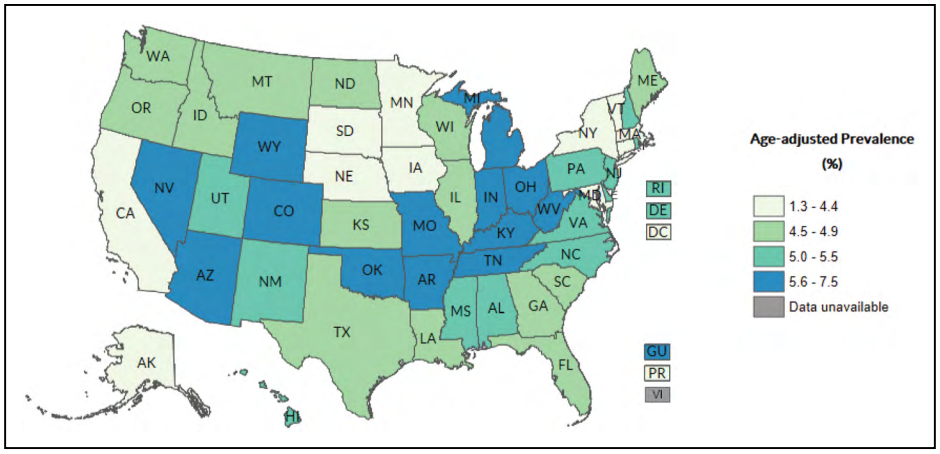

Chart 3-4. Prevalence (age-adjusted) of current e-cigarette use, United States (BRFSS, 2017).
White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.
BRFSS indicates Behavior Risk Factor Surveillance System.
Source: BRFSS Prevalence and Trends Data, 2017.[9]

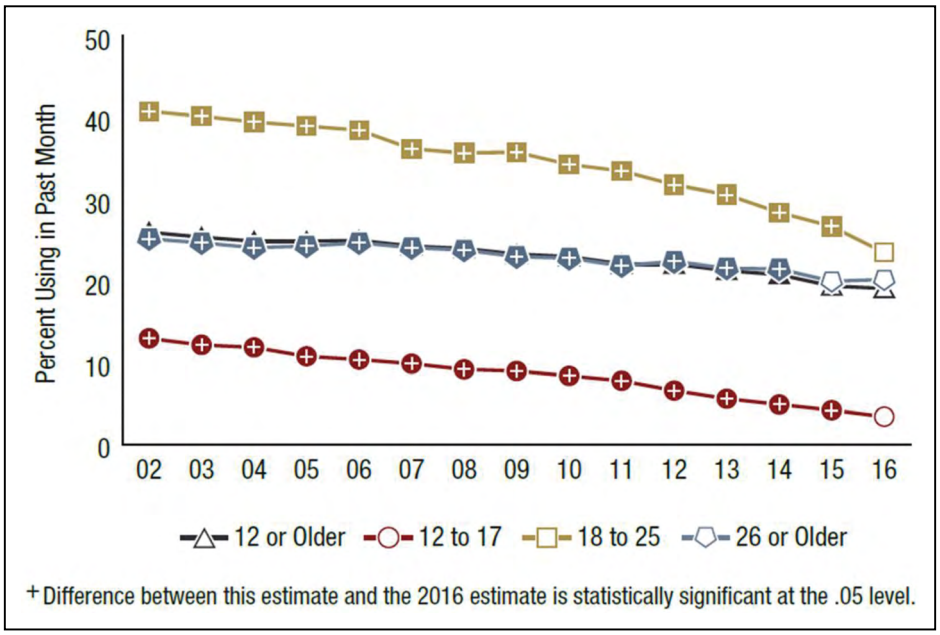

Chart 3-5. Past month cigarette use among people ≥12 years of age, by age group: percentages, 2002 to 2016 (NHIS, 2002–2016; NSDUH, 2002–2016).
NSDUH indicates National Survey on Drug Use and Health; and NHIS, National Health Interview Survey.
Source: Reprinted from NSDUH.[13]

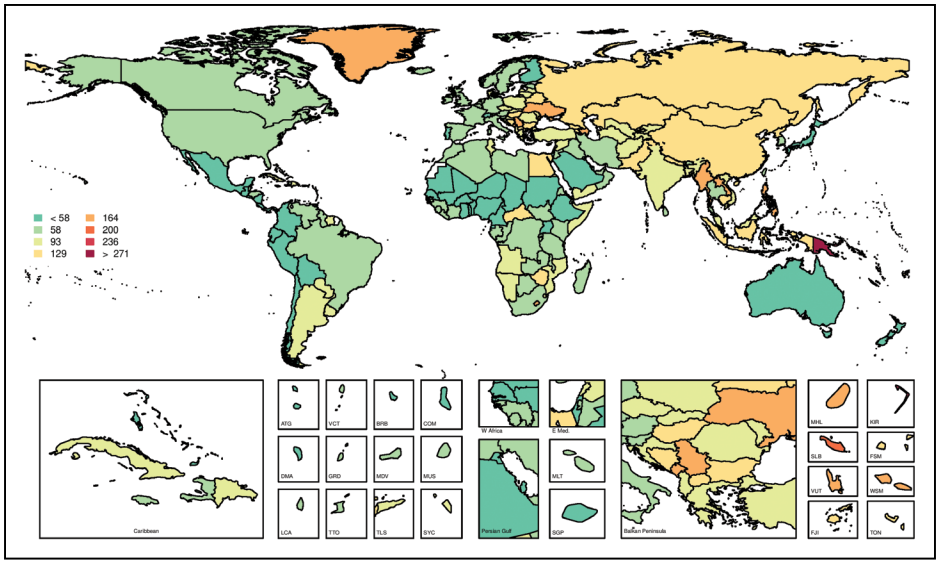

Chart 3-6. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2017.
East and Southeast Asia and Eastern Europe have the highest mortality rates attributable to tobacco.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[64] Printed with permission.

REFERENCES

1. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-year trends in smoking-related mortality in the United States. *N Engl J Med.* 2013;368:351–364. doi: 10.1056/NEJMsa1211127
2. American Heart Association. My Life Check - Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check–lifes-simple-7. Accessed July 1, 2019.
3. Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital signs: tobacco product use among middle and high school students: United States, 2011-2018. *MMWR Morb Mortal Wkly Rep.* 2019;68:157–164. doi: 10.15585/mmwr.mm6806e1
4. Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA. Tobacco product use among adults: United States, 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:1225–1232. doi: 10.15585/mmwr.mm6744a2
5. Electronic nicotine delivery systems key facts. Centers for Disease Control and Prevention website. https://chronicdata.cdc.gov/Policy/Electronic-Nicotine-Delivery-Systems-Key-Facts-Inf/nwhw-m4ki. Accessed May 6, 2019.
6. Barrington-Trimis JL, Leventhal AM. Adolescents' use of "Pod Mod" e-cigarettes: urgent concerns. *N Engl J Med.* 2018;379:1099–1102. doi: 10.1056/NEJMp1805758
7. Anic GM, Sawdey MD, Jamal A, Trivers KF. Frequency of use among middle and high school student tobacco product users: United States, 2015-2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:1353–1357. doi: 10.15585/mmwr.mm6749a1
8. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, Skarbinski J. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Ann Intern Med.* 2015;162:335–344. doi: 10.7326/M14-0954
9. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. BRFSS Prevalence & Trends Data [online]. 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed April 1, 2019.
10. Drake P, Driscoll AK, Mathews TJ. Cigarette smoking during pregnancy: United States, 2016. *NCHS Data Brief.* 2018;(305):1–8.
11. Center for Behavioral Statistics and Quality. 2017 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2018.
12. Berry KM, Fetterman JL, Benjamin EJ, Bhatnagar A, Barrington-Trimis JL, Leventhal AM, Stokes A. Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. *JAMA Netw Open.* 2019;2:e187794. doi: 10.1001/jamanetworkopen.2018.7794
13. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results From the 2016 National Survey on Drug Use and Health. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2017. HHS publication No. SMA 17-5044, NSDUH Series H-52. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf. Accessed May 6, 2019.
14. US Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress: A Report of the Surgeon General.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
15. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults: United States, 2005-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:1205–1211. doi: 10.15585/mmwr.mm6544a2
16. US Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
17. Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health.* 2015;15:390. doi: 10.1186/s12889-015-1617-5
18. Rasmussen LD, Helleberg M, May MT, Afzal S, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Nordestgaard BG, Obel N. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. *Clin Infect Dis.* 2015;60:1415–1423. doi: 10.1093/cid/civ013
19. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet.* 2011;378:1297–1305. doi: 10.1016/S0140-6736(11)60781-2
20. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular

and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046

21. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke.* 2013;44:2821–2828. doi: 10.1161/STROKEAHA.113.002342
22. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther.* 2010;8:917–932. doi: 10.1586/erc.10.56
23. Azar RR, Frangieh AH, Mroué J, Bassila L, Kasty M, Hage G, Kadri Z. Acute effects of waterpipe smoking on blood pressure and heart rate: a real-life trial. *Inhal Toxicol.* 2016;28:339–342. doi: 10.3109/08958378.2016.1171934
24. Yatsuya H, Folsom AR; ARIC Investigators. Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol.* 2010;172:600–605. doi: 10.1093/aje/kwq191
25. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation.* 2014;130:1418–1436. doi: 10.1161/CIR.0000000000000107
26. Bhatnagar A. E-cigarettes and cardiovascular disease risk: evaluation of evidence, policy implications, and recommendations. *Curr Cardiovasc Risk Rep*. 2016;10:24. doi: 10.1007/s12170-016-0505-6
27. Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet*. 2010;42:441–447. doi: 10.1038/ng.571
28. Brazel DM, Jiang Y, Hughey JM, Turcot V, Zhan X, Gong J, Batini C, Weissenkampen JD, Liu M, Barnes DR, et al; CHD Exome+ Consortium; Consortium for Genetics of Smoking Behaviour. Exome chip meta-analysis fine maps causal variants and elucidates the genetic architecture of rare coding variants in smoking and alcohol use. *Biol Psychiatry.* 2019;85:946–955. doi: 10.1016/j.biopsych.2018.11.024
29. Saleheen D, Zhao W, Young R, Nelson CP, Ho W, Ferguson JF, Rasheed A, Ou K, Nurnberg ST, Bauer RC, et al. Loss of cardioprotective effects at the ADAMTS7 locus as a result of gene-smoking interactions. *Circulation.* 2017;135:2336–2353. doi: 10.1161/CIRCULATIONAHA.116.022069
30. Kessel Schneider S, Buka SL, Dash K, Winickoff JP, O'Donnell L. Community reductions in youth smoking after raising the minimum tobacco sales age to 21. *Tob Control.* 2016;25:355–359. doi: 10.1136/tobaccocontrol-2014-052207
31. Morain SR, Winickoff JP, Mello MM. Have tobacco 21 laws come of age? *N Engl J Med.* 2016;374:1601–1604. doi: 10.1056/NEJMp1603294
32. Municipal Tobacco Control Technical Assistance Program. States and localities that have raised the minimum legal sale age for tobacco products to 21. https://www.tobaccofreekids.org/assets/content/what_we_do/state_local_issues/sales_21/states_localities_MLSA_21.pdf. Accessed May 7, 2019.
33. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults: United States, 2000-2015. *MMWR Morb Mortal Wkly Rep.* 2017;65:1457–1464. doi: 10.15585/mmwr.mm6552a1
34. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med.* 2013;368:341–350. doi: 10.1056/NEJMsa1211128
35. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9
36. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update: a U.S. Public Health Service report. *Am J Prev Med*. 2008;35:158–176. doi: 10.1016/j.amepre.2008.04.009
37. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published correction appears in *Circulation*. 2019;140:e649–e650]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
38. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, et al; for the EVITA Investigators. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation.* 2016;133:21–30. doi: 10.1161/CIRCULATIONAHA.115.019634
39. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;387:2507–2520. doi: 10.1016/S0140-6736(16)30272-0
40. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med.* 2015;175:504–511. doi: 10.1001/jamainternmed.2014.8313
41. Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, Loewenstein G, Brennan TA, Asch DA, Volpp KG. Randomized trial of four financial-incentive programs for smoking cessation. *N Engl J Med.* 2015;372:2108–2117. doi: 10.1056/NEJMoa1414293
42. Centers for Disease Control and Prevention. Quitting smoking among adults: United States, 2001–2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:1513–1519.
43. Xu X, Alexander RL Jr, Simpson SA, Goates S, Nonnemaker JM, Davis KC, McAfee T. A cost-effectiveness analysis of the first federally funded antismoking campaign. *Am J Prev Med.* 2015;48:318–325. doi: 10.1016/j.amepre.2014.10.011
44. Antman E, Arnett D, Jessup M, Sherwin C. The 50th anniversary of the US surgeon general's report on tobacco: what we've accomplished and where we go from here. *J Am Heart Assoc.* 2014;3:e000740. doi: 10.1161/JAHA.113.000740
45. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med.* 2019;380:629–637. doi: 10.1056/NEJMoa1808779
46. Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, Mullany E, Lee A, Khan AR, Ahmadi A, Ferrari AJ, et al; U. S. Burden of Disease Collaborators. The state of US Health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319:1444–1472. doi: 10.1001/jama.2018.0158
47. National Center for Health Statistics. National Health Interview Survey, 2015 data release: public-use data file and documentation. Centers for Disease Control and Prevention website. http://www.cdc.gov/nchs/nhis/nhis_2015_data_release.htm. Accessed July 18, 2019.
48. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, et al; CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ.* 2015;350:h1551. doi: 10.1136/bmj.h1551
49. Zhang M, An Q, Yeh F, Zhang Y, Howard BV, Lee ET, Zhao J. Smoking-attributable mortality in American Indians: findings from the Strong Heart Study. *Eur J Epidemiol.* 2015;30:553–561. doi: 10.1007/s10654-015-0031-8
50. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, Levy DT. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA.* 2014;311:164–171. doi: 10.1001/jama.2013.285112
51. Bhatnagar A, Whitsel LP, Blaha MJ, Huffman MD, Krishan-Sarin S, Maa J, Rigotti N, Robertson RM, Warner JJ; on behalf of the American Heart Association. New and emerging tobacco products and the nicotine endgame: the role of robust regulation and comprehensive tobacco control and prevention: a presidential advisory from the American Heart Association. *Circulation*. 2019;139:e937–e958. doi: 10.1161/CIR.0000000000000669
52. Marynak K, Gentzke A, Wang TW, Neff L, King BA. Exposure to electronic cigarette advertising among middle and high school students: United States, 2014-2016. *MMWR Morb Mortal Wkly Rep.* 2018;67:294–299. doi: 10.15585/mmwr.mm6710a3
53. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23(suppl 3):iii3–iii9. doi: 10.1136/tobaccocontrol-2014-051670
54. Mirbolouk M, Charkhchi P, Kianoush S, Uddin SMI, Orimoloye OA, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. Prevalence and

distribution of e-cigarette use among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med.* 2018;169:429–438. doi: 10.7326/M17-3440

55. Food and Drug Administration, HHS. Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. *Fed Regist*. 2016;81:28973–29106. https://www.govinfo.gov/content/pkg/FR-2016-05-10/pdf/2016-10685.pdf. Accessed June 5, 2019.
56. Delnevo CD, Giovenco DP, Steinberg MB, Villanti AC, Pearson JL, Niaura RS, Abrams DB. Patterns of electronic cigarette use among adults in the United States. *Nicotine Tob Res.* 2016;18:715–719. doi: 10.1093/ntr/ntv237
57. Syamlal G, Jamal A, King BA, Mazurek JM. Electronic cigarette use among working adults: United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2016;65:557–561. doi: 10.15585/mmwr.mm6522a1
58. FDA's deeming regulations for e-cigarettes, cigars, and all other tobacco products. US Food & Drug Administration website. https://www. https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/fdas-deeming-regulations-e-cigarettes-cigars-and-all-other-tobacco-products. Accessed May 7, 2019.
59. Mackay DF, Irfan MO, Haw S, Pell JP. Meta-analysis of the effect of comprehensive smoke-free legislation on acute coronary events. *Heart.* 2010;96:1525–1530. doi: 10.1136/hrt.2010.199026
60. Homa DM, Neff LJ, King BA, Caraballo RS, Bunnell RE, Babb SD, Garrett BE, Sosnoff CS, Wang L; Centers for Disease Control and Prevention. Vital signs: disparities in nonsmokers' exposure to secondhand smoke-United States, 1999–2012. *MMWR Morb Mortal Wkly Rep*. 2015;64:103–108.
61. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *Am J Prev Med.* 2015;48:326–333. doi: 10.1016/j.amepre.2014.10.012
62. Economic trends in tobacco fact sheet. Centers for Disease Control and Prevention website. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/economics/econ_facts/index.htm. Accessed May 30, 2019.
63. Trends in State and Federal Cigarette Tax and Retail Price in the United States: 1970–2016. http://healtheducation.org/index.php/2019/01/24/trends-in-state-and-federal-cigarette-tax-and-retail-price-united-states-1970-2016/. Accessed May 30, 2019.
64. *Global Burden of Disease Study 2017 (GBD 2017)*. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
65. GBD Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 [published corrections appear in *Lancet*. 2019;393:132 and *Lancet*. 2019;393:e44]. *Lancet*. 2018;392:1923–1994. doi: 10.1016/S0140-6736(18)32225-6
66. GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;390:1644]. *Lancet*. 2017;389:1885–1906. doi: 10.1016/S0140-6736(17)30819-X
67. Tobacco fact sheet. World Health Organization website. http://www.who.int/mediacentre/factsheets/fs339/en/. Accessed May 7, 2019.
68. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases [published correction appears in *Tob Control*. 2018;27:478]. *Tob Control*. 2018;27:58–64. doi: 10.1136/tobaccocontrol-2016-053305
69. The WHO Framework Convention on Tobacco Control: an overview. World Health Organization website. http://www.who.int/fctc/about/en/index.html. Accessed May 7, 2019.

4. PHYSICAL INACTIVITY

See Charts 4-1 through 4-13

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Physical inactivity is a major risk factor for CVD (eg, CHD, stroke, PAD, HF).[1] Achieving the guideline recommendations for PA is one of the AHA's 7 components of ideal CVH for both children and adults.[2] The AHA and 2018 federal guidelines for PA recommend that children get at least 60 minutes of PA daily (including aerobic and muscle- and bone-strengthening activity).[3] In 2017, on the basis of survey interviews,[4] only 26.1% of high school students reported achieving at least 60 minutes of daily PA, which is likely an overestimation of those actually meeting the guidelines.[5,6] The 2018 federal guidelines[3] and the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[7] recommend that adults get at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity (or an equivalent combination) per week and perform muscle-strengthening activities at least 2 days per week. In a nationally representative sample of adults, only 24.3% reported participating in adequate leisure-time aerobic and muscle-strengthening activity to meet these criteria (Chart 4-1),[8] but they were not asked to report activity accumulated during occupational, transportation, or domestic duties.

Being physically active is an important aspect of overall health. Meeting recommendations for PA not only reduces premature mortality but also improves risk factors for CVD (such as HBP, type 2 DM, and high cholesterol) and reduces the likelihood of diseases related to CVD, including CHD, HF, stroke, and aging-related diseases, such as dementia.[7,9–11] Benefits from PA are seen for all ages and groups, including children and older adults, pregnant women, and people with disabilities and chronic conditions. Therefore, the 2018 federal guidelines recommend being as physically active as abilities and conditions allow and that some PA is better than none.[3] The PA Guidelines Advisory Committee published a scientific report providing a clearer message for individuals not meeting the 150

Abbreviations Used in Chapter 4

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
app	application
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CER	cost-effectiveness ratio
CHD	coronary heart disease
CI	confidence interval
CPS-II	Cancer Prevention Study II
CVD	cardiovascular disease
CVH	cardiovascular health
DBP	diastolic blood pressure
DM	diabetes mellitus
ED	emergency department
EF	ejection fraction
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GBD	Global Burden of Disease
HBP	high blood pressure
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
LDL-C	low-density lipoprotein cholesterol
LIFE	Lifestyle Interventions and Independence for Elders
MET	metabolic equivalent
MetS	metabolic syndrome
MI	myocardial infarction
MSA	Metropolitan Statistical Area
NAVIGATOR	Long-term Study of Nateglinide + Valsartan to Prevent or Delay Type II Diabetes Mellitus and Cardiovascular Complications
NH	non-Hispanic

(*Continued*)

Abbreviations Used in Chapter 4 Continued

NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIH-AARP	National Institutes of Health–American Association of Retired Persons
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PAF	population attributable fraction
QALY	quality-adjusted life-year
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
VTE	venous thromboembolism
WC	waist circumference
WHI	Women's Health Initiative
WHO	World Health Organization
WHS	Women's Health Study
YRBSS	Youth Risk Behavior Surveillance System

minutes of moderate PA per week guideline, stating that even small increases in moderate-intensity PA or replacing sedentary time with light-intensity PA could provide health benefits.[9]

Defining and Measuring PA

There are 4 dimensions of PA (mode or type, frequency, duration, and intensity) and 4 common domains for adults (occupational, domestic, transportation, and leisure time).[5] For children, there are additional considerations of structured PA in schools and communities. The federal guidelines specify the suggested frequency, duration, and intensity of activity. Historically, recommendations on PA for health purposes have focused on leisure-time activity. However, because all domains of PA could have an impact on health, and because an increase in 1 domain can sometimes be compensated for by a decrease in another domain, ideally data will be collected on all dimensions and domains of PA.[5]

There are 2 broad categories of methods to assess PA: (1) subjective methods that use questionnaires and diaries/logs and (2) objective methods that use wearable monitors (pedometers, accelerometers, etc). Studies that compare the findings between subjective and objective methods have found that there is marked discordance between self-reported and measured PA, with respondents often overstating their PA, especially the intensity.[5,6,12]

Another consideration in the measurement of PA is that surveys often ask only about leisure-time PA, which represents PA obtained from a single domain. People who obtain high PA in other domains might be less likely to engage in leisure-time PA. Although they might meet the federal PA guidelines, people who spend considerable time and physical effort in occupational, domestic, or transportation activities/domains might be less likely to be identified as meeting the guidelines.

PA and cardiorespiratory fitness provide distinct metrics in assessment of CVD risk.[13] Poor cardiorespiratory (or aerobic) fitness might be a stronger predictor of adverse cardiovascular outcomes than traditional risk factors.[14] Although many studies have shown that increasing the amount and quality of PA can improve cardiorespiratory fitness, other factors can contribute, such as a genetic predisposition to perform aerobic exercise.[15] Because cardiorespiratory fitness is directly measured and reflects both participation in PA and the state of physiological systems affecting performance, the relationship between cardiorespiratory fitness and clinical outcomes is stronger than the relationship of PA to a series of clinical outcomes.[13] Unlike health behaviors such as PA and risk factors that are tracked by federally funded programs (NHIS, NHANES, etc), there are no national data on adult cardiorespiratory fitness to-date, but the WHO has recently created a global action plan to approach cardiorespiratory fitness globally with a goal to reduce the prevalence of insufficient PA by 15% by 2030.[13,16] Such additional data on the cardiorespiratory fitness levels of populations could give a fuller and more accurate picture of physical fitness levels.[13]

Prevalence

Youth

Meeting the Activity Recommendations (See Charts 4-2 through 4-5)

- On the basis of self-reported PA (YRBSS, 2017)[4]:
  - The prevalence of high school students who met aerobic activity recommendations of ≥60 minutes of PA on all 7 days of the week was 26.1% nationwide and declined from 9th (30.6%) to 12th (22.9%) grades. At each grade level, the prevalence was higher in boys than in girls.
  - Almost double the percentage of high school–aged boys (35.3%) than girls (17.5%) reported having been physically active ≥60 min/d on all 7 days (Chart 4-2).
  - The prevalence of students meeting activity recommendations on ≥5 days per week was higher among NH white boys (59.4%), NH black boys (54.5%), and Hispanic boys (52.6%) than NH white girls (38.8%), NH black girls (29.9%), and Hispanic girls (36.9%; Chart 4-2).
  - 15.4% of students reported that they did not participate in ≥60 minutes of any kind of PA on any 1 of the previous 7 days. Girls were more likely than boys to report this level of inactivity (19.5% versus 11.0%), with black girls reporting the highest rate of inactivity (26.6%; Chart 4-3).
  - In the 2017 YRBSS, 28.5% of heterosexual students, 14.7% of gay, lesbian, and bisexual students, and 19.0% of students not sure about their sexual identity reported being physically active for at least 60 min/d on all 7 days. The difference between prevalence of being physically active in heterosexual versus gay, lesbian, and bisexual students was larger among male students (37.0% versus 15.0%, respectively) than among female students (19.0% versus 14.3%, respectively; Chart 4-4).
- With regard to objectively measured moderate to vigorous PA (based on age-specific criteria for accelerometer cut points; NHANES, 2003–2004)[17]:
  - Only 8% of 12- to 19-year-olds accumulated ≥60 minutes of moderate to vigorous PA on ≥5 days per week (counting every minute of activity), whereas 42% of 6- to 11-year-olds achieved similar activity levels.

- More boys than girls met PA recommendations (≥60 minutes of moderate to vigorous activity) on ≥5 days per week.
- With regard to objectively measured cardiorespiratory fitness (NHANES, 2012)[18]:
  - For adolescents 12 to 15 years of age, boys in all age groups were more likely to have adequate levels of cardiorespiratory fitness than girls (Chart 4-5).
- With regard to self-reported muscle-strengthening activities (YRBSS, 2017)[4]:
  - The proportion of high school students who participated in muscle-strengthening activities on ≥3 days of the week was 51.1% nationwide and declined from 9th grade (males 66.4%, females 49.3%) to 12th grade (males 56.6%, females 36.1%).
  - More high school boys (62.1%) than girls (40.8%) reported having participated in muscle-strengthening activities on ≥3 days of the week.

Structured Activity Participation in Schools and Sports

- In 2017, only 29.9% of students attended physical education classes in school daily (34.7% of boys and 25.3% of girls; YRBSS).[4]
- Daily physical education class participation declined from the 9th grade (45.5% for boys, 39.2% for girls) through the 12th grade (26.5% for boys, 15.9% for girls; YRBSS).[4]
- Just over half (54.3%) of high school students played on at least 1 school or community sports team in the previous year: 49.3% of girls and 59.7% of boys (YRBSS).[4]
- Data from the 2017 SummerStyles survey demonstrated that only 16.5% of parents (n=1137) reported that their child walked to school and reported safety concerns and living too far away as barriers limiting commuting as a means of engaging in an active lifestyle.[19]

Television/Video/Computers (See Chart 4-6)

- Research suggests that screen time (watching television or using a computer) can lead to less PA among children.[20] In addition, television viewing time is associated with poor nutritional choices, overeating, and weight gain (Chapter 5, Nutrition).
- In 2017 (YRBSS)[4]:
  - Nationwide, 43.0% of high school students used a computer, tablet, or smartphone for activities other than schoolwork (eg, videogames, texting, YouTube, or social media) for ≥3 h/d on an average school day.
  - The prevalence of using a computer, tablet, or smartphone ≥3 h/d (for activities other than schoolwork) was highest among NH black boys (47.7%), followed by Hispanic girls (46.8%), NH black girls (46.7%), Hispanic boys (43.9%), NH white boys (41.7%), and NH white girls (39.6%; Chart 4-6).
  - The prevalence of watching television ≥3 h/d was highest among NH black boys (37.8%) and girls (32.8%), followed by Hispanic boys (21.9%) and girls (19.5%) and NH white girls (18.4%) and boys (16.9%).
- A report from the Kaiser Family Foundation (using data from 2009) reported that 8- to 18-year-olds spent an average of 33 min/d talking on the phone and 49 minutes using their phone to access media (music, games, or videos).[21] In addition to other cell phone use, 7th to 12th graders spent an average of 95 min/d text messaging. Surveys such as YRBSS have not historically asked about cell phone use specifically and are thus likely underestimates of total screen-time use.

Adults

Meeting the Activity Recommendations (See Charts 4-1 and 4-7 through 4-12)

- With regard to self-reported leisure-time aerobic and muscle-strengthening PA (NHIS, 2017):
  - 24.3% of adults met the 2018 federal PA guidelines for both aerobic and strengthening activity, an important component of overall physical fitness, based on only reporting leisure-time activity (Chart 4-1).
- For self-reported leisure-time aerobic PA (NHIS, 2017):
  - The age-adjusted proportion who reported meeting the 2018 aerobic PA guidelines for Americans (≥150 minutes of moderate PA or 75 minutes of vigorous PA or an equivalent combination each week) through leisure-time activities was 62.0% and 55.1% for NH white males and females, 52.7% and 37.0% for NH black males and females, and 49.2% and 40.9% for Hispanic males and females, respectively. Among both males and females, NH whites were more likely to meet the PA aerobic guidelines with leisure-time activity than NH blacks and Hispanics. For each racial/ethnic group, males had higher PA than females (Chart 4-7).[22]
  - Among adults ≥25 years of age, 32.8% of participants with no high school diploma, 42.7% of those with a high school diploma or General Educational Development high school equivalency credential, 50.6% of those with some college, 54.5% of those with an associate's degree, 64.1% of those with a bachelor's degree, and 69.6% of

those with an advanced degree met the federal guidelines for aerobic PA through leisure-time activities (Chart 4-8).
- Adults residing in urban areas (metropolitan statistical areas) are more likely to meet the federal aerobic PA guidelines through leisure-time activities than those residing in rural areas (55.0% versus 47.2%; Chart 4-9).
- Adults living below 200% of the poverty level are less likely to meet the federal PA guidelines through leisure-time activities than adults living at >200% above the poverty level (Chart 4-10).
- In an analysis from the NIH-AARP Diet and Health Study, severe neighborhood socioeconomic deprivation was prospectively associated with less exercise time (highest quintile versus lowest quintile, −0.85 [95% CI, −0.95 to −0.75]) among 136 526 participants 51 to 70 years of age.[23]
- 13.0% of people with disabilities and 27.1% of people without disabilities meet both the aerobic and muscle-strengthening guidelines (Chart 4-11).[24]
- In 2017, 25.9% of adults reported that they do not engage in leisure-time PA (no sessions of leisure-time PA of ≥10 minutes in duration; Chart 4-12).
- With regard to objectively measured moderate to vigorous PA (accelerometer counts/min >2020; NHANES, 2003–2004)[6]:
  - The number of individuals meeting the federal PA guidelines, including all moderate to vigorous PA as recommended by the 2018 PA guidelines, declines from middle age (57% of 40- to 49-year-olds) to older age (26% of 60- to 69-year-olds).[6] Previous reports estimated that there were lower numbers of adults meeting the 2008 PA guidelines, which recommended only counting moderate to vigorous PA accumulated in 10-minute bouts (removing up to 75% of moderate activity).[25]
  - These accelerometer data also revealed that rural US residents performed less moderate to vigorous PA than urban residents, but rural residents spent more time in lighter-intensity PA (accelerometer counts/min, 760–2020) than their urban resident counterparts.[26]
  - On average, males and females self-report at least 5 times more moderate to vigorous PA than what is captured objectively when they wear an accelerometer using a traditional definition (≥2020 accelerometer counts/min),[6] but the magnitude of difference varies widely if using a different accelerometer definition of moderate to vigorous PA.[12]
  - In contrast to self-reported PA, which suggested that NH whites had higher levels of PA,[24] data from objectively measured PA revealed that Hispanic participants had higher total PA and moderate to vigorous PA than NH white or black participants (≥20 years old).[6]
- In a recent study of almost 5000 British males, among those with low PA in midlife, retirement and the development of cardiovascular-related conditions were identified as factors predicting a decrease in PA over 20 years of follow-up, but for males who were more active in middle age, retirement was observed to be a time of increasing PA.[27]
- A Nielsen report using data from 2017 reported that adults spent an average of 5 hours 5 minutes per day watching television (including live television and other television-connected devices such as DVDs or playing video games on a console) and an hour and a half each day on computers or tablets.[28] Adult smartphone app/web use was reported as 2 hours 28 minutes per day using data collected from 12 500 smartphone users in 2017.[28] These technology use behaviors could influence time spent in PA and sedentary time.
  - Of particular concern, black adults spent an average of 7 hours 13 minutes per day watching television. Black and Hispanic adults had the highest smartphone use compared with other racial/ethnic groups.[28]

Structured Activity Participation in Leisure-Time, Domestic, Occupational, and Transportation Activities and Sitting Time

- Individuals from urban areas who participated in NHANES 2003 to 2006 reported participating in more transportation activity, but rural individuals reported spending more time in household PA and more total PA than urban individuals, possibly explaining the higher levels of light activity of rural individuals observed by objective methods.[26]
  - The prevalence of walking for transportation also varies by geographic location, ranging from 43.5% of individuals living in New England reporting any walking for transportation compared with 17.8% of individuals living in the East South Central region of the United States.[29]
- At this time, it is unclear which construct of PA (domestic, occupational, or transportation) contributes to the higher objectively measured PA[30] but lower subjectively measured PA[24] for Hispanic individuals, or whether these differences are caused by overreporting or underreporting of leisure-time PA.
- A 1-day assessment indicated that the mean prevalence of any active transportation was

10.3% using 2012 data from the American Time Use Study. NH whites reported the lowest active transport, only 9.2%, of any racial/ethnic group. Roughly 11.0% of Hispanics, 13.4% of NH blacks, and 15.0% of other NH individuals reported participating in any active transportation on the previous day.[31]

- Using data from the 2015 to 2016 NHANES, prevalence of time spent sitting >8 h/d was reported at 25.7% (95% CI, 23.0%–28.5%) and increased with increasing age.[32]

Secular Trends

Youth

In 2017 (YRBSS)[4]:

- Among students nationwide, there was a significant increase in the number of individuals reporting participation in muscle-strengthening activities on ≥3 days per week, from 47.8% in 1991 to 51.1% in 2017; however, the prevalence did not change substantively from 2013 (51.7%) to 2017 (51.1%).[4,33]
- A significant increase occurred in the number of youth reporting having used computers for something other than schoolwork for ≥3 h/d compared with 2003 (22.1% versus 43.0% in 2017). The prevalence did not change significantly from 2015 to 2017 (41.7% versus 43.0%).[4]
  - From 2004 to 2009, the Kaiser Family Foundation reported that the proportion of 8- to 18-year-olds who owned their own cell phone increased from 39% to 66%,[21] which could also contribute to higher exposure to screen time in children.
- Nationwide, the number of high school students who reported attending physical education classes at least once per week did not change substantively between 2013 (48.0%) and 2017 (51.7%).[4,33]
  - The number of high school students reporting attending daily physical education classes changed in nonlinear ways over time. Attendance initially decreased from 1991 to 1995 (from 41.6% to 25.4%) and did not substantively change between 1995, 2013, and 2017 (25.4%, 29.4%, and 29.9%, respectively).
- The prevalence of high school students playing ≥1 team sport in the past year did not substantively change between 1999 (55.1%) and 2017 (54.3%).[4] In 2012, the prevalence of adolescents 12 to 15 years of age with adequate levels of cardiorespiratory fitness (based on age- and sex-specific standards) was 42.2% (Chart 4-5), down from 52.4% in 1999 to 2000.[18]

Adults (See Chart 4-12)

- The prevalence of physical inactivity among adults ≥18 years of age, overall and by sex, has decreased from 1998 to 2017, with the largest drop occurring in the past decade, from 40.2% to 25.9% between 2005 and 2017, respectively (Chart 4-12).
- The prevalence of physical inactivity has surpassed the target for Healthy People 2020, which was 32.6%.[34]
- The age-adjusted percentage of US adults who reported meeting both the muscle-strengthening and aerobic guidelines increased from 14.4% in 1998 to 21.4% in 2015 and 24.4% in 2017.[24] The percentage of US adults who reported meeting the aerobic guidelines increased from 40.1% in 1998 to 49.7% in 2015 and 54.0% in 2017.[24,35]
- The increase in those meeting the aerobic guidelines may be explained in part by the increased prevalence in self-reported transportation walking from 28.4% to 31.7% and leisure walking from 42.1% to 52.1% (2005 to 2015).[36]
- Although it appears that leisure-time PA has been increasing in recent years, trends in technology behavior could influence both PA and sedentary time. Nielsen reports of adult smartphone app/web use comparing data collected in 2012 and 2014 (48 min/d and 1 hour 25 minutes per day, respectively)[37] to 2017 (2 hours 28 minutes per day)[28] suggest extreme increases in use over the past few years. Although they acknowledge that there were inconsistent methods of data collection among these different reports, the reported changes in technology behavior over such a short period of time are striking.
  - During this time period, from 2012 to 2017, television viewing decreased from 5 hours 28 minutes per day to 5 hours 5 minutes per day. Time spent on a computer decreased from 1 hour 3 minutes to <52 minutes in 2017. However, in 2017, tablet use was also measured and contributed to screen time, at 34 min/d.
  - The relationships between changes in technology habits and sedentary time have not been measured systematically.

Promotion of PA

The US Surgeon General has introduced "Step It Up!, a Call to Action to Promote Walking and Walkable Communities" in recognition of the importance of PA.[38] There are roles for communities, schools, and worksites.

Communities

- Community-level interventions have been shown to be effective in promoting increased PA. Communities can encourage walking with street design that includes sidewalks, improved street lighting, and landscaping design that reduces traffic speed to improve pedestrian safety. Higher neighborhood walkability has been associated with lower prevalence of overweight, obesity, and lower incidence of DM.[39] Moving to a walkable neighborhood was associated with a lower risk for incident hypertension in the Canadian Community Health Survey.[40]
- Community-wide campaigns include a variety of strategies such as media coverage, risk factor screening and education, community events, and policy or environmental changes.

Schools

- Schools can provide opportunities for PA through physical education, recess, before- and after-school activity programs, and PA breaks.[41]
- According to the School Health Policies and Practices Study, <5% of elementary schools and junior and senior high schools required daily physical education in 2014.[34]
- In 2012, the School Health Policies and Practices Study also reported that 58.9% of school districts required regular elementary school recess.[34]
- Healthy after-school programs and active school-day policies have been shown to be cost-effective solutions to increase PA and prevent childhood obesity.[42]

Worksites

- Worksites can offer access to on-site exercise facilities or employer-subsidized off-site exercise facilities to encourage PA among employees.
- Worksite interventions for sedentary occupations, such as providing "activity-permissive" workstations and email contacts that promote breaks, have reported increased occupational light activity, and the more adherent individuals observed improvements in cardiometabolic outcomes.[43,44]

Family History and Genetics

- It is clear that environmental factors can play a role in PA and sedentary behavior and the context in which these behaviors occur. However, PA and sedentary behavior can also be determined in part by genetics, with heritability estimates of up to 47%, although few loci have been identified or replicated.[45–47]

Mortality

Self-Reported Physical Inactivity and Mortality

- In analysis from NHIS with >20 years of follow-up, 8.7% of all-cause mortality was attributed to a PA level of <150 minutes of moderate-intensity equivalent activity per week (N=67 762).[48]
- A meta-analysis of 9 cohort studies, representing 122 417 patients, found that as little as 15 minutes of daily moderate to vigorous PA reduced all-cause mortality in adults ≥60 years of age. This protective effect of PA was dose dependent; the most rapid reduction in mortality per minute of added PA was for those at the lowest levels of PA. These findings suggest that older adults can benefit from PA time far below the amount recommended by the federal guidelines.[49]
- In a pooled study of >600 000 participants,[50] an inverse dose-response relationship was observed between level of self-reported leisure-time PA (HR, 0.80 [95% CI, 0.78–0.82] for less than the recommended minimum of the PA guidelines; HR, 0.69 [95% CI, 0.67–0.70] for 1–2 times the recommended minimum; and HR, 0.63 [95% CI, 0.62–0.65] for 2–3 times the minimum) and mortality, with the upper threshold for mortality benefit occurring at 3 to 5 times the PA recommendations (HR, 0.61 [95% CI, 0.59–0.62]). Furthermore, there was no evidence of harm associated with performing ≥10 times the recommended minimum (HR, 0.68 [95% CI, 0.59–0.78]).[50]
- Similarly, a population-based cohort in New South Wales, Australia, of 204 542 adults followed up for an average of 6.5 years evaluated the relationship of PA to mortality risk. It found that compared with those who reported no moderate to vigorous PA, the adjusted HRs for all-cause mortality were 0.66 (95% CI, 0.61–0.71) for those reporting 10 to 149 min/wk, 0.53 (95% CI, 0.48–0.57) for those reporting 150 to 299 min/wk, and 0.46 (95% CI, 0.43–0.49) for those reporting ≥300 min/wk of activity.[51]
- In the WHS (N=28 879; mean age, 62 years), females participating in strength training (1–19, 20–59, and 60–149 min/wk compared with 0 min/wk) had lower risk of all-cause mortality (HR, 0.73 [95% CI, 0.65–0.82]; HR, 0.71 [95% CI, 0.62–0.82]; and HR, 0.81 [95% CI, 0.67–0.97], respectively) but performing ≥150 min/wk strength training was not associated with lower risk of all-cause mortality (HR, 1.10 [95% CI, 0.77–1.56]) because of very wide CIs.[52]
- A meta-analysis also revealed an association between participating in more transportation-related PA and lower all-cause mortality risk.[53] In contrast, higher occupational PA has been associated with higher mortality in males but not females.[54] It is unclear whether confounding factors such as fitness, SES, or other domains of PA might impact this relationship.
- In a longitudinal cohort study of 263 540 participants from the UK Biobank cohort, commuting by

bicycle was associated with a lower risk of CVD mortality and all-cause mortality (HR, 0.48 and 0.59, respectively). Commuting by walking was associated with a lower risk of CVD mortality (HR, 0.64) but not all-cause mortality.[55]

- In a meta-analysis of 13 studies, higher sedentary time was associated with a 22% higher risk of all-cause mortality (HR, 1.22 [95% CI, 1.09–1.41]). This association was more pronounced at lower levels of PA than at higher levels.[56]
- A meta-analysis that included >1 million participants across 16 studies compared the risk associated with sitting time and television viewing in physically active and inactive study participants. For inactive individuals (defined as the lowest quartile of PA), those sitting >8 h/d had a higher all-cause mortality risk than those sitting <4 h/d. For active individuals (top quartile for PA), sitting time was not associated with all-cause mortality, but active people who watched television ≥5 h/d did have higher mortality risk.[57]
- In a prospective US cohort study (CPS-II), prolonged leisure-time sitting (≥6 versus <3 h/d) was associated with higher risk of mortality from all causes and CVD (including CHD and stroke-specific mortality) among 127 554 males and females free of chronic disease at baseline.[58]
- Using an isotemporal substitution approach in a subsample of the CPS-II, among participants with the lowest level of PA, replacing 30 min/d of sitting with light-intensity PA or moderate to vigorous PA was associated with 14% (HR, 0.86 [95% CI, 0.81–0.89]) or 45% (HR, 0.55 [95% CI, 0.47–0.62]) lower mortality, respectively. For the individuals with the highest PA levels, substitution was not associated with differences in mortality risk.[59]

Objectively Measured Physical Inactivity/ Sedentary Time and Mortality

- In a subsample of NHANES 2003 to 2006 (participants with objectively measured PA and between 50 and 79 years of age [n=3029]), models that replaced sedentary time with 10 min/d of moderate to vigorous PA were associated with lower all-cause mortality (HR, 0.70 [95% CI, 0.57–0.85]) after 5 to 8 years of follow-up. Even substituting in 10 minutes of light activity per day was associated with lower all-cause mortality (HR, 0.91 [95% CI, 0.86–0.96]).[60]
- In an analysis from the WHS, objective measures of PA and sedentary behavior using an accelerometer were associated with all-cause mortality. The highest levels of overall PA volume, as measured by the accelerometer, were associated with 60% to 70% lower risk of all-cause mortality. This inverse association between overall PA and all-cause mortality was largely driven by the moderate to vigorous PA levels; light PA or sedentary behavior was not associated with mortality risk in this cohort after accounting for moderate to vigorous PA.[61]
- In the REGARDS cohort study of 7985 middle- and older-aged US adults, objectively measured total sedentary time was associated with higher risk of all-cause mortality, with an HR for highest versus lowest quartile of total sedentary time of 2.63 (95% CI, 1.60–4.30) and longer sedentary bouts (HR, 1.96 [95% CI, 1.31–2.93]).[62]

Cardiorespiratory Fitness and Mortality

- The Cooper Center Longitudinal Study, an analysis conducted on 16 533 participants, revealed that across all risk factor strata, the presence of low cardiorespiratory fitness was associated with a greater risk of CVD death over a mean follow-up of 28 years.[63]
- In a longitudinal cohort study from the UK Biobank data, the association between PA and all-cause mortality was strongest among those with lowest hand-grip strength and lowest cardiorespiratory fitness, which suggests that strength and possibly cardiorespiratory fitness could moderate the association between PA and mortality.[64]
- In a retrospective cohort study of 57 085 individuals who were clinically referred for stress testing (but without established CAD or HF), cardiorespiratory fitness–associated "biologic age" was a stronger predictor of mortality over 10 years of follow-up than chronological age.[65]

Complications of Physical Inactivity: The CVH Impact

Youth

- In a study from the NHANES 2003 to 2006 cohort of participants 6 to 17 years of age with objective measurement of PA levels by accelerometer, those with the highest levels of PA had lower SBP, lower glucose levels, and lower insulin levels than participants in the lowest PA group.[66]
- Similarly, a higher amount of objectively measured sedentary duration assessed by accelerometer among children 0 to 14 years of age is associated with greater odds of hypertriglyceridemia and cardiometabolic risk.[67]
- For elementary school children, engagement in organized sports for ≈1 year was associated with lower clustered cardiovascular risk.[68]
- In a study of 36 956 Brazilian adolescents, self-reported higher moderate to vigorous PA levels and lower amounts of screen time were associated with lower cardiometabolic risk. Furthermore, the association of screen time with cardiometabolic

risk was modified by BMI. In contrast, the association between moderate to vigorous PA and cardiometabolic risk was independent of BMI.[69]
- In a prospective study of 700 Norwegian 10-year-old children with objective measures of PA, higher levels of moderate PA at baseline were associated with lower triglyceride levels and lower insulin resistance at 7-month follow-up. In contrast, sedentary time duration was not associated with cardiometabolic risk factors on follow-up.[70]

Adults

Cardiovascular and Metabolic Risk

- In a meta-analysis of 11 studies investigating the role of exercise among individuals with MetS, aerobic exercise significantly improved DBP (–1.6 mm Hg, *P*=0.01), WC (–3.4 cm, *P*<0.01), fasting glucose (–0.15 mmol/L, *P*=0.03), and HDL-C (0.05 mmol/L, *P*=0.02).[71]
- Results from NHANES 2011 to 2014 demonstrated that the prevalence of low HDL-C was higher among adults who reported not meeting PA guidelines (21.0%) than among adults meeting guidelines (17.7%).[72]
- Engaging in active transport to work has been associated with lower cardiovascular risk factors.
  - In a large Swedish cohort of 23 732 individuals, bicycling to work at baseline was associated with a lower odds of developing incident obesity, hypertension, hypertriglyceridemia, and impaired glucose tolerance at 10 years' follow-up than among those using passive modes of transportation.[73]
- Even lighter-intensity activities, such as yoga, were reported to improve BMI, BP, triglycerides, LDL-C, and HDL-C but not fasting blood glucose in a meta-analysis of 32 RCTs comparing yoga to non-exercise control groups.[74]
- In a dose-response meta-analysis of 29 studies with 330 222 participants that evaluated the association between PA levels and risk of hypertension, each 10 MET h/wk–higher level of leisure-time PA was associated with a 6% lower risk of hypertension (RR, 0.94 [95% CI, 0.92–0.96]).[75]
- In a meta-analysis including 7 trials with 2517 pregnant female participants that evaluated the effects of exercise during pregnancy, aerobic exercise for ≈30 to 60 minutes 2 to 7 times per week during pregnancy was associated with significantly lower risk of gestational hypertensive disorders (RR, 0.70 [95% CI, 0.53–0.83]).[76]
- In a population-based study of Hispanic/Latino adults with objective assessment of sedentary time, higher levels of sedentary time were associated with lower levels of HDL-C, higher triglycerides, and higher measures of insulin resistance after adjustment for PA levels. Furthermore, the accrual of prolonged and uninterrupted bouts of sedentary time was particularly associated with greater abnormalities in measures of glucose regulation.[77,78]
- Intermittent breaks of 10 minutes standing or desk pedaling during each hour of sitting were insufficient to prevent endothelial dysfunction that developed over a period of 4 hours of sitting.[79]

Cardiovascular Events

- In a dose-response meta-analysis of 9 prospective cohort studies (N=720 425), higher levels of sedentary time were associated with greater risk of CVD in a nonlinear relationship (HR for highest versus lowest sedentary time, 1.14 [95% CI, 1.09–1.19]).[80]
- A study of the factors related to declining CVD among Norwegian adults ≥25 years of age found that increased PA (≥1 hour of strenuous PA per week) accounted for 9% of the decline in hospitalized and nonhospitalized fatal and nonfatal CHD events.[81]
- In a study that followed 1.1 million females in the United Kingdom without prior vascular disease for an average of 9 years, those who reported moderate activity were found to be at lower risk of CHD, a cerebrovascular event, or a thrombotic event. However, strenuous PA was not found to be as beneficial as moderate PA.[82]
- In a prospective cohort study of 130 843 participants from 17 countries, compared with low levels of self-reported PA (<150 min/wk of moderate-intensity PA), moderate (150–750 min/wk) and high (>750 min/wk) levels of PA were associated with a graded lower risk of major cardiovascular events (HR high versus low, 0.75 [95% CI, 0.69–0.82]; moderate versus low, 0.86 [95% CI, 0.78–0.93]; high versus moderate, 0.88 [95% CI, 0.82–0.94]) over an average 6.9 years of follow-up time.[83]
- In the 2-year LIFE study of older adults (mean age, 78.9 years), higher levels of PA, measured by accelerometer, were associated with lower risk of adverse cardiovascular events.[84]
- In a dose-response meta-analysis of 12 prospective cohort studies (N=370 460), there was an inverse dose-dependent association between PA levels and risk of HF. PA levels at the guideline-recommended minimum (500 MET min/wk) were associated with 10% lower risk of HF. PA at twice and 4 times the guideline-recommended levels was associated with 19% and 35% lower risk of HF, respectively.[85]
- Furthermore, a recent individual-level pooled analysis of 3 large cohort studies demonstrated that the strong, dose-dependent association between higher PA levels and lower risk of HF is largely

driven by lower risk of HF with preserved EF but not HF with reduced EF.[86]

- In a large clinical trial (NAVIGATOR) involving 9306 people with impaired glucose tolerance, ambulatory activity (in steps per day) as assessed by pedometer at baseline and 12 months was inversely associated with risk of a cardiovascular event.[87]
- In the WHI, every hour per day more of light-intensity PA was associated with lower CHD (HR, 0.86 [95% CI, 0.73–1.00]; *P*=0.05) and lower CVD (HR, 0.92 [95% CI, 0.85–0.99]; *P*=0.03).[88]
- Domains of PA, other than leisure time, are understudied and often overlooked. A meta-analysis reported a protective relation of transportation activity to cardiovascular risk, which was greater in females.[89] However, higher occupational PA has recently been associated with higher MI incidence in males 19 to 70 years old.[54,90] These relationships require further investigation, because a protective association of occupational activity with MI has been reported in young males (19–44 years).[90]
- A recent analysis from the Rotterdam Study evaluated the contribution of specific PA types on CVD-free life expectancy. Higher levels of cycling were associated with a greater CVD-free life span in males (3.1 years) and females (2.4 years). Furthermore, high domestic work in females (2.4 years) and high gardening in males (2 years) were also associated with an increased CVD-free life span.[91]
- Cardiorespiratory fitness and PA levels are important determinants of HF risk in the general population. In the Cooper Center Longitudinal Study population, higher levels of cardiorespiratory fitness in midlife were associated with lower risk of HF, MI, and stroke.[92]
  - The inverse association between higher fitness levels and risk of HF (HR per 1-MET higher fitness level, 0.79 [95% CI, 0.75–0.83] for males) was stronger than observed for risk of MI (HR, 0.91 [95% CI, 0.87–0.95]).[92]
  - Cardiorespiratory fitness accounted for 47% of the HF risk associated with higher BMI levels.[93]
  - Improvement in cardiorespiratory fitness in middle age was also strongly associated with lower risk of HF among the Cooper Center Longitudinal Study participants (HR per 1-MET increase in fitness levels, 0.83 [95% CI, 0.74–0.93]).[94]
- Lower levels of cardiorespiratory fitness have also been associated with higher risk of HF in a recent study of 21 080 veterans, with a 91% higher risk of HF noted among low-fitness participants (HR, 1.91 [95% CI, 1.74–2.09]).[95]
- In a Swedish cohort of 773 925 young males without history of VTE, cardiorespiratory fitness was associated with a reduced risk of VTE (HR, 0.81 [95% CI, 0.78–0.85]) at ≥20 years of follow-up.[96]
- In 5962 veterans, lower exercise capacity was associated with a higher risk of developing AF. For every 1-MET increase in exercise capacity, the risk of developing AF was 21% lower (HR, 0.79 [95% CI, 0.76–0.82]).[97]

Secondary Prevention

- A Cochrane systematic review of 63 studies concluded that exercise-based cardiac rehabilitation programs for CHD patients reduced cardiovascular mortality and hospital admissions but not overall mortality.[98]
- In a prospective study that monitored 902 HF patients (with preserved or reduced EF) for 3 years, reporting participation in any PA (≥1 min/wk) was associated with a lower risk of cardiac death and all-cause death than no PA. Less television screen time (<2 versus >4 h/d) was also associated with lower all-cause death.[99]
- In a prospective cohort study of 15 486 participants with stable CAD from 39 countries, higher levels of PA were associated with lower risk of mortality such that doubling the exercise volume was associated with 10% lower risk of all-cause mortality after adjustment for potential confounders.[100]
  - Among 1746 CAD patients followed up for 2 years, those who remained inactive or became inactive had a 4.9- and 2.4-fold higher risk of cardiac death, respectively, than patients who remained at least irregularly active during the follow-up period.[101]
  - In a prospective cohort study of 3307 individuals with CHD, participants who maintained high PA levels over longitudinal follow-up had a lower risk of mortality than those who were inactive over time (HR, 0.64 [95% CI, 0.50–0.83]).[102]
- In a cohort of patients with HF and preserved EF, compared with high levels of self-reported PA, poor and intermediate levels were associated with higher risk of HF hospitalization (HR, 1.93 [95% CI, 1.16–3.22] for poor versus high PA and HR, 1.84 [95% CI, 1.02–3.31] for intermediate versus high PA) and cardiovascular mortality (HR, 4.36 [95% CI, 1.37–13.83] for poor versus high PA and HR, 4.05 [95% CI, 1.17–14.04] for intermediate versus high PA).[103]
- Using data from a registry of stable outpatients with symptomatic coronary disease, cerebrovascular disease, or PAD, the mortality rate of patients with a recent MI was significantly lower in patients who participated in supervised (n=593) versus unsupervised (n=531) exercise programming.[104]

- Early mortality after a first MI was lower for patients who had higher exercise capacity before the MI event. Every 1-MET higher exercise capacity before the MI was associated with an 8% to 10% lower risk of mortality at 28 days, 90 days, and 365 days after MI.[105] A study of 3572 patients with recent MI demonstrated significant sex differences in PA after AMI. Females were more likely to be inactive than males within 12 months after the AMI episode (OR, 1.37 [95% CI, 1.21–1.55]).[106]
- A recent study of participants included in the WHI observational study who experienced a clinical MI during the study demonstrated that compared with those who maintained low PA levels after the MI event, participants had lower risk of mortality with improvement in PA levels (HR, 0.54 [95% CI, 0.36–0.86]) or with sustained high PA levels (HR, 0.52 [95% CI, 0.36–0.73]).[107]
- Among 2370 individuals with CVD who responded to the Taiwan National Health Interview Survey, achieving more total PA, leisure-time PA, and domestic and work-related PA was associated with lower mortality at 7-year follow-up.[108]

Brain Health

- Growing evidence suggests a link between vascular risk factors, cardiovascular/cerebrovascular disease and poor brain health, leading to cognitive and motor dysfunction. The AHA has proposed to use the Life's Simple 7 strategy not only to decrease cardiovascular risk, but also to maintain optimal brain health.[10]
- One of Life's Simple 7 strategies promotes achievement of adequate PA. Results from a meta-analysis including >33 000 participants suggest that individuals who self-report high PA levels have a 38% lower risk of cognitive decline.[109] Results from intervention trials have been more inconsistent.[110–113] However, there have been some promising results, including the FINGER study, which observed better executive function in those who adhered to a multidomain (exercise, cognitive training, and Mediterranean diet) intervention for 2 years.[110]
- Evidence from meta-analyses in stroke patients suggests that PA rehabilitation may also improve cognitive and motor function outcomes. An overall positive effect of PA training on cognitive performance was observed in stroke patients (Hedges' g, 0.30 [95% CI, 0.14–0.47]) in a meta-analysis representing data from 736 participants.[114] Another recent meta-analysis of studies involving stroke patients observed that treadmill training improved motor function compared with no training (standard mean difference, 0.60 [95% CI, 0.55–0.66]), with similar results in both low- and high-intensity and volume rehabilitation programs.[115]

Costs

- The economic consequences of physical inactivity are substantial. Using data derived primarily from WHO publications and data warehouses, one study estimated that the economic costs of physical inactivity account for 1.5% to 3.0% of total direct healthcare expenditures in developed countries such as the United States.[116]
- A global analysis of 142 countries (93.2% of the world's population) concluded that physical inactivity cost healthcare systems $53.8 billion in 2013, including $9.7 billion paid by individual households.[117]
- A study of American adults reported that inadequate levels of aerobic PA (after adjustment for BMI) were associated with an estimated 11.1% of aggregate healthcare expenditures (including expenditures for inpatient, outpatient, ED, office-based, dental, vision, home health, prescription drug, and other services).[118]
- An evaluation of healthcare costs based on the cardiovascular risk factor profile (including ≥30 minutes of moderate to vigorous PA ≥5 times per week) found that among adults ≥40 years of age with CVD, the highest marginal expenditures ($2853 per person in 2012) were for those not meeting the PA guidelines. Healthcare costs included hospitalizations, prescribed medications, outpatient visits (hospital outpatient visits and office-based visits), ED visits, and other expenditures (dental visits, vision aid, home health care, and other medical supplies).[119]
- A systematic review of population-based interventions to encourage PA found that improving biking trails, distributing pedometers, and school-based PA were most cost-effective.[120]
- Interventions and community strategies to increase PA have been shown to be cost-effective in terms of reducing medical costs[121]:
  - Nearly $3 in medical cost savings is realized for every $1 invested in building bike and walking trails.
  - The incremental CER ranges from $14 000 to $69 000 per QALY gained from interventions such as pedometer or walking programs compared with no intervention, especially in high-risk groups.

Global Burden (See Chart 4-13)

- Prevalence of physical inactivity in 2016 was reported to be 27.5% (95% CI, 25.0%–32.2%) of the population globally. These rates have not changed substantially since 2001, at which time prevalence of physical inactivity was 28.5% (95%

CI, 23.9%–33.9%). Critically, it appears that the number of women reporting insufficient PA is 8% higher than men, globally.[122]

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[123] Mortality rates attributable to low PA are highest in North Africa and the Middle East and in Central and Eastern Europe (Chart 4-13).
- Physical inactivity is among the leading behavioral risk factors for global death, responsible for 1.3 million deaths annually.[124] Other leading risk factors include diet, alcohol, tobacco, and child and maternal malnutrition. The adjusted PAF for achieving <150 minutes of moderate to vigorous PA per week was 8.0% for all-cause and 4.6% for major CVD in a study of 17 low-, middle-, and high-income countries in 130 843 participants without preexisting CVD.[83]

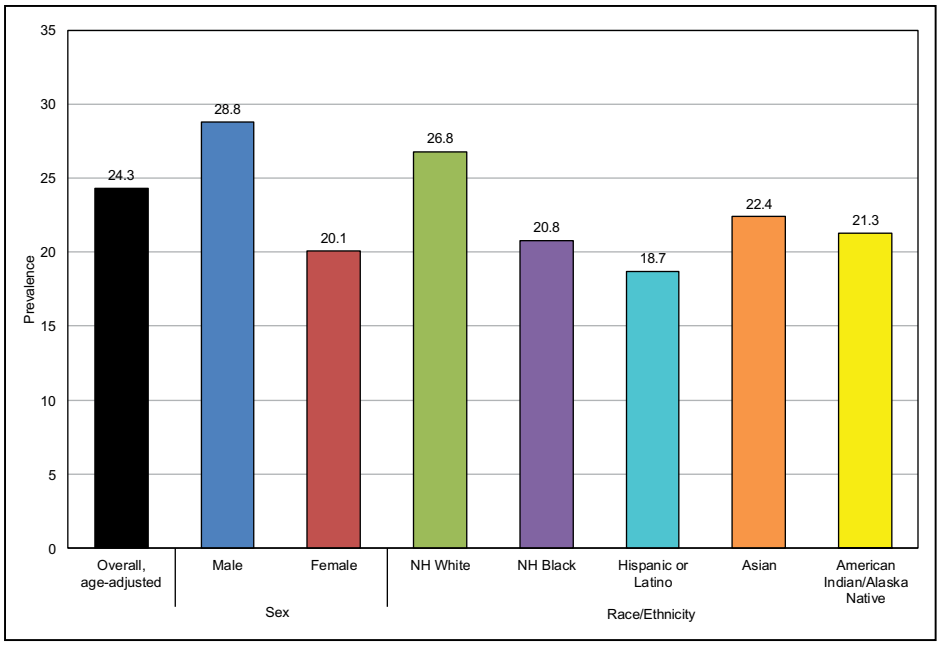

Chart 4-1. Prevalence of meeting both the aerobic and muscle-strengthening guidelines for the 2018 Physical Activity Guidelines for Americans among US adults ≥18 years of age, overall and by sex and race/ethnicity, 2017.
Data are age adjusted for adults ≥18 years of age.
NH indicates non-Hispanic.
Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2017.

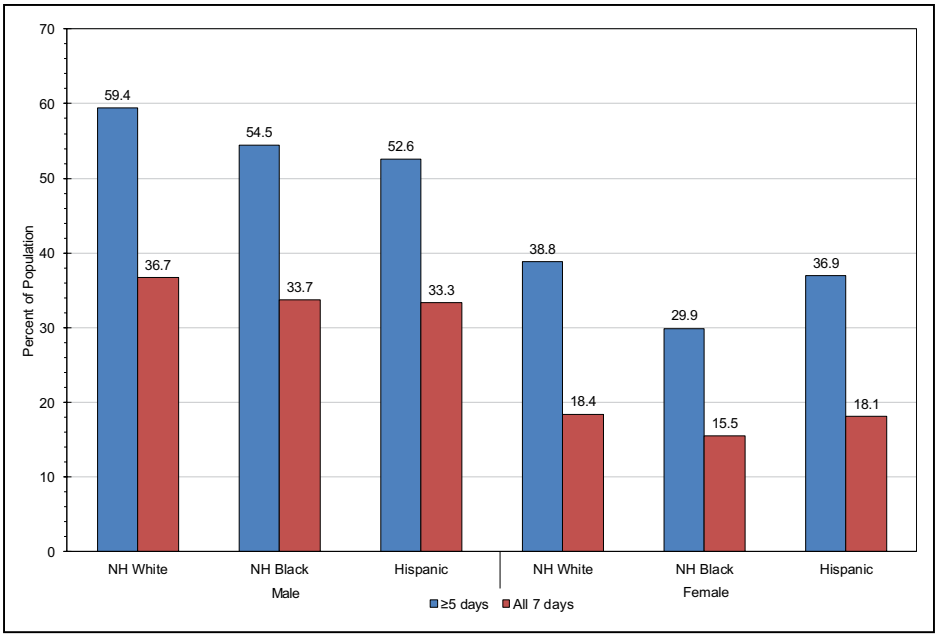

Chart 4-2. Prevalence of US students in grades 9 to 12 who were active at least 60 min/d on all 7 days by race/ethnicity and sex, 2017.
"Currently recommended levels" was defined as activity that increased their heart rate and made them breathe hard some of the time for a total of ≥60 min/d on all 7 days preceding the survey.
NH indicates non-Hispanic.
Source: Data derived from Kann et al[4] using Youth Risk Behavior Surveillance System, 2017.

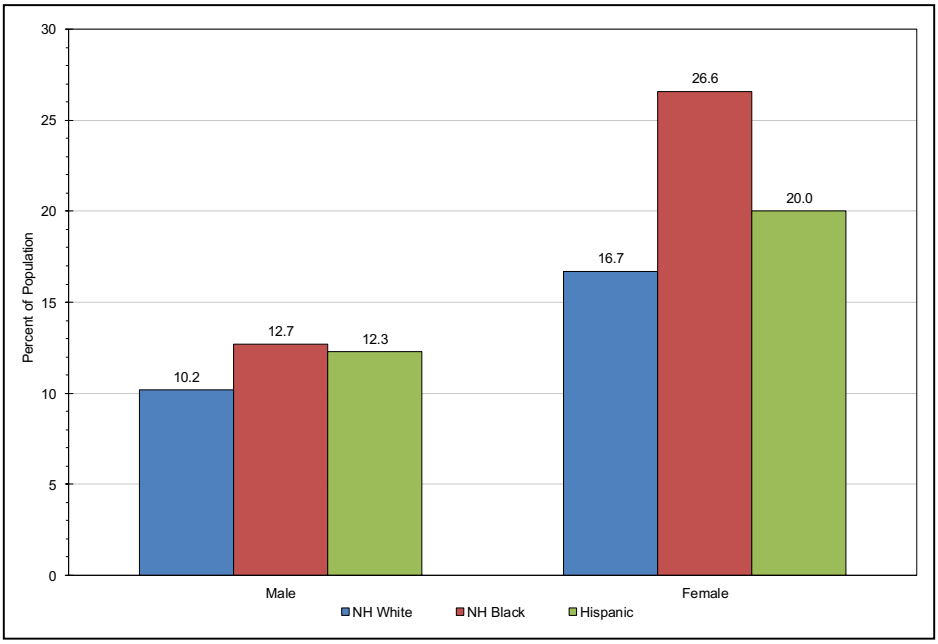

Chart 4-3. Prevalence of US students in grades 9 to 12 who did not participate in ≥60 minutes of physical activity on any day in the past 7 days by race/ethnicity and sex, 2017.
NH indicates non-Hispanic.
Source: Data derived from Kann et al[4] using Youth Risk Behavior Surveillance System, 2017.

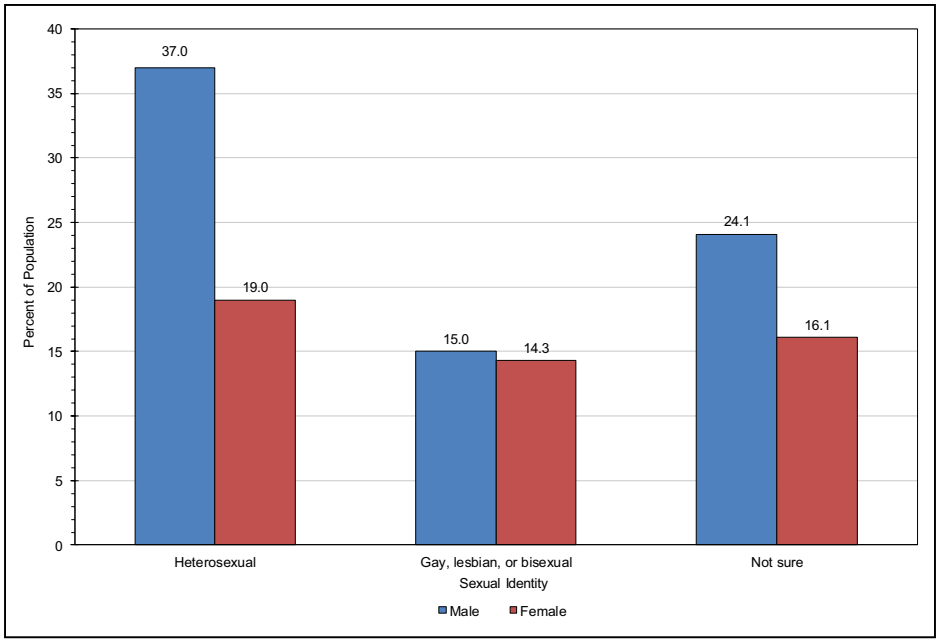

Chart 4-4. Prevalence of US students in grades 9 to 12 who were active at least 60 min/d on all 7 days by sexual identity and sex, 2017.
"Currently recommended levels" was defined as activity that increased their heart rate and made them breathe hard some of the time for a total of ≥60 min/d on all 7 days preceding the survey.
Source: Data derived from Kann et al[4] using Youth Risk Behavior Surveillance System, 2017.

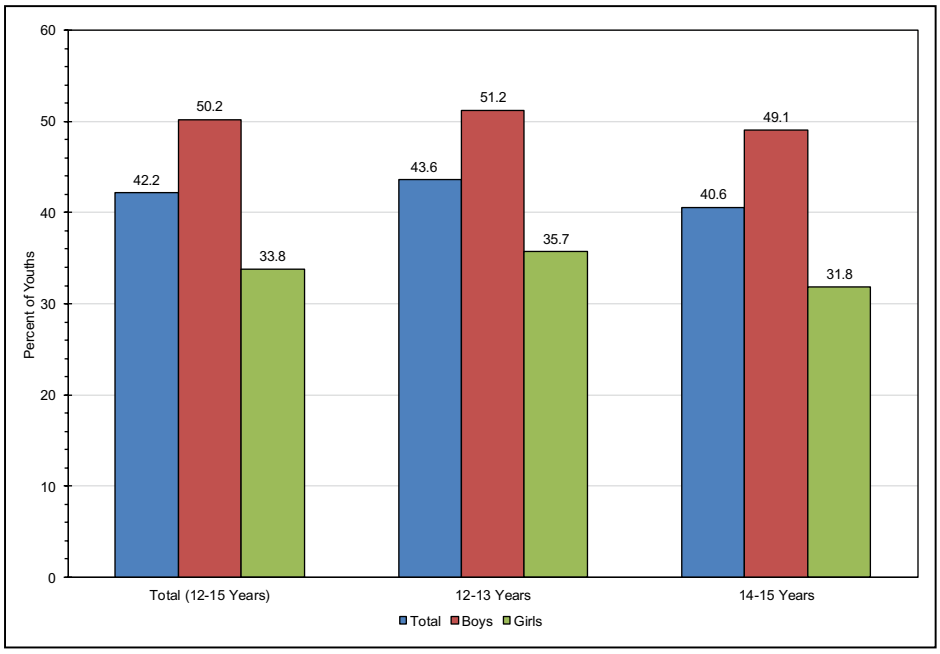

Chart 4-5. Prevalence of US children 12 to 15 years of age who had adequate levels of cardiorespiratory fitness by sex and age, 2012.
Source: Data derived from Gahche et al[18] using National Health and Nutrition Examination Survey, National Youth Fitness Survey, 2012.

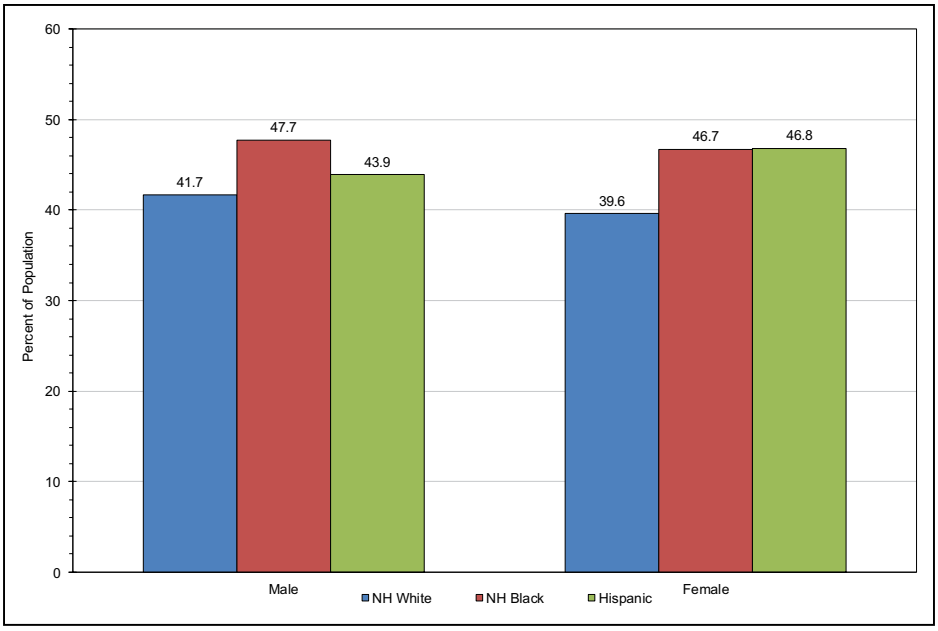

Chart 4-6. Percentage of US students in grades 9 to 12 who used a computer* for ≥3 hours on an average school day by race/ethnicity and sex, 2017.

NH indicates non-Hispanic.

*For something other than schoolwork.

Source: Data derived from Kann et al[4] using Youth Risk Behavior Surveillance System, 2017.

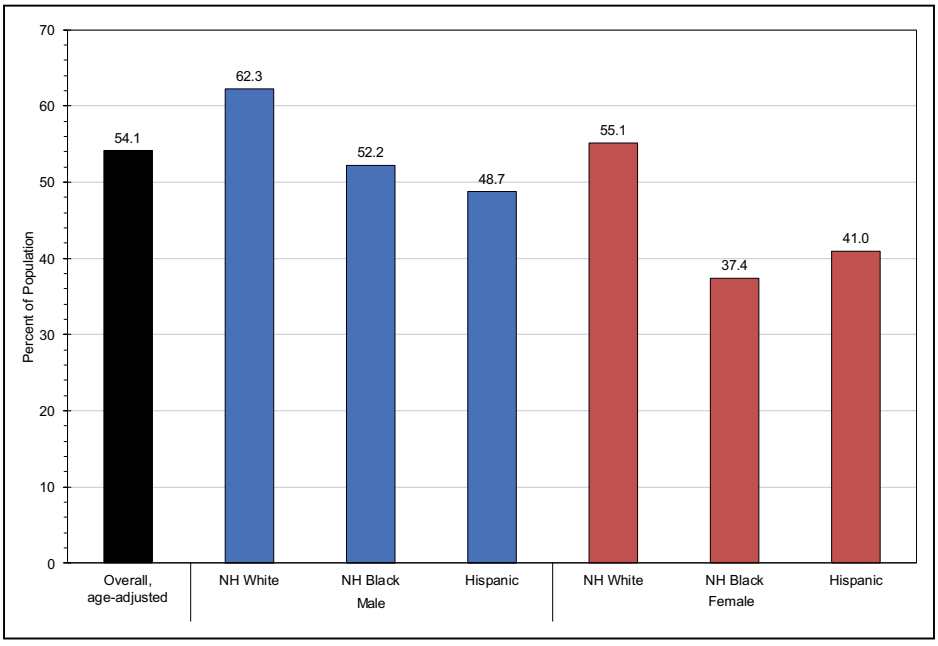

Chart 4-7. Prevalence of meeting the aerobic guidelines of the 2018 Physical Activity Guidelines for Americans among US adults ≥18 years of age by race/ethnicity and sex, 2017.

Percentages are age adjusted. The aerobic guidelines of the 2018 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.

NH indicates non-Hispanic.

Source: American Heart Association unpublished tabulation of National Health Interview Survey, 2017.[22]

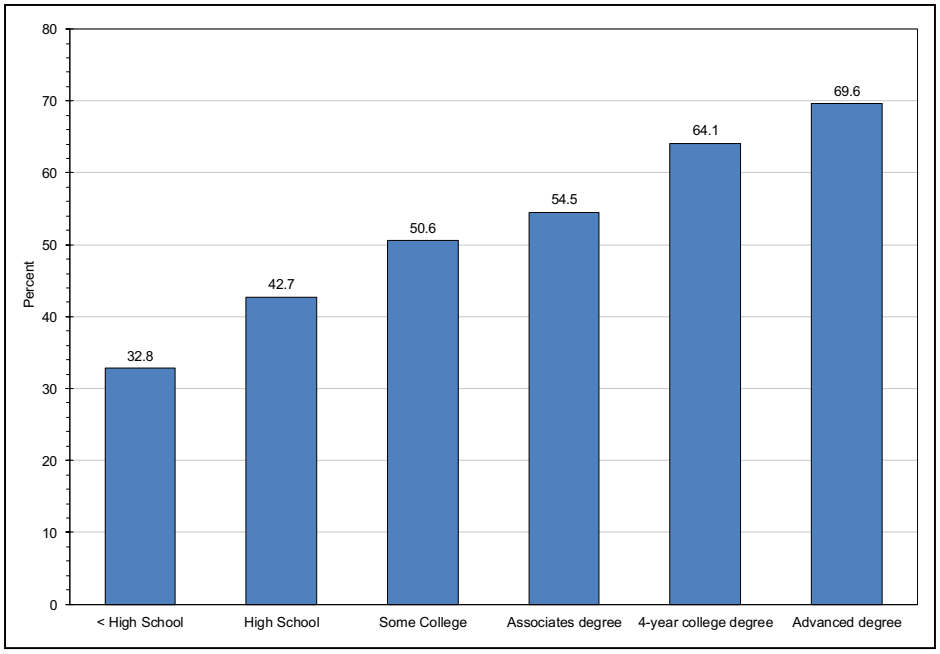

Chart 4-8. Prevalence of meeting the aerobic guidelines of the 2018 Physical Activity Guidelines for Americans among US adults ≥25 years of age by educational attainment, 2017.

Percentages are age adjusted. The aerobic guidelines of the 2018 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.

Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2017.

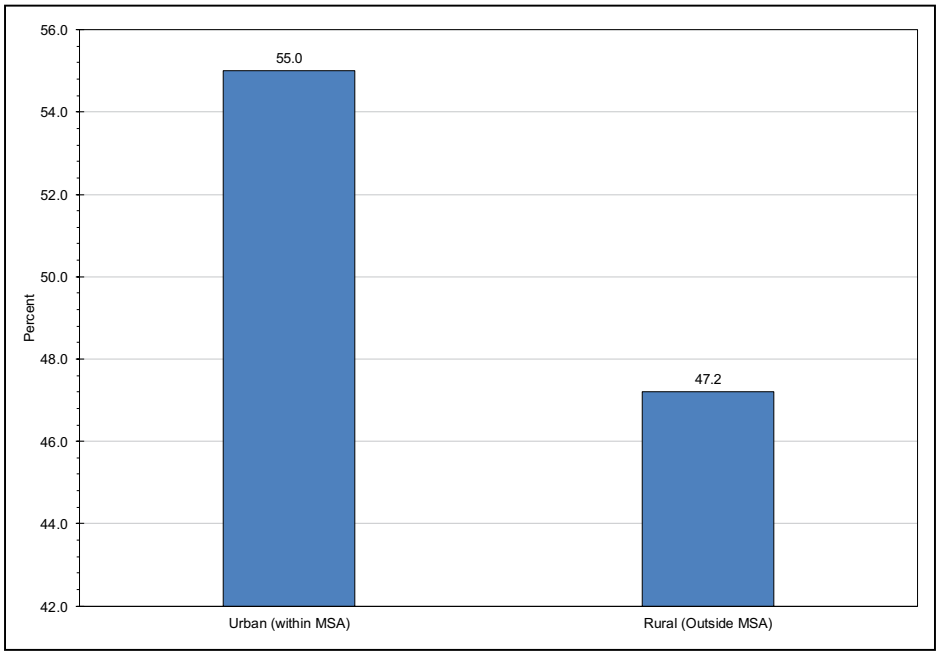

Chart 4-9. Prevalence of meeting the aerobic guidelines for the 2018 Physical Activity Guidelines for Americans among US adults ≥18 years of age by location of residence, 2017.

Percentages are age adjusted. The aerobic guidelines of the 2018 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.

MSA indicates metropolitan statistical area.

Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2017.

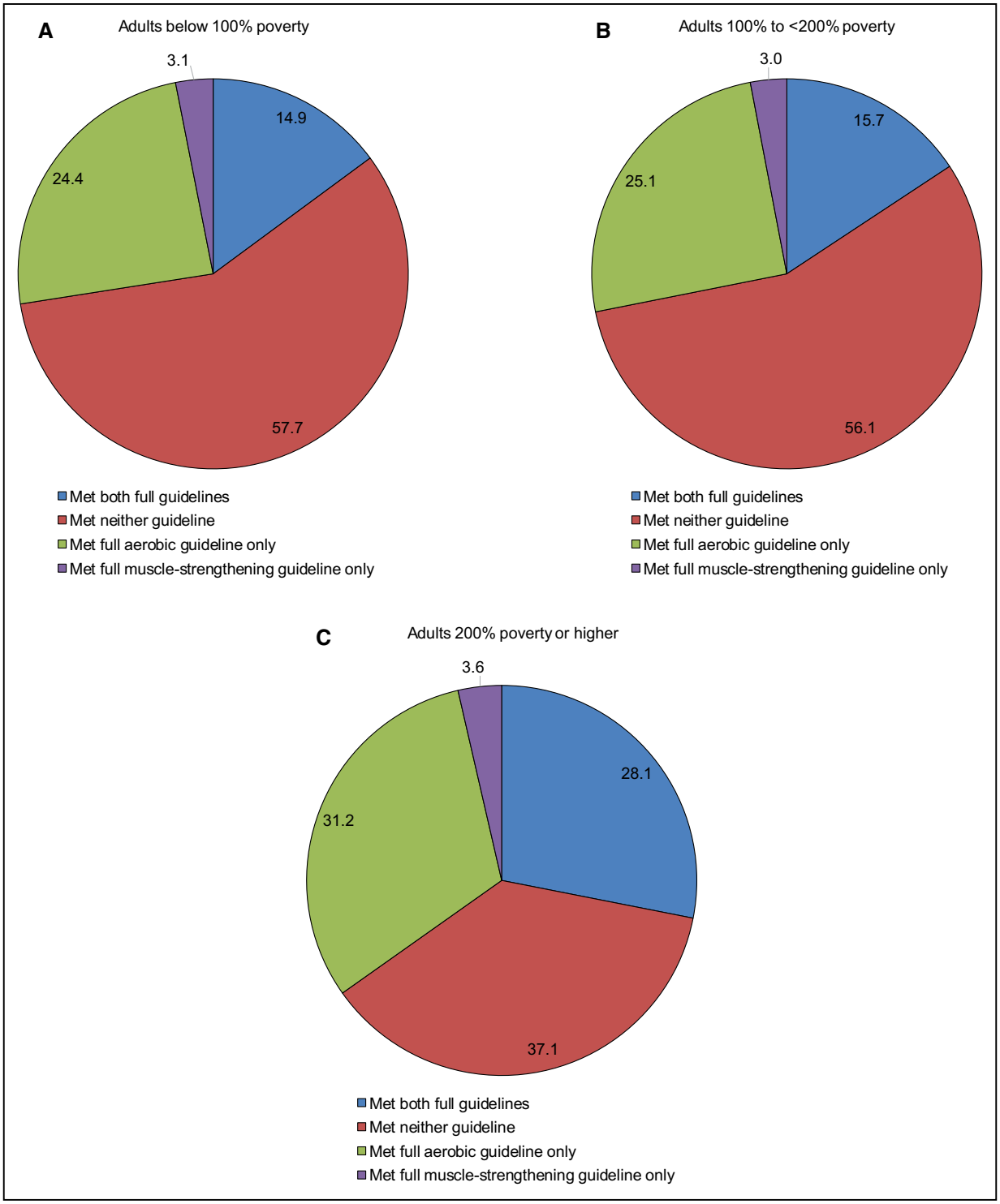

Chart 4-10. Prevalence of meeting the aerobic and muscle-strengthening guidelines for the 2018 Physical Activity Guidelines for Americans among US adults ≥18 years of age by poverty level and type of activity, 2017.

Percentages of American adults meeting guidelines are presented for (**A**) adults <100% poverty, (**B**) adults 100% to <200% poverty, and (**C**) adults ≥200% poverty. Percentages are age adjusted. The aerobic guidelines of the 2018 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination and performing muscle-strengthening activities at least 2 days per week.

Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 2017.

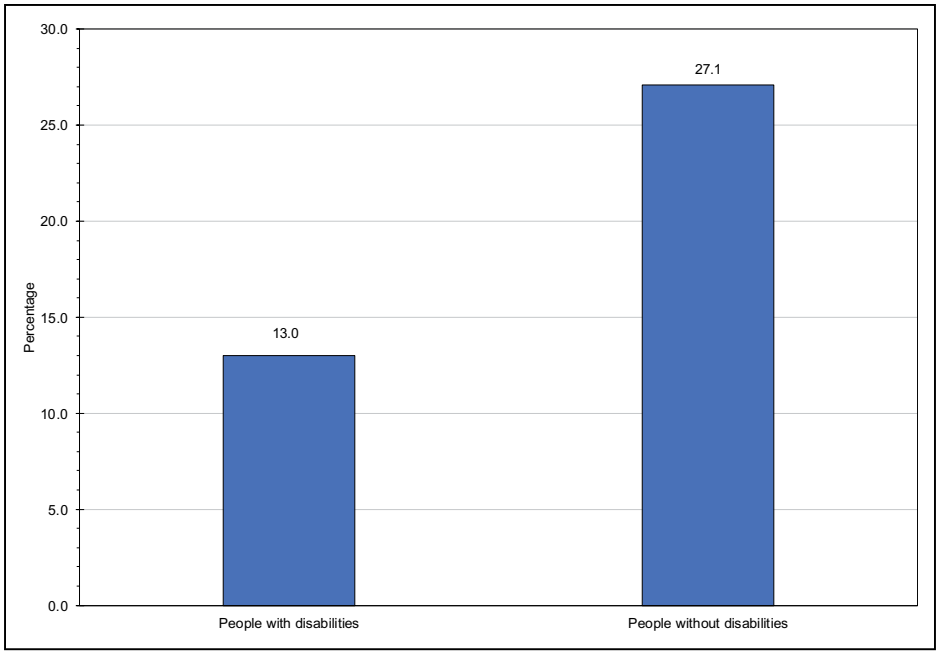

Chart 4-11. Prevalence of meeting both the aerobic and muscle-strengthening guidelines for the 2018 Physical Activity Guidelines for Americans among US adults ≥18 years of age by disability status, 2017.
Percentages are age adjusted. The aerobic guidelines of the 2008 Federal Physical Activity Guidelines for Americans recommend engaging in moderate leisure-time physical activity for ≥150 min/wk or vigorous activity ≥75 min/wk or an equivalent combination.
Source: National Health Interview Survey, 2017.[24]

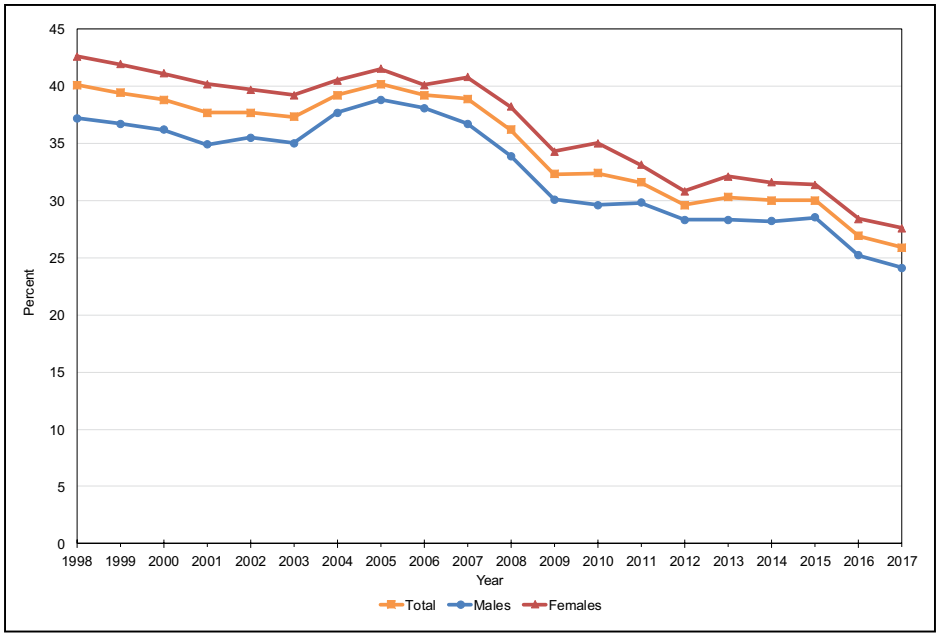

Chart 4-12. Trends in the prevalence of physical inactivity among US adults ≥18 years of age, overall and by sex, 1998 to 2017.
Percentages are age adjusted. Physical inactivity is defined as reporting no engagement in leisure-time physical activity in bouts lasting ≥10 minutes.
Source: Data derived from Healthy People 2020[8] using National Health Interview Survey, 1998 to 2017.

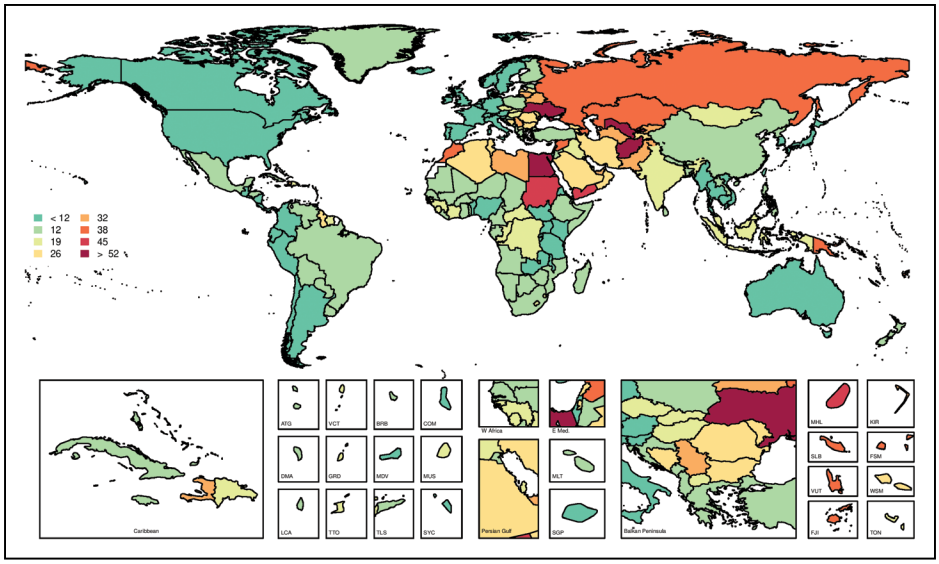

Chart 4-13. Age-standardized global mortality rates attributable to low physical activity per 100 000, both sexes, 2017.
Mortality rates attributable to low physical activity are highest in North Africa and the Middle East and in Central and Eastern Europe.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[123] Printed with permission.

REFERENCES

1. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS,et al; on behalf of the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122:406–441. doi: 10.1161/CIR.0b013e3181e8edf1
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
3. US Department of Health and Human Services. *Physical Activity Guidelines for Americans*. 2nd ed. Washington, DC: US Department of Health and Human Services; 2018.
4. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, Lowry R, Chyen D, Whittle L, Thornton J,et al. Youth risk behavior surveillance: United States, 2017. *MMWR Surveill Summ.* 2018;67:1–114. doi: 10.15585/mmwr.ss6708a1
5. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, Richardson CR, Smith DT, Swartz AM; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health and Cardiovascular, Exercise, and Cardiac Rehabilitation and Prevention Committee of the Council on Clinical Cardiology, and Council on Cardiovascular Stroke Nursing. Guide to the assessment of physical activity: clinical and research applications: a scientific statement from the American Heart Association. *Circulation*. 2013;128:2259–2579. doi: 10.1161/01.cir.0000435708.67487.da
6. Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S. adults: compliance with the Physical Activity Guidelines for Americans. *Am J Prev Med.* 2011;40:454–461. doi: 10.1016/j.amepre.2010.12.016
7. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW,et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published correction appears in *Circulation*. 2019;140:e649–e650]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
8. Office of Disease Prevention and Health Promotion. Healthy People 2020: Data 2020. HealthyPeople.gov website. https://www.healthypeople.gov/2020/data-search. Accessed March 27, 2019.
9. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: US Department of Health and Human Services; 2018.
10. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, et al; on behalf of the American Heart Association/American Stroke Association. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. *Stroke.* 2017;48:e284–e303. doi: 10.1161/STR.0000000000000148
11. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol.* 2017;74:1246–1254. doi: 10.1001/jamaneurol.2017.1658
12. Shiroma EJ, Cook NR, Manson JE, Buring JE, Rimm EB, Lee IM. Comparison of self-reported and accelerometer-assessed physical activity in older women. *PLoS One.* 2015;10:e0145950. doi: 10.1371/journal.pone.0145950
13. Kaminsky LA, Arena R, Beckie TM, Brubaker PH, Church TS, Forman DE, Franklin BA, Gulati M, Lavie CJ, Myers J, et al; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Clinical Cardiology, and Council on Nutrition, Physical Activity and Metabolism. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. *Circulation.* 2013;127:652–662. doi: 10.1161/CIR.0b013e31827ee100
14. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, et al; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation.* 2016;134:e653–e699. doi: 10.1161/CIR.0000000000000461
15. DeFina LF, Haskell WL, Willis BL, Barlow CE, Finley CE, Levine BD, Cooper KH. Physical activity versus cardiorespiratory fitness: two (partly)

distinct components of cardiovascular health? *Prog Cardiovasc Dis.* 2015;57:324–329. doi: 10.1016/j.pcad.2014.09.008
16. Lang JJ, Wolfe Phillips E, Orpana HM, Tremblay MS, Ross R, Ortega FB, Silva DAS, Tomkinson GR. Field-based measurement of cardiorespiratory fitness to evaluate physical activity interventions. *Bull World Health Organ.* 2018;96:794–796. doi: 10.2471/BLT.18.213728
17. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc.* 2008;40:181–188. doi: 10.1249/mss.0b013e31815a51b3
18. Gahche J, Fakhouri T, Carroll DD, Burt VL, Wang CY, Fulton JE. Cardiorespiratory fitness levels among U.S. youth aged 12–15 years: United States, 1999–2004 and 2012. *NCHS Data Brief*. 2014;(153):1–8.
19. Omura JD, Hyde ET, Watson KB, Sliwa SA, Fulton JE, Carlson SA. Prevalence of children walking to school and related barriers: United States, 2017. *Prev Med.* 2019;118:191–195. doi: 10.1016/j.ypmed.2018.10.016
20. Lieberman DA, Chamberlin B, Medina E Jr, Franklin BA, Sanner BM, Vafiadis DK; on behalf of the Power of Play: Innovations in Getting Active Summit Planning Committee. The power of play: Innovations in Getting Active Summit 2011: a science panel proceedings report from the American Heart Association. *Circulation*. 2011;123:2507–2516. doi: 10.1161/CIR.0b013e318219661d
21. Rideout V, Foher U, Roberts D. Generation M2: Media in the Lives of 8-18-Year-Olds: A Kaiser Family Foundation Study. Menlo Park, CA: Henry J. Kaiser Family Foundation; 2010.
22. National Center for Health Statistics. National Health Interview Survey, 2017 data release: public-use data file and documentation. Centers for Disease Control and Prevention website. http://www.cdc.gov/nchs/nhis/nhis_2017_data_release.htm. Accessed April 1, 2019.
23. Xiao Q, Keadle SK, Berrigan D, Matthews CE. A prospective investigation of neighborhood socioeconomic deprivation and physical activity and sedentary behavior in older adults. *Prev Med.* 2018;111:14–20. doi: 10.1016/j.ypmed.2018.02.011
24. National Center for Health Statistics. Summary Health Statistics: National Health Interview Survey, 2017: Table A-14. Centers for Disease Control and Prevention website. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-14.pdf. Accessed April 8, 2019.
25. Luke A, Dugas LR, Durazo-Arvizu RA, Cao G, Cooper RS. Assessing physical activity and its relationship to cardiovascular risk factors: NHANES 2003-2006. *BMC Public Health.* 2011;11:387. doi: 10.1186/1471-2458-11-387
26. Fan JX, Wen M, Kowaleski-Jones L. Rural-urban differences in objective and subjective measures of physical activity: findings from the National Health and Nutrition Examination Survey (NHANES) 2003-2006. *Prev Chronic Dis.* 2014;11:e141. doi: 10.5888/pcd11.140189
27. Aggio D, Papachristou E, Papacosta O, Lennon LT, Ash S, Whincup PH, Wannamethee SG, Jefferis BJ. Trajectories of self-reported physical activity and predictors during the transition to old age: a 20-year cohort study of British men. *Int J Behav Nutr Phys Act.* 2018;15:14. doi: 10.1186/s12966-017-0642-4
28. Nielsen Comparable Metrics Report Q2 2017. The Nielsen Company website. https://www.nielsen.com/us/en/insights/report/2017/the-nielsen-comparable-metrics-report-q2-2017/. Accessed April 1, 2019.
29. Carlson SA, Whitfield GP, Peterson EL, Ussery EN, Watson KB, Berrigan D, Fulton JE. Geographic and urban-rural differences in walking for leisure and transportation. *Am J Prev Med.* 2018;55:887–895. doi: 10.1016/j.amepre.2018.07.008
30. Hawkins MS, Storti KL, Richardson CR, King WC, Strath SJ, Holleman RG, Kriska AM. Objectively measured physical activity of USA adults by sex, age, and racial/ethnic groups: a cross-sectional study. *Int J Behav Nutr Phys Act.* 2009;6:31. doi: 10.1186/1479-5868-6-31
31. Whitfield GP, Paul P, Wendel AM. Active transportation surveillance: United States, 1999-2012. *MMWR Surveill Summ.* 2015;64:1–17.
32. Ussery EN, Fulton JE, Galuska DA, Katzmarzyk PT, Carlson SA. Joint prevalence of sitting time and leisure-time physical activity among US adults, 2015-2016 [published corrections appear in *JAMA*. 2019;321:209 and *JAMA*. 2019;321:1412]. *JAMA.* 2018;320:2036–2038. doi: 10.1001/jama.2018.17797
33. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Hawkins J, Queen B, Lowry R, Olsen EO, Chyen D, et al. Youth risk behavior surveillance: United States, 2015. *MMWR Surveill Summ*. 2016;65:1–174. doi: 10.15585/mmwr.ss6506a1
34. National Center for Health Statistics. Chapter 33: physical activity. *Healthy People 2020 Midcourse Review*. Hyattsville, MD; US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2016. DHHS publication No. 2017-1042.
35. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities.* Hyattsville, MD: National Center for Health Statistics; 2016. http://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed April 1, 2019.
36. Ussery EN, Carlson SA, Whitfield GP, Watson KB, Berrigan D, Fulton JE. Transportation and leisure walking among U.S. adults: trends in reported prevalence and volume, National Health Interview Survey 2005–2015. *Am J Prev Med*. 2018;55:533–540. doi: 10.1016/j.amepre.2018.05.027
37. Shifts in Viewing: The Cross-Platform Report Q2 2014: September 2014. New York, NY: Nielsen Company; 2014. https://www.nielsen.com/us/en/insights/report/2014/shifts-in-viewing-the-cross-platform-report-q2-2014/. Accessed April 1, 2019.
38. *Step It Up! The Surgeon General's Call to Action to Promote Walking and Walkable Communities*. Washington, DC: US Department of Health and Human Services, Office of the Surgeon General; 2015.
39. Creatore MI, Glazier RH, Moineddin R, Fazli GS, Johns A, Gozdyra P, Matheson FI, Kaufman-Shriqui V, Rosella LC, Manuel DG, et al. Association of neighborhood walkability with change in overweight, obesity, and diabetes. *JAMA.* 2016;315:2211–2220. doi: 10.1001/jama.2016.5898
40. Chiu M, Rezai MR, Maclagan LC, Austin PC, Shah BR, Redelmeier DA, Tu JV. Moving to a highly walkable neighborhood and incidence of hypertension: a propensity-score matched cohort study. *Environ Health Perspect.* 2016;124:754–760. doi: 10.1289/ehp.1510425
41. Centers for Disease Control and Prevention and SHAPE America–Society of Health and Physical Educators. Strategies for Recess in Schools. Atlanta, GA; Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.
42. Cradock AL, Barrett JL, Kenney EL, Giles CM, Ward ZJ, Long MW, Resch SC, Pipito AA, Wei ER, Gortmaker SL. Using cost-effectiveness analysis to prioritize policy and programmatic approaches to physical activity promotion and obesity prevention in childhood. *Prev Med.* 2017;95(suppl):S17–S27. doi: 10.1016/j.ypmed.2016.10.017
43. Carr LJ, Leonhard C, Tucker S, Fethke N, Benzo R, Gerr F. Total worker health intervention increases activity of sedentary workers. *Am J Prev Med.* 2016;50:9–17. doi: 10.1016/j.amepre.2015.06.022
44. Healy GN, Winkler EAH, Eakin EG, Owen N, Lamontagne AD, Moodie M, Dunstan DW. A cluster RCT to reduce workers' sitting time: impact on cardiometabolic biomarkers. *Med Sci Sports Exerc.* 2017;49:2032–2039. doi: 10.1249/MSS.0000000000001328
45. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, et al; on behalf of the Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–e279. doi: 10.1161/CIR.0000000000000440
46. den Hoed M, Brage S, Zhao JH, Westgate K, Nessa A, Ekelund U, Spector TD, Wareham NJ, Loos RJ. Heritability of objectively assessed daily physical activity and sedentary behavior. *Am J Clin Nutr.* 2013;98:1317–1325. doi: 10.3945/ajcn.113.069849
47. Lin X, Chan KK, Huang YT, Luo XI, Liang L, Wilson J, Correa A, Levy D, Liu S. Genetic determinants for leisure-time physical activity. *Med Sci Sports Exerc.* 2018;50:1620–1628. doi: 10.1249/MSS.0000000000001607
48. Carlson SA, Adams EK, Yang Z, Fulton JE. Percentage of deaths associated with inadequate physical activity in the United States. *Prev Chronic Dis.* 2018;15:e38. doi: 10.5888/pcd18.170354
49. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, Gaspoz JM, Barthélémy JC, Edouard P. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: a systematic review and meta-analysis. *Br J Sports Med.* 2015;49:1262–1267. doi: 10.1136/bjsports-2014-094306
50. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175:959–967. doi: 10.1001/jamainternmed.2015.0533
51. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older Australians [published correction appears in *JAMA Intern Med*. 2015;175:1248]. *JAMA Intern Med.* 2015;175:970–977. doi: 10.1001/jamainternmed.2015.0541
52. Kamada M, Shiroma EJ, Buring JE, Miyachi M, Lee IM. Strength training and all-cause, cardiovascular disease, and cancer mortality in older women: a cohort study. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.117.007677

53. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol.* 2011;40:1382–1400. doi: 10.1093/ije/dyr112
54. Holtermann A, Marott JL, Gyntelberg F, Søgaard K, Suadicani P, Mortensen OS, Prescott E, Schnohr P. Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study: a prospective cohort study. *BMJ Open.* 2012;2:e000556. doi: 10.1136/bmjopen-2011-000556
55. Celis-Morales CA, Lyall DM, Welsh P, Anderson J, Steell L, Guo Y, Maldonado R, Mackay DF, Pell JP, Sattar N, et al. Association between active commuting and incident cardiovascular disease, cancer, and mortality: prospective cohort study. *BMJ.* 2017;357:j1456. doi: 10.1136/bmj.j1456
56. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis [published correction appears in *Ann Intern Med*. 2015;163:400]. *Ann Intern Med.* 2015;162:123–132. doi: 10.7326/M14-1651
57. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, Bauman A, Lee IM; Lancet Physical Activity Series 2 Executive Committee; Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women [published correction appears in *Lancet*. 2016;388:e6]. *Lancet.* 2016;388:1302–1310. doi: 10.1016/S0140-6736(16)30370-1
58. Patel AV, Maliniak ML, Rees-Punia E, Matthews CE, Gapstur SM. Prolonged leisure time spent sitting in relation to cause-specific mortality in a large US cohort. *Am J Epidemiol.* 2018;187:2151–2158. doi: 10.1093/aje/kwy125
59. Rees-Punia E, Evans EM, Schmidt MD, Gay JL, Matthews CE, Gapstur SM, Patel AV. Mortality risk reductions for replacing sedentary time with physical activities. *Am J Prev Med.* 2019;56:736–741. doi: 10.1016/j.amepre.2018.12.006
60. Fishman EI, Steeves JA, Zipunnikov V, Koster A, Berrigan D, Harris TA, Murphy R. Association between objectively measured physical activity and mortality in NHANES. *Med Sci Sports Exerc.* 2016;48:1303–1311. doi: 10.1249/MSS.0000000000000885
61. Lee IM, Shiroma EJ, Evenson KR, Kamada M, LaCroix AZ, Buring JE. Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: the Women's Health Study. *Circulation.* 2018;137:203–205. doi: 10.1161/CIRCULATIONAHA.117.031300
62. Diaz KM, Howard VJ, Hutto B, Colabianchi N, Vena JE, Safford MM, Blair SN, Hooker SP. Patterns of sedentary behavior and mortality in U.S. middle-aged and older adults: a national cohort study. *Ann Intern Med.* 2017;167:465–475. doi: 10.7326/M17-0212
63. Wickramasinghe CD, Ayers CR, Das S, de Lemos JA, Willis BL, Berry JD. Prediction of 30-year risk for cardiovascular mortality by fitness and risk factor levels: the Cooper Center Longitudinal Study. *Circ Cardiovasc Qual Outcomes.* 2014;7:597–602. doi: 10.1161/CIRCOUTCOMES.113.000531
64. Celis-Morales CA, Lyall DM, Anderson J, Iliodromiti S, Fan Y, Ntuk UE, Mackay DF, Pell JP, Sattar N, Gill JM. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *Eur Heart J.* 2017;38:116–122. doi: 10.1093/eurheartj/ehw249
65. Blaha MJ, Hung RK, Dardari Z, Feldman DI, Whelton SP, Nasir K, Blumenthal RS, Brawner CA, Ehrman JK, Keteyian SJ, et al. Age-dependent prognostic value of exercise capacity and derivation of fitness-associated biologic age. *Heart.* 2016;102:431–437. doi: 10.1136/heartjnl-2015-308537
66. Jenkins GP, Evenson KR, Herring AH, Hales D, Stevens J. Cardiometabolic correlates of physical activity and sedentary patterns in U.S. youth. *Med Sci Sports Exerc.* 2017;49:1826–1833. doi: 10.1249/MSS.0000000000001310
67. Bailey DP, Charman SJ, Ploetz T, Savory LA, Kerr CJ. Associations between prolonged sedentary time and breaks in sedentary time with cardiometabolic risk in 10-14-year-old children: the HAPPY study. *J Sports Sci.* 2017;35:2164–2171. doi: 10.1080/02640414.2016.1260150
68. Hebert JJ, Klakk H, Møller NC, Grøntved A, Andersen LB, Wedderkopp N. The prospective association of organized sports participation with cardiovascular disease risk in children (the CHAMPS Study-DK). *Mayo Clin Proc.* 2017;92:57–65. doi: 10.1016/j.mayocp.2016.08.013
69. Cureau FV, Ekelund U, Bloch KV, Schaan BD. Does body mass index modify the association between physical activity and screen time with cardiometabolic risk factors in adolescents? Findings from a country-wide survey. *Int J Obes (Lond).* 2017;41:551–559. doi: 10.1038/ijo.2016.210
70. Skrede T, Stavnsbo M, Aadland E, Aadland KN, Anderssen SA, Resaland GK, Ekelund U. Moderate-to-vigorous physical activity, but not sedentary time, predicts changes in cardiometabolic risk factors in 10-y-old children: the Active Smarter Kids Study. *Am J Clin Nutr.* 2017;105:1391–1398. doi: 10.3945/ajcn.116.150540
71. Wewege MA, Thom JM, Rye KA, Parmenter BJ. Aerobic, resistance or combined training: a systematic review and meta-analysis of exercise to reduce cardiovascular risk in adults with metabolic syndrome. *Atherosclerosis.* 2018;274:162–171. doi: 10.1016/j.atherosclerosis.2018.05.002
72. Zwald ML, Akinbami LJ, Fakhouri TH, Fryar CD. Prevalence of low high-density lipoprotein cholesterol among adults, by physical activity: United States, 2011–2014. *NCHS Data Brief*. 2017;(276):1–8.
73. Grøntved A, Koivula RW, Johansson I, Wennberg P, Ostergaard L, Hallmans G, Renstrom F, Franks PW. Bicycling to work and primordial prevention of cardiovascular risk: a cohort study among Swedish men and women. *J Am Heart Assoc*. 2016;5:e004413. doi: 10.1161/JAHA.116.004413
74. Chu P, Gotink RA, Yeh GY, Goldie SJ, Hunink MG. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol.* 2016;23:291–307. doi: 10.1177/2047487314562741
75. Liu X, Zhang D, Liu Y, Sun X, Han C, Wang B, Ren Y, Zhou J, Zhao Y, Shi Y, et al. Dose-response association between physical activity and incident hypertension: a systematic review and meta-analysis of cohort studies. *Hypertension.* 2017;69:813–820. doi: 10.1161/HYPERTENSIONAHA.116.08994
76. Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand.* 2017;96:921–931. doi: 10.1111/aogs.13151
77. Qi Q, Strizich G, Merchant G, Sotres-Alvarez D, Buelna C, Castañeda SF, Gallo LC, Cai J, Gellman MD, Isasi CR, et al. Objectively measured sedentary time and cardiometabolic biomarkers in US Hispanic/Latino adults: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Circulation.* 2015;132:1560–1569. doi: 10.1161/CIRCULATIONAHA.115.016938
78. Diaz KM, Goldsmith J, Greenlee H, Strizich G, Qi Q, Mossavar-Rahmani Y, Vidot DC, Buelna C, Brintz CE, Elfassy T, et al. Prolonged, uninterrupted sedentary behavior and glycemic biomarkers among US Hispanic/Latino adults: the HCHS/SOL (Hispanic Community Health Study/Study of Latinos). *Circulation.* 2017;136:1362–1373. doi: 10.1161/CIRCULATIONAHA.116.026858
79. Kruse NT, Hughes WE, Benzo RM, Carr LJ, Casey DP. Workplace strategies to prevent sitting-induced endothelial dysfunction. *Med Sci Sports Exerc.* 2018;50:801–808. doi: 10.1249/MSS.0000000000001484
80. Pandey A, Salahuddin U, Garg S, Ayers C, Kulinski J, Anand V, Mayo H, Kumbhani DJ, de Lemos J, Berry JD. Continuous dose-response association between sedentary time and risk for cardiovascular disease: a meta-analysis. *JAMA Cardiol.* 2016;1:575–583. doi: 10.1001/jamacardio.2016.1567
81. Mannsverk J, Wilsgaard T, Mathiesen EB, Løchen ML, Rasmussen K, Thelle DS, Njølstad I, Hopstock LA, Bønaa KH. Trends in modifiable risk factors are associated with declining incidence of hospitalized and non-hospitalized acute coronary heart disease in a population. *Circulation.* 2016;133:74–81. doi: 10.1161/CIRCULATIONAHA.115.016960
82. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ; on behalf of the Million Women Study Collaborators. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation.* 2015;131:721–729. doi: 10.1161/CIRCULATIONAHA.114.010296
83. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, Casanova A, Swaminathan S, Anjana RM, Kumar R, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study [published correction appears in *Lancet*. 2017;390:2626]. *Lancet.* 2017;390:2643–2654. doi: 10.1016/S0140-6736(17)31634-3
84. Cochrane SK, Chen SH, Fitzgerald JD, Dodson JA, Fielding RA, King AC, McDermott MM, Manini TM, Marsh AP, Newman AB, et al. Association of accelerometry-measured physical activity and cardiovascular events in mobility-limited older adults: the LIFE (Lifestyle Interventions and Independence for Elders) study. *J Am Heart Assoc*. 2017;6:e007215. doi: 10.1161/JAHA.117.007215
85. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, de Lemos JA, Berry JD. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation.* 2015;132:1786–1794. doi: 10.1161/CIRCULATIONAHA.115.015853
86. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, et al. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol.* 2017;69:1129–1142. doi: 10.1016/j.jacc.2016.11.081

87. Yates T, Haffner SM, Schulte PJ, Thomas L, Huffman KM, Bales CW, Califf RM, Holman RR, McMurray JJ, Bethel MA, et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. *Lancet.* 2014;383:1059–1066. doi: 10.1016/S0140-6736(13)62061-9
88. LaCroix AZ, Bellettiere J, Rillamas-Sun E, Di C, Evenson KR, Lewis CE, Buchner DM, Stefanick ML, Lee IM, Rosenberg DE, et al; Women's Health Initiative (WHI). Association of light physical activity measured by accelerometry and incidence of coronary heart disease and cardiovascular disease in older women [published correction appears in *JAMA Netw Open*. 2019;2:e194476]. *JAMA Netw Open.* 2019;2:e190419. doi: 10.1001/jamanetworkopen.2019.0419
89. Hamer M, Chida Y. Active commuting and cardiovascular risk: a meta-analytic review. *Prev Med.* 2008;46:9–13. doi: 10.1016/j.ypmed.2007.03.006
90. Johnsen AM, Alfredsson L, Knutsson A, Westerholm PJ, Fransson EI. Association between occupational physical activity and myocardial infarction: a prospective cohort study. *BMJ Open.* 2016;6:e012692. doi: 10.1136/bmjopen-2016-012692
91. Dhana K, Koolhaas CM, Berghout MA, Peeters A, Ikram MA, Tiemeier H, Hofman A, Nusselder W, Franco OH. Physical activity types and life expectancy with and without cardiovascular disease: the Rotterdam Study. *J Public Health (Oxf).* 2017;39:e209–e218. doi: 10.1093/pubmed/fdw110
92. Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, DeFina L, Willis B. Physical fitness and risk for heart failure and coronary artery disease. *Circ Heart Fail.* 2013;6:627–634. doi: 10.1161/CIRCHEARTFAILURE.112.000054
93. Pandey A, Cornwell WK 3rd, Willis B, Neeland IJ, Gao A, Leonard D, DeFina L, Berry JD. Body mass index and cardiorespiratory fitness in mid-life and risk of heart failure hospitalization in older age: findings from the Cooper Center Longitudinal Study. *JACC Heart Fail.* 2017;5:367–374. doi: 10.1016/j.jchf.2016.12.021
94. Pandey A, Patel M, Gao A, Willis BL, Das SR, Leonard D, Drazner MH, de Lemos JA, DeFina L, Berry JD. Changes in mid-life fitness predicts heart failure risk at a later age independent of interval development of cardiac and noncardiac risk factors: the Cooper Center Longitudinal Study. *Am Heart J.* 2015;169:290–297.e1. doi: 10.1016/j.ahj.2014.10.017
95. Myers J, Kokkinos P, Chan K, Dandekar E, Yilmaz B, Nagare A, Faselis C, Soofi M. Cardiorespiratory fitness and reclassification of risk for incidence of heart failure: the Veterans Exercise Testing Study. *Circ Heart Fail.* 2017;10:e003780. doi: 10.1161/CIRCHEARTFAILURE.116.003780
96. Zöller B, Ohlsson H, Sundquist J, Sundquist K. Cardiovascular fitness in young males and risk of unprovoked venous thromboembolism in adulthood. *Ann Med.* 2017;49:176–184. doi: 10.1080/07853890.2016.1252057
97. Faselis C, Kokkinos P, Tsimploulis A, Pittaras A, Myers J, Lavie CJ, Kyritsi F, Lovic D, Karasik P, Moore H. Exercise capacity and atrial fibrillation risk in veterans: a cohort study. *Mayo Clin Proc.* 2016;91:558–566. doi: 10.1016/j.mayocp.2016.03.002
98. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol.* 2016;67:1–12. doi: 10.1016/j.jacc.2015.10.044
99. Doukky R, Mangla A, Ibrahim Z, Poulin MF, Avery E, Collado FM, Kaplan J, Richardson D, Powell LH. Impact of physical inactivity on mortality in patients with heart failure. *Am J Cardiol.* 2016;117:1135–1143. doi: 10.1016/j.amjcard.2015.12.060
100. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, Hagström E, Hochman JS, Koenig W, Lonn E, et al; STABILITY Investigators. Physical activity and mortality in patients with stable coronary heart disease. *J Am Coll Cardiol.* 2017;70:1689–1700. doi: 10.1016/j.jacc.2017.08.017
101. Lahtinen M, Toukola T, Junttila MJ, Piira OP, Lepojärvi S, Kääriäinen M, Huikuri HV, Tulppo MP, Kiviniemi AM. Effect of changes in physical activity on risk for cardiac death in patients with coronary artery disease. *Am J Cardiol.* 2018;121:143–148. doi: 10.1016/j.amjcard.2017.10.002
102. Moholdt T, Lavie CJ, Nauman J. Sustained physical activity, not weight loss, associated with improved survival in coronary heart disease [published correction appears in *J Am Coll Cardiol*. 2018;71:1499]. *J Am Coll Cardiol.* 2018;71:1094–1101. doi: 10.1016/j.jacc.2018.01.011
103. Hegde SM, Claggett B, Shah AM, Lewis EF, Anand I, Shah SJ, Sweitzer NK, Fang JC, Pitt B, Pfeffer MA, et al. Physical activity and prognosis in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist). *Circulation.* 2017;136:982–992. doi: 10.1161/CIRCULATIONAHA.117.028002
104. Coll-Fernández R, Coll R, Muñoz-Torrero JF, Aguilar E, Ramón Álvarez L, Sahuquillo JC, Yeste M, Jiménez PE, Mujal A, Monreal M; FRENA Investigators. Supervised versus non-supervised exercise in patients with recent myocardial infarction: a propensity analysis. *Eur J Prev Cardiol.* 2016;23:245–252. doi: 10.1177/2047487315578443
105. Shaya GE, Al-Mallah MH, Hung RK, Nasir K, Blumenthal RS, Ehrman JK, Keteyian SJ, Brawner CA, Qureshi WT, Blaha MJ. High exercise capacity attenuates the risk of early mortality after a first myocardial infarction: the Henry Ford Exercise Testing (FIT) Project. *Mayo Clin Proc.* 2016;91:129–139. doi: 10.1016/j.mayocp.2015.11.012
106. Minges KE, Strait KM, Owen N, Dunstan DW, Camhi SM, Lichtman J, Geda M, Dreyer RP, Bueno H, Beltrame JF, et al. Gender differences in physical activity following acute myocardial infarction in adults: a prospective, observational study. *Eur J Prev Cardiol.* 2017;24:192–203. doi: 10.1177/2047487316679905
107. Gorczyca AM, Eaton CB, LaMonte MJ, Manson JE, Johnston JD, Bidulescu A, Waring ME, Manini T, Martin LW, Stefanick ML, et al. Change in physical activity and sitting time after myocardial infarction and mortality among postmenopausal women in the Women's Health Initiative-Observational Study. *J Am Heart Assoc.* 2017;6:e005354. doi: 10.1161/JAHA.116.005354
108. Ku PW, Chen LJ, Fox KR, Chen YH, Liao Y, Lin CH. Leisure-time, domestic, and work-related physical activity and their prospective associations with all-cause mortality in patients with cardiovascular disease. *Am J Cardiol.* 2018;121:177–181. doi: 10.1016/j.amjcard.2017.10.003
109. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, Macchi C. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med.* 2011;269:107–117. doi: 10.1111/j.1365-2796.2010.02281.x
110. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385:2255–2263. doi: 10.1016/S0140-6736(15)60461-5
111. Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, Hoevenaar-Blom MP, Vermeulen M, van Gool WA. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet.* 2016;388:797–805. doi: 10.1016/S0140-6736(16)30950-3
112. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cufi MN, Dantoine T, Dartigues JF, et al; MAPT Study Group. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017;16:377–389. doi: 10.1016/S1474-4422(17)30040-6
113. Lamb SE, Sheehan B, Atherton N, Nichols V, Collins H, Mistry D, Dosanjh S, Slowther AM, Khan I, Petrou S, et al; DAPA Trial Investigators. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *BMJ.* 2018;361:k1675. doi: 10.1136/bmj.k1675
114. Oberlin LE, Waiwood AM, Cumming TB, Marsland AL, Bernhardt J, Erickson KI. Effects of physical activity on poststroke cognitive function: a meta-analysis of randomized controlled trials. *Stroke.* 2017;48:3093–3100. doi: 10.1161/STROKEAHA.117.017319
115. Abbasian S, Rastegar Mm M. Is the intensity or duration of treadmill training important for stroke patients? A meta-analysis. *J Stroke Cerebrovasc Dis.* 2018;27:32–43. doi: 10.1016/j.jstrokecerebrovasdis.2017.09.061
116. Oldridge NB. Economic burden of physical inactivity: healthcare costs associated with cardiovascular disease. *Eur J Cardiovasc Prev Rehabil.* 2008;15:130–139. doi: 10.1097/HJR.0b013e3282f19d42
117. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, Pratt M; Lancet Physical Activity Series 2 Executive Committee. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet.* 2016;388:1311–1324. doi: 10.1016/S0140-6736(16)30383-X
118. Carlson SA, Fulton JE, Pratt M, Yang Z, Adams EK. Inadequate physical activity and health care expenditures in the United States. *Prog Cardiovasc Dis.* 2015;57:315–323. doi: 10.1016/j.pcad.2014.08.002
119. Valero-Elizondo J, Salami JA, Ogunmoroti O, Osondu CU, Aneni EC, Malik R, Spatz ES, Rana JS, Virani SS, Blankstein R, et al. Favorable cardiovascular risk profile is associated with lower healthcare costs and resource utilization: the 2012 Medical Expenditure Panel Survey. *Circ Cardiovasc Qual Outcomes.* 2016;9:143–153. doi: 10.1161/CIRCOUTCOMES.115.002616
120. Laine J, Kuvaja-Köllner V, Pietilä E, Koivuneva M, Valtonen H, Kankaanpää E. Cost-effectiveness of population-level physical activity

interventions: a systematic review. *Am J Health Promot.* 2014;29:71–80. doi: 10.4278/ajhp.131210-LIT-622

121. Weintraub WS, Daniels SR, Burke LE, Franklin BA, Goff DC Jr, Hayman LL, Lloyd-Jones D, Pandey DK, Sanchez EJ, Schram AP, et al; on behalf of the American Heart Association Advocacy Coordinating Committee; Council on Cardiovascular Disease in the Young; Council on the Kidney in Cardiovascular Disease; Council on Epidemiology and Prevention; Council on Cardiovascular Nursing; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Clinical Cardiology, and Stroke Council. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation.* 2011;124:967–990. doi: 10.1161/CIR.0b013e3182285a81
122. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants [published correction appears in *Lancet Glob Health*. 2019;7:e36]. *Lancet Glob Health*. 2018;6:e1077-e1086. doi: 10.1016/S2214-109X(18)30357-7
123. *Global Burden of Disease Study 2017 (GBD 2017)*. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
124. GBD Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 [published corrections appear in *Lancet*. 2019;393:132 and *Lancet*. 2019;393:e44]. *Lancet*. 2018;392:1923–1994. doi: 10.1016/S0140-6736(18)32225-6

5. NUTRITION

See Tables 5-1 through 5-3 and Charts 5-1 through 5-6

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This chapter of the Update highlights national dietary habits, focusing on key foods, nutrients, dietary patterns, and other dietary factors related to cardiometabolic health. It is intended to examine current intakes, trends and changes in intakes, and estimated effects on disease to support and further stimulate efforts to monitor and improve dietary habits in relation to CVH.

Abbreviations Used in Chapter 5

AHA	American Heart Association
AHEI	Alternate Healthy Eating Index
ALA	α-linoleic acid
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CER	cost-effectiveness ratio
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DHA	docosahexaenoic acid
DM	diabetes mellitus
EPA	eicosapentaenoic acid
GBD	Global Burden of Disease
GRS	genetic risk score
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HDL-C	high-density lipoprotein cholesterol
HEI	Healthy Eating Index
HF	heart failure
HR	hazard ratio
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MI	myocardial infarction
MUFA	monounsaturated fatty acid
MVMM	multivitamin/mineral
NA	not available
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
PREDIMED	Prevención con Dieta Mediterránea
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SD	standard deviation
SES	socioeconomic status
SFA	saturated fatty acid
SNP	single-nucleotide polymorphism
SSB	sugar-sweetened beverage
TC	total cholesterol
TOHP	Trials of Hypertension Prevention
UI	uncertainty interval
WHI	Women's Health Initiative

Prevalence and Trends in the AHA 2020 Healthy Diet Metrics (See Table 5-1 and Charts 5-1 and 5-2)

The AHA's 2020 Impact Goals prioritize improving CVH,[1] which includes following a healthy diet pattern characterized by 5 primary and 3 secondary metrics (Table 5-1) that should be consumed within a context that is appropriate in energy balance and consistent with a DASH-type eating plan.[1]

The AHA scoring system for ideal, intermediate, and poor diet patterns uses a binary-based scoring system, which awards 1 point for meeting the ideal target for each metric and 0 points otherwise.[2] For better consistency with other dietary pattern scores such as DASH, an alternative continuous scoring system has been developed to measure small improvements over time toward the AHA ideal target levels (Table 5-1). The dietary targets remain the same, and progress toward each of these targets is assessed by use of a more granular range of 1 to 10 (rather than 0 to 1).

Using the alternative scoring system, the mean AHA healthy diet score improved between 2003 to 2004 and 2015 to 2016 in the United States for adults. In adults, the prevalence of a poor diet improved from 56.0% to 47.8% for the primary score and 43.7% to 36.4% for the secondary score (Table 5-2). Changes in score were largely attributable to increased consumption of whole grains and nuts, seeds, and legumes and decreased consumption of SSBs. No significant changes were observed for consumption of total fruits and vegetables, fish and shellfish, sodium, processed meat, and saturated fat.

Similar changes in AHA healthy diet scores between 2003 to 2004 and 2015 to 2016 were seen in minority groups and those with lower income or education, although significant disparities persisted (Charts 5-1 and 5-2). The proportion with a poor diet decreased from 64.7% to 58.3% for NH blacks, from 66.0% to 57.5% for Mexican Americans, and from 54.0% to 45.9% for NH whites (Chart 5-1). The proportion with a poor diet (<40% adherence) decreased from 50.7% to 38.8% in adults with income-to-poverty ratio ≥3.0, but only from 67.7% to 59.7% in adults with income-to-poverty ratio <1.3 (Chart 5-2).

Dietary Habits in the United States: Current Intakes of Foods and Nutrients

Adults (See Table 5-3)

The average dietary consumption by US adults of selected foods and nutrients related to cardiometabolic

health based on data from 2015 to 2016 NHANES is detailed below (Table 5-3):

- Consumption of whole grains was 1.1 and 0.9 servings per day by NH white males and females, 0.7 and 0.8 servings per day by NH black males and females, and 0.6 and 0.7 servings per day by Mexican American males and females, respectively. For each of these groups, <10% of adults in 2011 to 2012 met guidelines of ≥3 servings per day.
- Whole fruit consumption ranged from 1.0 to 1.6 servings per day in racial or ethnic subgroups: ≈10% of NH whites, ≈6% of NH blacks, and ≈9% of Mexican Americans met guidelines of ≥2 cups per day. When 100% fruit juices were included, the number of servings increased and the proportions of adults consuming ≥2 cups per day increased to ≈13% in NH whites, ≈12% in NH blacks, and ≈18% in Mexican Americans.
- Nonstarchy vegetable consumption ranged from 1.6 to 2.4 servings per day in these racial or ethnic subgroups: ≈8% of NH whites, ≈3% of NH blacks, and ≈5% of Mexican Americans met guidelines of ≥2.5 cups per day.
- Consumption of fish and shellfish ranged from 1.0 to 1.8 servings per week in these racial or ethnic subgroups: ≈17% of NH whites, ≈23% of NH blacks, and ≈18% of Mexican Americans met guidelines of ≥2 servings per week.
- Weekly consumption of nuts and seeds was ≈6 servings among NH whites and ≈3 servings among NH blacks and Mexican Americans. Approximately 1 in 3 whites, 1 in 6 NH blacks, and 1 in 5 Mexican Americans met guidelines of ≥4 servings per week.
- Consumption of processed meats was lowest among Mexican American females (1.0 servings per week) and highest among NH white males (≈2.5 servings per week). Between 57% (NH white males) and 80% (Mexican American females) of adults consumed ≤2 servings per week.
- Consumption of SSBs ranged from 5.8 servings per week among NH white females to 10 servings per week among NH black males and females and Mexican American males. The majority of NH whites (≈63%) consumed <36 oz/wk, whereas only the minority of NH blacks (37%) and Mexican Americans (42%) met this target.
- Consumption of sweets and bakery desserts ranged from 4.7 servings per week among Mexican American females to 3.3 servings per week among NH black males. The majority of NH whites, NH blacks, and Mexican Americans consumed <2.5 servings per week.
- The proportion of total energy intake from added sugars ranged from 10.8% for Mexican American males to 22.1% for NH black females. Between 12% of NH black females and 38.1% of Mexican American males consumed ≤6.5% of total energy intake from added sugars.
- Consumption of eicosapentaenoic acid and docosahexaenoic acid ranged from 0.075 to 0.103 g/d in each sex and racial or ethnic subgroup. Fewer than ≈9% of NH whites, ≈9% of NH blacks, and ≈7% of Mexican Americans consumed ≥0.250 g/d.
- One-quarter to two-fifths of adults in each sex and racial or ethnic subgroup consumed <10% of total calories from saturated fat, and approximately one-half to two-thirds consumed <300 mg of dietary cholesterol per day.
- The ratio of (PUFAs+MUFAs)/SFAs ranged from 1.8 in NH white males and Mexican American males to 2.6 in NH black females. The proportion with a ratio ≥2.5 ranged from 40% in NH black females to 12.6% in NH white males.
- Only ≈8% of NH whites, ≈5% of blacks, and ≈12% of Mexican Americans consumed ≥28 g of dietary fiber per day.
- Only ≈4% to ≈8% of adults in each racial or ethnic subgroup consumed <2.3 g of sodium per day. Estimated mean sodium intake in the United States by 24-hour urinary excretion was 4205 mg/d for males and 3039 mg/d for females in 2013 to 2014. Estimates of sodium intake by race, sex, and source are shown in Charts 5-3 and 5-4. Sodium added to food outside the home accounts for more than two-thirds of total sodium intake in the United States (Chart 5-4).[3] Top sources of sodium intake vary by race/ethnicity, with the largest contributor being yeast breads for NH whites, sandwiches for NH blacks, burritos and tacos for Hispanics, and soups for NH Asians.[4]

Children and Teenagers

On the basis of NHANES 2011 to 2012, the average dietary consumption by US children and teenagers of selected foods and nutrients related to cardiometabolic health is detailed below[5]:

- Whole grain consumption was <1 serving per day in all age and sex groups, with <5% of all children in different age and sex subgroups meeting guidelines of ≥3 servings per day.
- Fruit consumption was low and decreased with age: 1.7 to 1.9 servings per day in younger boys and girls (5–9 years of age), 1.4 servings per day in adolescent boys and girls (10–14 years of age), and 0.9 to 1.3 servings per day in teenage boys and girls (15–19 years of age). The proportion meeting guidelines of ≥2 cups per day was also low and decreased with age: ≈8% to 14% in those 5 to 9 years of age, 3% to 8% in those 10 to 14 years of age, and 5% to 6% in those 15 to 19 years of age. When 100% fruit juices were included,

the number of servings consumed increased by ≈50%, and proportions consuming ≥2 cups per day increased to nearly 25% of those 5 to 9 years of age, 20% of those 10 to 14 years of age, and 15% of those 15 to 19 years of age.
- Nonstarchy vegetable consumption was low, ranging from 1.1 to 1.5 servings per day, with <1.5% of children in different age and sex subgroups meeting guidelines of ≥2.5 cups per day.
- Consumption of fish and shellfish was low, ranging between 0.3 and 1.0 servings per week in all age and sex groups. Among all ages, only 7% to 14% of youths consumed ≥2 servings per week.
- Consumption of nuts, seeds, and beans ranged from 1.1 to 2.7 servings per week among different age and sex groups, and generally <15% of children in different age and sex subgroups consumed ≥4 servings per week.
- Consumption of unprocessed red meats was higher in boys than in girls and increased with age, up to 3.6 and 2.5 servings per week in 15- to 19-year-old boys and girls, respectively.
- Consumption of processed meats ranged from 1.4 to 2.3 servings per week, and the majority of children consumed <2 servings per week of processed meats.
- Consumption of SSBs was higher in boys than in girls in the 5- to 9-year-old (7.7 versus 6.0 servings per week) and 10- to 14-year-old (11.6 versus 9.7 servings per week) groups, but it was higher in girls than in boys in the 15- to 19-year-old group (14 versus 12.4 servings per week). Only about half of children 5 to 9 years of age and one-quarter of boys 15 to 19 years of age consumed <4.5 servings per week.
- Consumption of sweets and bakery desserts was higher among 5- to 9-year-old and 10- to 14-year-old (6.6 to 8.3 servings per week) boys and girls and modestly lower (4.7 to 6 servings per week) among 15- to 19-year-olds. A minority of children in all age and sex subgroups consumed <2.5 servings per week.
- Consumption of eicosapentaenoic acid and docosahexaenoic acid was low, ranging from 0.034 to 0.065 g/d in boys and girls in all age groups. Fewer than 7% of children and teenagers at any age consumed ≥0.250 g/d.
- Consumption of SFAs was ≈11% of calories in boys and girls in all age groups, and average consumption of dietary cholesterol ranged from ≈210 to 270 mg/d, increasing with age. Approximately 25% to 40% of youths consumed <10% energy from SFAs, and ≈70% to 80% consumed <300 mg of dietary cholesterol per day.
- Consumption of dietary fiber ranged from ≈14 to 16 g/d. Fewer than 3% of children in all age and sex subgroups consumed ≥28 g/d.
- Consumption of sodium ranged from 3.1 to 3.5 g/d. Only 2% to 11% of children in different age and sex subgroups consumed <2.3 g/d.

Secular Trends

In addition to individual foods and nutrients, overall dietary patterns can be another useful tool for assessing diet quality.[6] The 2015 US Dietary Guidelines Advisory Committee summarized the evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes.[7] They concluded that a healthy dietary pattern is higher in vegetables, fruits, whole grains, low-fat or nonfat dairy, seafood, legumes, and nuts; moderate in alcohol (among adults); lower in red and processed meat; and low in sugar-sweetened foods and drinks and refined grains. The 2015 US Dietary Guidelines also describe a healthy vegetarian dietary pattern, which includes more legumes, soy products, nuts and seeds, and whole grains but does not include meats, poultry, or seafood. Different dietary patterns have been defined, such as HEI-2010, AHEI, Mediterranean, DASH-type, Western, prudent, and vegetarian patterns.

Between 1999 and 2010, the average AHEI-2010 score of US adults improved from 39.9 to 46.8.[8] This was related to reduced intake of *trans* fat (accounting for more than half of the improvement), SSBs, and fruit juice, as well as an increased intake of whole fruit, whole grains, PUFAs, and nuts and legumes. Adults with greater family income and education had higher scores, and the gap between low and high SES widened over time, from 3.9 points in 1999 to 2000 to 7.8 points in 2009 to 2010.

Between 1999 and 2012, the mean HEI-2010 score in US children and adolescents 2 to 18 years of age improved from 42.5 to 50.9.[9] One-third of the improvement was attributable to reduction in empty calorie intake; other HEI categories that improved included whole grains, fruit, seafood and plant proteins, greens and beans, and fatty acids. Participants in the National School Lunch Program and the School Breakfast Program had lower HEI-2010 scores than nonparticipants. There was also a trend toward lower HEI-2010 scores in Supplemental Nutrition Assistance Program participants after the 2003 to 2004 cycle. HEI-2010 scores have remained consistently lower in NH blacks (1999–2000: 39.6; 2011–2012: 48.4) than in NH whites (1999–2000: 42.1; 2011–2012: 50.2) and highest in Mexican Americans (1999–2000: 44.1; 2011–2012: 51.9). In a study that used household store purchase data (N=98 256 household-by-quarter observations), Supplemental Nutrition Assistance Program participants purchased more calories from SSBs (15–20 kcal per person per day), more sodium (174–195 mg per person per day), and fewer calories from fiber (–0.52 kcal per person per day) than income-eligible and higher-income nonparticipants.[10]

The impact of the October 2009 Special Supplemental Nutrition Program for Women, Infants, and Children food package revision (more fruits, vegetables, whole grains, and lower-fat milk) was examined using 2003 to 2008 and 2011 to 2012 NHANES data in 2- to 4-year-old children from low-income households.[11] The Women, Infants, and Children food package revisions were associated with significant improvements in HEI-2010 score (3.7-higher HEI points [95% CI, 0.6–6.9]), with the greatest improvement coming from a 3.4-fold increase (95% CI, 1.3–9.4) in the greens and beans category.

In a study using data from the Food and Agriculture Organization Food Balance Sheets from 1961 to 1965, 2000 to 2003, and 2004 to 2011 in 41 countries, a Mediterranean adequacy index was calculated based on available energy intake for food groups consistent or inconsistent with the Mediterranean dietary pattern.[12] Adherence to the Mediterranean dietary pattern decreased from 1961 to 1965 to 2000 to 2003, with stabilization overall from 2004 to 2011.

Trends in Dietary Supplement Intake (See Chart 5-5)

Use of dietary supplements is common in the United States among both adults and children despite lack of evidence to support the use of most dietary supplements in reducing risks of CVD or death.[13] From 1999 to 2000 to 2011 to 2012, use of multivitamins/multiminerals decreased from 37% to 31%, use of omega-3 fatty acids increased from 1.4% to 11%, and use of vitamin D supplements remained stable (34% to 38%; Chart 5-5). Fifty-two percent of US adults reported using any supplement, including multivitamins/multiminerals (31%), vitamin D (38%), and omega-3 fatty acids (11%).[14] Trends in any supplement use over time were increasing in older adults, stable among middle-aged adults, and decreasing in younger adults.

Social Determinants

- Societal and environmental factors independently associated with diet quality, adiposity, or weight gain include education, income, race/ethnicity, and (at least cross-sectionally) neighborhood availability of supermarkets.[15–17]
- Other local food-environment characteristics, such as availability of grocery stores (ie, smaller stores than supermarkets), convenience stores, and fast food restaurants, are not consistently associated with diet quality or adiposity and could be linked to social determinants of health for CVD.[18]
- Disparities may be driven in part by overabundance of unhealthy food options. In a study of neighborhood-level data from 4 US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California), past neighborhood-level income was inversely associated with current density of convenience stores.[19] In low-income neighborhoods, the percentage of white population was inversely associated with density of fast food restaurants and smaller grocery stores.
- In a study using NHANES and Nielsen Homescan data to examine disparities in calories from store-bought consumer packaged goods over time, calories from store-bought beverages decreased between 2003 to 2006 and 2009 to 2012. However, the decline in calories from consumer packaged goods was slower for NH blacks, Mexican Americans, and lowest-income households.[20]

Genetics/Family History

- Genetic factors may contribute to food preferences and modulate the association between dietary components and adverse CVH outcomes.[21–23] However, there is a paucity of gene-diet interaction studies with independent replication to support personalizing dietary recommendations according to genotype.
- In a randomized trial of 609 overweight-obese, nondiabetic participants that compared the effects of healthy low-fat versus healthy low-carbohydrate weight loss diets, neither genotype pattern (3 SNP multilocus genotype responsiveness pattern) nor insulin secretion (30 minutes after glucose challenge) modified the effects of diet on weight loss.[24]
- The interactions between a GRS composed of 97 BMI-associated variants and 3 diet-quality scores were examined in a pooled analysis of 30 904 participants from the Nurses' Health Study, the Health Professional Follow-up Study, and the Women's Genome Health Study. Higher diet quality was found to attenuate the association between GRS and BMI (*P* for interaction terms <0.005 for AHEI-2010 score, Alternative Mediterranean Diet score, and DASH diet score).[25] A 10-U increase in the GRS was associated with a 0.84-U (95% CI, 0.72–0.96) increase in BMI for those in the highest tertile of AHEI score, compared with a 1.14-U (95% CI, 0.99–1.29) increase in BMI in those in the lowest tertile of AHEI score.

Impact on US Mortality

Comparable risk assessment methods and nationally representative data were used to estimate the impact of 10 specific dietary factors on cardiometabolic mortality in the United States in 2002 and 2012.[26] In 2012, 318 656 (45.4%) of 702 308 cardiometabolic deaths were estimated to be attributable to poor dietary habits. The largest numbers of deaths attributable to diet were

estimated to be from high sodium intake (66 508; 9.5% of all cardiometabolic deaths), low consumption of nuts/seeds (59 374; 8.5%), high consumption of processed meats (57 766; 8.2%), low intake of seafood omega-3 fats (54 626; 7.8%), low consumption of vegetables (53 410; 7.6%) and fruits (52 547; 7.5%), and high consumption of SSBs (51 694; 7.4%). Between 2002 and 2012, population-adjusted US cardiometabolic deaths decreased by 26.5%, with declines in estimated diet-associated cardiometabolic deaths for PUFAs (–20.8%), nuts/seeds (–18.0%), and SSBs (–14.5%) and increases in diet-associated cardiometabolic deaths for sodium (5.8%) and unprocessed red meats (14.4%). Estimated cardiometabolic mortality related to whole grains, fruits, vegetables, seafood, omega-3 fats, and processed meats remained relatively stable.

CVH Impact of Diet

Dietary Patterns

- The observational findings for benefits of a healthy food–based dietary pattern have been confirmed in 2 randomized clinical trials, including a small secondary prevention trial in France among patients with recent MI[27] and a large primary prevention trial in Spain among patients with CVD risk factors.[28] The latter trial, PREDIMED, demonstrated an ≈30% reduction in the risk of stroke, MI, and death attributable to cardiovascular causes in those patients randomized to Mediterranean-style diets supplemented with extra-virgin olive oil or mixed nuts.
- In a randomized crossover trial of 118 overweight omnivores at low-moderate CVD risk, a reduced-calorie lacto-ovo vegetarian diet was compared with a reduced-calorie Mediterranean diet by providing face-to-face, individual counseling sessions. Both diets were equally successfully in reducing body weight and fat mass. LDL-C, uric acid, and vitamin B12 were lower during the vegetarian diet, whereas triglycerides were lower during the Mediterranean diet, without substantial differences between oxidative stress markers and inflammatory cytokines.[29]
- In the PREDIMED RCT, a significantly smaller decrease in central adiposity occurred in the Mediterranean diet with nuts group (–0.92 cm [95% CI, –1.6 to –0.2 cm]) but not the Mediterranean diet with olive oil group (–0.47 [95% CI, –1.1 to 0.2 cm]) compared with the control group.[30] In a subgroup analysis of 3541 patients in PREDIMED without DM, HRs for incident DM were 0.60 (95% CI, 0.43–0.85) for the Mediterranean diet with olive oil arm and 0.82 (95% CI, 0.61–1.10) for the Mediterranean diet with nuts arm compared with the control arm.
- Compared with a usual Western diet, a DASH-type dietary pattern with low sodium reduced SBP by 5.3, 7.5, 9.7, and 20.8 mm Hg in adults with baseline SBP <130, 130 to 139, 140 to 149, and ≥150 mm Hg, respectively.[31]
- Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher protein lowered BP by 1.4 mm Hg, LDL-C by 3.3 mg/dL, and triglycerides by 16 mg/dL but also lowered HDL-C by 1.3 mg/dL. Compared with a higher-carbohydrate DASH diet, a DASH-type diet with higher unsaturated fat lowered BP by 1.3 mm Hg, increased HDL-C by 1.1 mg/dL, and lowered triglycerides by 10 mg/dL.[32] The DASH-type diet higher in unsaturated fat also improved glucose-insulin homeostasis compared with the higher-carbohydrate DASH diet.[33]
- In a systematic review and meta-analysis of controlled clinical trials of dietary pattern interventions, the DASH diet had the largest net effect on SBP (–7.6 mm Hg) and DBP (–4.2 mm Hg), whereas the Mediterranean diet had an effect on DBP (–1.4 mm Hg) but not SBP.[34]
- In a meta-analysis of 8 observational studies (3 Seventh-day Adventist cohorts [N=110 723] and 5 other cohorts [N=72 598]), vegetarians had a 40% lower risk of CHD in the Seventh-day Adventist studies (RR, 0.60 [95% CI, 0.43–0.80]) and a 16% lower risk of CHD (RR, 0.84 [95% CI, 0.74–0.96]) in the other studies.[35]
- In a cohort of 200 272 US males and females, greater adherence to a plant-based dietary pattern, defined by higher intake of plant-based foods and low intake of animal-based foods, was associated with a 20% lower risk of DM (HR, 0.80 [95% CI, 0.74–0.87]).[36]

Fats and Carbohydrates

- In meta-analyses of RCTs comparing higher versus lower fiber intake, higher fiber intake lowered body weight (–0.37 kg [95% CI, –0.63 to –0.11 kg]), TC (–0.15 mmol/L [95% CI, –0.22 to –0.07 mmol/L]), and SBP (–1.27 mm Hg [95% CI, –2.50 to –0.04 mm Hg]) and tended to lower HbA_{1c} (–0.54% [95% CI, –1.28% to 0.20%]).[37] In similar meta-analyses of RCTs for whole grains and glycemic index, higher whole grain intake only significantly reduced body weight (–0.62 kg [95% CI, –1.19 to –0.05 kg]), whereas no consistent health effects were found for glycemic index.
- In meta-analyses of observational studies, higher total dietary fiber intake was associated with a lower risk of incident CHD (RR, 0.76 [95% CI, 0.69–0.83]), CHD mortality (RR, 0.69 [95% CI, 0.60–0.81]), and incident stroke (RR, 0.78 [95% CI, 0.69–0.88]).[37] Higher whole grain intake was associated with a lower risk of incident CHD (RR,

0.80 [95% CI, 0.70–0.91]), CHD mortality (RR, 0.66 [95% CI, 0.56–0.77]), and stroke death (RR, 0.74 [95% CI, 0.58–0.94]). Evidence for associations between glycemic index, glycemic load, and source of dietary fiber and CVD outcomes was less robust.

- In a randomized trial of 609 nondiabetic participants with BMI 28 to 40 kg/m^2 that compared the effects of healthy low-fat versus healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups.[24]
- In a meta-analysis of RCTs, consumption of 1% of calories from *trans* fat in place of SFAs, MUFAs, or PUFAs, respectively, increased the ratio of TC to HDL-C by 0.031, 0.054, and 0.67; increased apolipoprotein B levels by 3, 10, and 11 mg/L; decreased apolipoprotein A-1 levels by 7, 5, and 3 mg/L; and increased Lp(a) levels by 3.8, 1.4, and 1.1 mg/L.[38]
- A meta-analysis of 102 randomized controlled feeding trials evaluated the effects of exchanging different dietary fats and carbohydrates on markers of glucose-insulin homeostasis.[39] Replacing 5% energy from carbohydrates with SFAs generally had no significant effects, whereas replacing carbohydrates with unsaturated fats lowered both HbA_{1c} and insulin. On the basis of "gold standard" short-term insulin response in 10 trials, PUFAs improved insulin secretion compared with carbohydrates, SFAs, and even MUFAs.
- In a randomized crossover trial of 92 adults with abdominal obesity, LDL-C was highest after a butter-rich diet, followed by a cheese-rich diet, high-carbohydrate diet, MUFA-rich diet, and PUFA-rich diet. The butter-rich and cheese-rich diets similarly increased HDL-C (by 4.7% and 3.8%, respectively) compared with the high-carbohydrate diet.[40]
- In a meta-analysis of 61 trials (N=2582), tree nut consumption lowered TC by 4.7 mg/dL, LDL-C by 4.8 mg/dL, apolipoprotein B by 3.7 mg/dL, and triglycerides by 2.2 mg/dL. No heterogeneity by nut type was observed.[41]
- In the WHI RCT (N=48 835), reduction of total fat consumption from 37.8% energy (baseline) to 24.3% energy (at 1 year) and 28.8% energy (at 6 years) had no effect on incidence of CHD (RR, 0.98 [95% CI, 0.88–1.09]), stroke (RR, 1.02 [95% CI, 0.90–1.15]), or total CVD (RR, 0.98 [95% CI, 0.92–1.05]) over a mean follow-up of 8.1 years.[42]
- In a meta-analysis of RCTs in which increased PUFA consumption in place of SFAs reduced CHD events, there was 10% lower risk for each 5% energy exchange (RR, 0.90 [95% CI, 0.83–0.97]).[43]
- In a meta-analysis of 13 prospective cohort studies, increased intake of PUFAs was associated with lower risk of CHD, whether it replaced SFAs or carbohydrates.[44]

Foods and Beverages

- In a systematic review and meta-analysis, RCTs in children demonstrated reductions in BMI gain when SSBs were replaced with noncaloric beverages, and RCTs in adults showed weight gain when SSBs were added.[45]
- In a meta-analysis of 16 prospective cohort studies, each daily serving of fruits or vegetables was associated with a 4% lower risk of cardiovascular mortality (RR, 0.96 [95% CI, 0.92–0.99]).[46]
- In a prospective study of 512 891 adults in China (only 18% consumed fresh fruit daily), individuals who ate fresh fruit daily had 40% lower risk of CVD death (RR, 0.60 [95% CI, 0.54–0.67]), 34% lower risk of incident CHD (RR, 0.66 [95% CI, 0.58–0.75]), 25% lower risk of ischemic stroke (RR, 0.75 [95% CI, 0.72–0.79]), and 36% lower risk of hemorrhagic stroke (RR, 0.64 [95% CI, 0.56–0.74]).[47]
- In a meta-analysis of 45 prospective studies, whole grain intake was associated with a lower risk of CHD (HR, 0.81 [95% CI, 0.75–0.87]) and CVD (HR, 0.78 [95% CI, 0.73–0.85]) but was not significantly associated with stroke (HR, 0.88 [95% CI, 0.75–1.03]).[48]
- In a meta-analysis of 14 prospective cohort studies, every 20 g/d higher intake of fish was associated with 4% reduced risk of CVD mortality (RR, 0.96 [95% CI, 0.94–0.98]).[49] The association was stronger in Asian cohorts than Western cohorts. In the REGARDS study, individuals who consumed ≥2 servings of fried fish per week had a greater risk of CVD over 5.1 years of follow-up than those who consumed <1 serving per month (HR, 1.63 [95% CI, 1.11–2.40]).[50]
- In a meta-analysis of prospective cohort and case-control studies from multiple countries, consumption of unprocessed red meat was not significantly associated with incidence of CHD. In contrast, each 50-g serving per day of processed meats was associated with a higher incidence of CHD (RR, 1.42 [95% CI, 1.07–1.89]).[51]
- In a study of 169 310 female nurses and 41 526 male health professionals, consumption of 1 serving of nuts ≥5 times per week was associated with lower risk of CVD (HR, 0.86 [95% CI, 0.79–0.93]) and CHD (HR, 0.80 [95% CI, 0.72–0.89]) compared with those who never or almost never consumed nuts. Results were largely consistent for peanuts, tree nuts, and walnuts.[52]
- In a meta-analysis of 5 prospective observational studies, consumption of legumes (beans) was associated with lower incidence of CHD (RR per 4 weekly 100-g servings, 0.86 [95% CI, 0.78–0.94]).[53]
- Results from a meta-analysis of 17 prospective observational studies showed that neither dairy consumption nor dairy fat was significantly associated with higher or lower risk of CHD.[54]

Sodium and Potassium

- In a meta-analysis of 34 RCTs with modest reduction of sodium for ≥4 weeks, a 100-mmol/d (2300-mg/d) reduction in sodium was associated with a 5.8-mm Hg lower SBP.[55] The effects of sodium reduction on BP appear to be stronger in individuals who are older, hypertensive, and black.[56,57]
- Nearly all observational studies demonstrate an association between higher estimated sodium intakes (eg, >4000 mg/d) and a higher risk of CVD events, in particular stroke.[58–64] Some studies have also observed higher CVD risk at estimated low intakes (eg, <3000 g/d), which suggests a potential J-shaped relationship with risk.
- An AHA science advisory suggested that variation in methodology might account for inconsistencies in the relationship between sodium and CVD in observational studies. Increased risk at low sodium intake in some observational studies could be related to reverse causation (illness causing low intake) or imprecise estimation of sodium intake through a single dietary recall or a single urine excretion.[62]
- Post hoc analyses of the TOHP with 10 to 15 years of follow-up found that participants randomized to sodium reduction had a 25% decrease in CVD risk (RR, 0.75 [95% CI, 0.57–0.99]) compared with those randomized to control.[63]
- In an observational analysis of TOHP participants not assigned to an active sodium reduction intervention, sodium-potassium ratio was linearly associated with risk of CVD over 10 to 15 years of follow-up (RR, 1.24 per unit [95% CI, 1.05–1.46]; *P*=0.01).[63]
- In a longer-term (median 24 years) post hoc analysis of the TOHP (median of five 24-hour urine measurements), every 1-U increase in sodium-potassium ratio was associated with a 13% higher risk of death (HR, 1.13 [95% CI, 1.01–1.27]; *P*=0.04).[64]

Dietary Supplements

- In an RCT of 15 480 adults with DM and no history of ASCVD, 1 g of n-3 fatty acids had no effect on first serious vascular event (RR, 0.97 [95% CI, 0.87–1.08]) or a composite outcome of first serious vascular event or revascularization (RR, 1.00 [95% CI, 0.91–1.09]) or mortality (RR, 0.95 [95% CI, 0.86–1.05]) compared with placebo (1 g of olive oil).[65]
- In an RCT of 25 871 adults (males ≥50 years of age and females ≥55 years of age), the effects of daily supplementation of 2000 IU of vitamin D and 1 g of marine n-3 fatty acids were examined on prevention of cancer and CVD.[66] Vitamin D had no effect on major cardiovascular events (HR, 0.97 [95% CI, 0.85–1.12]), cancer (HR, 0.96 [95% CI, 0.88–1.06]), or any secondary outcomes. Marine n-3 fatty acid supplementation had no effect on major cardiovascular events (HR, 0.92 [95% CI, 0.80–1.06]), invasive cancer (HR, 1.03 [95% CI, 0.93–1.13]), or any secondary outcomes.
- A 2017 AHA scientific advisory statement summarized available evidence and suggested fish oil supplementation only for secondary prevention of CHD and SCD (Class IIa recommendation) and for secondary prevention of outcomes in patients with HF (Class IIa recommendation).[67]
- A meta-analysis of 77 917 participants in 10 RCTs with ≥500 participants treated for ≥1 year found that fish oil supplementation (eicosapentaenoic acid dose range 226–1800 mg/d; docosahexaenoic acid dose range 0–1700 mg/d) had no significant effect on CHD death (RR, 0.94 [95% CI, 0.81–1.03]), nonfatal MI (RR, 0.97 [95% CI, 0.87–1.08]), or any CHD events (RR, 0.97 [95% CI, 0.93–1.01]).[68]
- Meta-analyses of RCTs examining the effects of multivitamins, vitamin D, calcium, vitamin C, B-complex, antioxidants, and vitamin B3 (niacin) have demonstrated no salutary cardiovascular benefits.[69] Meta-analyses of folic acid RCTs suggested reductions in stroke risk (RR, 0.80 [95% CI, 0.69–0.93]) and CVD (RR, 0.83 [95% CI, 0.73–0.93]), although the benefit was mainly driven by the China Stroke Primary Prevention Trial, a large RCT of 20 702 adults with hypertension and no history of stroke or MI.[70]

Cost

The US Department of Agriculture reported that the Consumer Price Index for all food increased by 1.4% in 2018.[71] Prices for foods eaten at home increased by 0.4% in 2018, whereas prices for foods eaten away from home increased by 2.6%. Using data from Euromonitor International, the US Department of Agriculture calculated the share of consumer expenditures attributed to food in multiple countries in 2016. The proportion of consumer expenditures spent on food ranged from 6.3% in the United States to 9.1% in Canada, 23.1% in Mexico, and 58.9% in Nigeria.[72]

Cost of a Healthy Diet

- A meta-analysis of price comparisons of healthy versus unhealthy diet patterns found that the healthiest diet patterns cost, on average, ≈$1.50 more per person per day to consume.[73]
- In a 1-year (2013–2014) RCT of 30 after-school programs in South Carolina, site leaders in the intervention group received assistance in establishing snack budgets and menus and identifying low-cost outlets to purchase snacks that met healthy eating standards. The intervention was successful in increasing the number of days fruits and vegetables were served (3.9 versus 0.7 d/wk) and decreasing the number of days SSBs (0.1 versus 1.8 d/wk) and

sugary foods (0.3 versus 2.7 d/wk) were served.[74] Cost in the intervention group was minimized by identifying low-cost grocery outlets or large bulk warehouse stores; cost increased by $0.02 per snack in the intervention group compared with a $0.01 per snack decrease in the control group.

Cost-Effectiveness of Sodium Reduction

- A global cost-effectiveness analysis modeled the cost-effectiveness of a so-called soft regulation national policy to reduce sodium intake in countries around the world, based on the United Kingdom experience (government-supported industry agreements, government monitoring of industry compliance, public health campaign).[75] Model estimates were based on sodium intake, BP, and CVD data from 183 countries. Country-specific cost data were used to estimate the CER, defined as purchasing power parity–adjusted international dollars (I$, equivalent to country-specific purchasing power of $1 US) per DALY saved over 10 years. Globally, the estimated average CER was I$204 per DALY (95% CI, I$149–I$322) saved. The estimated CER was highly favorable in high-, middle-, and low-income countries.

Global Trends in Key Dietary Factors

Analysis of SSB sales data suggests that the regions in the world with the highest SSB consumption are North America, Latin America, Australasia, and Western Europe.[76] A number of countries and US cities have implemented SSB taxes. In Mexico, a 1 peso per liter excise tax was implemented in January 2014. In a study using store purchase data from 6645 Mexican households, posttax volume of beverages purchased decreased by 5.5% in 2014 and by 9.7% in 2015 compared with predicted volume of beverages purchased based on pretax trends. Although all socioeconomic groups experienced declines in SSB purchases, the lowest socioeconomic group had the greatest decline in SSB purchases (9.0% in 2014 and 14.3% in 2015).[77] In Berkeley, CA, a 1 cent per ounce SSB excise tax was implemented in January 2015.[78] Using store-level data, posttax year 1 SSB sales declined by 9.6% compared with predicted SSB sales based on pretax trends. By comparison, SSB sales increased by 6.9% in non-Berkeley stores in adjacent cities.

In 2010, mean sodium intake among adults worldwide was 3950 mg/d.[79] Across world regions, mean sodium intakes were highest in Central Asia (5510 mg/d) and lowest in eastern sub-Saharan Africa (2180 mg/d). Across countries, the lowest observed mean national intakes were ≈1500 mg/d. Between 1990 and 2010, global mean sodium intake appeared to remain relatively stable, although data on trends in many world regions were suboptimal.

In a systematic review of population-level sodium initiatives, reduction in mean sodium intake occurred in 5 of 10 initiatives.[80] Successful population-level sodium initiatives tended to use multiple strategies and included structural activities, such as food product reformulation. For example, the United Kingdom initiated a nationwide salt reduction program in 2003 to 2004 that included consumer awareness campaigns, progressively lower salt targets for various food categories, clear nutritional labeling, and working with industry to reformulate foods. Mean sodium intake in the United Kingdom decreased by 15% from 2003 to 2011,[81] along with concurrent decreases in BP (3.0/1.4 mm Hg) in patients not taking antihypertensive medication, stroke mortality (42%), and CHD mortality (40%; $P<0.001$ for all comparisons); these findings remained statistically significant after adjustment for changes in demographics, BMI, and other dietary factors.

Global Burden (See Chart 5-6)

- The GBD 2017 Study[82] used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories. The age-standardized mortality attributable to dietary risks is highest in Oceania and Central Asia (Chart 5-6).
- An updated report from the GBD 2017 Study estimated the impact of 15 dietary risk factors on mortality and DALYs worldwide, using a comparative risk assessment approach.[83] In 2017, an estimated 11 million deaths (95% UI, 10–12 million; 22% of all deaths) and 255 million DALYs (95% UI, 234–274 million; 15% of all DALYs) were attributable to dietary risks. The leading dietary risk factors were high sodium intake (3 million [95% UI, 1–5 million] deaths), low whole grain intake (3 million [95% UI, 2–4 million] deaths), and low fruit intake (2 million [95% UI, 1–4 million] deaths). Low-middle Socio-demographic Index and high-middle Socio-demographic Index countries had the highest age-standardized rates of diet-related deaths (344 [95% UI, 319–369] and 347 [95% UI, 324–369] deaths per 100 000 population), whereas high Socio-demographic Index countries had the lowest age-standardized rates of diet-related deaths (113 [95% UI, 104–122] deaths per 100 000 population). Age-standardized diet-related death rates decreased between 1990 to 2017 from 406 (95% UI, 381–430) to 275 (95% UI, 258–292) deaths per 100 000 population, although the proportion of deaths attributable to dietary risks was largely stable.

Table 5-1. AHA Dietary Targets and Healthy Diet Score for Defining Cardiovascular Health

	AHA Target	Consumption Range for Alternative Healthy Diet Score*	Alternative Scoring Range*
Primary dietary metrics†			
Fruits and vegetables	≥4.5 cups/d‡	0 to ≥4.5 cups/d‡	0–10
Fish and shellfish	2 or more 3.5-oz servings/wk (≥200 g/wk)	0 to ≥7 oz/wk	0–10
Sodium	≤1500 mg/d	≤1500 to >4500 mg/d	10–0
SSBs	≤36 fl oz/wk	≤36 to >210 fl oz/wk	10–0
Whole grains	3 or more 1-oz-equivalent servings/d	0 to ≥3 oz/d	0–10
Secondary dietary metrics†			
Nuts, seeds, and legumes	≥4 servings/wk (nuts/seeds: 1 oz; legumes: ½ cup)	0 to ≥4 servings/d	0–10
Processed meats	2 or fewer 1.75-oz servings/wk (≤100 g/wk)	≤3.5 to >17.5 oz/wk	10–0
Saturated fat	≤7% energy	≤7 to >15 (% energy)	10–0
AHA Diet Score (primary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40%–79%) Poor: <2 dietary targets (<40%)	Sum of scores for primary metrics	0 (worst) to 100 (best)§ Ideal: 80–100 Intermediate: 40–79 Poor: <40
AHA Diet Score (secondary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40%–79%) Poor: <2 dietary targets (<40%)	Sum of scores for primary and secondary metrics	0 (worst) to 100 (best)§ Ideal: 80–100 Intermediate: 40–79 Poor: <40

AHA indicates American Heart Association; and SSBs, sugar-sweetened beverages.

*Consistent with other dietary pattern scores, the highest score (10) was given for meeting or exceeding the AHA target (eg, at least 4.5 cups of fruit and vegetables per day; no more than 1500 mg/d of sodium), and the lowest score (0) was given for zero intake (protective factors) or for very high intake (harmful factors). The score for each metric was scaled continuously within this range. For harmful factors, the level of high intake that corresponded to a zero score was identified as approximately the 90th percentile distribution of US population intake.

†Selected by the AHA based on evidence for likely causal effects on cardiovascular events, diabetes mellitus, or obesity; a general prioritization of food rather than nutrient metrics; consistency with US and AHA dietary guidelines; ability to measure and track these metrics in the US population; and parsimony, that is, the inclusion of as few components as possible that had minimal overlap with each other while at the same time having some overlap with the many other relevant dietary factors that were not included.[2] The AHA dietary metrics should be targeted in the context of a healthy diet pattern that is appropriate in energy balance and consistent with a DASH (Dietary Approaches to Stop Hypertension)-type eating plan, including but not limited to these metrics.

‡Including up to one 8-oz serving per day of 100% fruit juice and up to 0.42 cups/d (3 cups/wk) of starchy vegetables such as potatoes or corn.

§The natural range of the primary AHA Diet Score is 0 to 50 (5 components), and the natural range of the secondary AHA Diet Score is 0 to 80 (8 components). Both scores are then rescaled to a range of 0 to 100 for comparison purposes. The ideal range of the primary AHA Diet Score corresponds to the AHA scoring system of meeting at least 4 of 5 binary dietary targets (≥80%), the intermediate range corresponds to meeting 2 or 3 dietary targets (40%–79%), and the poor range corresponds to meeting <2 dietary targets (<40%). The same ranges are used for the secondary AHA Diet Score for consistency and comparison.

Sources: AHA's My Life Check – Life's Simple 7[1]; Lloyd-Jones et al[2]; Rehm et al.[84]

Table 5-2. Trends in Key Dietary Components Among US Adults, NHANES 2003 to 2004 to NHANES 2015 to 2016

AHA Score	Survey-Weighted Mean/Percentages (95% CI)*							
	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P* for Trend
Primary	19.0 (18.1–20.0)	19.9 (19.2–20.6)	19.5 (18.7–20.3)	20.9 (20.5–21.4)	21.2 (20.4–21.9)	21.0 (20.3–21.7)	20.8 (19.9–21.6)	<0.001
Fruits and vegetables	5.0 (4.7–5.3)	5.0 (4.8–5.3)	4.9 (4.7–5.2)	5.1 (4.9–5.3)	5.1 (4.9–5.3)	4.9 (4.7–5.0)	4.8 (4.5–5.0)	0.18
Whole grains	2.1 (1.9–2.3)	2.4 (2.3–2.6)	2.4 (2.2–2.6)	2.8 (2.7–2.9)	3.1 (2.9–3.3)	3.0 (2.8–3.1)	3.0 (2.8–3.2)	<0.001
Fish and shellfish	2.5 (2.2–2.8)	2.6 (2.4–2.8)	2.5 (2.2–2.7)	2.8 (2.4–3.1)	2.5 (2.2–2.8)	2.5 (2.2–2.9)	2.3 (1.9–2.6)	0.23
SSBs	5.6 (5.2–6.0)	6.3 (6.0–6.6)	6.2 (5.9–6.5)	6.6 (6.4–6.8)	6.7 (6.4–7.0)	6.9 (6.5–7.3)	7.1 (6.8–7.3)	<0.001
Sodium	3.8 (3.6–3.9)	3.5 (3.4–3.6)	3.5 (3.4–3.6)	3.6 (3.5–3.8)	3.8 (3.7–3.9)	3.8 (3.6–3.9)	3.7 (3.5–3.8)	0.17
Secondary	34.6 (33.4–35.8)	35.6 (34.5–36.6)	35.5 (34.2–36.7)	37.3 (36.6–38.0)	38.0 (36.9–39.2)	37.5 (36.6–38.3)	37.1 (35.8–38.3)	<0.001
Nuts, seeds and legumes	4.1 (3.9–4.4)	4.4 (4.1–4.7)	4.3 (3.9–4.7)	4.4 (4.2–4.6)	4.8 (4.6–5.0)	4.7 (4.4–5.0)	5.0 (4.6–5.4)	<0.001
Processed meat	6.6 (6.4–6.8)	6.5 (6.1–6.8)	6.7 (6.5–6.9)	6.6 (6.4–6.9)	6.7 (6.4–6.9)	6.7 (6.5–7.0)	6.7 (6.5–7.0)	0.09
Saturated fat	4.9 (4.7–5.1)	4.8 (4.7–5.0)	5.0 (4.8–5.2)	5.3 (5.1–5.5)	5.4 (5.2–5.6)	5.0 (4.8–5.2)	4.5 (4.3–4.8)	0.48
Diet quality by primary and secondary scores (%)								
Primary score								
Poor	56.0 (51.6–60.2)	52.4 (48.3–56.5)	53.9 (49.9–57.9)	47.8 (45.3–50.3)	45.8 (41.8–49.9)	46.6 (42.7–50.7)	47.8 (43.1–52.6)	<0.001
Intermediate	43.4 (39.2–47.6)	46.9 (43.0–50.8)	45.3 (41.5–49.1)	50.7 (48.0–53.3)	52.7 (48.8–56.6)	51.8 (47.7–55.9)	50.8 (46.2–55.4)	0.001
Ideal	0.7 (0.5–1.0)	0.7 (0.4–1.3)	0.8 (0.5–1.6)	1.5 (1.0–2.2)	1.5 (0.9–2.4)	1.6 (1.0–2.5)	1.4 (1.0–2.1)	0.001
Secondary score								
Poor	43.7 (39.6–47.8)	41.7 (38.1–45.4)	41.3 (37.1–45.7)	36.1 (34.0–38.3)	33.9 (31.2–36.7)	35.8 (33.3–38.3)	36.4 (32.6–40.4)	<0.001
Intermediate	55.2 (51.2–59.2)	56.8 (53.1–60.4)	57.5 (53.1–61.7)	61.6 (59.3–63.8)	64.1 (61.6–66.5)	62.0 (59.5–64.4)	62.0 (58.1–65.7)	<0.001
Ideal	1.1 (0.7–1.7)	1.5 (1.0–2.2)	1.3 (0.9–1.8)	2.3 (1.5–3.3)	2.0 (1.4–2.9)	2.3 (1.8–2.9)	1.6 (1.0–2.5)	0.02

AHA indicates American Heart Association; NHANES, National Health and Nutrition Examination Survey; and SSBs, sugar sweetened beverages.

*All dietary variables were adjusted for energy to 2000 kcal/d using the residual method before the analysis. Each AHA consumption target was evaluated based on a continuous scoring system. Intake of each dietary component was scored from 0 to 10 (beneficial components) and from 10 to 0 (harmful components). For beneficial dietary components, individuals with zero intake received the lowest score (0). For harmful dietary components, the lowest score (0) was assigned to a higher level approximately equivalent to the 80th to 90th percentile of intake among US adults and rounded to a practical value (eg, 4500 mg/d sodium, one 50-g serving/d of processed meat, two 8-oz servings/d of sugar-sweetened beverages, and 15% energy of saturated fat). Intermediate dietary intake was scored linearly between 0 and 10. For example, an adult consuming 3000 mg/d of sodium would receive 5 sodium points (ie, his or her sodium consumption was halfway between 1500 mg/d and the maximum value of 4500 mg/d).

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using NHANES, 2003 to 2016. [85]

Table 5-3. Population Mean Consumption* of Food Groups and Nutrients of Interest by Sex and Race/Ethnicity Among US Adults ≥20 Years of Age, NHANES 2015 to 2016

	NH White Males		NH Black Males		Mexican American Males		NH White Females		NH Black Females		Mexican American Females	
	Average Consumption	% Meeting Guidelines	Average Consumption	% Meeting Guidelines	Average Consumption	% Meeting Guidelines	Average Consumption	% Meeting Guidelines	Average Consumption	% Meeting Guidelines	Average Consumption	% Meeting Guidelines
Foods												
Whole grains, servings/d	1.1±0.7	7.5	0.7±1.5	5.5	0.6±1.1	3.0	0.9±0.6	4.7	0.8±1.4	4.0	0.7±1.1	3.2
Whole fruit, servings/d	1.4±1.2	10.0	1.0±2.0	4.3	1.4±2.1	9.5	1.5±1.1	9.9	1.1±2	6.8	1.6±2.3	8.7
Total fruit, servings/d	1.8±1.4	13.7	1.7±2.6	8.9	2±2.7	16.5	1.9±1.2	12.0	1.9±2.5	14.6	2.2±2.9	18.6
Nonstarchy vegetables, servings/d	2.2±1.2	6.4	1.6±1.9	2.2	2±1.8	3.2	2.4±1.3	9.1	1.8±1.8	3.2	2.3±2	6.0
Starchy vegetables,† servings/d	0.9±0.7	NA	1.0±1.5	NA	0.5±1	NA	0.9±0.7	NA	0.9± 1.2	NA	0.8± 1.2	NA
Legumes, servings/wk	1.5±2.1	29.9	1.0±3.4	15.2	3.4±6.4	46.4	1.2± 1.6	25.3	1.1± 3.2	21.2	2.9±5.7	45.6
Fish and shellfish, servings/wk	1.0±1.8	16.0	1.4±3.9	21.1	1.2±4.1	18.2	1.0±1.5	18.6	1.8±4.1	24.5	1.2±4	17.3
Nuts and seeds, servings/wk	5.8±6.5	37.3	2.8±9.5	13.4	2.5±7.5	20.5	6.2±6.1	36.8	3.4±8.3	20.5	3±8.9	17.5
Unprocessed red meats, servings/wk	3.5±2.7	NA	3.4±5.7	NA	3.9±5.1	NA	2.4±1.9	NA	2.4±3.6	NA	3.1±4.5	NA
Processed meat, servings/wk	2.5±1.9	56.7	2.1±3.2	62.0	1.8±3.1	67.2	1.8±1.5	65.7	1.4±2.4	70.9	1±1.8	79.8
SSBs, servings/wk	8.3±8.7	57.6	10.3±12.5	32.9	10±12.4	39.2	5.8±6.6	67.7	9.7±13.5	41.2	8±12.6	45.3
Sweets and bakery desserts, servings/wk	3.7±3.6	57.8	3.3±6.8	62.2	4.2±7.6	61.7	4.2±4.1	56.2	3.7±7.2	59.1	4.7±8.5	52.2
Refined grain, servings/d	4.8±1.4	9.4	5.2±3.1	7.5	7.0 ±3.2	0.82	4.8±1.4	9.8	4.9±2.6	7.1	6.7±3.5	3.0
Nutrients												
Total calories, kcal/d	2418±522	NA	2211±1086	NA	2485±1140	NA	1742±344	NA	1762±824	NA	1852±803	NA
EPA/DHA, mg/d	0.079±0.103	9.0	0.101±0.247	10.6	0.075±0.159	6.9	0.084±0.111	8.8	0.103±0.251	8.2	0.090±0.241	7.9
ALA, g/d	1.65±0.55	42.4	1.69±1.12	43.8	1.56±0.73	41.6	1.95±0.71	87.9	1.86±1.02	86.7	1.72±0.88	87.1
n-6 PUFA, % energy	7.4± 2.9	NA	8.8 ± 6.8	NA	7.3±5.8	NA	11.6±5.1	NA	11.9±14.8	NA	10.1±6.7	NA
Saturated fat, % energy	12±2	26.0	11±4	36.2	11.4±3.6	30.7	12±2.1	26.8	10.9±3.9	37.3	11.2±3.7	37.5
Ratio of (PUFAs + MUFAs)/SFAs	1.8±0.6	12.6	2.2±1.6	25.1	1.8±1.3	13.6	2.3±0.8	29.7	2.6±2.2	40.0	2.3±1.4	31.3
Dietary cholesterol, mg/d	280±107	66.2	313±216	54.6	331±213	54.9	307±115	61.9	315±199	55.6	342±244	54.3
Carbohydrate, % energy	45.3±6.2	NA	46.3±12.2	NA	47.3±10.6	NA	46.2±5.8	NA	48.7±11.3	NA	49.3±10.5	NA
Dietary fiber, g/d	16.4±4.8	6.7	14.1±8.3	4.8	18.2±9.7	9.7	17.8±4.7	10.0	15±8.1	4.7	20.2±10	14.8
sodium, g/d	3.4±0.58	7.7	3.5±1.11	4.7	3.4±1.06	7.4	3.5±0.54	5.6	3.4±0.91	7.0	3.4±0.98	4.4
Added sugar, % energy	11.1±9.5	36.9	13.8±17.5	23.0	10.8±13.2	38.1	16.7±9.6	20.0	22.1±33.6	11.8	15.3±16.5	22.6

Values for average consumption are mean±SD. Data are from NHANES 2015 to 2016, derived from two 24-hour dietary recalls per person, with population SD adjusted for within-person vs between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability, means and proportions are reported for a 2000-kcal/d diet. To obtain actual mean consumption levels, the group means for each food or nutrient can be multiplied by the group-specific total calories (kcal/d) divided by 2000 kcal/d. The calculations for foods use the US Department of Agriculture (USDA)'s Food Patterns Equivalent Database on composition of various mixed dishes, which incorporates partial amounts of various foods (eg, vegetables, nuts, processed meats) in mixed dishes; in addition, the characterization of whole grains is now derived from the USDA database instead of the ratio of total carbohydrate to fiber.

ALA indicates α-linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; NA, not available; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; n-6-PUFA, ω-6-polyunsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; and SSBs, sugar-sweetened beverages.

*All intakes and guidelines adjusted to a 2000 kcal/d diet. Servings are defined as follows: whole grains, 1-oz equivalents; fruits and vegetables, 1/2-cup equivalents; legumes, 1/2 cup; fish/shellfish, 3.5 oz or 100 g; nuts and seeds, 1 oz; unprocessed red or processed meat, 3.5 oz or 100 g; sugar-sweetened beverages, 8 fl oz; sweets and bakery desserts, 50 g. Guidelines defined as follows: whole grains, 3 or more 1-oz equivalent (eg, 21 g of whole wheat bread, 82 g of cooked brown rice, 31 g of Cheerios) servings/d; fruits, ≥2 cups/d; nonstarchy vegetables, ≥2.5 cups/d; legumes, ≥1.5 cups/wk; fish or shellfish, 2 or more 100-g (3.5-oz) servings/wk; nuts and seeds, 4 or more 1-oz servings/wk; processed meats (bacon, hot dogs, sausage, processed deli meats), 2 or fewer 100-g (3.5-oz) servings/wk (1/4 of discretionary calories); sugar-sweetened beverages (defined as ≥50 cal/8 oz, excluding 100% fruit juices), ≤36 oz/wk (≈1/4 of discretionary calories); sweets and bakery desserts, 2.5 or fewer 50-g servings/wk (≈1/4 of discretionary calories); EPA/DHA, ≥0.250 g/d[51]; ALA, ≥1.6/1.1 g/d (males/females); saturated fat, <10% energy; dietary cholesterol, <300 mg/d; dietary fiber, ≥28 g/d; sodium, <2.3 g/d; ratio of (PUFAs + MUFAs)/SFAs ≥2.5; added sugars ≤6.5% total energy intake. No dietary targets are listed for starchy vegetables and unprocessed red meats because of their positive association with long-term weight gain and their positive or uncertain relation with diabetes mellitus and cardiovascular disease.

†Including white potatoes (chips, fries, mashed, baked, roasted, mixed dishes), corn, plantains, green peas, etc. Sweet potatoes, pumpkin, and squash are considered red-orange vegetables by the USDA and are included in nonstarchy vegetables.

Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using NHANES, 2015 to 2016.[85]

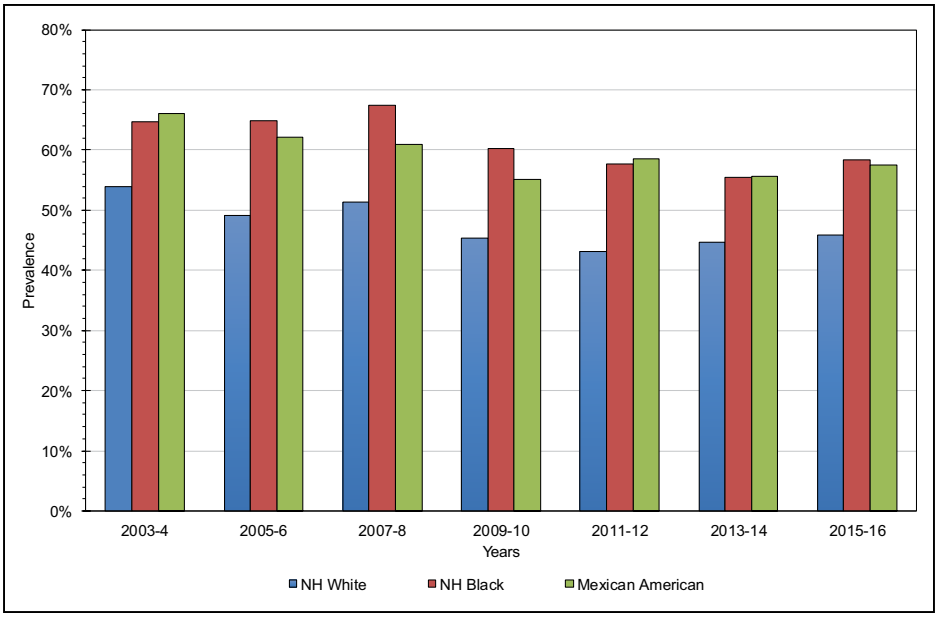


Chart 5-1. Trends in prevalence of poor AHA healthy diet score, by race/ethnicity, United States, 2003 to 2016.
Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence, based on primary AHA continuous diet score. AHA indicates American Heart Association; and NH, non-Hispanic.
Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using National Health and Nutrition Examination Survey data, 2003 to 2016.[85]

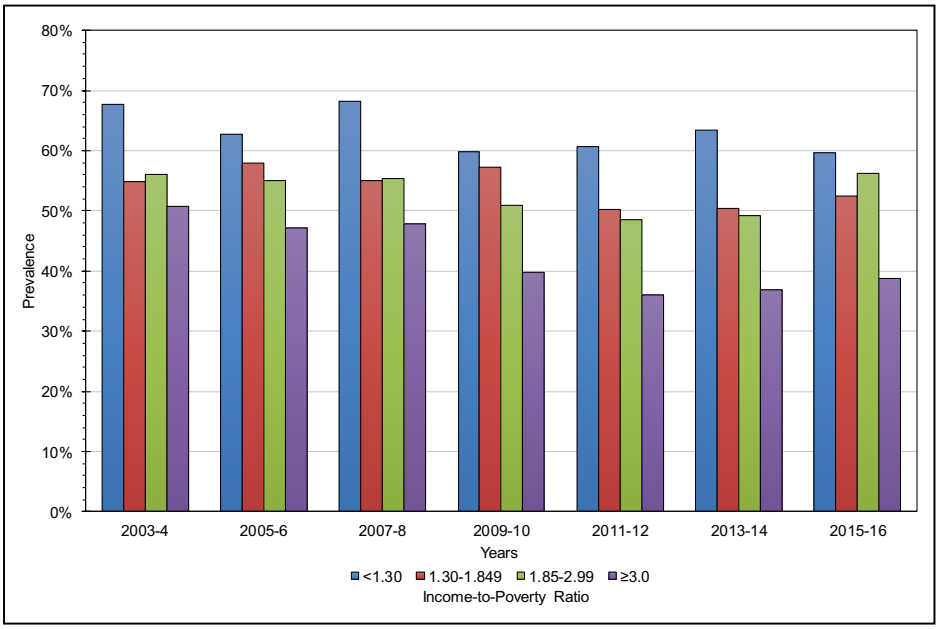


Chart 5-2. Trends in prevalence of poor AHA healthy diet score in the United States, by ratio of family income to poverty level, 2003 to 2016.
Components of AHA healthy diet score are defined in Table 5-1. Poor diet was defined as <40% adherence, based on primary AHA continuous diet score. AHA indicates American Heart Association.
Source: Unpublished analyses courtesy of Dr Junxiu Liu, Tufts University, using National Health and Nutrition Examination Survey data, 2003 to 2016.[85]

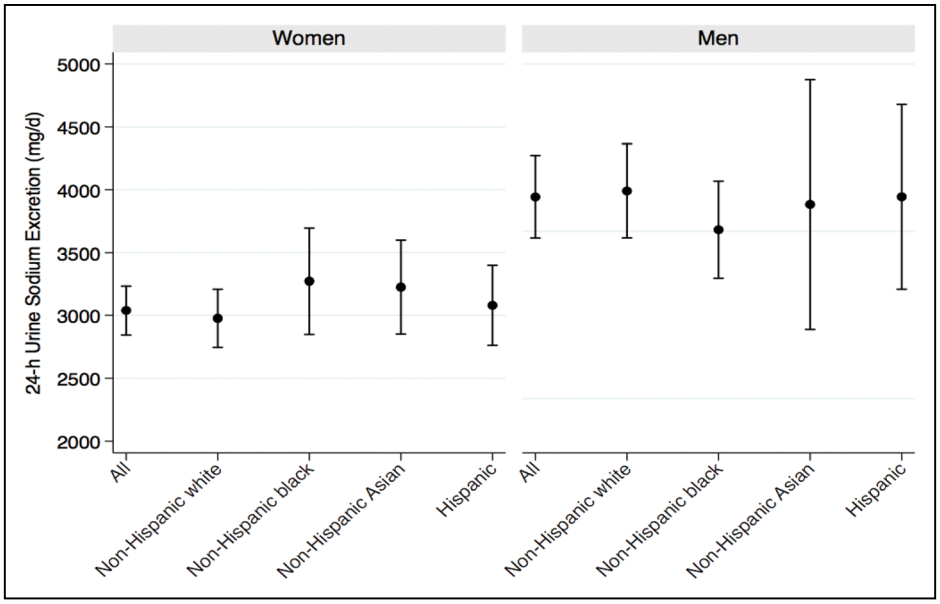
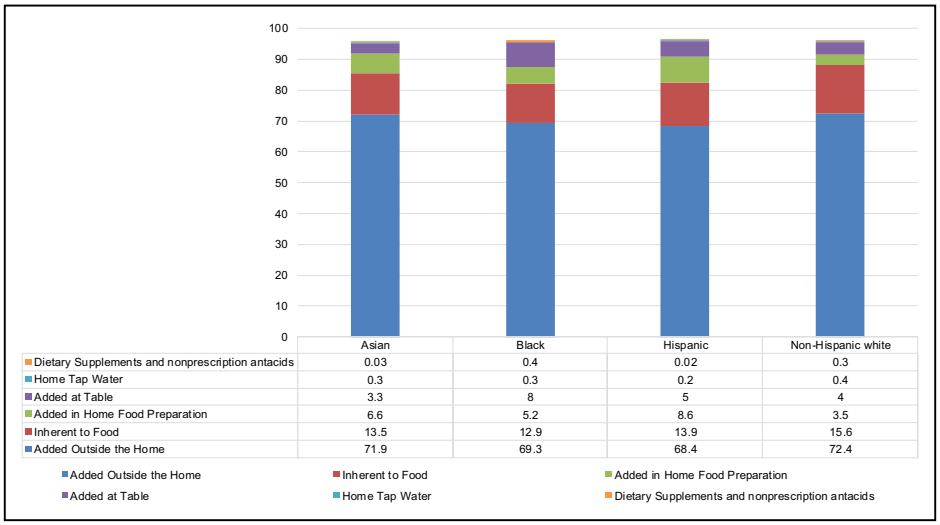


Chart 5-3. Estimated mean sodium intake by 24-hour urinary excretion, United States, 2013 to 2014.
Estimates based on nationally representative sample of 827 nonpregnant, noninstitutionalized US adults 20 to 69 years of age who completed a 24-hour urine collection in NHANES 2013 to 2014.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Data derived from Cogswell et al[86] using NHANES 2013 to 2014.[85]



	Asian	Black	Hispanic	Non-Hispanic white
Dietary Supplements and nonprescription antacids	0.03	0.4	0.02	0.3
Home Tap Water	0.3	0.3	0.2	0.4
Added at Table	3.3	8	5	4
Added in Home Food Preparation	6.6	5.2	8.6	3.5
Inherent to Food	13.5	12.9	13.9	15.6
Added Outside the Home	71.9	69.3	68.4	72.4

Chart 5-4. Sources of sodium intake in adults in 3 geographic regions in the United States, 2013 to 2014.
Sources of sodium intake determined by four 24-hour dietary recalls with special procedures, in which duplicate samples of salt added to food at the table and in home food preparation were collected in 450 adults recruited in 3 geographic regions (Birmingham, AL; Palo Alto, CA; and Minneapolis-St. Paul, MN) with equal numbers of males and females from 4 racial/ethnic groups (Asians, blacks, Hispanics, non-Hispanic whites).
Source: Reprinted from Harnack et al.[3] Copyright © 2017, American Heart Association, Inc.

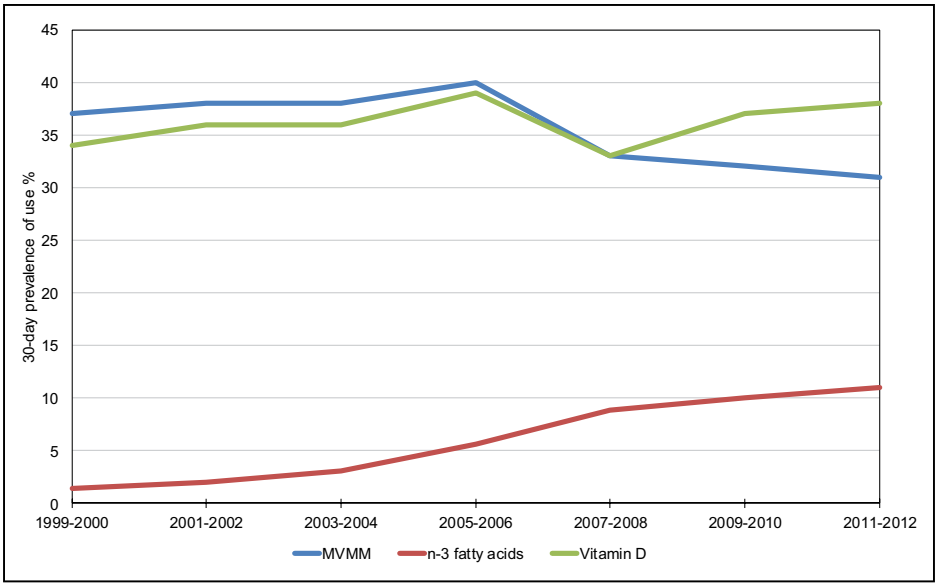


Chart 5-5. Trends in use of MVMM, vitamin D, and n-3 fatty acid supplements among adults in the United States (NHANES, 1999–2012).
MVMM indicates multivitamin/mineral; and NHANES, National Health and Nutrition Examination Survey.
Source: Data derived from Kantor et al.[14]

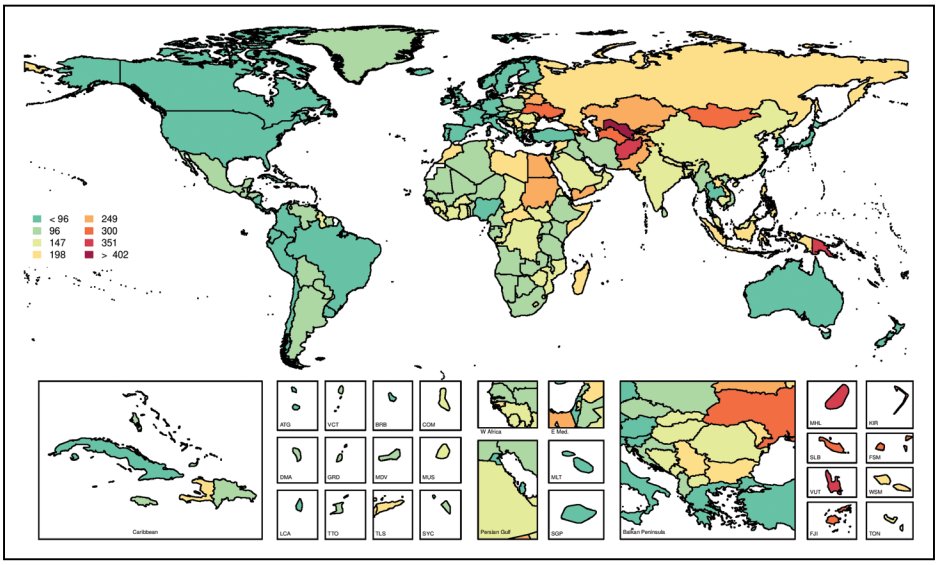


Chart 5-6. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2017.
The age-standardized mortality attributable to dietary risks is highest in Oceania and Central Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[82] Printed with permission.

REFERENCES

1. American Heart Association. My Life Check – Life's Simple 7. https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check–lifes-simple-7. Accessed March 11, 2019.
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
3. Harnack LJ, Cogswell ME, Shikany JM, Gardner CD, Gillespie C, Loria CM, Zhou X, Yuan K, Steffen LM. Sources of sodium in US adults from 3 geographic regions. *Circulation.* 2017;135:1775–1783. doi: 10.1161/CIRCULATIONAHA.116.024446
4. Quader ZS, Zhao L, Gillespie C, Cogswell ME, Terry AL, Moshfegh A, Rhodes D. Sodium intake among persons aged ≥2 years: United States, 2013-2014. *MMWR Morb Mortal Wkly Rep.* 2017;66:324–328. doi: 10.15585/mmwr.mm6612a3
5. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2018 update: a report from the American Heart Association [published correction appears in *Circulation*. 2018;137:e493]. *Circulation.* 2018;137:e67–e492. doi: 10.1161/CIR.0000000000000558
6. Ahluwalia N, Andreeva VA, Kesse-Guyot E, Hercberg S. Dietary patterns, inflammation and the metabolic syndrome. *Diabetes Metab.* 2013;39:99–110. doi: 10.1016/j.diabet.2012.08.007
7. US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2015–2020*. 8th ed. Washington, DC: US Government Printing Office; December 2015. https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf. Accessed March 11, 2019.
8. Wang DD, Leung CW, Li Y, Ding EL, Chiuve SE, Hu FB, Willett WC. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern Med.* 2014;174:1587–1595. doi: 10.1001/jamainternmed.2014.3422
9. Gu X, Tucker KL. Dietary quality of the US child and adolescent population: trends from 1999 to 2012 and associations with the use of federal nutrition assistance programs. *Am J Clin Nutr.* 2017;105:194–202. doi: 10.3945/ajcn.116.135095
10. Grummon AH, Taillie LS. Nutritional profile of Supplemental Nutrition Assistance Program household food and beverage purchases. *Am J Clin Nutr.* 2017;105:1433–1442. doi: 10.3945/ajcn.116.147173
11. Tester JM, Leung CW, Crawford PB. Revised WIC food package and children's diet quality. *Pediatrics*. 2016;137:e20153557. doi: 10.1542/peds.2015-3557
12. Vilarnau C, Stracker DM, Funtikov A, da Silva R, Estruch R, Bach-Faig A. Worldwide adherence to Mediterranean Diet between 1960 and 2011. *Eur J Clin Nutr*. 2019;72(suppl 1):83-91. doi: 10.1038/s41430-018-0313-9
13. Schwingshackl L, Boeing H, Stelmach-Mardas M, Gottschald M, Dietrich S, Hoffmann G, Chaimani A. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr.* 2017;8:27–39. doi: 10.3945/an.116.013516
14. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999–2012. *JAMA*. 2016;316:1464–1474. doi: 10.1001/jama.2016.14403
15. Kumanyika S, Grier S. Targeting interventions for ethnic minority and low-income populations. *Future Child*. 2006;16:187–207.
16. Li F, Harmer PA, Cardinal BJ, Bosworth M, Acock A, Johnson-Shelton D, Moore JM. Built environment, adiposity, and physical activity in adults aged 50-75. *Am J Prev Med.* 2008;35:38–46. doi: 10.1016/j.amepre.2008.03.021
17. Sallis JF, Glanz K. The role of built environments in physical activity, eating, and obesity in childhood. *Future Child.* 2006;16:89–108.
18. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, Jacobs DR Jr, Kraus WE, Kris-Etherton PM, Krummel DA, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovasc. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. *Circulation.* 2012;126:1514–1563. doi: 10.1161/CIR.0b013e318260a20b
19. Rummo PE, Guilkey DK, Ng SW, Popkin BM, Evenson KR, Gordon-Larsen P. Beyond supermarkets: food outlet location selection in four U.S. cities over time. *Am J Prev Med.* 2017;52:300–310. doi: 10.1016/j.amepre.2016.08.042
20. Ng SW, Poti JM, Popkin BM. Trends in racial/ethnic and income disparities in foods and beverages consumed and purchased from stores among US households with children, 2000-2013. *Am J Clin Nutr.* 2016;104:750–759. doi: 10.3945/ajcn.115.127944
21. Ferguson JF, Allayee H, Gerszten RE, Ideraabdullah F, Kris-Etherton PM, Ordovás JM, Rimm EB, Wang TJ, Bennett BJ; on behalf of the American Heart Association Council on Functional Genomics and Translational Biology, Council on Epidemiology and Prevention, and Stroke Council. Nutrigenomics, the microbiome, and gene-environment interactions: new directions in cardiovascular disease research, prevention, and treatment: a scientific statement from the American Heart Association. *Circ Cardiovasc Genet.* 2016;9:291–313. doi: 10.1161/HCG.0000000000000030
22. Pirastu N, Kooyman M, Traglia M, Robino A, Willems SM, Pistis G, Amin N, Sala C, Karssen LC, Van Duijn C, et al. A genome-wide association study in isolated populations reveals new genes associated to common food likings. *Rev Endocr Metab Disord.* 2016;17:209–219. doi: 10.1007/s11154-016-9354-3
23. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, et al. Personalized nutrition by prediction of glycemic responses. *Cell.* 2015;163:1079–1094. doi: 10.1016/j.cell.2015.11.001
24. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial [published corrections appear in *JAMA*. 2018;319:1386 and *JAMA*. 2018;319:1728]. *JAMA.* 2018;319:667–679. doi: 10.1001/jama.2018.0245
25. Ding M, Ellervik C, Huang T, Jensen MK, Curhan GC, Pasquale LR, Kang JH, Wiggs JL, Hunter DJ, Willett WC, et al. Diet quality and genetic association with body mass index: results from 3 observational studies. *Am J Clin Nutr.* 2018;108:1291–1300. doi: 10.1093/ajcn/nqy203
26. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA.* 2017;317:912–924. doi: 10.1001/jama.2017.0947
27. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999;99:779–785. doi: 10.1161/01.cir.99.6.779
28. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90. *N Engl J Med* 2018;378:2241–2442. doi: 10.1056/NEJMc1806491
29. Sofi F, Dinu M, Pagliai G, Cesari F, Gori AM, Sereni A, Becatti M, Fiorillo C, Marcucci R, Casini A. Low-calorie vegetarian versus Mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation.* 2018;137:1103–1113. doi: 10.1161/CIRCULATIONAHA.117.030088
30. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Fitó M, Chiva-Blanch G, Fiol M, Gómez-Gracia E, Arós F, Lapetra J, et al; PREDIMED Study Investigators. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol.* 2019;7:e6–e17. doi: 10.1016/S2213-8587(19)30074-9
31. Juraschek SP, Miller ER 3rd, Weaver CM, Appel LJ. Effects of sodium reduction and the DASH diet in relation to baseline blood pressure. *J Am Coll Cardiol.* 2017;70:2841–2848. doi: 10.1016/j.jacc.2017.10.011
32. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, et al; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA.* 2005;294:2455–2464. doi: 10.1001/jama.294.19.2455
33. Gadgil MD, Appel LJ, Yeung E, Anderson CA, Sacks FM, Miller ER 3rd. The effects of carbohydrate, unsaturated fat, and protein intake on measures of insulin sensitivity: results from the OmniHeart trial. *Diabetes Care.* 2013;36:1132–1137. doi: 10.2337/dc12-0869

34. Gay HC, Rao SG, Vaccarino V, Ali MK. Effects of different dietary interventions on blood pressure: systematic review and meta-analysis of randomized controlled trials. *Hypertension.* 2016;67:733–739. doi: 10.1161/HYPERTENSIONAHA.115.06853
35. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol.* 2014;176:680–686. doi: 10.1016/j.ijcard.2014.07.080
36. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, Willett WC, Manson JE, Sun Q, Hu FB. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med.* 2016;13:e1002039. doi: 10.1371/journal.pmed.1002039
37. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses [published correction appears in *Lancet*. 2019;393:406]. *Lancet.* 2019;393:434–445. doi: 10.1016/S0140-6736(18)31809-9
38. Uauy R, Aro A, Clarke R. WHO Scientific Update on trans fatty acids: summary and conclusions. *Eur J Clin Nutr*. 2009;63:S68–S75.
39. Imamura F, Micha R, Wu JH, de Oliveira Otto MC, Otite FO, Abioye AI, Mozaffarian D. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials. *PLoS Med.* 2016;13:e1002087. doi: 10.1371/journal.pmed.1002087
40. Brassard D, Tessier-Grenier M, Allaire J, Rajendiran E, She Y, Ramprasath V, Gigleux I, Talbot D, Levy E, Tremblay A, et al. Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. *Am J Clin Nutr.* 2017;105:800–809. doi: 10.3945/ajcn.116.150300
41. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am J Clin Nutr.* 2015;102:1347–1356. doi: 10.3945/ajcn.115.110965
42. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA.* 2006;295:655–666. doi: 10.1001/jama.295.6.655
43. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med.* 2010;7:e1000252. doi: 10.1371/journal.pmed.1000252
44. Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, Willett WC, Hu FB. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation.* 2014;130:1568–1578. doi: 10.1161/CIRCULATIONAHA.114.010236
45. Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am J Clin Nutr.* 2013;98:1084–1102. doi: 10.3945/ajcn.113.058362
46. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, Hu FB. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies [published correction appears in *BMJ*. 2014;349:5472.]. *BMJ.* 2014;349:g4490. doi: 10.1136/bmj.g4490
47. Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, Sherliker P, Gao H, Chen Y, Yang L, et al; China Kadoorie Biobank Study. Fresh fruit consumption and major cardiovascular disease in China. *N Engl J Med.* 2016;374:1332–1343. doi: 10.1056/NEJMoa1501451
48. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ.* 2016;353:i2716. doi: 10.1136/bmj.i2716
49. Jayedi A, Shab-Bidar S, Eimeri S, Djafarian K. Fish consumption and risk of all-cause and cardiovascular mortality: a dose-response meta-analysis of prospective observational studies. *Public Health Nutr.* 2018;21:1297–1306. doi: 10.1017/S1368980017003834
50. Nahab F, Pearson K, Frankel MR, Ard J, Safford MM, Kleindorfer D, Howard VJ, Judd S. Dietary fried fish intake increases risk of CVD: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Public Health Nutr.* 2016;19:3327–3336. doi: 10.1017/S136898001600152X
51. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation.* 2010;121:2271–2283. doi: 10.1161/CIRCULATIONAHA.109.924977
52. Guasch-Ferré M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol.* 2017;70:2519–2532. doi: 10.1016/j.jacc.2017.09.035
53. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr.* 2014;100:278–288. doi: 10.3945/ajcn.113.076901
54. Chen M, Li Y, Sun Q, Pan A, Manson JE, Rexrode KM, Willett WC, Rimm EB, Hu FB. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. *Am J Clin Nutr.* 2016;104:1209–1217. doi: 10.3945/ajcn.116.134460
55. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ.* 2013;346:f1325. doi: 10.1136/bmj.f1325
56. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med.* 2014;371:624–634. doi: 10.1056/NEJMoa1304127
57. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, et al; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med.* 2001;344:3–10. doi: 10.1056/NEJM200101043440101
58. Kalogeropoulos AP, Georgiopoulou VV, Murphy RA, Newman AB, Bauer DC, Harris TB, Yang Z, Applegate WB, Kritchevsky SB. Dietary sodium content, mortality, and risk for cardiovascular events in older adults: the Health, Aging, and Body Composition (Health ABC) Study. *JAMA Intern Med.* 2015;175:410–419. doi: 10.1001/jamainternmed.2014.6278
59. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, et al; PURE, EPIDREAM and ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet.* 2016;388:465–475. doi: 10.1016/S0140-6736(16)30467-6
60. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, et al; PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events [published correction appears in *N Engl J Med*. 2014;371:1267]. *N Engl J Med.* 2014;371:612–623. doi: 10.1056/NEJMoa1311889
61. Whelton PK, Appel LJ, Sacco RL, Anderson CA, Antman EM, Campbell N, Dunbar SB, Frohlich ED, Hall JE, Jessup M, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations [published correction appears in *Circulation*. 2013;27:e263]. *Circulation*. 2012;126:2880–2889. doi: 10.1161/CIR.0b013e318279acbf
62. Cobb LK, Anderson CA, Elliott P, Hu FB, Liu K, Neaton JD, Whelton PK, Woodward M, Appel LJ; on behalf of the American Heart Association Council on Lifestyle and Metabolic Health. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation.* 2014;129:1173–1186. doi: 10.1161/CIR.0000000000000015
63. Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK; Trials of Hypertension Prevention Collaborative Research Group. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med.* 2009;169:32–40. doi: 10.1001/archinternmed.2008.523
64. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the Trials of Hypertension Prevention. *J Am Coll Cardiol.* 2016;68:1609–1617. doi: 10.1016/j.jacc.2016.07.745
65. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540–1550. doi: 10.1056/NEJMoa1804989
66. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, et al; VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* 2019;380:33–44. doi: 10.1056/NEJMoa1809944
67. Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, et al; on behalf

of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. *Circulation.* 2017;135:e867–e884. doi: 10.1161/CIR.0000000000000482

68. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, et al; Omega-3 Treatment Trialists' Collaboration. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. *JAMA Cardiol.* 2018;3:225–234. doi: 10.1001/jamacardio.2017.5205
69. Jenkins DJA, Spence JD, Giovannucci EL, Kim YI, Josse R, Vieth R, Blanco Mejia S, Viguiliouk E, Nishi S, et al. Supplemental vitamins and minerals for CVD prevention and treatment. *J Am Coll Cardiol.* 2018;71:2570–2584. doi: 10.1016/j.jacc.2018.04.020
70. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, Tang G, Wang B, Chen D, He M, et al; CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA.* 2015;313:1325–1335. doi: 10.1001/jama.2015.2274
71. Food price outlook: changes in food price indexes, 2015 through 2018. USDA Economic Research Service website. https://www.ers.usda.gov/data-products/food-price-outlook.aspx. Accessed March 11, 2019.
72. Food expenditure series. USDA Economic Research Service website. https://www.ers.usda.gov/data-products/food-expenditures.aspx. Accessed March 11, 2019.
73. Rao M, Afshin A, Singh G, Mozaffarian D. Do healthier foods and diet patterns cost more than less healthy options? A systematic review and meta-analysis. *BMJ Open.* 2013;3:e004277. doi: 10.1136/bmjopen-2013-004277
74. Beets MW, Weaver RG, Turner-McGrievy G, Huberty J, Ward DS, Freedman D, Hutto B, Moore JB, Beighle A. Making healthy eating policy practice: a group randomized controlled trial on changes in snack quality, costs, and consumption in after-school programs. *Am J Health Promot.* 2016;30:521–531. doi: 10.4278/ajhp.141001-QUAN-486
75. Webb M, Fahimi S, Singh GM, Khatibzadeh S, Micha R, Powles J, Mozaffarian D. Cost effectiveness of a government supported policy strategy to decrease sodium intake: global analysis across 183 nations. *BMJ.* 2017;356:i6699. doi: 10.1136/bmj.i6699
76. Popkin BM, Hawkes C. Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses. *Lancet Diabetes Endocrinol.* 2016;4:174–186. doi: 10.1016/S2213-8587(15)00419-2
77. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW. In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. *Health Aff (Millwood).* 2017;36:564–571. doi: 10.1377/hlthaff.2016.1231
78. Silver LD, Ng SW, Ryan-Ibarra S, Taillie LS, Induni M, Miles DR, Poti JM, Popkin BM. Changes in prices, sales, consumer spending, and beverage consumption one year after a tax on sugar-sweetened beverages in Berkeley, California, US: A before-and-after study. *PLoS Med.* 2017;14:e1002283. doi: 10.1371/journal.pmed.1002283
79. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open.* 2013;3:e003733. doi: 10.1136/bmjopen-2013-003733
80. Barberio AM, Sumar N, Trieu K, Lorenzetti DL, Tarasuk V, Webster J, Campbell NRC, McLaren L. Population-level interventions in government jurisdictions for dietary sodium reduction: a Cochrane Review. *Int J Epidemiol.* 2017;46:1551–1563. doi: 10.1093/ije/dyw361
81. He FJ, Brinsden HC, MacGregor GA. Salt reduction in the United Kingdom: a successful experiment in public health. *J Hum Hypertens.* 2014;28:345–352. doi: 10.1038/jhh.2013.105
82. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
83. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2019;393:1958–1972. doi: 10.1016/S0140-6736(19)30041-8
84. Rehm CD, Peñalvo JL, Afshin A, Mozaffarian D. Dietary intake among US adults, 1999-2012. *JAMA.* 2016;315:2542–2553. doi: 10.1001/jama.2016.7491
85. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
86. Cogswell ME, Loria CM, Terry AL, Zhao L, Wang CY, Chen TC, Wright JD, Pfeiffer CM, Merritt R, Moy CS, et al. Estimated 24-hour urinary sodium and potassium excretion in US adults. *JAMA.* 2018;319:1209–1220. doi: 10.1001/jama.2018.1156

6. OVERWEIGHT AND OBESITY

See Table 6-1 and Charts 6-1 through 6-8

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Overweight and obesity are major risk factors for CVD, including CHD, stroke,[1,2] AF,[3] VTE,[4,5] and CHF. According to NHANES 2015 to 2016, the prevalence of obesity was 39.6% of US adults and 18.5% of youth, with 7.7% of adults and 5.6% of youth having severe obesity.[6–8] The AHA has identified BMI <85th percentile in youth (2–19 years of age) and <25 kg/m^2 in adults (≥20 years of age) as 1 of the 7 components of ideal CVH.[9] In 2015 to 2016, 60.1% of youth, 32.0% of adults 20 to 49 years of age, and 24.4% of adults ≥50 years of age met these criteria (Chapter 2, Cardiovascular Health, Charts 2-2 and 2-3).

Abbreviations Used in Chapter 6

AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AHA	American Heart Association
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
ARIC	Atherosclerosis Risk in Communities Study
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ATP III	Adult Treatment Panel III
BMI	body mass index
BRFSS	Behavioral Risk Factor Surveillance System
CABG	coronary artery bypass graft
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
DBP	diastolic blood pressure
DM	diabetes mellitus
DNA	deoxyribonucleic acid
GBD	Global Burden of Disease
GWAS	genome-wide association study
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
IMT	intima-media thickness
IRR	incidence rate ratio
LDL-C	low-density lipoprotein cholesterol
Look AHEAD	Look: Action for Health in Diabetes
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	metabolic syndrome
MHO	metabolically healthy obesity
MI	myocardial infarction

(*Continued*)

Abbreviations Used in Chapter 6 Continued

NCHS	National Center for Health Statistics
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
OR	odds ratio
PA	physical activity
PCI	percutaneous coronary intervention
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SE	standard error
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SOS	Swedish Obese Subjects
UI	uncertainty interval
VTE	venous thromboembolism
WC	waist circumference
WHI	Women's Health Initiative
YRBSS	Youth Risk Behavior Surveillance System

Classification of Overweight and Obesity

- For adults, NHLBI weight categories are as follows: overweight (25.0 ≤ BMI ≤ 29.9 kg/m^2) and obese class I (BMI 30–35 kg/m^2), class II (BMI >35–39.9 kg/m^2), and class III (BMI ≥40 kg/m^2). BMI cutoffs often misclassify obesity in those with muscle mass on the upper and lower tails of the distribution. BMI categories also vary in prognostic value by race/ethnicity; they appear to overestimate risk in blacks and underestimate risk in Asians.[10] For this reason, lower BMI cutoffs have been recommended to identify increased health risks for Asian and South Asian populations.[11]
- For youth, sex-specific BMI-for-age 2000 CDC growth charts for the United States are used,[12] and overweight is defined as 85th to <95th percentile and obesity as ≥95th percentile. A 2013 AHA scientific statement recommended that the definition of severe obesity for children ≥2 years old and adolescents be changed to BMI ≥120% of the 95th percentile for age and sex or an absolute BMI ≥35 kg/m^2, whichever is lower.[13] This definition of severe obesity among children could better identify this small but important group compared with the other common definition of BMI ≥99th percentile for age and sex.[13]
- Current obesity guidelines define WC ≥40 inches (102 cm) for males and ≥35 inches (88 cm) for

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females as being associated with increased cardiovascular risk[14]; however, lower cutoffs have been recommended for various racial/ethnic groups, for example, ≥80 cm for Asian females and ≥90 cm for Asian males.[10,15] WC measurement is recommended for those with BMI of 25 to 34.9 kg/m^2, to provide additional information on CVD risk.[16]

Prevalence

Youth
(See Table 6-1 and Chart 6-1)

- According to 2015 to 2016 data from NHANES, the overall prevalence of obesity (≥95th percentile) was 18.5%. By age group, the prevalence of obesity for children 2 to 5 years of age was 13.9%; for children 6 to 11 years of age, the prevalence was 18.4%; and for adolescents 12 to 19 years of age, the prevalence was 20.6% (Chart 6-1).[17,18]
- According to 2013 to 2016 data from NHANES, the overall prevalence of overweight, including obesity, in children and adolescents 2 to 19 years of age was 34.2% based on a BMI-for-age value ≥85th percentile of the 2000 CDC growth charts. There were no significant differences in overweight (including obesity) prevalence for boys and girls (Table 6-1).[19] Among all children 2 to 19 years of age, the prevalence of obesity was lower for NH Asian boys (11.9%) and girls (7.4%) than for NH white (15.3%, 14.1%), NH black (17.9%, 23.0%), and Hispanic (24.3%, 22.9%) boys and girls, respectively (Table 6-1).
- The prevalence of childhood obesity varies by SES. According to 2011 to 2014 NHANES data, for children 2 to 19 years old, the prevalence of obesity by percentage of poverty level was 18.9% for ≤130%, 19.9% for 131% to 350%, and 10.9% for >350% of the federal poverty level.[20]
  - In addition, obesity prevalence among children 2 to 19 years of age was higher for those whose parents had a high school diploma or less education (21.6%) than for adolescents whose parents had a bachelor's degree or higher (9.6%).[20]
- According to NHANES 1999 to 2014, the prevalence of obesity among adolescents 12 to 19 years of age was 21.6% in the South region, 20.8% in the Midwest region, 18.2% in the Northeast region, and 15.8% in the West region.[21]
- According to self-reported height and weight data from the YRBSS 2015,[22] 13.9% of US high school students had obesity and 16.0% were overweight. The percentages of obesity were higher in boys (16.8%) than girls (10.8%) and in blacks (16.8%) and Hispanics (16.4%) than in whites (12.4%). Obesity rates varied by states: The highest rates of obesity in girls were observed in Kentucky and Mississippi (16.2%), and in boys, West Virginia (23.4%); the lowest rates in girls were observed in Nevada (6.3%), whereas for boys, the lowest rates were seen in Montana (13.0%).

Adults
(See Table 6-1 and Charts 6-2 through 6-6)

- According to NHANES 2013 to 2016, among US adults ≥20 years of age (Table 6-1):
  - The prevalence of obesity was 38.3% (36.0% of males and 40.4% of females), including 7.7% with class III obesity (5.5% of males and 9.8% of females).
  - Among men, the prevalence of obesity was 35.8% in NH whites, 37.0% in NH blacks, 11.1% in NH Asians, and 40.1% in Hispanics.
  - Among women, the prevalence of obesity was 37.8% in NH whites, 55.3% in NH blacks, 13.5% in NH Asians, and 48.4% in Hispanics.
- According to NHANES 2011 to 2014, the age-adjusted prevalence of obesity was higher among middle-aged (40–59 years of age, 40.2%) and older (≥60 years of age, 37.0%) adults than younger (20–39 years of age, 32.3%) adults. This pattern (lower prevalence of obesity among younger adults) was similar for males and females, although the prevalence of obesity was higher among females.[7]
- Females have had a higher prevalence of class III obesity and a lower prevalence of overweight than males in all NHANES surveys from 1999 through 2016 (Chart 6-2).[23]
- In the United States, the prevalence of obesity, as estimated from self-reported height and weight in the BRFSS (2017),[24] varies by region and state. Self-reported estimates usually underestimate BMI and obesity. In 2017, by state, the prevalence of obesity was highest in West Virginia (37.7%) and Mississippi (37.2%) and lowest in Colorado (22.4%; Chart 6-3).[25] When BRFSS data from 2015 to 2017 were combined, prevalence of obesity exceeded 35% in a greater number of states for Hispanic adults and NH black adults than for white adults (Charts 6-4 through 6-6).

Secular Trends
(See Chart 6-7)

Youth

- According to NHANES data, overall prevalence of obesity and severe obesity in youth (2–19 years of age) did not increase significantly between 2007 to 2008 and 2015 to 2016 (Chart 6-7). Among children 2 to 5 years of age, a quadratic trend was seen, with obesity decreasing from 10.1% in 2007 to 2008 to 8.4% in 2011 to 2012 and increasing to 13.9% in 2015 to 2016.[8]

- According to NHANES 2011 to 2014 data, prevalence of obesity in youth (2–19 years of age) increased from 1988 to 1994 until 2003 to 2004 but did not change significantly afterward. The prevalence of severe obesity increased between 1988 to 1994 and 2013 to 2014.[19]
- According to NCHS/CDC surveys and NHANES, the prevalence of obesity among children and adolescents increased substantially from 1963 to 1965 through 2009 to 2010, but this increase has slowed.[26]
- Specifically, according to NHANES data, from 1988 to 1994, 2003 to 2006, and 2011 to 2014, the percentage of children 12 to 19 years of age with obesity increased from 10.5% to 17.6% to 20.5%, respectively[26]; however, during the same time periods, among children 2 to 5 years of age, the prevalence of obesity changed from 7.2% in 1988 to 1994 to 12.5% in 2003 to 2006 to 8.9% in 2011 to 2014.[19,26] Another analysis of NHANES data showed that between 1988 to 1994 and 2013 to 2014, extreme obesity (defined as a BMI at or above 120% of the sex-specific 95th percentile on the CDC BMI-for-age growth charts) increased among children 6 to 11 years of age (from 3.6% to 4.3%) and among adolescents 12 to 19 years of age (from 2.6% to 9.1%).[19]
- Among infants and children from birth to >2 years old, the prevalence of high weight for recumbent length (ie, ≥95th percentile of sex-specific CDC 2000 growth charts) was 9.5% in 2003 to 2004 and 8.1% in 2011 to 2014. The decrease of 1.4% was not statistically significant.[27]
- According to the YRBSS, among US high school students between 1999 and 2015, there was a significant linear increase in the prevalence of obesity (from 10.6% to 13.9%) and in the prevalence of overweight (from 14.1% to 16.0%). Between 1991 and 2015, there was a corresponding significant linear increase of students who reported they were trying to lose weight, from 41.8% to 45.6%.[22]

Adults

- In the United States, the age-standardized prevalence of obesity and severe obesity increased significantly in the past decade (from 2007–2008 to 2015–2016) among adults (Chart 6-7).[8]
- In the United States, the prevalence of obesity among adults, estimated using NHANES data, increased from 1999 to 2000 through 2013 to 2014 from 30.5% to 37.7%[6]; however, from 2005 to 2006 through 2013 to 2014, there was a significant linear trend for the increase in obesity and class III obesity for females (from 35.6% to 41.1% and from 7.5% to 10.0%, respectively) but not males (from 33.4% to 35.1% and from 7.5% to 10.0%, respectively).[6]
- From NHANES 1999 to 2002 to NHANES 2007 to 2010, the prevalence of total and undiagnosed DM, total hypertension, total dyslipidemia, and smoking did not change significantly within any of the BMI categories, but there was a lower prevalence of dyslipidemia (–3.4% [95% CI, –6.3% to –0.5%]) among overweight adults. However, the prevalence of untreated hypertension decreased among adults with overweight or obesity, and the prevalence of untreated dyslipidemia decreased for all BMI categories (normal, overweight, obesity, and BMI ≥35 kg/m^2).[28]
- Another study reported that for females, but not males, the increase in WC from NHANES 1999 to 2000 to NHANES 2010 to 2011 was greater than expected based on the increase in BMI.[29]

Family History and Genetics

- Overweight and obesity have considerable genetic components, with heritability estimates ranging from ≈30% to 75%.[30,31] However, only ≈1.5% of interindividual variation of BMI is explained by commonly occurring SNPs, which suggests a role for DNA methylation variants to explain the genetic contributions to obesity.[32]
- Monogenic or mendelian causes of obesity include mutations with strong effects in genes that control appetite and energy balance (eg, *LEP*, *MC4R*) and obesity that occurs in the context of genetic syndromes (eg, Prader-Willi syndrome).[33]
- GWASs in diverse populations have implicated multiple loci for obesity, mostly defined by BMI, WC, or waist-hip ratio. The FTO locus is the most well-established obesity locus, first reported in 2007[34,35] and replicated in many studies with diverse populations and age groups since then.[36–40] The mechanisms underlying the association remain incompletely elucidated but could be related to mitochondrial thermogenesis[11] or food intake.[41]
- Other GWASs have reported numerous additional loci,[42] with >300 putative loci, most of which explain only a small proportion of the variance in obesity, have not been mechanistically defined, and have unclear clinical significance. Variants associated with lean mass have also been reported.[43,44] Fine mapping of loci, including recent efforts focused on GWASs in African ancestry, in addition to mechanistic studies, is required to define functionality of obesity-associated loci.[45]
- A large GWAS of obesity in >240 000 individuals of predominately European ancestry revealed an interaction with smoking, which highlights the

need to consider gene-environment interactions in genetic studies of obesity.[46]
- Genetic variants also associate with weight loss response to dietary intervention.[47]
- Epigenetic modifications such as DNA methylation have both genetic and environmental contributors and may contribute to risk of and adverse consequences of obesity. An epigenome-wide association study in 479 people demonstrated that increased methylation at the HIF3A locus in circulating white blood cells and in adipose tissue was associated with increased BMI.[48]

Prevention

- Prenatal environmental exposures related to excessive gestational weight gain, independent of maternal obesity, are associated with increased risk of childhood obesity (OR, 1.21 [95% CI, 1.05–1.40])[49]; preconception counseling strategies to promote healthy maternal weight before conception and interventions during pregnancy to prevent excess weight gain are needed.
- 70% of adults with obesity did not have obesity in childhood or adolescence, so reducing the overall burden of adult obesity might require interventions beyond targeting obesity reduction solely at overweight children and children with obesity.[50]
- In adults, 2 prevention targets are the built environment and the workplace. The built environment plays a role in promoting healthy lifestyles and preventing obesity.[51] Similar to schools for children, the workplace can provide an opportunity to educate adults on methods to reduce weight and can also motivate individuals to lose weight through group participation.[52]
- The CDC Prevention Status Reports highlight the status of public health policies and practices to address public health problems, including obesity, by state. Reports rate the extent to which the state has implemented the policies or practices identified from systemic reviews, national strategies or action plans, or expert bodies.[53] Obesity reduction policies and programs implemented by country are also available online.[54]

Awareness

- According to NHANES 2003 to 2006 data, ≈23% of adults who were overweight and with obesity misperceived themselves to be at a healthier weight status, and those people were less likely to have tried to lose weight in the prior year.[55]
- Recent studies show that parents' perceptions of overweight and obesity differ according to the child's race and sex. Boys 6 to 15 years of age with obesity were more likely than girls to be misperceived as being "about the right weight" by their parents (OR, 1.40 [95% CI, 1.12–1.76]; *P*=0.004). Obesity was significantly less likely to be misperceived among girls 11 to 15 years of age than among girls 6 to 10 years of age (OR, 0.46 [95% CI, 0.29–0.74]; *P*=0.002) and among Hispanic males than among white males (OR, 0.58 [95% CI, 0.36–0.93]; *P*=0.02).[55] Notification of a child's unhealthy weight by healthcare practitioners increased from 22% in 1999 to 34% in 2014.[56]

Treatment and Control

- The randomized trial Look AHEAD showed that among adults who were overweight, had obesity, and had type 2 DM, an intensive lifestyle intervention produced a greater percentage of weight loss at 4 years than DM support education.[57]
  - After 8 years of intervention, the percentage of weight loss ≥5% and ≥10% was greater in the intensive lifestyle intervention than in DM support education groups (50.3% and 26.9% versus 35.7% and 17.2%, respectively).[58]
  - Look AHEAD was stopped early, with a median 9.6 years of follow-up, for failure to show a significant difference in CVD events between the intensive lifestyle intervention and the control group.[57]
  - Intensive lifestyle interventions produced greater weight loss than education alone among those with class III obesity[59] and childhood obesity.[60]
- A comprehensive review and meta-analysis of 54 RCTs suggested that dietary weight loss interventions reduce all-cause mortality (34 trials, 685 events; RR, 0.82 [95% CI, 0.71–0.95]), but the benefit on lowering cardiovascular mortality was less clear.[61]
- Ten-year follow-up data from the nonrandomized SOS bariatric intervention study (see Bariatric Surgery) suggested that to maintain a favorable effect on cardiovascular risk factors, more than the short-term goal of 5% weight loss is needed to overcome secular trends and aging effects.[62] Long-term follow-up might be necessary to show reductions in CVD risk.
- Lifestyle and surgical interventions are both beneficial: After gastric bypass, individuals with regular PA had improved fat mass, insulin sensitivity, and HDL-C levels.[63]

Bariatric Surgery

- Lifestyle interventions often do not provide sustained significant weight loss for people with obesity. Among adults with obesity, bariatric surgery

produces greater weight loss and maintenance of lost weight than lifestyle intervention, with some variations depending on the type of procedure and the patient's initial weight.[64] Gastric bypass surgery is typically performed as a Roux-en-Y gastric bypass, vertical sleeve gastrectomy, adjustable gastric banding, or biliopancreatic diversion with duodenal switch.

- Benefits reported for bariatric surgery include substantial weight loss; remission of DM, hypertension, and dyslipidemia; reduced incidence of mortality; reduction in microvascular disease; and fewer CVD events.[65] Long-term follow-up of the Longitudinal Assessment of Bariatric Surgery-2 study, a multicenter observational cohort study of 1300 participants who underwent bariatric surgery, demonstrated that most participants maintained the majority of their weight loss. However, at 7 years after surgery, lower prevalence rates of DM and hypertension were only achieved among those who underwent Roux-en-Y gastric bypass and not among those who underwent laparoscopic gastric banding.[66]
- Reported risks with bariatric surgery include not only perioperative mortality and adverse events but also weight regain, DM recurrence (particularly for those with longer DM duration before surgery), bone loss, increases in substance use disorders, suicide, and nutritional deficiencies. Outcomes vary by bariatric surgery technique.[67]
- Outcomes must be assessed cautiously, because most bariatric surgery data come from nonrandomized observational studies, with only a few RCTs comparing bariatric surgery to medical treatment for patients with DM. Furthermore, studies have not always reported their definition of remission or partial remission for comorbidities such as DM, hypertension, and dyslipidemia, and many have not reported laboratory values or medication use.[67,68]
- In a large bariatric surgery cohort, the prevalence of high 10-year predicted CVD risk (using the ATP III definition, ≥10%)[69] was 36.5%,[70] but 76% of those with low 10-year risk had high lifetime predicted CVD risk (defined as predicted lifetime risk ≥39%).[71] The corresponding prevalence in US adults is 18% and 56%, respectively.[72]
- A meta-analysis of RCTs also showed substantially higher weight loss and DM remission for bariatric surgery than for conventional medical therapy, with follow-up of ≤2 years.[73]
- The longest follow-up to date of 12 years in 1156 patients with severe obesity, including 418 individuals who underwent gastric bypass, demonstrated sustained weight loss and both remission and prevention of incident type 2 DM, hypertension, and dyslipidemia.[74]
- An RCT demonstrated that weight loss from laparoscopic sleeve gastrectomy was similar to that achieved by traditional (Roux-en-Y) gastric bypass surgery, although the latter achieved greater improvement in lipid levels.[75,76]
- According to retrospective data, among 9949 patients who underwent gastric bypass surgery, after a mean of 7 years, long-term mortality was 40% lower among the surgically treated patients than among control subjects with obesity. Specifically, cancer mortality was reduced by 60%, DM mortality by 92%, and CAD mortality by 56%. Nondisease death rates (eg, accidents, suicide) were 58% higher in the surgery group.[77]
- A recent DM consensus statement recommended bariatric surgery to treat type 2 DM among adults with class III obesity and recommended it be considered to treat type 2 DM among adults with class I obesity.[59]
- The role of bariatric surgery to treat type 2 DM in adolescence is controversial.[78] Although bariatric surgery improves insulin requirements and comorbidities in type 1 DM, there was minimal sustained effect in glycemic control in long-term follow-up in a small series.[79]

Mortality

- Childhood BMI in the highest quartile was associated with premature death as an adult in a cohort of 4857 American Indian children during a median follow-up of 23.9 years (BMI for quartile 4 versus quartile 1: IRR, 2.30 [95% CI, 1.46–3.62]).[80]
- According to NHIS-linked mortality data, among young adults 18 to 39 years of age, the HR for all-cause mortality was 1.07 (95% CI, 0.91–1.26) for self-reported overweight (not including obesity), 1.41 (95% CI, 1.16–1.73) for obesity, and 2.46 (95% CI, 1.91–3.16) for extreme obesity.[81]
- A systematic review (2.88 million people and >270 000 deaths) showed that relative to normal BMI (18.5 to <25 kg/m^2), all-cause mortality was lower for overweight individuals (BMI 25 to <30 kg/m^2: HR, 0.94 [95% CI, 0.91–0.96]) and was not elevated for class I obesity (HR, 0.95 [95% CI, 0.88–1.01]). All-cause mortality was higher for obesity overall (HR, 1.18 [95% CI, 1.12–1.25]) and for the subset of class II and III obesity (HR, 1.29 [95% CI, 1.18–1.41]).[82]
- Fluctuation of weight is associated with cardiovascular events and death. In 9509 participants of the Treating to New Targets trial, those in the quintile of highest body weight fluctuation had the highest rates of cardiovascular events, MI, stroke, and death.[83]

- A meta-analysis of 3.74 million deaths among 30.3 million participants found that overweight and obesity were associated with higher risk of all-cause mortality, with the lowest mortality observed at BMI 22 to 23 kg/m^2 among healthy never-smokers.[84]
- In 10 large population cohorts in the United States, individual-level data from adults 20 to 79 years of age with 3.2 million person-years of follow-up (1964–2015) demonstrated that overweight and obesity were associated with early development of CVD and reinforced the greater mortality associated with obesity.[85]
- In the APPROACH registry of individuals after CABG and PCI, overweight and class I obesity (BMI 20–24.9 kg/m^2) were associated with lower mortality, whereas BMI ≥40 kg/m^2 was associated with elevated mortality.[86] According to data from the National Adult Cardiac Surgery registry from 2002 to 2013, there was lower mortality in overweight and obesity class I and II (OR, 0.81 [95% CI, 0.76–0.86] and 0.83 [95% CI, 0.74–0.94], respectively) relative to normal-weight individuals and greater mortality risk with underweight (OR, 1.51 [95% CI, 1.41–1.62), with these results persisting after adjustment for residual confounding and reverse causation.[87]
- In a study of 22 203 females and males from England and Scotland, metabolically unhealthy obese individuals were at an increased risk of all-cause mortality compared with MHO individuals (HR, 1.72 [95% CI, 1.23–2.41]).[88]

Complications

Youth

- According to the National Longitudinal Study of Adolescent Health, compared with those with normal weight or those who were overweight, adolescents who were obese had a 16-fold increased risk of having severe obesity as adults, and 70.5% of adolescents with severe obesity maintained this weight status into adulthood.[89]
- A systematic review and meta-analysis of 15 prospective cohort studies with 200 777 participants showed that children and adolescents who had obesity were ≈5 times more likely to have obesity in adulthood than those who did not have obesity. Approximately 55% of children with obesity will remain with obesity in adolescence, 80% of adolescents with obesity will remain with obesity in their adulthood, and 70% of these adolescents will remain with obesity at over 30 years of age.[50]
- Children and adolescents who are overweight and have obesity are at increased risk for future adverse health effects, including the following[90]:
  - Increased prevalence of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, and DM. Among 8579 youths in NHANES, higher BMI was associated with higher SBP and DBP, lower HDL-C, and high triglycerides and HbA_{1c} levels.[91,92]
  - Poor school performance, tobacco use, alcohol use, premature sexual behavior, and poor diet.
  - Other associated health conditions, such as asthma, hepatic steatosis, sleep apnea, stroke, some cancers (breast, colon, and kidney), renal insufficiency, musculoskeletal disorders, gallbladder disease, and reproductive abnormalities.
- Data from 4 Finnish cohort studies examining childhood and adult BMI with a mean follow-up of 23 years found that children who were overweight or had obesity and had obesity in their adulthood had an increased risk of type 2 DM (RR, 5.4), hypertension (RR, 2.7), dyslipidemia (high LDL-C: RR, 1.8; low HDL-C: RR, 2.1; high triglycerides: RR, 3.0), and carotid atherosclerosis (RR, 1.7), whereas those who achieved normal weight by adulthood had risks comparable to individuals who never had obesity.[93]
- The CARDIA study showed that young adults who were overweight or had obesity had lower self-reported physical health–related quality of life than normal-weight participants 20 years later.[94]

Adults

- Obesity is associated with increased lifetime risk of CVD and increased prevalence of type 2 DM, hypertension, dyslipidemia, sleep-disordered breathing, VTE, AF, and dementia.[85,95]
- Analyses of continuous BMI show the risk of type 2 DM increases with increasing BMI.[64]
- A systematic review and meta-analysis of 37 studies showed that high childhood BMI was associated with an increased incidence of adult DM (OR, 1.70 [95% CI, 1.30–2.22]) and CHD (OR, 1.20 [95% CI, 1.10–1.31]), but not stroke; however, the accuracy of childhood BMI predicting any adult morbidity was low. Only 31% of future DM and 22% of future hypertension and CHD occurred in those who as youth ≥12 years of age had been classified as overweight or who had obesity.[96]
- Another study examining longitudinal data from 2.3 million adolescents (16–19 years of age) demonstrated increased cardiovascular mortality in adulthood among youth with obesity compared with youth with BMI in the 5th to 24th percentile, with an HR of 4.9 (95% CI, 3.9–6.1) for death attributable to CHD, 2.6 (95% CI, 1.7–4.1) for death attributable to stroke, 2.1 (95% CI, 1.5–2.9) for sudden death, and 3.5 (95% CI, 2.9–4.1) for death attributable to total cardiovascular causes,

after adjustment for sex, age, birth year, sociodemographic characteristics, and height.[97]

- Cardiovascular risks are even higher with class III obesity than with class I or class II obesity.[98] Among 156 775 postmenopausal females in the WHI, for severe obesity versus normal BMI, HRs (95% CIs) for mortality were 1.97 (1.77–2.20) in white females, 1.55 (1.20–2.00) in black females, and 2.59 (1.55–4.31) in Hispanic females; for CHD, HRs were 2.05 (1.80–2.35), 2.24 (1.57–3.19), and 2.95 (1.60–5.41), respectively; and for CHF, HRs were 5.01 (4.33–5.80), 3.60 (2.30–5.62), and 6.05 (2.49–14.69), respectively. However, CHD risk was strongly related to CVD risk factors across BMI categories, even in class III obesity, and CHD incidence was similar by race/ethnicity with adjustment for differences in BMI and CVD risk factors.[98]
- Obesity was cross-sectionally associated with subclinical atherosclerosis, including CAC and carotid IMT, among older adults in MESA, and this association persisted after adjustment for CVD risk factors.[99] In a prospective analysis of younger adults through midlife, greater duration of overall and abdominal obesity was associated with presence of and progression of subclinical atherosclerosis in the CARDIA study.[100]
- A recent meta-analysis of 10 case-referent studies and 4 prospective cohort studies (including ARIC)[5] reported that when individuals with BMI ≥30 kg/m^2 were compared with those with BMI <30 kg/m^2, obesity was associated with a significantly higher prevalence (OR, 2.45 [95% CI, 1.78–3.35]) and incidence (RR, 2.39 [95% CI, 1.79–3.17]) of VTE, although there was significant heterogeneity in the studies.[4]
- Obesity in females is associated with increased risk of adverse pregnancy outcomes, (eg, preeclampsia, gestational hypertension, gestational DM).
  - The risk of preeclampsia was higher in females who were overweight (OR 1.73 [95% CI, 1.59–1.87]) or obese (OR, 3.15 [95% CI, 2.96–3.35]) in a systematic review of 23 studies including 1.4 million females.[101]
  - The risk of gestational hypertension was higher among females with obesity (OR 2.91 [95% CI, 2.76–3.07]) than among females with a normal prepregnancy BMI.[102]
  - The risk of gestational DM was 2.14 (95% CI, 1.82–2.53), 3.56 (95% CI, 3.05- 4.21), and 8.56 (95% CI, 5.07–16.04) among overweight, obese, and severely obese females, respectively compared with females with normal prepregnancy BMI.[103]
- A recent meta-analysis of 15 prospective studies of midlife BMI demonstrated that the increased risk for Alzheimer disease or any dementia was 1.35 and 1.26 for overweight, respectively, and 2.04 and 1.64 for obesity, respectively.[104] The inclusion of obesity in dementia forecast models increased the estimated prevalence of dementia through 2050 by 9% in the United States and 19% in China.[105]
- A BMI paradox is often reported, with higher-BMI patients demonstrating favorable outcomes among adults with prevalent CHF, hypertension, peripheral vascular disease, and CAD; similar findings have been seen for percent body fat. However, recent studies suggest that the obesity paradox might be explained by lead-time bias, because it is not present before the development of CVD.[85,106]
- The ARISTOTLE trial reported that in adjusted analyses, higher BMI was associated with lower all-cause mortality (overweight HR, 0.67 [95% CI, 0.59–0.78]; obesity HR, 0.63 [95% CI, 0.54–0.74]), similar to an earlier study from the AFFIRM trial.[107]
- In a study of 2625 participants with new-onset DM pooled from 5 longitudinal cohort studies, rates of total, CVD, and non-CVD mortality were higher among normal-weight people than among overweight participants and participants with obesity, with adjusted HRs of 2.08 (95% CI, 1.52–2.85), 1.52 (95% CI, 0.89–2.58), and 2.32 (95% CI, 1.55–3.48), respectively.[108]
- In a study of 189 672 participants from 10 US longitudinal cohort studies, obesity was associated with a shorter total longevity and greater proportion of life lived with CVD, and higher BMI was associated with significantly higher risk of death attributable to CVD.[85]
- Recent studies have evaluated risks for MHO versus "metabolically unhealthy" or "metabolically abnormal" obesity. The definition of MHO has varied across studies, but it has often comprised 0 or 1 metabolic abnormality by MetS criteria, sometimes excluding WC.
  - Using strict criteria of 0 MetS components and no previous CVD diagnosis, a recent report of 10 European cohort studies (N=163 517 people) reported that the prevalence of MHO varied from 7% to 28% in females and from 2% to 19% in males.[109]
  - MHO appears to be unstable over time, with 1 study showing that 44.5% of MHO individuals transitioned to metabolically unhealthy obesity over 8 years of follow-up.[110]
  - Among younger adults in the CARDIA study, after 20 years of follow-up, 47% of people were defined as being metabolically healthy overweight (presence of 0 or 1 metabolic risk factor).[111] Among older adults in MESA, approximately half of participants with MHO developed MetS and had increased odds of CVD (OR, 1.60 [95% CI, 1.14–2.25]) compared

with those with stable MHO or healthy normal weight.[112]
  - A recent meta-analysis of 22 prospective studies suggested that CVD risk was higher in MHO than metabolically healthy normal-weight participants (RR, 1.45 [95% CI, 1.20–1.70]); however, the risk in MHO individuals was lower than in individuals who were metabolically unhealthy and normal weight (RR, 2.07 [95% CI, 1.62–2.65]) or obese (RR, 2.31 [95% CI, 1.99–2.69]).[95]
  - Other reports suggest that obesity, especially long-lasting or severe obesity, without metabolic abnormalities might not increase risk for MI but does increase risk for HF.[113,114]

Cost

Obesity costs the healthcare system, healthcare payers, and individuals with obesity.

- In the United States, the estimated annual medical cost of obesity in 2008 was $147 billion; the annual medical costs for individuals with obesity were $1429 higher than for normal-weight individuals.[115] A more recent study estimated mean annual per capita healthcare expenses associated with obesity were $1160 for males and $1525 for females.[116]
- According to NHANES I data linked to Medicare and mortality records, 45-year-old individuals with obesity had lifetime Medicare costs of $163 000 compared with $117 000 for those who were at normal weight at 65 years of age.[117]
- According to data from the Medicare Current Beneficiary Survey from 1997 to 2006, in 1997, expenditures for Part A and Part B services per beneficiary were $6832 for a normal-weight person, which was more than for overweight people ($5473) or people with obesity ($5790); however, over time, expenses increased more rapidly for overweight people and people with obesity.[118]
- The costs of obesity are high: People with obesity paid on average $1429 (42%) more for healthcare costs than normal-weight people in 2006. For beneficiaries who are obese, Medicare pays $1723 more, Medicaid pays $1021 more, and private insurers pay $1140 more annually than for beneficiaries who are at normal weight. Similarly, people with obesity have 46% higher inpatient costs and 27% more outpatient visits and spend 80% more on prescription drugs.[115]
- Using 4 waves of NHANES data (through 2000), the total excess cost in 2007 US dollars related to the current prevalence of adolescent overweight and obesity was estimated to be $254 billion ($208 billion in lost productivity secondary to premature morbidity and mortality and $46 billion in direct medical costs).[119]
- A recent study recommended the use of $19 000 (2012 US dollars) as the incremental lifetime medical cost of a child with obesity relative to a normal-weight child who maintains normal weight throughout adulthood.[120]
- According to the 2006 NHDS, the incidence of bariatric surgery was estimated at 113 000 cases per year, with costs of nearly $1.5 billion annually.[121]
- A recent cost-effectiveness study of laparoscopic adjustable gastric banding showed that after 5 years, $4970 was saved in medical expenses; if indirect costs were included (absenteeism and presenteeism), savings increased to $6180 and $10 960, respectively.[122] However, when expressed per QALY, only $6600 was gained for laparoscopic gastric bypass, $6200 for laparoscopic adjustable gastric band, and $17 300 for open Roux-en-Y gastric bypass, none of which exceeded the standard $50 000 per QALY gained.[123] Two other recent large studies failed to demonstrate a cost benefit for bariatric surgery versus matched patients over 6 years of follow-up.[124,125]
- The cost effectiveness of bariatric surgery among individuals with DM is unclear, with 2 studies showing cost savings[126,127] but a recent study demonstrating no improvement compared with intensive lifestyle and medical interventions.[128]
- Bariatric surgery appears to be cost-effective for the treatment of nonalcoholic steatohepatitis, with increasing degree of obesity associated with decreasing cost per QALY ($19 222/QALY in the severely obese), which suggests that subsets of indications for bariatric surgery may be more cost-effective.[129]

Global Burden (See Chart 6-8)

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[130]
  - Age-standardized mortality rates attributable to high BMI are generally lower in Northern Europe, sub-Saharan Africa, and East Asia (Chart 6-8).
- Although there is considerable variability in overweight and obesity data methodology and quality worldwide, cross-country comparisons can help reveal different patterns. Worldwide, from 1975 to 2014, the prevalence of obesity increased from 3.2% in 1975 to 10.8% in 2014 in males and from 6.4% to 14.9% in females, and mean age-standardized BMI increased from 21.7 to 24.2 kg/m^2 in males and from 22.1 to 24.4 kg/m^2 in females.[131] Worldwide, between 1980 and 2013,

the proportion of adults with overweight or obesity increased from 28.8% (95% UI, 28.4%–29.3%) to 36.9% (95% UI, 36.3%–37.4%) among males and from 29.8% (95% UI, 29.3%–30.2%) to 38.0% (95% UI, 37.5%–38.5%) among females. Since 2006, the increase in adult obesity in developed countries has slowed. The estimated prevalence of adult obesity exceeded 50% of males in Tonga and females in Kuwait, Kiribati, the Federated States of Micronesia, Libya, Qatar, Tonga, and Samoa. In the sub-Saharan African country of Malawi, representative of rural but developing countries, the prevalence of overweight or obesity was 18% and 44% of urban males and females, respectively, and 9% and 27% of rural males and females, respectively. Associated hypertension and DM are highly prevalent and underdiagnosed.[132] As of 2013, around the world, obesity rates are higher for females than males and in developed countries than in developing countries. Higher obesity rates for females than for males occur for those ≥45 years of age in developed countries but for those ≥25 years of age in developing countries.[133]

- Between 1980 and 2013, the prevalence of overweight and obesity rose by 27.5% for adults.[133] Over this same period, no declines in obesity prevalence were detected. In 2008, an estimated 1.46 billion adults were overweight or obese. The prevalence of obesity was estimated at 205 million males and 297 million females in 2013. The highest prevalence of male obesity is in the United States, Southern and Central Latin America, Australasia, and Central and Western Europe, and the lowest prevalence is in South and Southeast Asia and East, Central, and West Africa. For females, the highest prevalence of obesity is in Southern and North Africa, the Middle East, Central and Southern Latin America, and the United States, and the lowest is in South, East, and Southeast Asia, the high-income Asia-Pacific subregion, and East, Central, and West Africa.[134]
- An appraisal of the prevalence of obesity in sub-Saharan Africa from 2009 to 2012 suggests an increase in BMI and WC, associated with hypertension. In 2726 university students in Cameroon, the prevalence of obesity, overweight and obesity (combined), and hypertension was 3.5%, 21%, and 6.3%, respectively. There was an increase over time in overweight and obesity in males and an increase in prevalence of abdominal obesity in females, which were both associated with incident hypertension.[135]
- In 2015, a total of 107.7 million youth and 603.7 million adults had obesity, with an overall obesity prevalence of 5.0% among children and 12.0% among adults. High BMI contributed to 4.0 million deaths globally, with the leading cause of death and disability being attributable to CVD.[136]

Table 6-1. Prevalence of Overweight, Obesity, and Severe Obesity in Youth and Adults, United States, 2013 to 2016

	Prevalence of Overweight and Obesity,* Age 2-19 y		Prevalence of Obesity,* Age 2-19 y		Prevalence of Overweight and Obesity,* Age ≥20 y		Prevalence of Obesity,* Age ≥20 y		Prevalence of Extreme Obesity,* Age ≥20 y	
	n†	%	n†	%	n†	%	n†	%	n†	%
Total	25396610	34.2	13218119	17.8	168124846	69.9	73776304	38.3	17971151	7.7
Male	12976634	34.2	6867751	18.1	85319221	73.2	35712352	36.0	6315689	5.5
Female	12456292	34.3	6355251	17.5	82831254	66.9	38070753	40.4	11798284	9.8
NH white										
Male	6181303	30.9	3060645	15.3	57009715	73.6	23603229	35.8	4147532	5.5
Female	5408658	28.5	2675862	14.1	52655558	64.3	23508364	37.8	7306654	9.4
NH black										
Male	1696311	32.4	937159	17.9	9135568	69.1	3939550	37.0	968527	7.2
Female	2146338	42.2	1169805	23.0	12095004	79.5	6100089	55.3	2328852	15.3
Hispanic										
Male	3973860	43.8	2204676	24.3	14518219	80.8	6303729	40.1	1053598	5.6
Female	3818241	43.8	1996295	22.9	13722325	77.8	6667145	48.4	1869623	10.3
NH Asian										
Male	432521	24.2	212686	11.9	2964505	48.8	676746	11.1	23956	0.4
Female	335568	19.2	129334	7.4	2503175	36.3	912116	13.5	20574	0.3

NH indicates non-Hispanic.

*Overweight and obesity in adults is defined as body mass index (BMI) ≥25 kg/m^2. Obesity in adults is defined as BMI ≥30 kg/m^2. Extreme obesity is defined as BMI ≥40 kg/m^2. Prevalence estimates for adults were age-adjusted using the direct method to standardize estimates to the projected 2000 US census population with age categories of 20 to 39, 40 to 59, and ≥60 years of age. In children, overweight and obesity are based on BMI-for-age values ≥85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. In children, obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.[16] Prevalence estimates for youth are unadjusted.

†n is population counts applied to the average of the 2013 and 2015 Census Bureau population estimates.

Source: Unpublished tabulation using National Health and Nutrition Examination Survey, 2013 to 2016.[18]

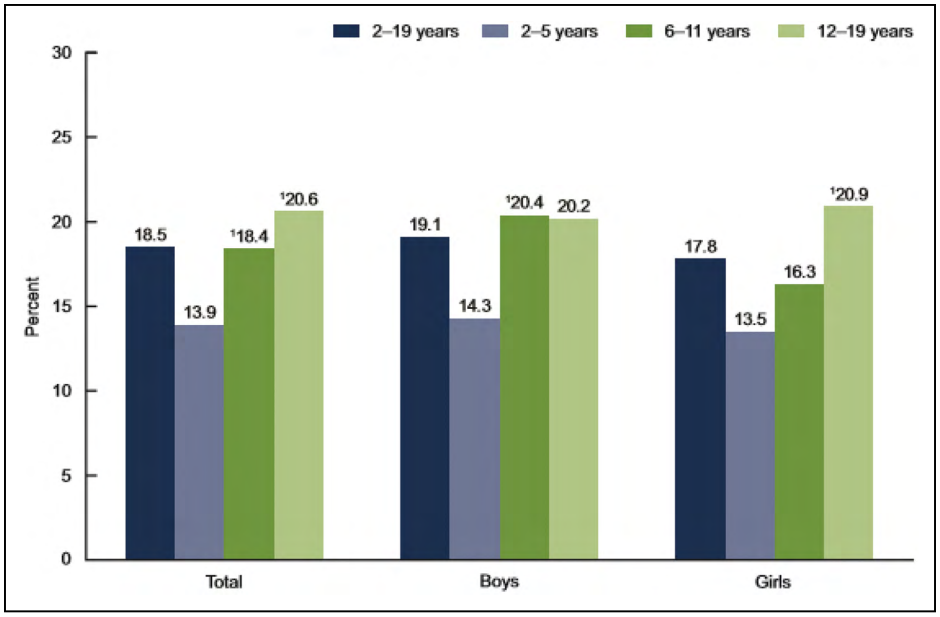

Chart 6-1. Prevalence of obesity among US youth 2 to 19 years of age, by sex and age, 2015 to 2016.
[1]Significantly different from those 2 to 5 years of age.
Source: Reprinted from Hales et al[17] using National Health and Nutrition Examination Survey, 2015 to 2016.

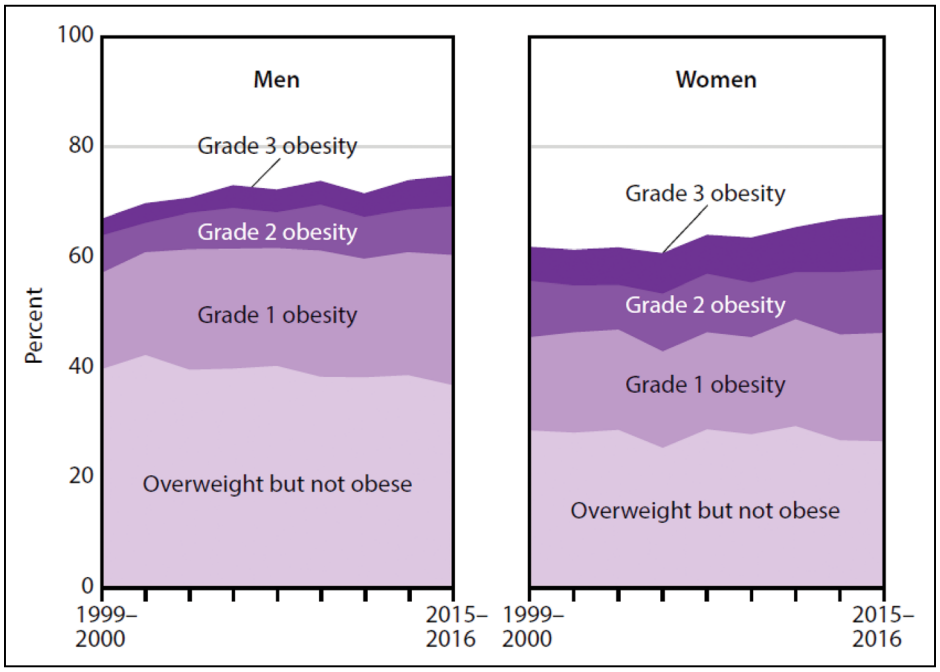

Chart 6-2. Overweight and obesity among US adults ≥20 years of age, by sex and grade of obesity, 1999 to 2000 through 2015 to 2016.
Estimates are age adjusted. *Overweight but not obese* is defined as a body mass index (BMI) ≥25.0 to 29.9 kg/m^2. Grade 1 obesity is a BMI ≥30.0 to 34.9 kg/m^2, grade 2 obesity is a BMI from 35.0 to 39.9 kg/m^2, and grade 3 obesity is a BMI ≥40.0 kg/m^2.
Source: Reprinted from *Health, United States, 2017*[23] using data from National Health and Nutrition Examination Survey, 1999 to 2016.

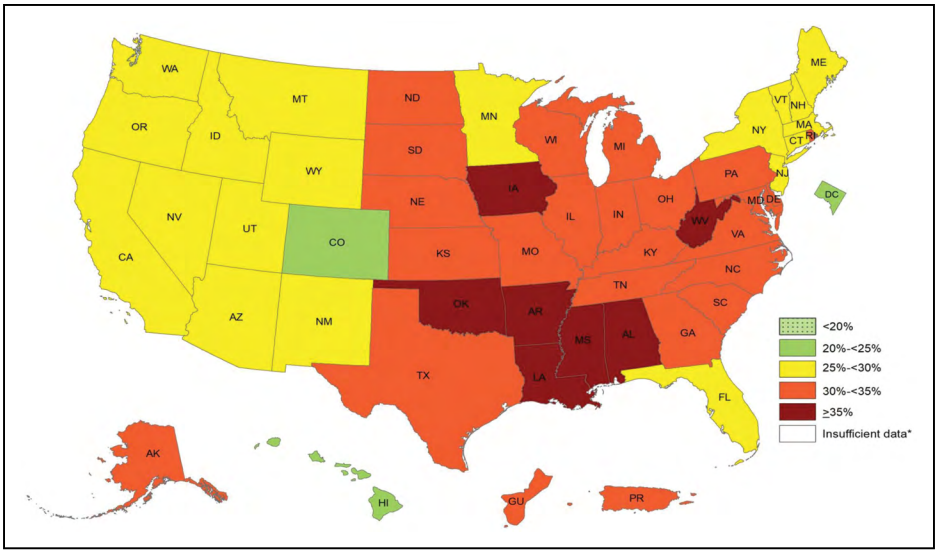

Chart 6-3. Prevalence of self-reported obesity among adults by US state and territory, 2015 to 2017.
Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011. BRFSS indicates Behavioral Risk Factor Surveillance System.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using BRFSS, 2015 to 2017.[25]

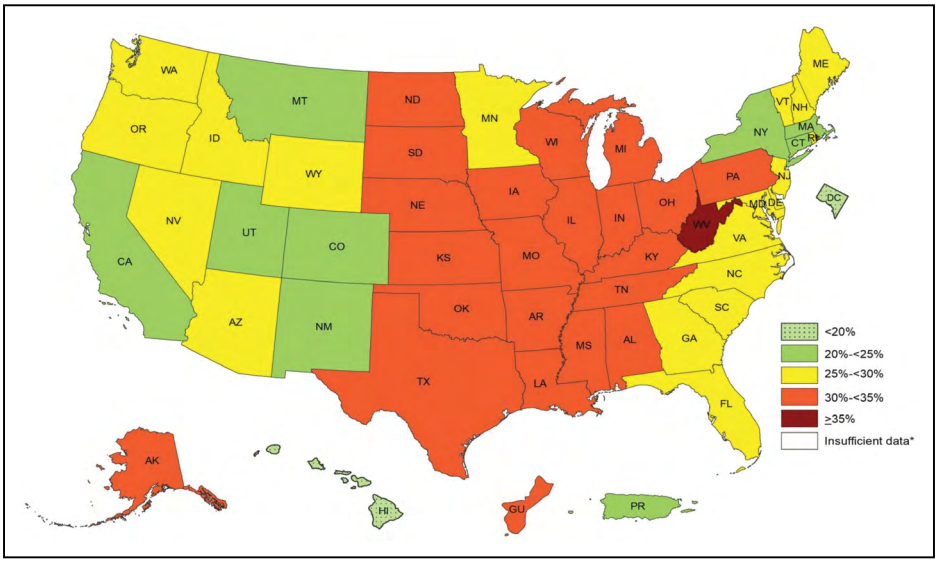

Chart 6-4. Prevalence of self-reported obesity among non-Hispanic white adults, by US state and territory, 2015 to 2017.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System, 2015 to 2017.[25]

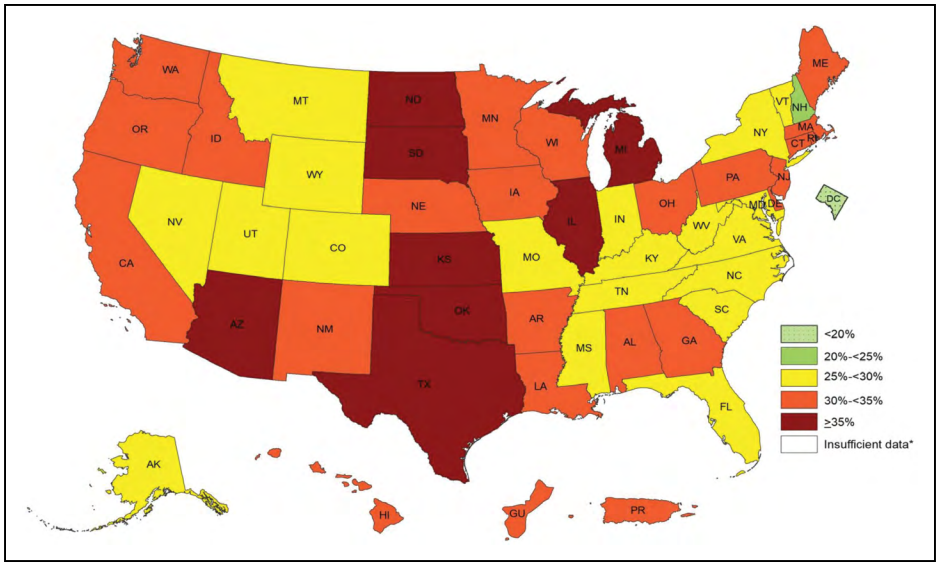

Chart 6-5. Prevalence of self-reported obesity among Hispanic adults, by US state and territory, 2015 to 2017.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System, 2015 to 2017.[25]

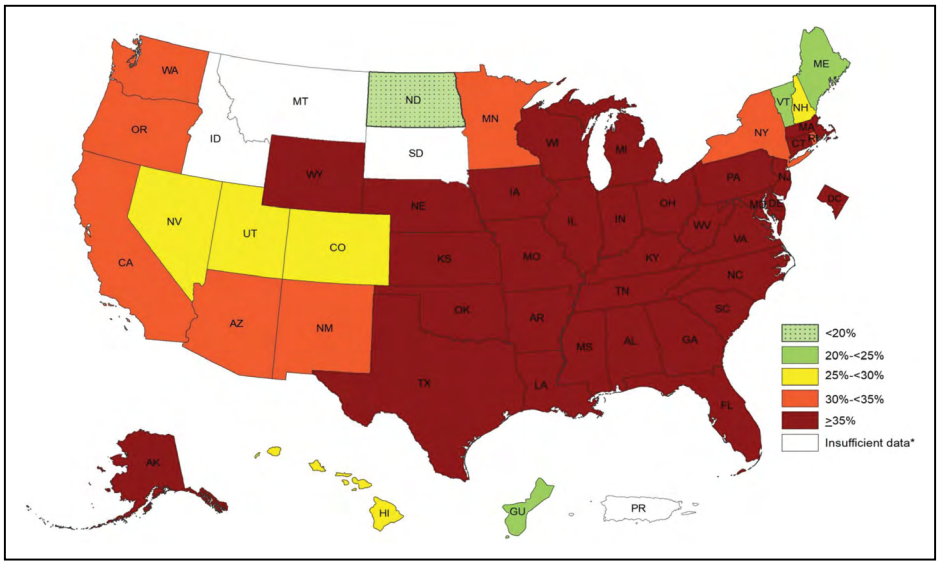

Chart 6-6. Prevalence of self-reported obesity among non-Hispanic black adults, by US state and territory, 2015 to 2017.
*Sample size <50 or the relative SE (dividing the SE by the prevalence) ≥ 30%.
Source: Reprinted from Centers for Disease Control and Prevention, Obesity Prevalence Map using Behavioral Risk Factor Surveillance System, 2015 to 2017.[25]

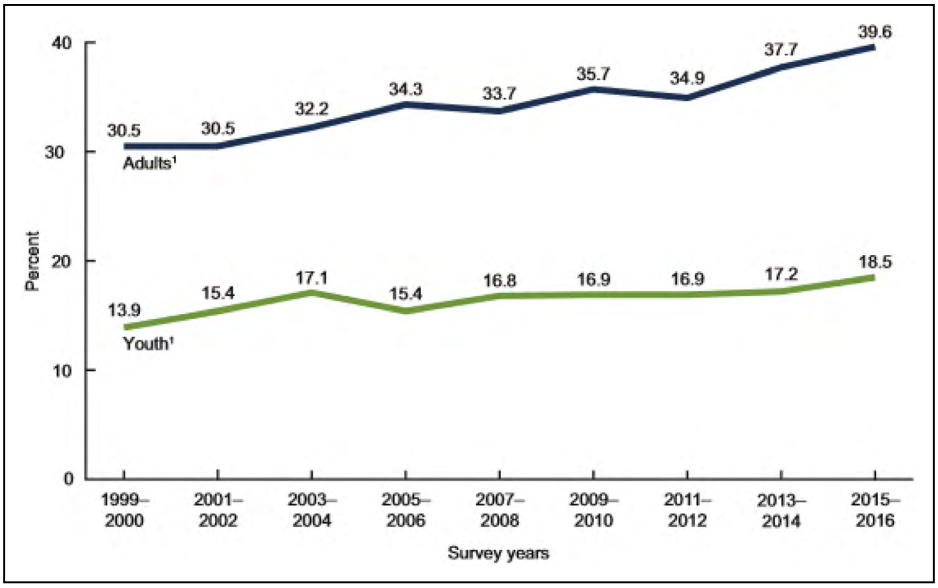

Chart 6-7. Trends in obesity prevalence among US adults ≥20 years of age (age adjusted) and US youth 2 to 19 years of age, 1999 to 2000 through 2015 to 2016.

All estimates for adults are age adjusted by the direct method to the 2000 US census population using the age groups 20 to 39, 40 to 59, and ≥60 years of age.
[1]Significant increasing linear trend from 1999 to 2000 through 2015 to 2016.
Source: Reprinted from Hales et al[17] using National Health and Nutrition Examination Survey, 1999 to 2016.

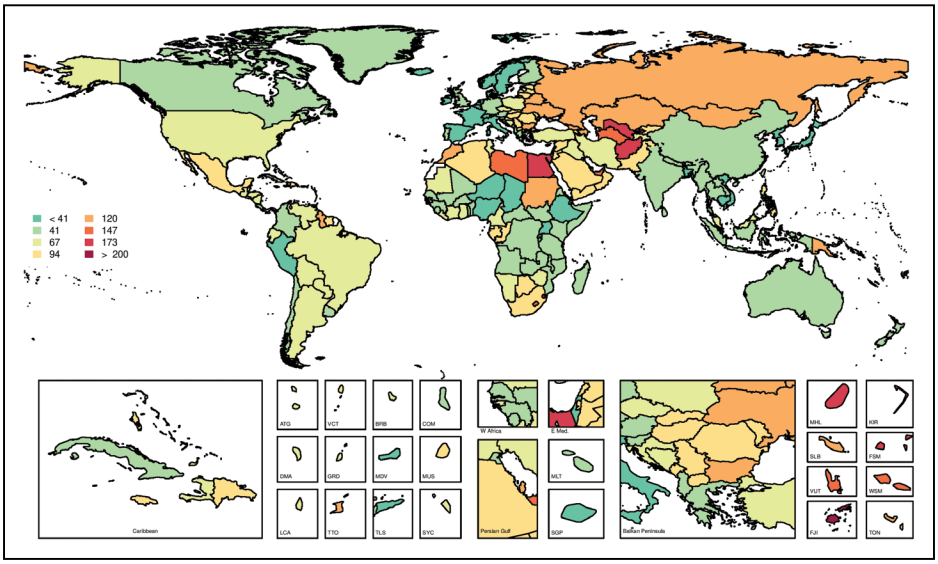

Chart 6-8. Age-standardized mortality rates attributable to high body mass index (BMI) per 100 000, both sexes, 2017.

Age-standardized mortality rates attributable to high BMI are generally lower in Northern Europe, sub-Saharan Africa and East Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[130] Printed with permission.

REFERENCES

1. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH; on behalf of the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation.* 2004;110:2952–2967. doi: 10.1161/01.CIR.0000145546.97738.1E
2. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH; on behalf of the American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2006;113:898–918. doi: 10.1161/CIRCULATIONAHA.106.171016
3. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol.* 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
4. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis: a PRISMA-compliant systemic review and meta-analysis. *Medicine (Baltimore).* 2016;95:e4495. doi: 10.1097/MD.0000000000004495
5. Wattanakit K, Lutsey PL, Bell EJ, Gornik H, Cushman M, Heckbert SR, Rosamond WD, Folsom AR. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism: a time-dependent analysis. *Thromb Haemost.* 2012;108:508–515. doi: 10.1160/TH11-10-0726
6. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA.* 2016;315:2284–2291. doi: 10.1001/jama.2016.6458
7. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. *NCHS Data Brief*. 2015;(219):1–8.
8. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA*. 2018:1723–1725. doi: 10.1001/jama.2018.3060
9. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
10. Rao G, Powell-Wiley TM, Ancheta I, Hairston K, Kirley K, Lear SA, North KE, Palaniappan L, Rosal MC; on behalf of the American Heart Association Obesity Committee of the Council on Lifestyle and Cardiometabolic Health. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2015;132:e130]. *Circulation*. 2015;132:457–472. doi: 10.1161/CIR.0000000000000223
11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies [published correction appears in *Lancet*. 2004;363:902]. *Lancet*. 2004;363:157–163. doi: 10.1016/S0140-6736(03)15268-3
12. CDC growth charts. Centers for Disease Control and Prevention website. http://www.cdc.gov/growthcharts/cdc_charts.htm. Accessed March 29, 2019
13. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation.* 2013;128:1689–1712. doi: 10.1161/CIR.0b013e3182a5cfb3
14. Cornier MA, Després JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, Lopez-Jimenez F, Rao G, St-Onge MP, Towfighi A, et al; on behalf of the American Heart Association Obesity Committee of the Council on Nutrition; Physical Activity and Metabolism; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing, Council on Epidemiology and Prevention; Council on the Kidney in Cardiovascular Disease, and Stroke Council. Assessing adiposity: a scientific statement from the American Heart Association. *Circulation.* 2011;124:1996–2019. doi: 10.1161/CIR.0b013e318233bc6a
15. World Health Organization. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8–11 December 2008. Geneva, Switzerland: World Health Organization; 2011.
16. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, et al; on behalf of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [published correction appears in *Circulation*. 2014;129(suppl 2):S139–S140]. *Circulation*. 2014;129(suppl 2):S102–S138. doi: 10.1161/01.cir.0000437739.71477.ee
17. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. *NCHS Data Brief*. 2017;(288):1–8.
18. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
19. Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, Flegal KM. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. *JAMA.* 2016;315:2292–2299. doi: 10.1001/jama.2016.6361
20. Ogden CL, Carroll MD, Fakhouri TH, Hales CM, Fryar CD, Li X, Freedman DS. Prevalence of obesity among youths by household income and education level of head of household: United States 2011-2014. *MMWR Morb Mortal Wkly Rep.* 2018;67:186–189. doi: 10.15585/mmwr.mm6706a3
21. DeBoer MD, Filipp SL, Gurka MJ. Geographical variation in the prevalence of obesity and metabolic syndrome among US adolescents. *Pediatr Obes.* 2019;14:e12483. doi: 10.1111/ijpo.12483
22. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Hawkins J, Queen B, Lowry R, Olsen EO, Chyen D, et al. Youth risk behavior surveillance: United States, 2015. *MMWR Surveill Summ*. 2016;65:1–174. doi: 10.15585/mmwr.ss6506a1
23. National Center for Health Statistics. *Health, United States, 2017: With Special Feature on Mortality*. Hyattsville, MD: National Center for Health Statistics; 2018. https://www.cdc.gov/nchs/data/hus/hus17.pdf. Accessed April 1, 2019.
24. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Behavioral Risk Factor Surveillance System (BRFSS). BRFSS prevalence & trends data [online] (2017). Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed April 1, 2019.
25. National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. Prevalence of self-reported obesity among U.S. adults by state and territory, BRFSS, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/obesity/data/prevalence-maps.html. Accessed April 1, 2019.
26. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: National Center for Health Statistics; 2015. http://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed April 1, 2019.
27. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA.* 2014;311:806–814. doi: 10.1001/jama.2014.732
28. Saydah S, Bullard KM, Cheng Y, Ali MK, Gregg EW, Geiss L, Imperatore G. Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999-2010. *Obesity (Silver Spring).* 2014;22:1888–1895. doi: 10.1002/oby.20761
29. Freedman DS, Ford ES. Are the recent secular increases in the waist circumference of adults independent of changes in BMI? *Am J Clin Nutr.* 2015;101:425–431. doi: 10.3945/ajcn.114.094672
30. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr.* 2008;87:398–404. doi: 10.1093/ajcn/87.2.398

31. Riveros-McKay F, Mistry V, Bounds R, Hendricks A, Keogh JM, Thomas H, Henning E, Corbin LJ, O'Rahilly S, Zeggini E, et al; Understanding Society Scientific Group. Genetic architecture of human thinness compared to severe obesity. *PLoS Genet.* 2019;15:e1007603. doi: 10.1371/journal.pgen.1007603
32. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, Lindgren CM, Luan J, Mägi R, et al; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010;42:937–948. doi: 10.1038/ng.686
33. Kaur Y, de Souza RJ, Gibson WT, Meyre D. A systematic review of genetic syndromes with obesity. *Obes Rev.* 2017;18:603–634. doi: 10.1111/obr.12531
34. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science.* 2007;316:889–894. doi: 10.1126/science.1141634
35. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orrú M, Usala G, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet.* 2007;3:e115. doi: 10.1371/journal.pgen.0030115
36. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, et al. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet.* 2009;41:527–534. doi: 10.1038/ng.357
37. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, Chen CH, Delahanty RJ, Okada Y, Tabara Y, et al; Genetic Investigation of ANthropometric Traits (GIANT) Consortium. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet.* 2012;44:307–311. doi: 10.1038/ng.1087
38. Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ, et al; GIANT Consortium. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet.* 2012;44:302–306. doi: 10.1038/ng.1086
39. Monda KL, Chen GK, Taylor KC, Palmer C, Edwards TL, Lange LA, Ng MC, Adeyemo AA, Allison MA, Bielak LF, et al; NABEC Consortium; UKBEC Consortium; BioBank Japan Project; AGEN Consortium. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat Genet.* 2013;45:690–696. doi: 10.1038/ng.2608
40. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. *Nat Rev Endocrinol.* 2014;10:51–61. doi: 10.1038/nrendo.2013.227
41. Speakman JR. The "fat mass and obesity related" (FTO) gene: mechanisms of impact on obesity and energy balance. *Curr Obes Rep.* 2015;4:73–91. doi: 10.1007/s13679-015-0143-1
42. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. *Mol Cell Endocrinol.* 2014;382:740–757. doi: 10.1016/j.mce.2012.08.018
43. Karasik D, Zillikens MC, Hsu YH, Aghdassi A, Akesson K, Amin N, Barroso I, Bennett DA, Bertram L, Bochud M, et al. Disentangling the genetics of lean mass. *Am J Clin Nutr.* 2019;109:276–287. doi: 10.1093/ajcn/nqy272
44. Zillikens MC, Demissie S, Hsu YH, Yerges-Armstrong LM, Chou WC, Stolk L, Livshits G, Broer L, Johnson T, Koller DL, et al. Large meta-analysis of genome-wide association studies identifies five loci for lean body mass [published correction apears in *Nat Commun*. 2017;8:1414]. *Nat Commun.* 2017;8:80. doi: 10.1038/s41467-017-00031-7
45. Ng MCY, Graff M, Lu Y, Justice AE, Mudgal P, Liu CT, Young K, Yanek LR, Feitosa MF, Wojczynski MK, et al; Bone Mineral Density in Childhood Study (BMDCS) Group. Discovery and fine-mapping of adiposity loci using high density imputation of genome-wide association studies in individuals of African ancestry: African Ancestry Anthropometry Genetics Consortium. *PLoS Genet.* 2017;13:e1006719. doi: 10.1371/journal.pgen.1006719
46. Justice AE, Winkler TW, Feitosa MF, Graff M, Fisher VA, Young K, Barata L, Deng X, Czajkowski J, Hadley D, et al. Genome-wide meta-analysis of 241,258 adults accounting for smoking behaviour identifies novel loci for obesity traits. *Nat Commun.* 2017;8:14977. doi: 10.1038/ncomms14977
47. Valsesia A, Wang QP, Gheldof N, Carayol J, Ruffieux H, Clark T, Shenton V, Oyston LJ, Lefebvre G, Metairon S, et al. Genome-wide gene-based analyses of weight loss interventions identify a potential role for NKX6.3 in metabolism. *Nat Commun.* 2019;10:540. doi: 10.1038/s41467-019-08492-8
48. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aïssi D, Wahl S, Meduri E, Morange PE, Gagnon F, Grallert H, et al. DNA methylation and body-mass index: a genome-wide analysis. *Lancet.* 2014;383:1990–1998. doi: 10.1016/S0140-6736(13)62674-4
49. Tie HT, Xia YY, Zeng YS, Zhang Y, Dai CL, Guo JJ, Zhao Y. Risk of childhood overweight or obesity associated with excessive weight gain during pregnancy: a meta-analysis. *Arch Gynecol Obstet.* 2014;289:247–257. doi: 10.1007/s00404-013-3053-z
50. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev.* 2016;17:95–107. doi: 10.1111/obr.12334
51. Feng J, Glass TA, Curriero FC, Stewart WF, Schwartz BS. The built environment and obesity: a systematic review of the epidemiologic evidence. *Health Place.* 2010;16:175–190. doi: 10.1016/j.healthplace.2009.09.008
52. Cooklin A, Joss N, Husser E, Oldenburg B. Integrated approaches to occupational health and safety: a systematic review. *Am J Health Promot.* 2017;31:401–412. doi: 10.4278/ajhp.141027-LIT-542
53. Prevention Status Reports. Centers for Disease Control and Prevention website. Atlanta, GA: US Department of Health and Human Services; 2016. http://www.cdc.gov/psr/. Accessed March 29, 2019.
54. World Obesity Federation. Policies and interventions. World Obesity Federation website. https://www.worldobesity.org/resources#Global-Obesity-Observatory. Accessed March 29. 2018
55. Duncan DT, Wolin KY, Scharoun-Lee M, Ding EL, Warner ET, Bennett GG. Does perception equal reality? Weight misperception in relation to weight-related attitudes and behaviors among overweight and obese US adults. *Int J Behav Nutr Phys Act.* 2011;8:20. doi: 10.1186/1479-5868-8-20
56. Hansen AR, Duncan DT, Baidal JA, Hill A, Turner SC, Zhang J. An increasing trend in health care professionals notifying children of unhealthy weight status: NHANES 1999–2014. *Int J Obes (Lond).* 2016;40:1480-1485. doi: 10.1038/ijo.2016.85
57. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, et al; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes [published correction appears in *N Engl J Med*. 2014;370:1866]. *N Engl J Med*. 2013;369:145–154. doi: 10.1056/NEJMoa1212914
58. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. *Obesity (Silver Spring).* 2014;22:5–13. doi: 10.1002/oby.20662
59. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, Del Prato S, Ji L, Sadikot SM, et al; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. *Diabetes Care.* 2016;39:861–877. doi: 10.2337/dc16-0236
60. Ho M, Garnett SP, Baur L, Burrows T, Stewart L, Neve M, Collins C. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. *Pediatrics.* 2012;130:e1647–e1671. doi: 10.1542/peds.2012-1176
61. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ.* 2017;359:j4849. doi: 10.1136/bmj.j4849
62. Sjöström CD, Lystig T, Lindroos AK. Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. *Int J Obes (Lond).* 2011;35:1413–1420. doi: 10.1038/ijo.2010.282
63. Wefers JF, Woodlief TL, Carnero EA, Helbling NL, Anthony SJ, Dubis GS, Jakicic JM, Houmard JA, Goodpaster BH, Coen PM. Relationship among physical activity, sedentary behaviors, and cardiometabolic risk factors during gastric bypass surgery-induced weight loss. *Surg Obes Relat Dis.* 2017;13:210–219. doi: 10.1016/j.soard.2016.08.493
64. Guidelines (2013) for managing overweight and obesity in adults: preface to the Expert Panel Report (comprehensive version which includes systematic evidence review, evidence statements, and recommendations). *Obesity (Silver Spring).* 2014;22(suppl 2):S40. doi: 10.1002/oby.20822
65. Shubeck S, Dimick JB, Telem DA. Long-term outcomes following bariatric surgery. *JAMA.* 2018;319:302–303. doi: 10.1001/jama.2017.20521
66. Courcoulas AP, King WC, Belle SH, Berk P, Flum DR, Garcia L, Gourash W, Horlick M, Mitchell JE, Pomp A, et al. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) Study. *JAMA Surg.* 2018;153:427–434. doi: 10.1001/jamasurg.2017.5025
67. Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ.* 2014;349:g3961. doi: 10.1136/bmj.g3961
68. Puzziferri N, Roshek TB 3rd, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. *JAMA.* 2014;312:934–942. doi: 10.1001/jama.2014.10706

69. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
70. Mackey RH, Belle SH, Courcoulas AP, Dakin GF, Deveney CW, Flum DR, Garcia L, King WC, Kuller LH, Mitchell JE, et al; Longitudinal Assessment of Bariatric Surgery Consortium Writing Group. Distribution of 10-year and lifetime predicted risk for cardiovascular disease prior to surgery in the longitudinal assessment of bariatric surgery-2 study. *Am J Cardiol.* 2012;110:1130–1137. doi: 10.1016/j.amjcard.2012.05.054
71. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation.* 2006;113:791–798. doi: 10.1161/CIRCULATIONAHA.105.548206
72. Marma AK, Berry JD, Ning H, Persell SD, Lloyd-Jones DM. Distribution of 10-year and lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes.* 2010;3:8–14. doi: 10.1161/CIRCOUTCOMES.109.869727
73. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ.* 2013;347:f5934. doi: 10.1136/bmj.f5934
74. Adams TD, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, Gutierrez JM, Frogley SJ, Ibele AR, Brinton EA, et al. Weight and metabolic outcomes 12 years after gastric bypass. *N Engl J Med.* 2017;377:1143–1155. doi: 10.1056/NEJMoa1700459
75. Salminen P, Helmiö M, Ovaska J, Juuti A, Leivonen M, Peromaa-Haavisto P, Hurme S, Soinio M, Nuutila P, Victorzon M. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS Randomized Clinical Trial. *JAMA.* 2018;319:241–254. doi: 10.1001/jama.2017.20313
76. Van Osdol AD, Grover BT, Borgert AJ, Kallies KJ, Kothari SN. Impact of laparoscopic Roux-en-Y Gastric bypass versus sleeve gastrectomy on postoperative lipid values. *Surg Obes Relat Dis.* 2017;13:399–403. doi: 10.1016/j.soard.2016.09.031
77. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357:753–761. doi: 10.1056/NEJMoa066603
78. Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. *Lancet.* 2017;389:2252–2260. doi: 10.1016/S0140-6736(17)31371-5
79. Vilarrasa N, Rubio MA, Miñambres I, Flores L, Caixàs A, Ciudin A, Bueno M, García-Luna PP, Ballesteros-Pomar MD, Ruiz-Adana M, et al. Long-term outcomes in patients with morbid obesity and type 1 diabetes undergoing bariatric surgery. *Obes Surg.* 2017;27:856–863. doi: 10.1007/s11695-016-2390-y
80. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med.* 2010;362:485–493. doi: 10.1056/NEJMoa0904130
81. Ma J, Flanders WD, Ward EM, Jemal A. Body mass index in young adulthood and premature death: analyses of the US National Health Interview Survey linked mortality files. *Am J Epidemiol.* 2011;174:934–944. doi: 10.1093/aje/kwr169
82. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA.* 2013;309:71–82. doi: 10.1001/jama.2012.113905
83. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med.* 2017;376:1332–1340. doi: 10.1056/NEJMoa1606148
84. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ.* 2016;353:i2156. doi: 10.1136/bmj.i2156
85. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol.* 2018;3:280–287. doi: 10.1001/jamacardio.2018.0022
86. Terada T, Forhan M, Norris CM, Qiu W, Padwal R, Sharma AM, Nagendran J, Johnson JA. Differences in short- and long-term mortality associated with BMI following coronary revascularization. *J Am Heart Assoc.* 2017;6:e005335. doi: 10.1161/JAHA.116.005335
87. Mariscalco G, Wozniak MJ, Dawson AG, Serraino GF, Porter R, Nath M, Klersy C, Kumar T, Murphy GJ. Body mass index and mortality among adults undergoing cardiac surgery: a nationwide study with a systematic review and meta-analysis. *Circulation.* 2017;135:850–863. doi: 10.1161/CIRCULATIONAHA.116.022840
88. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab.* 2012;97:2482–2488. doi: 10.1210/jc.2011-3475
89. The NS, Suchindran C, North KE, Popkin BM, Gordon-Larsen P. Association of adolescent obesity with risk of severe obesity in adulthood. *JAMA.* 2010;304:2042–2047. doi: 10.1001/jama.2010.1635
90. Daniels SR, Jacobson MS, McCrindle BW, Eckel RH, Sanner BM. American Heart Association Childhood Obesity Research Summit: executive summary. *Circulation.* 2009;119:2114–2123. doi: 10.1161/CIRCULATIONAHA.09.192215
91. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med.* 2015;373:1307–1317. doi: 10.1056/NEJMoa1502821
92. Umer A, Kelley GA, Cottrell LE, Giacobbi P Jr, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. *BMC Public Health.* 2017;17:683. doi: 10.1186/s12889-017-4691-z
93. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med.* 2011;365:1876–1885. doi: 10.1056/NEJMoa1010112
94. Kozak AT, Daviglus ML, Chan C, Kiefe CI, Jacobs DR Jr, Liu K. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults study. *Int J Obes (Lond).* 2011;35:134–141. doi: 10.1038/ijo.2010.120
95. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2016;23:956–966. doi: 10.1177/2047487315623884
96. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev.* 2016;17:56–67. doi: 10.1111/obr.12316
97. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, Ben-Ami Shor D, Tzur D, Afek A, Shamiss A, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med.* 2016;374:2430–2440. doi: 10.1056/NEJMoa1503840
98. McTigue KM, Chang YF, Eaton C, Garcia L, Johnson KC, Lewis CE, Liu S, Mackey RH, Robinson J, Rosal MC, et al. Severe obesity, heart disease, and death among white, African American, and Hispanic postmenopausal women. *Obesity (Silver Spring).* 2014;22:801–810. doi: 10.1002/oby.20224
99. Burke GL, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, Chung H, Carnethon MR. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med.* 2008;168:928–935. doi: 10.1001/archinte.168.9.928
100. Reis JP, Loria CM, Lewis CE, Powell-Wiley TM, Wei GS, Carr JJ, Terry JG, Liu K. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. *JAMA.* 2013;310:280–288. doi: 10.1001/jama.2013.7833
101. Poorolajal J, Jenabi E. The association between body mass index and preeclampsia: a meta-analysis. *J Matern Fetal Neonatal Med.* 2016;29:3670–3676. doi: 10.3109/14767058.2016.1140738
102. Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-for-gestational-age infants. *J Matern Fetal Neonatal Med.* 2015;28:1679–1686. doi: 10.3109/14767058.2014.964675
103. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM. Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care.* 2007;30:2070–2076. doi: 10.2337/dc06-2559a
104. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev.* 2011;12:e426–e437. doi: 10.1111/j.1467-789X.2010.00825.x

105. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. *Obesity (Silver Spring).* 2013;21:E51–E55. doi: 10.1002/oby.20037
106. Chang VW, Langa KM, Weir D, Iwashyna TJ. The obesity paradox and incident cardiovascular disease: a population-based study. *PLoS One.* 2017;12:e0188636. doi: 10.1371/journal.pone.0188636
107. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, Jacob S. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med.* 2010;123:646–651. doi: 10.1016/j.amjmed.2009.11.026
108. Carnethon MR, De Chavez PJ, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, Golden SH, Liu K, Mukamal KJ, Campbell-Jenkins B, et al. Association of weight status with mortality in adults with incident diabetes [published correction appears in *JAMA*. 2012;308:2085]. *JAMA.* 2012;308:581–590. doi: 10.1001/jama.2012.9282
109. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, Gaye A, Gögele M, Heier M, Hiekkalinna T, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord.* 2014;14:9. doi: 10.1186/1472-6823-14-9
110. Hamer M, Bell JA, Sabia S, Batty GD, Kivimäki M. Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Ageing. *Eur J Endocrinol.* 2015;173:703–708. doi: 10.1530/EJE-15-0449
111. Fung MD, Canning KL, Mirdamadi P, Ardern CI, Kuk JL. Lifestyle and weight predictors of a healthy overweight profile over a 20-year follow-up. *Obesity (Silver Spring).* 2015;23:1320–1325. doi: 10.1002/oby.21087
112. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, Ouyang P, Sibley CT, Tracy R, Woodward M, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol.* 2018;71:1857–1865. doi: 10.1016/j.jacc.2018.02.055
113. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. *J Am Coll Cardiol.* 2014;63:1071–1078. doi: 10.1016/j.jacc.2013.11.035
114. Janszky I, Romundstad P, Laugsand LE, Vatten LJ, Mukamal KJ, Mørkedal B. Weight and weight change and risk of acute myocardial infarction and heart failure: the HUNT Study. *J Intern Med.* 2016;280:312–322. doi: 10.1111/joim.12494
115. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff (Millwood).* 2009;28:w822–w831. doi: 10.1377/hlthaff.28.5.w822
116. An R. Health care expenses in relation to obesity and smoking among U.S. adults by gender, race/ethnicity, and age group: 1998-2011. *Public Health.* 2015;129:29–36. doi: 10.1016/j.puhe.2014.11.003
117. Cai L, Lubitz J, Flegal KM, Pamuk ER. The predicted effects of chronic obesity in middle age on Medicare costs and mortality. *Med Care.* 2010;48:510–517. doi: 10.1097/MLR.0b013e3181dbdb20
118. Alley D, Lloyd J, Shaffer T, Stuart B. Changes in the association between body mass index and Medicare costs, 1997-2006. *Arch Intern Med.* 2012;172:277–278. doi: 10.1001/archinternmed.2011.702
119. Lightwood J, Bibbins-Domingo K, Coxson P, Wang YC, Williams L, Goldman L. Forecasting the future economic burden of current adolescent overweight: an estimate of the coronary heart disease policy model. *Am J Public Health.* 2009;99:2230–2237. doi: 10.2105/AJPH.2008.152595
120. Finkelstein EA, Graham WC, Malhotra R. Lifetime direct medical costs of childhood obesity. *Pediatrics.* 2014;133:854–862. doi: 10.1542/peds.2014-0063
121. Livingston EH. The incidence of bariatric surgery has plateaued in the U.S. *Am J Surg.* 2010;200:378–385. doi: 10.1016/j.amjsurg.2009.11.007
122. Finkelstein EA, Allaire BT, Dibonaventura MD, Burgess SM. Incorporating indirect costs into a cost-benefit analysis of laparoscopic adjustable gastric banding. *Value Health.* 2012;15:299–304. doi: 10.1016/j.jval.2011.12.004
123. Wang BC, Wong ES, Alfonso-Cristancho R, He H, Flum DR, Arterburn DE, Garrison LP, Sullivan SD. Cost-effectiveness of bariatric surgical procedures for the treatment of severe obesity. *Eur J Health Econ.* 2014;15:253–263. doi: 10.1007/s10198-013-0472-5
124. Maciejewski ML, Livingston EH, Smith VA, Kahwati LC, Henderson WG, Arterburn DE. Health expenditures among high-risk patients after gastric bypass and matched controls. *Arch Surg.* 2012;147:633–640. doi: 10.1001/archsurg.2012.818
125. Weiner JP, Goodwin SM, Chang HY, Bolen SD, Richards TM, Johns RA, Momin SR, Clark JM. Impact of bariatric surgery on health care costs of obese persons: a 6-year follow-up of surgical and comparison cohorts using health plan data. *JAMA Surg.* 2013;148:555–562. doi: 10.1001/jamasurg.2013.1504
126. Makary MA, Clark JM, Shore AD, Magnuson TH, Richards T, Bass EB, Dominici F, Weiner JP, Wu AW, Segal JB. Medication utilization and annual health care costs in patients with type 2 diabetes mellitus before and after bariatric surgery [published correction appears in *Arch Surg*. 2011;146:659]. *Arch Surg.* 2010;145:726–731. doi: 10.1001/archsurg.2010.150
127. Keating C, Neovius M, Sjöholm K, Peltonen M, Narbro K, Eriksson JK, Sjöström L, Carlsson LM. Health-care costs over 15 years after bariatric surgery for patients with different baseline glucose status: results from the Swedish Obese Subjects study [published correction appears in *Lancet Diabetes Endocrinol*. 2015;3:e11]. *Lancet Diabetes Endocrinol.* 2015;3:855–865. doi: 10.1016/S2213-8587(15)00290-9
128. Banerjee S, Garrison LP Jr, Flum DR, Arterburn DE. Cost and health care utilization implications of bariatric surgery versus intensive lifestyle and medical intervention for type 2 diabetes. *Obesity (Silver Spring).* 2017;25:1499–1508. doi: 10.1002/oby.21927
129. Klebanoff MJ, Corey KE, Chhatwal J, Kaplan LM, Chung RT, Hur C. Bariatric surgery for nonalcoholic steatohepatitis: a clinical and cost-effectiveness analysis. *Hepatology.* 2017;65:1156–1164. doi: 10.1002/hep.28958
130. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
131. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants [published correction appears in *Lancet*. 2016;387:1998]. *Lancet*. 2016;387:1377–1396. doi: 10.1016/S0140-6736(16)30054-X
132. Price AJ, Crampin AC, Amberbir A, Kayuni-Chihana N, Musicha C, Tafatatha T, Branson K, Lawlor DA, Mwaiyeghele E, Nkhwazi L, et al. Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi. *Lancet Diabetes Endocrinol.* 2018;6:208–222. doi: 10.1016/S2213-8587(17)30432-1
133. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013 [published correction appears in *Lancet*. 2014;384:746]. *Lancet*. 2014;384:766–781. doi: 10.1016/S0140-6736(14)60460-8
134. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet.* 2011;377:557–567. doi: 10.1016/S0140-6736(10)62037-5
135. Choukem SP, Kengne AP, Nguefack ML, Mboue-Djieka Y, Nebongo D, Guimezap JT, Mbanya JC. Four-year trends in adiposity and its association with hypertension in serial groups of young adult university students in urban Cameroon: a time-series study. *BMC Public Health.* 2017;17:499. doi: 10.1186/s12889-017-4449-7
136. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13–27. doi: 10.1056/NEJMoa1614362

7. HIGH BLOOD CHOLESTEROL AND OTHER LIPIDS

See Table 7-1 and Charts 7-1 through 7-5

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Cholesterol is one of the primary causal risk factors for the development of ASCVD and is 1 of 7 critical metrics the AHA has used to define CVH in adults and children. The AHA updated the guideline for treatment of cholesterol in 2018.[1] There is substantial interest in lowering average cholesterol levels in populations and in identifying individuals likely to benefit from targeted cholesterol-lowering interventions.

US-based population estimates of mean levels and prevalence reported in this chapter are derived from NHANES data for youth and adults.[2]

Abbreviations Used in Chapter 7

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
apoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
ATP III	Adult Treatment Panel III
BMI	body mass index
CAC	coronary artery calcification
CAD	coronary artery disease
CASCADE FH	Cascade Screening for Awareness and Detection of FH
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DM	diabetes mellitus
FH	familial hypercholesterolemia
GBD	Global Burden of Disease
GWAS	genome-wide association study
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NNT	number needed to treat
OR	odds ratio
PCSK9	proprotein convertase subtilisin/kexin type 9
PESA	Progression of Early Subclinical Atherosclerosis
QALY	quality-adjusted life-year
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SE	standard error
TC	total cholesterol
UI	uncertainty interval
VLDL	very-low-density lipoprotein
WHO	World Health Organization

Prevalence of High TC

Youth (See Chart 7-1)

- Among children 6 to 11 years of age, the mean TC level in 2013 to 2016 was 157.8 mg/dL. For males, it was 157.9 mg/dL; for females, it was 157.7 mg/dL. The racial/ethnic breakdown in NHANES 2013 to 2016[2] was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH whites, 157.1 mg/dL for males and 159.1 mg/dL for females
  - For NH blacks, 158.8 mg/dL for males and 158.2 mg/dL for females
  - For Hispanics, 158.7 mg/dL for males and 153.9 mg/dL for females
  - For NH Asians, 160.1 mg/dL for males and 161.5 mg/dL for females
- Among adolescents 12 to 19 years of age,[2] the mean TC level in 2013 to 2016 was 154.4 mg/dL; for males, it was 151.6 mg/dL; for females, it was 157.5 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH whites, 150.6 mg/dL for males and 157.2 mg/dL for females
  - For NH blacks, 150.8 mg/dL for males and 156.0 mg/dL for females
  - For Hispanics, 152.7 mg/dL for males and 156.0 mg/dL for females
  - For NH Asians, 155.4 mg/dL for males and 170.2 mg/dL for females
- Among youth 6 to 19 years of age, the prevalence of adverse TC levels (TC ≥200 mg/dL) in 2009 to 2016 was 7.1% (95% CI, 6.4%–7.8%). Conversely, ideal levels of lipids (as opposed to adverse or borderline levels) may be a particularly relevant target for youth. Among youth 6 to 19 years of age, the prevalence of ideal TC levels (TC <170 mg/dL) in 2015 to 2016 was 71.4% (95% CI, 69.0%–73.8%; Chart 7-1).[3] The remainder of youth had borderline levels (TC 170–199 mg/dL).

Adults (≥20 Years of Age) (See Table 7-1 and Charts 7-2 through 7-4)

- Among adults ≥20 years of age, the mean TC level in 2013 to 2016 was 190.8 mg/dL. For males, it

was 187.9 mg/dL; for females, it was 193.1 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH whites, 187.7 mg/dL for males and 194.9 mg/dL for females
  - For NH blacks, 182.5 mg/dL for males and 185.4 mg/dL for females
  - For Hispanics, 192.6 mg/dL for males and 191.2 mg/dL for females
  - For NH Asians, 189.5 mg/dL for males and 191.9 mg/dL for females
- In 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]):
  - An estimated 28.5 million adults ≥20 years of age had serum TC levels ≥240 mg/dL, with a prevalence of 11.7%, and 92.8 million (38.2%) had serum TC levels ≥200 mg/dL (Table 7-1).
  - The percentage of adults with high TC (≥240 mg/dL or ≥200 mg/dL) was lower for NH black than for NH white and Asian and Hispanic adults; NH black males had the lowest age-adjusted prevalence for both categories of TC (Table 7-1 and Charts 7-2 and 7-3).
  - Females had higher prevalence of TC ≥240 mg/dL (12.4%) and TC ≥200 mg/dL (40.4%) than males (10.7% and 35.4%, respectively; Table 7-1).
- The Healthy People 2010 guideline of an age-adjusted mean TC level of ≤200 mg/dL has been achieved in adults, in males, in females, and in all race/ethnicity subgroups.[2,4] The Healthy People 2020 target is a mean total blood cholesterol of 177.9 mg/dL for adults, which had not been achieved in adults, in males, in females, or in any race/ethnicity subgroup as of 2013 to 2016 NHANES data (Chart 7-4).[5] Conversely, the Healthy People 2020 target of ≤13.5% for the proportion of adults with high TC ≥240 mg/dL has been achieved as of 2013 to 2016 for adults overall and all race-sex subgroups except NH white females (Table 7-1 and Chart 7-3).[6]

Prevalence of Abnormal Levels of Lipid Subfractions

LDL Cholesterol

Youth

- There are limited data available on LDL-C for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age, the mean LDL-C level in 2013 to 2016 was 86.7 mg/dL (males, 85.6 mg/dL; females, 87.8 mg/dL). The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH whites, 86.7 mg/dL for males and 87.9 mg/dL for females
  - For NH blacks, 81.7 mg/dL for males and 88.4 mg/dL for females
  - For Hispanic Americans, 85.0 mg/dL for males and 84.2 mg/dL for females
  - For NH Asians, 81.7 mg/dL for males and 103.3 mg/dL for females; however, these values are based on data from small sample sizes (50 NH Asian males and 53 NH Asian females)
- High levels of LDL-C (≥130 mg/dL) occurred in 5.9% of male adolescents and 5.2% of female adolescents during 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- Conversely, ideal levels of LDL-C (<110 mg/dL) were present in 84.1% (95% CI, 79.8%–88.4%) of all adolescents in 2013 to 2014 (Chart 7-1).[3]

Adults

- In 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]), the mean level of LDL-C for American adults ≥20 years of age was 112.1 mg/dL. The racial/ethnic breakdown was as follows:
  - Among NH whites, 112.3 mg/dL for males and 112.3 mg/dL for females
  - Among NH blacks, 111.0 mg/dL for males and 108.1 mg/dL for females
  - Among Hispanics, 117.5 mg/dL for males and 109.3 mg/dL for females
  - Among NH Asians, 113.8 mg/dL for males and 108.2 mg/dL for females
- In 2015 to 2016, the age-adjusted prevalence of high LDL-C (≥130 mg/dL) was 29.4% (unpublished NHLBI tabulation using NHANES[2]).

HDL Cholesterol

Youth

- Among children 6 to 11 years of age, the mean HDL-C level in 2013 to 2016 was 56.0 mg/dL. For males, it was 57.4 mg/dL, and for females, it was 54.5 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - For NH whites, 56.6 mg/dL for males and 54.7 mg/dL for females
  - For NH blacks, 62.5 mg/dL for males and 58.1 mg/dL for females
  - For Hispanics, 55.9 mg/dL for males and 52.2 mg/dL for females
  - For NH Asians, 58.1 mg/dL for males and 54.4 mg/dL for females
- Among children 6 to 11 years of age, low levels of HDL-C (<40 mg/dL) occurred in 6.9% of males and 10.8% of females in 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- Among adolescents 12 to 19 years of age, the mean HDL-C level was 51.8 mg/dL. For males, it was 49.9 mg/dL, and for females, it was 53.8 mg/dL. The racial/ethnic breakdown was as

follows (NHANES 2013–2016,[2] unpublished NHLBI tabulation):
  - For NH whites, 49.2 mg/dL for males and 53.5 mg/dL for females
  - For NH blacks, 54.4 mg/dL for males and 56.9 mg/dL for females
  - For Hispanics, 49.6 mg/dL for males and 52.2 mg/dL for females
  - For NH Asians, 52.8 mg/dL for males and 56.6 mg/dL for females
- Low levels of HDL-C (<40 mg/dL) occurred in 20.4% of male adolescents and 10.4% of female adolescents in 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- Conversely, ideal levels of HDL-C (>45 mg/dL) were present in 75.4% (95% CI, 72.1% –78.7%) of all youth 6 to 19 years of age in 2015 to 2016 (Chart 7-1).[3]

Adults

- In 2013 to 2016 (unpublished NHLBI tabulation using NHANES[2]), the mean level of HDL-C for American adults ≥20 years of age was 54.2 mg/dL. The racial/ethnic breakdown was as follows:
  - Among NH whites, 48.4 mg/dL for males and 60.9 mg/dL for females
  - Among NH blacks, 52.8 mg/dL for males and 60.1 mg/dL for females
  - Among Hispanics, 45.8 mg/dL for males and 54.4 mg/dL for females
  - Among NH Asians, 47.7 mg/dL for males and 60.2 mg/dL for females
- According to NHANES 2015 to 2016,[7] the age-adjusted prevalence rates for HDL-C <40 mg/dL were:
  - 28.5% in males and 8.9% in females
  - Among NH whites, 28.2% in males and 7.3% in females
  - Among NH blacks, 17.3% in males and 8.2% in females
  - Among Hispanics, 36.2 % in males and 13.8% in females
  - Among NH Asians, 26.4% in males and 7.7% in females

Triglycerides

Youth

- There are limited data available on triglycerides for children 6 to 11 years of age.
- Among adolescents 12 to 19 years of age, the geometric mean triglyceride level in 2013 to 2016 was 61.8 mg/dL. For males, it was 62.2 mg/dL, and for females, it was 61.3 mg/dL. The racial/ethnic breakdown was as follows (unpublished NHLBI tabulation using NHANES[2]):
  - Among NH whites, 63.8 mg/dL for males and 61.6 mg/dL for females
  - Among NH blacks, 45.6 mg/dL for males and 48.4 mg/dL for females
  - Among Hispanics, 70.2 mg/dL for males and 68.4 mg/dL for females
  - Among NH Asians, 59.0 mg/dL for males and 74.0 mg/dL for females
- High levels of triglycerides (≥130 mg/dL) occurred in 11.9% of male adolescents and 7.6% of female adolescents during 2013 to 2016 (unpublished NHLBI tabulation using NHANES 2013–2016[2]).
- Conversely, ideal levels of triglycerides (<90 mg/dL) were present in 76.7% (95% CI, 70.8%–82.5%) of all adolescents in 2013 to 2014 (Chart 7-1).[3]

Adults

- Among American adults ≥20 years of age, the geometric mean triglyceride level in 2013 to 2016 was 95.6 mg/dL (unpublished NHLBI tabulation using NHANES[2]). The geometric mean triglyceride levels were 103.0 mg/dL for males and 89.1 mg/dL for females. The racial/ethnic breakdown was as follows:
  - Among NH whites, 103.4 mg/dL for males and 92.1 mg/dL for females
  - Among NH blacks, 82.2 mg/dL for males and 66.7 mg/dL for females
  - Among Hispanics, 113.5 mg/dL for males and 99.7 mg/dL for females
  - Among NH Asians, 109.9 mg/dL for males and 84.6 mg/dL for females
- In 2013 to 2016, ≈22.2% of adults had high triglyceride levels (≥150 mg/dL; unpublished NHLBI tabulation using NHANES[2]).
  - The prevalence of high triglycerides (≥150 mg/dL) was higher (25.5%) among those with lower education (<12 years) than among those with higher education (>12 years; 21.2%; unpublished NHLBI tabulation using NHANES 2013-2016[2]).

Secular Trends in TC and Lipid Subfractions

Youth (See Chart 7-1)

- Between 1999 and 2016, there were favorable trends in mean levels of TC, HDL-C, and non–HDL-C among youth 6 to 19 years of age. There were also favorable trends in levels of LDL-C, triglycerides, and apolipoprotein B among adolescents 12 to 19 years of age over a similar period (data not available for younger children). The proportion of youths 6 to 19 years of age with all ideal levels of TC, HDL-C, and non–HDL-C increased significantly from 42.1% (95% CI, 39.6%–44.7%) in 2007 to 2008 to 51.4% (95% CI, 48.5%–54.2%) in 2015 to 2016,

and the proportion with at least 1 adverse level decreased from 23.1% (95% CI, 21.5%–24.7%) in 2007 to 2010 to 19.2% (95% CI, 17.6%–20.8%) in 2013 to 2016 (Chart 7-1). The proportion of adolescents 12 to 19 years of age with all ideal levels of TC, HDL-C, non–HDL-C, LDL-C, triglycerides, and apolipoprotein B did not change significantly, from 39.6% (95% CI, 33.7%–45.4%) in 2007 to 2008 to 46.8% (95% CI, 40.9%–52.6%) in 2013 to 2014, and the proportion with at least 1 adverse level remained stable from 2007 to 2010 to 2011 to 2014 at 25.2% (25.2% in 2011–2014 [95% CI, 22.2%–28.2%]; Chart 7-1).[3]

Adults (≥20 Years of Age)

- The prevalence of high TC (≥240 mg/dL) has decreased over time, from 18.3% of adults in 1999 to 2000 to 12.4% in 2015 to 2016.[7]
- From 1999 to 2016, mean serum TC for adults ≥20 years of age decreased across all subgroups of race (Chart 7-4).
- Overall, the decline in mean cholesterol levels in recent years likely reflects greater uptake of cholesterol-lowering medications rather than changes in dietary patterns.[8]
- Mean levels of LDL-C decreased from 126.2 mg/dL during 1999 to 2000 to 112.8 mg/dL during 2015 to 2016. The age-adjusted prevalence of high LDL-C (≥130 mg/dL) decreased from 42.9% during 1999 to 2000 to 29.4% during 2015 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- Low HDL-C prevalence declined between 2007 to 2008 and 2015 to 2016 (unpublished NHLBI tabulation using NHANES[2]).
- Geometric mean levels of triglycerides declined from 123 mg/dL in 1999 to 2000 to 97 mg/dL in 2013 to 2014.[9]

Family History and Genetics

- There are several known monogenic or mendelian causes of high blood cholesterol and lipids, the most common of which is FH, which affects up to ≈1 in 200 individuals.[10]
- High cholesterol is heritable even in families that do not harbor one of these monogenic forms of disease.
  - In a study of >100 000 individuals of European origin, 95 loci were identified using GWASs.[11] Additional studies with even larger sample sizes and including individuals of diverse ancestry, use of electronic health record–based samples, and the addition of whole-exome sequencing (which offers more comprehensive coverage of the coding regions of the genome) have brought the number of known lipid loci to >200.[12–15] The loci associated with blood lipid levels are often associated with cardiovascular and metabolic traits, including CAD, type 2 DM, hypertension, waist-hip ratio, and BMI.[12]
  - As expected for a causal biomarker, there is considerable overlap between the genetics of LDL-C and the genetics of CHD. Furthermore, overlap between genetic loci for triglyceride-rich lipoproteins and disease implicate triglycerides as causal in CVD.[16,17]

Familial Hypercholesterolemia

- FH is a monogenic disorder that has been associated with mutations in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9*, which affect uptake and clearance of LDL-C.[10,18]
- Based on data from NHANES (N=42 471, weighted to represent 212 million US adults) during 1999 to 2014, the estimated US prevalence of definite/probable FH using the Dutch Lipid Clinic criteria was 0.47% (SE, 0.03%), and the estimated prevalence of severe dyslipidemia (LDL-C ≥190 mg/dL) was 6.6% (SE, 0.2%) among adults.[19] Based on data from NHANES 1999 to 2012, the estimated US prevalence of LDL-C ≥190 mg/dL was 0.42% (95% CI, 0.15%–0.70%) among adolescents.[20]
- Individuals with the FH phenotype (LDL-C ≥190 mg/dL) experience an acceleration in CHD risk by 10 to 20 years in males and 20 to 30 years in females.[21]
- However, individuals with LDL-C ≥190 mg/dL and a confirmed FH mutation representing lifelong elevation of LDL-C levels have substantially higher odds for CAD than those with LDL-C ≥190 mg/dL without pathogenic mutations.[18]
  - Compared with individuals with LDL-C <130 mg/dL and no mutation, those with both LDL-C ≥190 mg/dL and an FH mutation had a 22-fold increased risk for CAD (OR, 22.3 [95% CI, 10.7–53.2]).
  - Compared with individuals with LDL-C <130 mg/dL and no mutation, individuals with LDL-C ≥190 mg/dL and no FH mutation had a 6-fold higher risk for CAD (OR, 6.0 [95% CI, 5.2–6.9]).
- Based on NHANES 1999 to 2014 data, despite high frequency of cholesterol screening and awareness (>80%), statin use was uniformly low in adults with definite/probable FH (52.3% [SE, 8.2%]) and with severe dyslipidemia (37.6% [SE, 1.2%]).[19] Among adults with diagnosed FH in the CASCADE FH Registry, 25% achieved LDL-C <100 mg/dL and 41% achieved LDL-C reduction ≥50%; factors associated with ≥50% reduction from untreated LDL-C levels were high-intensity statin use (OR, 7.33 [95% CI, 1.86–28.86]; used in 42%) and use

of >1 medication to lower LDL-C (OR, 1.80 [95% CI, 1.34–2.41]; used in 45%).[22]

- Individuals who are homozygous for an FH mutation have severe CAD that becomes apparent in childhood and requires plasmapheresis; it may be best treated using novel therapies, including gene therapy.[23]
- Cascade screening, which recommends cholesterol testing for all first-degree relatives of FH patients, can be an effective strategy to identify affected family members who would benefit from therapeutic intervention.[24]

Familial Combined Hyperlipidemia

- Familial combined hyperlipidemia is a complex oligogenic disorder that affects 1% to 3% of the general population, which makes it the most prevalent primary dyslipidemia. In individuals with premature CAD, the prevalence is up to 10% to 14%. Familial combined hyperlipidemia has a heterogeneous clinical presentation within families and within individuals, including fluctuating elevations in LDL-C or triglycerides, as well as elevated apolipoprotein B levels. Environmental interactions are important in familial combined hyperlipidemia, and metabolic comorbidities are common. Probably because of its complex nature, familial combined hyperlipidemia remains underdiagnosed.[25]

Lipid Genetics and Drug Development

- Genetic studies of lipid traits have had some success in identifying new drug targets, particularly the genetic interrogation of extremely high and low LDL-C,[26–28] which led to the development of PCSK9 inhibitors. Furthermore, identification of variants in *ANGPTL4*, *ANGPTL3*, and *APOC-III* that associate with increased triglycerides and CAD risk highlight inhibition of these genes as potentially therapeutic.[17,29,30]
- As highly effective LDL-C–lowering drugs, statins are widely prescribed to reduce CVD risk, but response to statins varies among individuals. Genetic variants that affect statin responsiveness could predict the lipid-modulating ability of statins[31–33] and modulate cardioprotection.[34]

Screening

- Nearly 70% of adults (67% of males and 72% of females) had been screened for cholesterol (defined as reporting they had their cholesterol checked with the past 5 years) according to data from NHANES 2011 to 2012, which was unchanged since 2009 to 2010.[35]
  - — Among NH whites, 71.8% were screened (70.6% of males and 72.9% of females).
  - — Among NH blacks, 71.9% were screened (66.8% of males and 75.9% of females).
  - — Among NH Asians, 70.8% were screened (70.6% of males and 70.9% of females).
  - — Among Hispanic adults, 59.3% were screened (54.6% of males and 64.2% of females).
- In the United States, universal cholesterol screening is recommended for all children between 9 and 11 years and again between 17 and 21 years of age, and reverse-cascade screening of family members is recommended for children found to have moderate to severe hypercholesterolemia.[1,36]
  - — Despite published guidelines, in a 2013 to 2014 survey of 614 practicing pediatricians in the United States, only 30.3% and 42.4% of pediatricians reported that they usually/most/all of the time screened healthy 9- to 11-year-olds and 17- to 21-year-olds, respectively.[37]
  - — Data from Slovenia's universal screening program demonstrate the potential utility of this approach for detection of FH. Genetic testing was performed in 272 5-year-old children identified by the screening program to have TC >231.7 mg/dL or TC >193.1 mg/dL plus a family history of premature cardiovascular complications. Between 2009 and 2013, 57.0% of these children were identified as having an FH-causing mutation, only 40.6% of whom had a family history of cardiovascular complications (thus, targeted screening would likely have missed the majority). Based on commonly reported FH incidence, the estimated detection rate of FH was 53.6% (95% CI, 34.5%–72.8%) for 2009 to 2013 and peaked at 96.3% in 2013.[38]
  - — It has been estimated that in the United States, the numbers of 10-year-old children needed to universally screen to identify 1 case of severe hyperlipidemia (LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL plus family history) or any hyperlipidemia (LDL-C ≥130 mg/dL) were 111 and 12, respectively. These numbers were 49 and 7, respectively, for a targeted screening program based on parental dyslipidemia or early CVD in a first-degree relative. The incremental costs of detection per case for universal (versus targeted) screening were $32 170 for severe and $1980 for any hyperlipidemia, and the universal (versus targeted) strategy would annually detect about 8000 more children with severe hyperlipidemia and 126 000 more children with any hyperlipidemia.[39]

Awareness

- Based on NHANES data, awareness of high cholesterol among adults with high LDL-C (based on

ATP III guidelines) increased from 48.9% to 62.8% from NHANES 1999 to 2000 to NHANES 2003 to 2004 but did not increase further through 2009 to 2010 (61.5%).[40]

- Between 2001 and 2012, awareness increased among uninsured adults 21 to 64 years of age but remained significantly lower than among insured adults, whereas awareness was similar between publicly and privately insured adults.[41]
- Based on NHANES 2005 to 2014 data, awareness among young adults 18 to 39 years of age with high (≥240 mg/dL) or borderline (200–239 mg/dL) TC was 56.9% (SE, 2.4%) and 22.5% (SE, 1.4%), respectively.[42] Independent predictors of awareness included older age (OR, 2.35 [95% CI, 1.53–3.61] for 30–39 versus 18–29 years of age), having insurance (OR, 2.14 [95% CI, 1.25–3.65]), and private clinic or doctor's office as usual source of care (OR, 2.09 [95% CI, 1.24–3.53] versus no usual source).

Treatment

- ODYSSEY OUTCOMES,[43] a multicenter, double-blinded RCT of alirocumab among 18 924 patients with ACS already taking maximum doses of statins, found the following:
  - After 2.8 years, alirocumab treatment significantly reduced cardiovascular death, MI, stroke, or hospitalization, from 11% to 9.5% compared with placebo (HR, 0.85 [95% CI, 0.78–0.93]; *P*<0.001).
  - To prevent 1 MACE, the NNT was 49 patients for 4 years.
  - Mortality was reduced from 4.1% to 3.5% (HR, 0.85 [95% CI, 0.73–0.98]). This was a nominal finding.
  - For patients with LDL-C >100 mg/dL, absolute risk reductions were 3.4% for MACE and 1.4% for mortality. The NNT was 16 patients for 4 years to prevent 1 MACE.
- LDL-C lowering in adults with LDL-C ≤70 mg/dL was safe and effective in a recent meta-analysis. Among adults with starting LDL-C as low as a median of 63 mg/dL and who achieved levels as low as a median of 21 mg/dL, the RR for major vascular events was consistently reduced (RR per 38.7-mg/dL reduction, 0.79 [95% CI, 0.71–0.87]), and no adverse effects were observed.[44]

Control

- From 2001 to 2012, disparities in LDL-C control widened between insured and uninsured US adults 21 to 64 years of age with high LDL-C (based on ATP III). LDL-C control was 21.4% (SE, 1.6%) among insured versus 10.5% (SE, 2.6%) among uninsured adults in 2001 to 2004 (*P*<0.01), and 35.1% (SE, 1.9%) versus 11.3% (SE, 2.2%), respectively (*P*<.0001), in 2009 to 2012. Additional independent predictors of LDL-C control included more frequent health care, increasing age, higher income (≥200% versus <200% of federal poverty level), white race (versus black or Hispanic), and hypertension.[41]
- Data are not yet available regarding statin eligibility and LDL-C control under the 2018 Cholesterol Clinical Practice Guideline.[1] However, the 2013 ACC/AHA guideline on treatment of blood cholesterol[44a] was found to increase statin eligibility most among nonwhite adults (eligibility among black adults: 25.8% [adjusted OR, 3.8; *P*<0.001]; other races: 18.7% [adjusted OR, 2.5; *P*<0.001]), adults with no more than high-school education (17.3% [adjusted OR, 1.7; *P*=0.001]), and uninsured adults (17.6% [adjusted OR, 1.5; *P*<0.001]) versus white adults (14.5%), adults who completed college (13.0%), and those with insurance (15.6%), respectively.[45] Differences were driven by the prevalence of elevated predicted cardiac risk and DM. Among the US adults newly eligible for treatment with statins, 12.4 million (66.3%) were nonwhite and had lower education or lower income, and 3.0 million (16.1%) had no health insurance.
  - In a separate analysis of Hispanic/Latino adults, eligibility for treatment with statins increased from 15.9% (95% CI, 15.0%–16.7%) to 26.9% (95% CI, 25.7%–28.0%), mainly driven by the ≥7.5% CAD risk criteria (prevalence, 13.9% [95% CI, 13.0%–14.7%]). However, among Hispanic/Latino adults eligible for treatment with statins under National Cholesterol Education Program/ATP III and the 2013 ACC/AHA guideline, only 28.2% (95% CI, 26.3%–30.0%) and 20.6% (95% CI, 19.4%–21.9%) were taking statins, respectively.[46]
- Data from the REGARDS[47] study indicated that even after accounting for access to medical care, there were disparities in statin use among individuals with DM.
  - White males or females with DM and LDL-C >100 mg/dL (66.0% and 55.0%, respectively) were more likely to be prescribed statins than black males or females (57.8% and 53.6%, respectively).
  - White males were more likely to have LDL-C at goal than white females or black males and females.

Mortality and Complications

- Among 4184 individuals free of conventional cardiovascular risk factors in the PESA study, subclinical atherosclerosis (plaque or CAC) was present in 49.7% and was associated with LDL-C at levels currently considered normal.[48]

- There was a linear and significant increase in the prevalence of atherosclerosis from the LDL-C 60 to 70 mg/dL category to the 150 to 160 mg/dL category (from 11% to 64%, respectively, $P<0.001$).
- A similar pattern was seen for the extent of atherosclerosis (focal, intermediate, or generalized disease), as well as the number of vascular sites affected.

- Long-term exposure to even modestly elevated cholesterol levels can lead to CAD later in life.[49] In the Framingham Offspring Cohort, CAD rates were significantly elevated among adults with prolonged hyperlipidemia (non–HDL-C ≥160 mg/dL):
  - Over a median 15-year follow-up, CAD rates were 4.4% for those with no exposure, 8.1% for those with 1 to 10 years of exposure, and 16.5% for those with 11 to 20 years of exposure to hyperlipidemia by 55 years of age ($P<0.001$).
  - The risk persisted after adjustment for other risk factors including non–HDL-C level at 55 years of age (adjusted HR, 1.39 [95% CI, 1.05–1.85] per decade of hyperlipidemia).
- In a large study of Health Survey for England and Scottish Health Survey participants (N=37 059), based on 2250 deaths of all causes during 326 016 person-years of follow-up[50]:
  - A U-shaped association of all-cause mortality was seen with the lowest HDL-C (<58 mg/dL; HR, 1.23 [95% CI, 1.06–1.44]) and highest HDL-C (≥77 mg/dL; HR, 1.25 [95% CI, 0.97–1.62]).
  - Association with CAD was linear, with increased risk in those with the lowest HDL-C (HR, 1.49 [95% CI, 1.15–1.94]).
- Triglyceride concentration has strong associations with ASCVD risk, but in most studies the association is attenuated after adjustment for other traditional risk factors.[51] However, a recent mendelian randomization analysis of data from 654 783 participants including 91 129 cases of CHD demonstrated that triglyceride-lowering variants in the lipoprotein lipase gene and LDL-C–lowering variants in the LDL receptor gene were associated with similarly lower CHD risk when evaluated per 10-mg/dL lower apolipoprotein B level. This suggested that the clinical benefit of both triglycerides and LDL-C lowering might be related to the absolute reduction in apolipoprotein B–containing lipoprotein particles (VLDL and LDL particles, respectively).[52]

Healthcare Utilization

- NHANES data show that from 1999 to 2000 to 2011 to 2012, the use of cholesterol-lowering treatment increased from 8% to 18% among adults, with the use of statins increasing from 7% to 17%.[53]

Cost

- In a 2017 analysis, it was estimated that under the 2013 ACC/AHA guideline on treatment of blood cholesterol, compared with ATP III guidelines, 12.3 million more Americans would be treated with statins over years 2016 to 2025, increasing treatment costs by $13.3 billion.
  - Despite the higher screening and treatment costs, the 2013 ACC/AHA guideline was projected to save 43 100 lives and 183 000 QALYs and result in a net cost savings of $3.9 billion.[54]
- In the United States, only 47% of prescriptions for PCSK9 inhibitors were approved between July 2015 and August 2016.[55] Approval rates were highest for Medicare (60.9%) and lowest for private third-party payers (24.4%).

Global Burden of Hypercholesterolemia (See Chart 7-5)

- According to the GBD 2017 study of leading risk factors for global mortality, high LDL-C remained the fifth-leading risk factor for mortality in 1990 and 2017. In 2017, high LDL-C accounted for 4.3 million (95% UI, 3.3–5.4 million) deaths and 94.9 million (95% UI, 78.8–112.0 million) DALYs worldwide. From 2007 to 2017, the percent change in total number of deaths was 20.8 (18.2–23.2), and the percent change in age-standardized mortality rate was −10.6 (−11.8 to −9.4).[56,57]
- In 2017, among WHO regions, the mortality rate (per 100 000) attributable to LDL-C was highest in the European region (125.9 [95% UI, 93.4–161.9]) and lowest in the African region (16.1 [95% UI, 12.1–20.5]; driven by very low rates in sub-Saharan Africa). The remainder of the regions had rates clustered between 46.3 and 58.1 per 100 000 (Chart 7-5).
- A report on trends in TC in 199 countries and territories indicated that between 1980 and 2008, mean TC levels declined in high-income regions of the world (Australasia, North America, and Western Europe), as well as in Central and Eastern Europe, but increased in East and Southeast Asia and the Pacific.[58] Nevertheless, mean TC levels in 2008 were highest in the high-income region of Australasia, North America, and Western Europe (regional mean, 202.6 mg/dL [95% CI, 196.4–208.4 mg/dL] for males and 202.2 mg/dL [95% CI, 194.5–210.0 mg/dL] for females) and lowest in sub-Saharan Africa (157.8 mg/dL [95% CI, 147.7–167.8 mg/dL] for males and 165.1 mg/dL [95% CI, 154.3–176.3 mg/dL] for females).

Table 7-1. High TC and LDL-C and Low HDL-C, United States, 2013 to 2016 (Age ≥20 Years)

Population Group	Prevalence of TC ≥200 mg/dL	Prevalence of TC ≥240 mg/dL	Prevalence of LDL-C ≥130 mg/ dL	Prevalence of HDL-C <40 mg/dL
Both sexes	92 800 000 (38.2)	28 500 000 (11.7)	69 600 000 (28.9)	45 600 000 (19.2)
Males	41 200 000 (35.4)	12 400 000 (10.7)	34 800 000 (30.1)	33 700 000 (29.0)
Females	51 600 000 (40.4)	16 100 000 (12.4)	34 800 000 (27.6)	11 900 000 (9.9)
NH white males	35.4	10.5	29.4	29.7
NH white females	41.8	13.6	29.7	9.3
NH black males	29.8	8.9	29.5	19.8
NH black females	33.1	9.0	23.4	8.1
Hispanic males	39.9	13.0	33.5	32.6
Hispanic females	38.9	10.1	23.8	13.1
NH Asian males	38.7	11.7	32.2	25.9
NH Asian females	39.6	10.8	25.1	7.9

Values are n (%) or %. Prevalence of TC ≥200 mg/dL includes people with TC ≥240 mg/dL. In adults, levels of 200 to 239 mg/dL are considered borderline high. Levels of ≥240 mg/dL are considered high. Data for TC, LDL-C, and HDL-C are age adjusted. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NH, non-Hispanic; and TC, total cholesterol.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Health and Nutrition Examination Survey (2013–2016),[2] applied to 2016 population estimates.

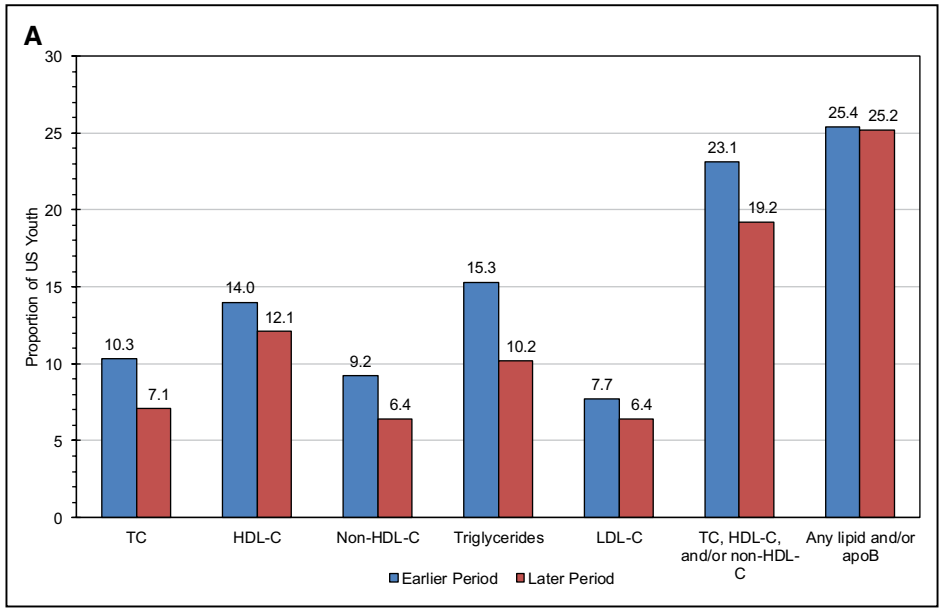

Chart 7-1. Proportions of US youth with adverse and ideal lipid levels in the period 1999 to 2016, NHANES.
A, Adverse lipid levels. **B**, Ideal lipid levels. TC, HDL-C, and non–HDL-C are shown for all youth 6 to 19 years of age, and triglycerides, LDL-C, and any/all lipids plus apoB are shown for fasting adolescents 12 to 19 years of age. **A**, For adverse lipid levels, the "earlier" and "later" periods shown for each lipid, respectively, are as follows: 1999 to 2006 and 2009 to 2016 for TC; 2007 to 2010 and 2013 to 2016 for HDL-C; 2007 to 2010 and 2013 to 2016 for non–HDL-C; 1999 to 2006 and 2007 to 2014 for triglycerides; 1999 to 2006 and 2007 to 2014 for LDL-C; 2007 to 2010 and 2013 to 2016 for any of TC, HDL-C, or non–HDL-C; and 2007 to 2010 and 2011 to 2014 for any lipid or apoB. (*Continued*)

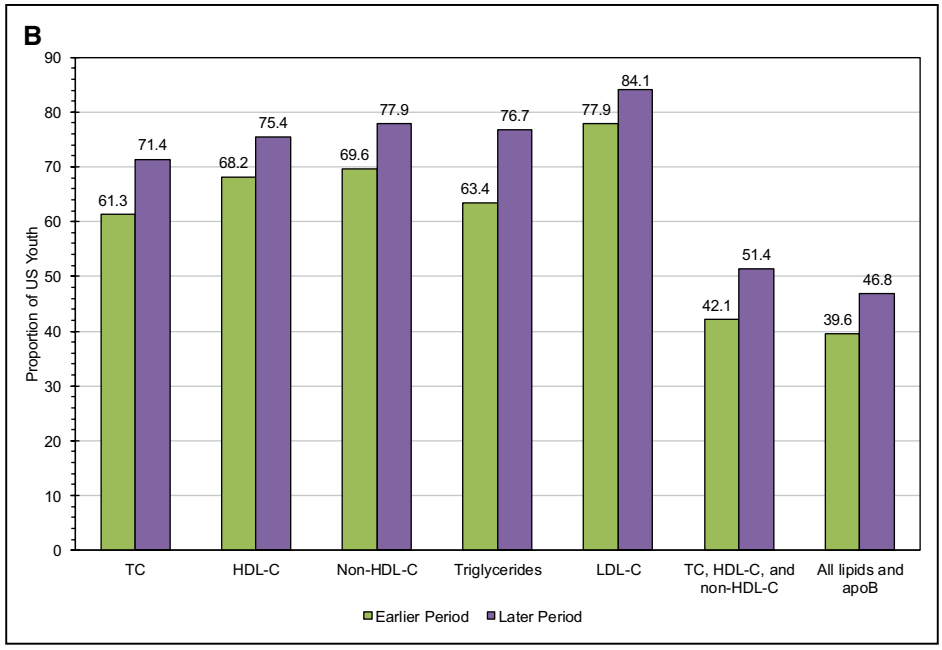

Chart 7-1 Continued. B, For ideal lipid levels, the "earlier" and "later" periods shown for each lipid, respectively, are as follows: 1999 to 2000 and 2015 to 2016 for TC; 2007 to 2008 and 2015 to 2016 for HDL-C; 2007 to 2008 and 2015 to 2016 for non–HDL-C; 1999 to 2000 and 2013 to 2014 for triglycerides; 1999 to 2000 and 2013 to 2014 for LDL-C; 2007 to 2008 and 2015 to 2016 for TC, HDL-C, and non–HDL-C; and 2007 to 2008 and 2013 to 2014 for all lipids and apoB. apoB indicates apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; and TC, total cholesterol.
Source: Data derived from Perak et al.[3]

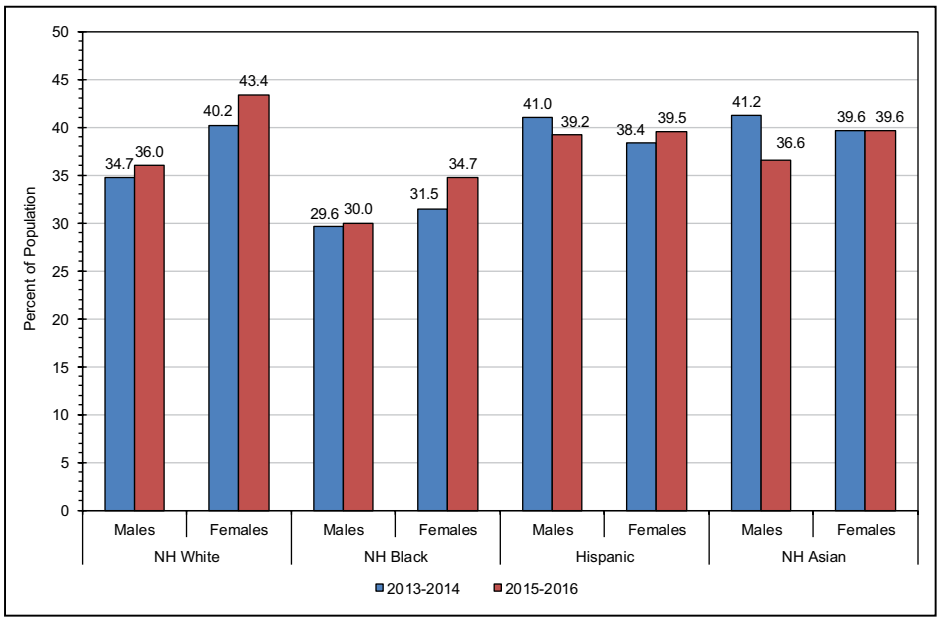

Chart 7-2. Age-adjusted trends in the prevalence of serum total cholesterol ≥200 mg/dL in US adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 2013–2014 and 2015–2016).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[2]

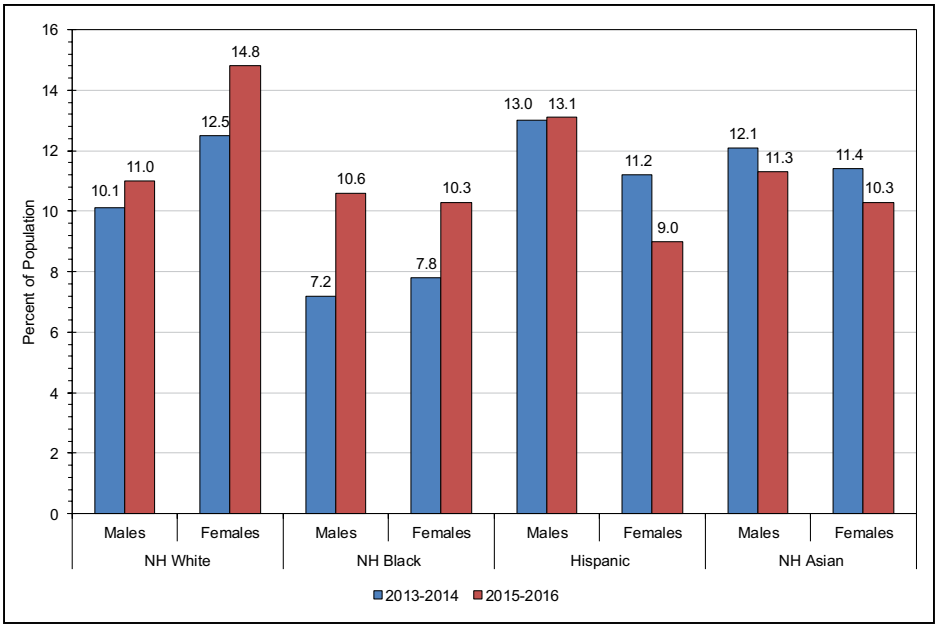

Chart 7-3. Age-adjusted trends in the prevalence of serum total cholesterol ≥240 mg/dL in US adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 2013–2014 and 2015–2016).

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[2]

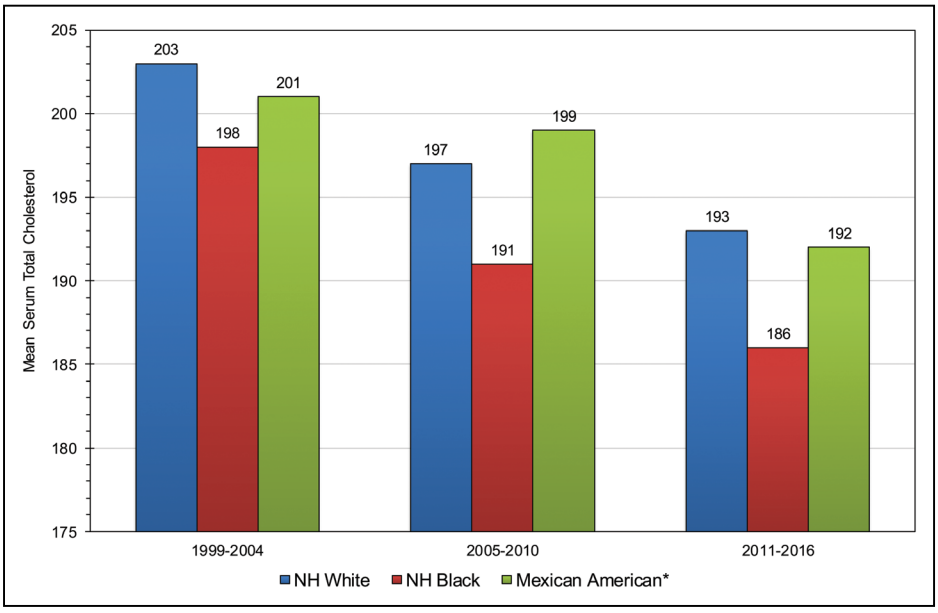

Chart 7-4. Age-adjusted trends in mean serum total cholesterol among US adults ≥20 years old by race and survey year (NHANES, 1999–2004, 2005–2010, and 2011–2016).

Values are in mg/dL.

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 1999 to 2016.[2]

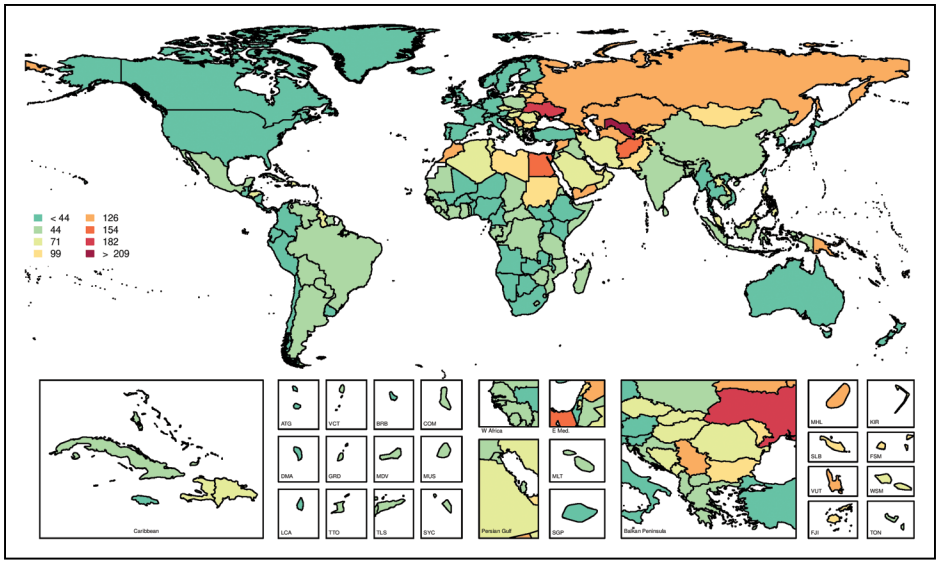

Chart 7-5. Age-standardized global mortality rates attributable to high low-density lipoprotein cholesterol (LDL-C) per 100 000, both sexes, 2017.
Age-standardized mortality rates attributable to high LDL-C are generally higher in Eastern Europe and North (but not sub-Saharan) Africa.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[56] Printed with permission.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2019;139:e1182–e1186]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
2. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
3. Perak AM, Ning H, Kit BK, de Ferranti SD, Van Horn LV, Wilkins JT, Lloyd-Jones DM. Trends in levels of lipids and apolipoprotein B in US youths aged 6 to 19 years, 1999-2016. *JAMA*. 2019;321:1895–1905. doi: 10.1001/jama.2019.4984
4. QuickStats: average total cholesterol level among men and women aged 20–74 years: National Health and Nutrition Examination Survey, United States, 1959–1962 to 2007–2008. *MMWR Morb Mortal Wkly Rep*. 2009;58:1045. Centers for Disease Control and Prevention website. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5837a9.htm. Accessed July 1, 2019.
5. US Department of Health and Human Services. Healthy People 2020 HDS-8: reduce the mean total blood cholesterol levels among adults. Healthy People.gov website. https://www.healthypeople.gov/node/4600/data_details. Accessed April 3, 2019.
6. US Department of Health and Human Services. Healthy People 2020 HDS-7: reduce the proportion of adults with high total blood cholesterol levels. Healthy People.gov website. https://www.healthypeople.gov/node/4599. Accessed April 3, 2019.
7. Carroll MD, Fryar CD, Nguyen DT. Total and high-density lipoprotein cholesterol in adults: United States, 2015–2016. *NCHS Data Brief*. 2017:1–8.
8. Ford ES, Capewell S. Trends in total and low-density lipoprotein cholesterol among U.S. adults: contributions of changes in dietary fat intake and use of cholesterol-lowering medications. *PLoS One*. 2013;8:e65228. doi: 10.1371/journal.pone.0065228
9. Rosinger A, Carroll MD, Lacher D, Ogden C. Trends in total cholesterol, triglycerides, and low-density lipoprotein in US adults, 1999-2014 [published correction appears in *JAMA Cardiol*. 2017;2:346]. *JAMA Cardiol*. 2017;2:339–341. doi: 10.1001/jamacardio.2016.4396
10. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34:3478–3490a. doi: 10.1093/eurheartj/eht273
11. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466:707–713. doi: 10.1038/nature09270
12. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, et al; Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274–1283. doi: 10.1038/ng.2797
13. Peloso GM, Auer PL, Bis JC, Voorman A, Morrison AC, Stitziel NO, Brody JA, Khetarpal SA, Crosby JR, Fornage M, et al; NHLBI GO Exome Sequencing Project. Association of low-frequency and rare coding-sequence variants with blood lipids and coronary heart disease in 56,000 whites and blacks. *Am J Hum Genet*. 2014;94:223–232. doi: 10.1016/j.ajhg.2014.01.009
14. Dewey FE, Murray MF, Overton JD, Habegger L, Leader JB, Fetterolf SN, O'Dushlaine C, Van Hout CV, Staples J, Gonzaga-Jauregui C, et al. Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. *Science*. 2016;354:aaf6814. doi: 10.1126/science.aaf6814
15. Natarajan P, Peloso GM, Zekavat SM, Montasser M, Ganna A, Chaffin M, Khera AV, Zhou W, Bloom JM, Engreitz JM, et al; NHLBI TOPMed Lipids Working Group. Deep-coverage whole genome sequences and blood lipids among 16,324 individuals. *Nat Commun*. 2018;9:3391. doi: 10.1038/s41467-018-05747-8
16. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, et al; Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies [published correction appears in *Lancet*. 2010;376:90]. *Lancet*. 2010;375:1634–1639. doi: 10.1016/S0140-6736(10)60545-4
17. The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31. doi: 10.1056/NEJMoa1307095

18. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol.* 2016;67:2578–2589. doi: 10.1016/j.jacc.2016.03.520
19. Bucholz EM, Rodday AM, Kolor K, Khoury MJ, de Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999–2014). *Circulation.* 2018;137:2218–2230. doi: 10.1161/CIRCULATIONAHA.117.032321
20. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation.* 2016;133:1067–1072. doi: 10.1161/CIRCULATIONAHA.115.018791
21. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation.* 2016;134:9–19. doi: 10.1161/CIRCULATIONAHA.116.022335
22. deGoma EM, Ahmad ZS, O'Brien EC, Kindt I, Shrader P, Newman CB, Pokharel Y, Baum SJ, Hemphill LC, Hudgins LC, et al. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH Registry. *Circ Cardiovasc Genet.* 2016;9:240–249. doi: 10.1161/CIRCGENETICS.116.001381
23. Ajufo E, Cuchel M. Recent developments in gene therapy for homozygous familial hypercholesterolemia. *Curr Atheroscler Rep.* 2016;18:22. doi: 10.1007/s11883-016-0579-0
24. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA.* 2017;318:381–382. doi: 10.1001/jama.2017.8543
25. Bello-Chavolla OY, Kuri-García A, Ríos-Ríos M, Vargas-Vázquez A, Cortés-Arroyo JE, Tapia-González G, Cruz-Bautista I, Aguilar-Salinas CA. Familial combined hyperlipidemia: current knowledge, perspectives, and controversies. *Rev Invest Clin.* 2018;70:224–236. doi: 10.24875/RIC.18002575
26. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet.* 2003;34:154–156. doi: 10.1038/ng1161
27. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med.* 2006;354:1264–1272. doi: 10.1056/NEJMoa054013
28. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9 [published correction appears in *Nat Genet*. 2005;37:328]. *Nat Genet.* 2005;37:161–165. doi: 10.1038/ng1509
29. Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, Yu R, Hurh E, Paz E, McEvoy BW, et al. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med.* 2017;377:222–232. doi: 10.1056/NEJMoa1701329
30. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease [published correction appears in *N Engl J Med*. 2016;374:1898]. *N Engl J Med*. 2016;374:1134–1144. doi: 10.1056/NEJMoa1507652
31. Postmus I, Trompet S, Deshmukh HA, Barnes MR, Li X, Warren HR, Chasman DI, Zhou K, Arsenault BJ, Donnelly LA, et al; Welcome Trust Case Control Consortium. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nat Commun.* 2014;5:5068. doi: 10.1038/ncomms6068
32. Postmus I, Warren HR, Trompet S, Arsenault BJ, Avery CL, Bis JC, Chasman DI, de Keyser CE, Deshmukh HA, Evans DS, et al. Meta-analysis of genome-wide association studies of HDL cholesterol response to statins. *J Med Genet.* 2016;53:835–845. doi: 10.1136/jmedgenet-2016-103966
33. Chu AY, Giulianini F, Barratt BJ, Ding B, Nyberg F, Mora S, Ridker PM, Chasman DI. Differential genetic effects on statin-induced changes across low-density lipoprotein-related measures. *Circ Cardiovasc Genet.* 2015;8:688–695. doi: 10.1161/CIRCGENETICS.114.000962
34. Shiffman D, Trompet S, Louie JZ, Rowland CM, Catanese JJ, Iakoubova OA, Kirchgessner TG, Westendorp RG, de Craen AJ, Slagboom PE, et al. Genome-wide study of gene variants associated with differential cardiovascular event reduction by pravastatin therapy. *PLoS One.* 2012;7:e38240. doi: 10.1371/journal.pone.0038240
35. Carroll MD, Kit BK, Lacher DA, Yoon SS. Total and high-density lipoprotein cholesterol in adults: National Health and Nutrition Examination Survey, 2011–2012. *NCHS Data Brief*. 2013;(132):1–8.
36. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256. doi: 10.1542/peds.2009-2107C
37. de Ferranti SD, Rodday AM, Parsons SK, Cull WL, O'Connor KG, Daniels SR, Leslie LK. Cholesterol screening and treatment practices and preferences: a survey of United States pediatricians. *J Pediatr.* 2017;185:99–105.e2. doi: 10.1016/j.jpeds.2016.12.078
38. Klančar G, Grošelj U, Kovač J, Bratanič N, Bratina N, Trebušak Podkrajšek K, Battelino T. Universal screening for familial hypercholesterolemia in children. *J Am Coll Cardiol.* 2015;66:1250–1257. doi: 10.1016/j.jacc.2015.07.017
39. Smith AJ, Turner EL, Kinra S, Bodurtha JN, Chien AT. A cost analysis of universal versus targeted cholesterol screening in pediatrics. *J Pediatr.* 2018;196:201–207.e2. doi: 10.1016/j.jpeds.2018.01.027
40. Muntner P, Levitan EB, Brown TM, Sharma P, Zhao H, Bittner V, Glasser S, Kilgore M, Yun H, Woolley JM, et al. Trends in the prevalence, awareness, treatment and control of high low density lipoprotein-cholesterol among United States adults from 1999-2000 through 2009-2010. *Am J Cardiol.* 2013;112:664–670. doi: 10.1016/j.amjcard.2013.04.041
41. Egan BM, Li J, Sarasua SM, Davis RA, Fiscella KA, Tobin JN, Jones DW, Sinopoli A. Cholesterol control among uninsured adults did not improve from 2001–2004 to 2009–2012 as disparities with both publicly and privately insured adults doubled. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.117.006105
42. Bucholz EM, Gooding HC, de Ferranti SD. Awareness of cardiovascular risk factors in U.S. young adults aged 18-39 years. *Am J Prev Med.* 2018;54:e67–e77. doi: 10.1016/j.amepre.2018.01.022
43. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med.* 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174
44. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. *JAMA Cardiol.* 2018;3:823–828. doi: 10.1001/jamacardio.2018.2258

44a. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2014;129(suppl 2):S46–S48 and *Circulation*. 2015;132:e396]. *Circulation*. 2014;129(suppl 2):S1–45. doi: 10.1161/01.cir.0000437738.63853.7a

45. Verma AA, Jimenez MP, Subramanian SV, Sniderman AD, Razak F. Race and socioeconomic differences associated with changes in statin eligibility under the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003764. doi: 10.1161/CIRCOUTCOMES.117.003764
46. Qureshi WT, Kaplan RC, Swett K, Burke G, Daviglus M, Jung M, Talavera GA, Chirinos DA, Reina SA, Davis S, et al. American College of Cardiology/American Heart Association (ACC/AHA) class I guidelines for the treatment of cholesterol to reduce atherosclerotic cardiovascular risk: implications for US Hispanics/Latinos based on findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *J Am Heart Assoc*. 2017;6:e005045. doi: 10.1161/JAHA.116.005045
47. Gamboa CM, Colantonio LD, Brown TM, Carson AP, Safford MM. Race-sex differences in statin use and low-density lipoprotein cholesterol control among people with diabetes mellitus in the Reasons for Geographic and Racial Differences in Stroke Study. *J Am Heart Assoc*. 2017;6:e004264. doi: 10.1161/JAHA.116.004264
48. Fernández-Friera L, Fuster V, López-Melgar B, Oliva B, García-Ruiz JM, Mendiguren J, Bueno H, Pocock S, Ibáñez B, Fernández-Ortiz A, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors [published correction appears in *J Am Coll Cardiol*. 2018;71:588–589.]. *J Am Coll Cardiol.* 2017;70:2979–2991. doi: 10.1016/j.jacc.2017.10.024

49. Navar-Boggan AM, Peterson ED, D'Agostino RB Sr, Neely B, Sniderman AD, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. *Circulation*. 2015;131:451–458. doi: 10.1161/CIRCULATIONAHA.114.012477
50. Hamer M, O'Donovan G, Stamatakis E. High-density lipoprotein cholesterol and mortality: too much of a good thing? *Arterioscler Thromb Vasc Biol*. 2018;38:669–672. doi: 10.1161/ATVBAHA.117.310587
51. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, et al; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000. doi: 10.1001/jama.2009.1619
52. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364–373. doi: 10.1001/jama.2018.20045
53. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. *JAMA*. 2015;314:1818–1831. doi: 10.1001/jama.2015.13766
54. Heller DJ, Coxson PG, Penko J, Pletcher MJ, Goldman L, Odden MC, Kazi DS, Bibbins-Domingo K. Evaluating the impact and cost-effectiveness of statin use guidelines for primary prevention of coronary heart disease and stroke. *Circulation*. 2017;136:1087–1098. doi: 10.1161/CIRCULATIONAHA.117.027067
55. Hess GP, Natarajan P, Faridi KF, Fievitz A, Valsdottir L, Yeh RW. Proprotein convertase subtilisin/kexin type 9 inhibitor therapy: payer approvals and rejections, and patient characteristics for successful prescribing. *Circulation*. 2017;136:2210–2219. doi: 10.1161/CIRCULATIONAHA.117.028430
56. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
57. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 [published corrections appear in *Lancet*. 2019;393:132 and *Lancet*. 2019;393:e44]. *Lancet*. 2018;392:1923–1994. doi: 10.1016/S0140-6736(18)32225-6
58. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, Singh GM, Lin JK, Stevens GA, Riley LM, et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Cholesterol). National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. *Lancet*. 2011;377:578–586. doi: 10.1016/S0140-6736(10)62038-7

8. HIGH BLOOD PRESSURE

ICD-9 401 to 404; ICD-10 I10 to I15. See Tables 8-1 and 8-2 and Charts 8-1 through 8-6

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HBP is a major risk factor for CVD and stroke.[1] The AHA has identified untreated BP <90th percentile (for children) and <120/<80 mm Hg (for adults ≥20 years of age) as 1 of the 7 components of ideal CVH.[2] In 2015 to 2016, 85.2% of children 12 to 19 years of age, 55.1% of adults 20 to 49 years of age, and 19.9% of adults ≥50 years of age met these criteria (Chapter 2, Cardiovascular Health, Charts 2-2 and 2-3).

Abbreviations Used in Chapter 8

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DM	diabetes mellitus
ED	emergency department
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GBD	Global Burden of Disease
GRS	genetic risk score(s)
GWAS	genome-wide association study
HBP	high blood pressure
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*

(*Continued*)

Abbreviations Used in Chapter 8 Continued

ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
IDACO	International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes
JHS	Jackson Heart Study
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NVSS	National Vital Statistics System
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAF	population attributable fraction
PAR	population attributable risk
QALY	quality-adjusted life-year
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SPRINT	Systolic Blood Pressure Intervention Trial
SSB	sugar-sweetened beverage

Prevalence (See Table 8-1 and Charts 8-1 and 8-2)

- Although surveillance definitions vary widely in the published literature, including for the CDC and NHLBI, as of the 2017 Hypertension Clinical Practice Guidelines the following definition of HBP has been proposed for surveillance[3]:
  - SBP ≥130 mm Hg or DBP ≥80 mm Hg or self-reported antihypertensive medicine use, or
  - Having been told previously, at least twice, by a physician or other health professional that one has HBP.
- Other important BP classifications, or phenotypes, assessed via 24-hour ambulatory BP monitoring include:
  - *Sustained hypertension*, defined as elevated clinic BP with elevated 24-hour ambulatory BP

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  - — *White-coat hypertension*, defined as elevated clinic BP with normal 24-hour ambulatory BP
  - — *Masked hypertension*, defined as normal clinic BP with elevated 24-hour ambulatory BP
- Using data from the 2011 to 2014 NHANES (N=9623), the prevalence of hypertension among US adults was 45.6% (95% CI, 43.6%–47.6%) using BP thresholds from the the 2017 Hypertension Clinical Practice Guidelines versus 31.9% (95% CI, 30.1%–33.7%) using guideline thresholds from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[4]
- Using the most recent 2017 definition, the age-adjusted prevalence of hypertension among US adults ≥20 years of age was estimated to be 46.0% in NHANES in 2013 to 2016 (49.0% for males and 42.8% for females).[5] This equates to an estimated 116.4 million adults ≥20 years of age who have HBP (58.7 million males and 57.7 million females; Table 8-1).
- In NHANES 2013 to 2016,[5] the prevalence of HBP was 26.1% among those 20 to 44 years of age, 59.2% among those 45 to 64 years of age, and 78.2% among those ≥65 years of age (unpublished NHLBI tabulation).
- In NHANES 2013 to 2016,[5] a higher percentage of males than females had hypertension up to 64 years of age. For those ≥65 years of age, the percentage of females with hypertension was higher than for males (unpublished NHLBI tabulation).
- The prevalence of HBP in adults ≥20 years of age is presented by both age and sex in Chart 8-1.
- Data from the 2017 BRFSS (unpublished NHLBI tabulation) indicate that the age-adjusted percentage of adults ≥18 years of age who had been told that they had HBP ranged from 24.3% in Minnesota to 38.6% in Alabama and West Virginia among US states, and the percentage was highest, at 41.0%, in Puerto Rico. The crude percentage (median) for the total United States was 32.3%.[6]
- Data from NHANES 2013 to 2016[5] indicate that 35.3% of US adults with hypertension are not aware they have it (unpublished NHLBI tabulation).
- The age-adjusted prevalence of hypertension in 1999 to 2004, 2005 to 2010, and 2011 to 2016 is shown in race/ethnicity and sex subgroups in Chart 8-2.
- Among 1677 participants in the IDACO cohort database 40 to 79 years of age with clinic-measured SBP ≥140 mm Hg or DBP ≥90 mm Hg and not taking antihypertensive medication, 35.7% (95% CI, 23.5%–56.2%) had white-coat hypertension. Among 3320 participants from the same database with clinic SBP <140 mm Hg and clinic DBP <90 mm Hg and not taking antihypertensive medication, 16.9% (95% CI, 8.8%–30.5%) had masked hypertension.[7]
- A meta-analysis of 20 observational studies and 4 RCTs with a total sample size of 961 035 estimated the prevalence of apparent treatment-resistant hypertension in the observational studies to be 13.7% (95% CI, 11.2%–16.2%).[8]
- In a cohort of 3367 patients with established kidney disease, 40.4% had resistant hypertension, which was defined as having SBP ≥140 mm Hg or DBP ≥90 mm Hg on ≥3 antihypertensive medications or use of ≥4 antihypertensive medications and SBP <140 mm Hg and DBP <90 mm Hg.[9]
- An analysis of the Spanish Ambulatory Blood Pressure Monitoring Registry using 70 997 patients treated for hypertension estimated the prevalence of resistant hypertension (SBP/DBP ≥140/90 mm Hg on at least 3 antihypertensive medications) was 16.9%, whereas the prevalence of white-coat resistant hypertension was 37.1%.[10] The prevalence of refractory hypertension (SBP/DBP ≥140/90 mm Hg on ≥5 antihypertensive medications) was 1.4%, whereas the prevalence of white-coat refractory hypertension was 26.7%.[10]
- SPRINT demonstrated that an SBP goal of <120 mm Hg resulted in fewer CVD events and a greater reduction in mortality than an SBP goal of <140 mm Hg among people with SBP ≥130 mm Hg and increased cardiovascular risk.[11] Using NHANES 2007 to 2012 data, it was estimated that 7.6% (95% CI, 7.0%–8.3%) of US adults (16.8 million [95% CI, 15.7–17.8 million]) met the SPRINT inclusion and exclusion criteria.[12]
- In a meta-analysis of people ≥16 years of age with HIV (49 studies with data collected from 1996–2014; N=63 554), the prevalence of hypertension was 25.2% (95% CI, 21.2%–29.6%) overall, 34.7% (95% CI, 27.4%–42.8%) among those who had been treated with antiretroviral therapy, and 12.7% (95% CI, 7.4%–20.8%) among those who had not received antiretroviral therapy.[13]

Older Adults

- The white-coat effect (clinic minus out-of-clinic BP) is larger at older ages. In IDACO, a pooled analysis of 11 cohorts (n=656 untreated participants with white-coat hypertension and n=653 participants with sustained normotension), the white-coat effect for SBP was 3.8 mm Hg (95% CI, 3.1–4.6 mm Hg) larger for each 10-year increase in age.[14]
- Among 5236 adults in the REGARDS study ≥65 years of age currently taking antihypertensive medications and enrolled in Medicare fee-for-service, having more indicators of frailty (low BMI, cognitive impairment, depressive symptoms,

exhaustion, impaired mobility, and history of falls) was associated with an increased risk for serious fall injuries. The HR associated with 1 versus 0 indicators of frailty was 1.18 (95% CI, 0.99–1.40), 2 versus 0 was 1.49 (95% CI, 1.19–1.87), and ≥3 versus 0 was 2.04 (95% CI, 1.56–2.67). In contrast, on-treatment SBP, DBP, and number of antihypertensive medications were not statistically significantly associated with risk for serious fall injuries.[15]

Children and Adolescents

- In NHANES 2011 to 2012, 11.0% (95% CI, 8.8%–13.4%) of children and adolescents 8 to 17 years of age had either HBP (SBP or DBP at the 95th percentile or higher) or borderline HBP (SBP or DBP between the 90th and 95th percentile or BP levels of 120/80 mm Hg or higher but <95th percentile).[16]
- In NHANES 2011 to 2012, HBP was more common among boys (1.8%) than girls (1.4%) and among Hispanics (2.4%) than among NH blacks (1.9%), NH whites (1.1%), and NH Asians (1.7%). Having either HBP or borderline HBP was more common among boys (15.4%) than girls (6.8%). Also, NH blacks (15.3%) were more likely to have either HBP or borderline HBP than Hispanic (11.5%), NH white (9.4%), or NH Asian (8.5%) boys or girls.[16]
- In 2003 to 2010, for girls 8 to 11 years of age, 3.5% had poor BP (SBP or DBP >95th percentile), 5.0% had intermediate BP (SBP ≥120 mm Hg or 90th–95th percentile or DBP ≥80 mm Hg or 90th–95th percentile), and 91.5% had ideal BP levels (SBP and DBP, 90th percentile) according to the AHA 2020 Strategic Impact Goals. For boys 8 to 11 years of age, 2.8% had poor BP, 4.8% had intermediate BP, and 92.5% had ideal BP according to Life's Simple 7.[17]
- In NHANES 1999 to 2012, the prevalence of HBP was 9.9% among severely obese US adolescents (BMI ≥120% of 95th percentile of sex-specific BMI for age or BMI ≥35 kg/m^2). The OR for HBP was 5.3 (95% CI, 3.8–7.3) when comparing severely obese versus normal-weight adolescents.[18]
- In a retrospective study of 500 children screened for potential hypertension with ambulatory BP monitoring at a single pediatric nephrology unit in Italy, 12% had white-coat hypertension and 10% had masked hypertension.[19]
- Among 30 565 children and adolescents (3–17 years of age) receiving health care between 2012 and 2015, 51.2% of those with a first BP reading ≥95th percentile for age, sex, and height and who had a repeated BP measurement during the same visit had a mean BP based on 2 consecutive readings that was <95th percentile. Of those with a visit BP ≥95th percentile, 67.8% did not have a follow-up visit within 3 months, and only 2.3% of those individuals with a follow-up visit had a BP ≥95th percentile at this visit.[20]

Race/Ethnicity (See Table 8-1 and Chart 8-2)

- Table 8-1 includes statistics on prevalence of HBP, mortality from HBP, hospital discharges for HBP, and cost of HBP for different race, ethnicity, and sex groups.
- The prevalence of hypertension in blacks in the United States is among the highest in the world. Using NHANES 2011 to 2016 data,[5] the age-adjusted prevalence of hypertension among NH blacks was 57.6% among males and 53.2% among females (Chart 8-2).
- In an analysis of NHANES participants 22 to 79 years of age from 2003 to 2014, foreign-born NH blacks (n=522) had lower adjusted odds of having hypertension than US-born NH blacks (n=4511; OR, 0.61 [95% CI, 0.49–0.77]).[21]
- Data from the 2014 NHIS showed that black adults ≥18 years of age were more likely (33.0%) to have been told on ≥2 occasions that they had hypertension than American Indian/Alaska Native adults (26.4%), white adults (23.5%), Hispanic or Latino adults (22.9%), or Asian adults (19.5%).[22]
- Among >4 million adults who were overweight or obese in 10 healthcare systems and had continuous insurance coverage or had at least 1 primary care encounter from 2012 to 2013, the prevalence of hypertension was 47.3% among blacks, 39.6% among whites, 38.6% among Native Hawaiians/Pacific Islanders, 38.3% among American Indians/Native Americans, 34.8% among Asians, and 27.7% among Hispanics. Within categories defined by BMI and after adjustment for age, sex, and healthcare system, each racial/ethnic group except Hispanics was more likely to have hypertension than whites.[23]
- Among 441 blacks in the JHS not taking antihypertensive medication, the prevalence of clinic hypertension (mean SBP ≥140 mm Hg or mean DBP ≥90 mm Hg) was 14.3%, the prevalence of daytime hypertension (mean daytime SBP ≥135 mm Hg or mean daytime DBP ≥85 mm Hg) was 31.8%, and the prevalence of nighttime hypertension (mean nighttime SBP ≥120 mm Hg or mean nighttime DBP ≥70 mm Hg) was 49.4%. Among 575 blacks taking antihypertensive medication, the prevalence estimates were 23.1% for clinic hypertension, 43.0% for daytime hypertension, and 61.7% for nighttime hypertension.[24]

Incidence

- Among 3890 adults 18 to 30 years of age participating in the CARDIA study who were free of hypertension at baseline, the incidence of hypertension (SBP ≥130 mm Hg, DBP ≥80 mm Hg, or self-reported antihypertensive medication use) by 55 years of age was 75.7% in black females, 75.5% in black males, 54.5% in white males, and 40.0% in white females.[25]

Lifetime Risk and Cumulative Incidence

- Data from 13 160 participants in cohorts in the Cardiovascular Lifetime Risk Pooling Project (ie, the Framingham Offspring Study, CARDIA, and ARIC) found that the lifetime risk of hypertension from 20 to 85 years of age using the 2017 Hypertension Clinical Practice Guidelines was 86.1% (95% CI, 84.1%–88.1%) for black males, 85.7% (95% CI, 84.0%–87.5%) for black females, 83.8% (95% CI, 82.5%–85.0%) for white males, and 69.3% (95% CI, 67.8%–70.7%) for white females.[26]
- Among 32 887 participants of the Kailuan study in Tangshan City, Hebei Province, China, with prehypertension (SBP 120–239 mm Hg or DBP 80–89 mm Hg and not taking antihypertensive medications) who were 18 to 98 years of age in 2006 to 2007 and were followed up until 2012 to 2013, the cumulative incidence of hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medications) varied according to the number of ideal CVH factors. The cumulative incidence of hypertension was 78.6% for those with 0 or 1 ideal factors, 71.1% for those with 2 ideal factors, 63.2% for those with 3 ideal factors, 56.1% for those with 4 ideal factors, and 61.6% for those with ≥5 ideal factors.[27]
- In the Aerobics Center Longitudinal Study, a longitudinal study of the age-related trajectories of BP among males 20 to 90 years of age without hypertension, CVD, or cancer conducted from 1970 to 2006 at the Cooper Clinic in Dallas, TX, the mean SBP increased 0.30 mm Hg (95% CI, 0.29–0.31 mm Hg) per year. The mean increase in SBP per year was dependent on percentile of physical fitness, measured by age-specific treadmill time, with higher physical fitness associated with lower mean increases in SBP per year.[28]

Secular Trends

- In NHANES, the prevalence of prehypertension decreased in all age groups for US adults between 1999 to 2000 and 2013 to 2014, with the largest decline occurring among those 18 to 39 years of age (from 32.2% in 1999–2000 to 23.4% in 2013–2014).[29]
- Among US children and adolescents between 1999 to 2000 and 2011 to 2012, there was no evidence of a change in the prevalence of borderline HBP (from 7.6% [95% CI, 5.8%–9.8%] to 9.4% [95% CI, 7.2%–11.9%]; *P*=0.90) or either HBP or borderline HBP (from 10.6% [95% CI, 8.4%–13.1%] to 11.0% [95% CI, 8.8%–13.4%]; *P*=0.26).[16] In this age group, HBP declined from 3.0% (95% CI, 2.0%–4.3%) to 1.6% (95% CI, 1.0%–2.4%; *P*=0.003).[16]
- Analysis of data for children and adolescents 8 to 17 years of age (n=14 720) from NHANES 1999 to 2002 through NHANES 2009 to 2012 found that mean SBP decreased from 105.6 to 104.9 mm Hg, and DBP decreased from 60.3 to 56.1 mm Hg.[30]
- In NHANES, among normal-weight and overweight/obese US adolescents (12–19 years of age), there was no statistically significant evidence that mean SBP and DBP changed between 1988 to 1994 and 2007 to 2012. Among normal-weight adolescents, the unadjusted prevalence of pre-HBP was 11.4% (95% CI, 9.6%–13.6%) and the prevalence of HBP was 0.9% (95% CI, 0.5%–1.5%) in 1988 to 1994; the prevalence of pre-HBP was 11.1% (95% CI, 9.3%–13.1%) and that of HBP was 1.4% (95% CI, 0.9%–2.1%) in 2007 to 2012. Among overweight/obese adolescents, the unadjusted prevalence of pre-HBP was 15.5% (95% CI, 11.1%–22.3%) and that of HBP was 6.4% (95% CI, 3.6%–11.0%) in 1988 to 1994; the unadjusted prevalence of pre-HBP was 21.4% (95% CI, 18.2%–25.0%) and that of HBP was 3.4% (95% CI, 2.3%–4.9%) in 2007 to 2012.[31]
- In a systematic review of studies evaluating secular trends in BP among children and adolescents (N=18 studies with >2 million participants), BP decreased between 1963 and 2012 in 13 studies, increased in 4 studies, and did not change in 1 study conducted.[32] No formal pooling of data was conducted.

Risk Factors

- Among 60 027 participants in the Norwegian Mother and Child Cohort Study who were normotensive before pregnancy, the PAF for pharmacologically treated hypertension within 10 years postpartum was 28.6% (95% CI, 25.5%–30.3%) for complications of pregnancy (preeclampsia/eclampsia, gestational hypertension, preterm delivery, and pregestational or gestational DM).[33]
- In a cohort of 58 671 parous females participating in the Nurses' Health Study II without CVD or hypertension at baseline, gestational hypertension

and preeclampsia during first pregnancy were associated with a higher rate of self-reported physician-diagnosed chronic hypertension over a 25- to 32-year follow-up (HR, 2.8 [95% CI, 2.6–3.0] for gestational hypertension and HR, 2.2 [95% CI, 2.1–2.3] for preeclampsia).[34]

- Among 6897 black and white participants in the REGARDS cohort who were free from hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg) at baseline, the Southern dietary pattern accounted for 51.6% (95% CI, 18.8%–84.4%) of the excess risk of incident hypertension in black males compared with white males and 29.2% (95% CI, 13.4%–44.9%) of the risk in black females compared with white females.[35]
- In NHANES 2013 to 2014, among 766 participants, each additional 1000 mg of usual 24-hour sodium excretion (a marker of sodium consumption) was associated with 4.58 mm Hg (95% CI, 2.64–6.51 mm Hg) higher SBP and 2.25 mm Hg (95% CI, 0.83–3.67 mm Hg) higher DBP. Each additional 1000 mg of potassium excretion was associated with 3.72 mm Hg (95% CI, 1.42–6.01 mm Hg) lower SBP.[36]
- In a meta-analysis of 240 508 individuals enrolled in 6 prospective cohorts, participants with SSB consumption in the highest versus lowest quantile had a risk ratio for hypertension of 1.12 (95% CI, 1.06–1.17).[37] This equated to an 8.2% increased risk for hypertension for each additional SSB consumed per day.
- In a meta-analysis of 5 studies, each additional 250 mL of SSBs per day was associated with an RR for incident hypertension of 1.07 (95% CI, 1.04–1.10).[38]
- In the JHS, intermediate and ideal versus poor levels of moderate to vigorous PA were associated with HRs of hypertension of 0.84 (95% CI, 0.67–1.05) and 0.76 (95% CI, 0.58–0.99), respectively.[39]
- In a meta-analysis of 24 cohort studies (N=330 222), each 10 additional MET h/wk in leisure-time PA was associated with reduced risk for hypertension (RR, 0.94 [95% CI, 0.92–0.96]). In 5 cohort studies, each additional 50 MET h/wk in total PA time was associated with an RR for hypertension of 0.93 (95% CI, 0.88–0.98).[40]
- In a meta-analysis of 9 population-based studies (N=102 408), the OR for having hypertension among participants with versus without restless leg syndrome was 1.36 (95% CI, 1.18–1.57).[41]
- In the HCHS/SOL Sueño Sleep Ancillary Study of Hispanics (N=2148), a 10% higher sleep fragmentation and frequent napping versus not napping were associated with a 5.2% and 11.6% higher prevalence of hypertension, respectively. A 10% higher sleep efficiency was associated with a 7.2% lower prevalence of hypertension.[42]
- In the JHS ancillary sleep study conducted from 2012 to 2016 among 913 participants, those with moderate or severe OSA had a 2-fold higher odds (95% CI, 1.14–3.67) of resistant hypertension than participants without sleep apnea.[43]
- Among 1741 participants in the JHS with hypertension, 20.1% of those without versus 30.5% of those with CKD developed apparent treatment-resistant hypertension (multivariable-adjusted HR, 1.45 [95% CI, 1.12–1.86]).[44]

Social Determinants

- In a meta-analysis of 51 studies, lower SES measured by income, occupation, or education was linked to increased risk of hypertension. Findings were particularly pronounced for education, with a 2-fold higher odds of hypertension (95% CI, 1.55–2.63) observed in lower- compared with higher-educated individuals. Associations were stronger among females and in higher-income countries.[45]
- Recent data from 2280 black participants of the CARDIA study found that moving from highly segregated census tracts to low-segregation tracts, without returning to a high-segregation tract over a 25-year follow-up, was associated with a 5.71 mm Hg–lower mean SBP (95% CI, 3.5–8.0 mm Hg), even after adjustment for poverty and other relevant risk factors.[46]
- Self-reported experiences of discrimination and unfair treatment have also been linked to hypertension and BP. In a meta-analysis of 44 studies (N=32 651), higher reports of discrimination were linked to a greater prevalence of hypertension (Fisher *Z*, 0.048 [95% CI, 0.013–0.087]), particularly among blacks (compared with other racial/ethnic groups), participants of older ages, males, and individuals with a lower versus higher level of education. Associations between reports of discrimination and BP were most striking for ambulatory nighttime BP; effect sizes for overall associations between self-reported experiences of discrimination and resting SBP or DBP were not significant.[47]
- At least 1 study has found that social integration, defined as the number of social contacts of an individual, may be an important factor to consider in treatment-resistant hypertension. In the JHS, a study of blacks, each additional social contact was associated with a 13% lower prevalence (95% CI, 0.74–1.00) of treatment-resistant hypertension in multivariable adjusted models.[48]
- In a subsample of 528 females and males 45 to 84 years of age who did not have hypertension at baseline from the Chicago, IL, MESA field center, higher levels of self-reported neighborhood safety

were associated with lower levels of SBP (1.54 mm Hg per 1-SD increase [95% CI, 0.25–2.83]) in both sexes and lower levels of DBP (1.24 mm Hg [95% CI, 0.37–2.12]) among females only.[49]

Risk Prediction

- A systematic review identified 48 hypertension risk prediction models reported in 26 studies (N=162 358 enrolled participants). The C statistics from these models ranged from 0.60 to 0.90, with a pooled C statistic of 0.77 (95% CI, 0.74–0.79).[50]
- Using a total study sample of ≈1.5 million individuals in the Health Information Exchange data set of Maine, which covers ≈95% of Maine residents, the additive regression tree model software XGBoost achieved an AUC of 0.87 for predicting incident hypertension cases in 2015, having been trained on data from 2013 and 2014.[51] This AUC is likely optimistic, given the high probability that the same person could be present in both the training and validation data sets.

Borderline Risk Factors/Subclinical/Unrecognized Disease

- Using data from NHANES 2011 to 2014, among US adults not taking antihypertensive medication, the prevalence of elevated BP (SBP 120–129 mm Hg, DBP <80 mm Hg) was 12.1% (95% CI, 11.0%–13.3%).[4]
- Among 17 747 participants in NHANES 2007 to 2012 who were 8 to 80 years of age, the yearly net transition probabilities for ideal BP (<90th percentile by age and sex for individuals 8–19 years of age; SBP <120 mm Hg and DBP <80 mm Hg for individuals 20–80 years of age) to prehypertension (90th–95th percentile or SBP ≥120 mm Hg or DBP ≥80 mm Hg for individuals 8–19 years of age; SBP 120–129 mm Hg or DBP 80–89 mm Hg for individuals 20–80 years of age) among African American and white American males were highest from 30 years of age to 40 years of age, and highest after 40 years of age among Mexican American males. Yearly net transition probabilities for ideal BP to prehypertension among females increased monotonically from 8 to 80 years of age.[52]

Genetics/Family History

- Genetic studies have been conducted to identify the genetic architecture of hypertension. Several large-scale GWASs, whole-exome, and whole-genome sequencing studies, with interrogation of common and rare variants in >300 000 individuals, have established >100 well-replicated hypertension loci, with several hundred additional suggestive loci.[53–60]
- GRS for hypertension are also associated with increased risk of CVD and MI.[53]
- Given strong effects of environmental factors on hypertension, gene-environment interactions are important in the pathophysiology of hypertension. Large-scale gene-environment interaction studies have not yet been conducted; however, studies of several thousand people have to date revealed several loci of interest that interact with smoking[61,62] and sodium.[63]
- The clinical implications and utility of hypertension genes remain unclear, although some genetic variants have been shown to influence response to antihypertensive agents.[64]

Prevention

- In NHANES 2011 to 2014 (N=10 958), US NH blacks (13.2%) were more likely than NH Asians (11.0%), NH whites (8.6%), or Hispanics (7.4%) to use home BP monitoring on a weekly basis.[65]
- Among 6328 participants in the International Childhood Cardiovascular Cohort Consortium, which included 4 cohort studies conducted from as early as 1970 with follow-up as late as 2007, the RR for adult-onset incident hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or antihypertensive medication use) ranged from 1.5 to 2.3 among the 4 studies for participants who were overweight or obese in childhood compared with participants who were normal weight in childhood. The pooled RR was 1.8 (95% CI, 1.5–2.1).[66]

Awareness, Treatment, and Control (See Table 8-2 and Charts 8-3 through 8-5)

- Using NHANES 2013 to 2016 data,[5] the extent of awareness, treatment, and control of HBP is provided by race/ethnicity in Chart 8-3, by age in Chart 8-4, and by race/ethnicity and sex in Chart 8-5. Awareness, treatment, and control of hypertension were higher at older ages (Chart 8-4). Overall, females were more likely than males in all race/ethnicity groups to be aware of their condition, under treatment, or in control of their hypertension (Chart 8-5).
- Analysis of NHANES 1999 to 2004, 2005 to 2010, and 2011 to 2016[5] found the proportion of adults aware of their hypertension increased within each race/ethnicity and sex subgroup. Similarly, large increases in hypertension treatment and control (≈10%) occurred in each of these groups (Table 8-2).
- According to NHANES data on 22 911 adults with hypertension in 1999 to 2000 (SBP ≥130 mm Hg, DBP ≥80 mm Hg, or self-reported antihypertensive

medication use), the prevalence of hypertension control among males increased from 8.6% to 20.5% in 2015 to 2016, and it increased among females from 10.8% to 23.8%.[67]

- In a multinational study of 63 014 adults at least 50 years of age from high-, middle-, and low-income countries, 55.6% of participants were aware of their diagnosis of hypertension, 44.1% were treated, and 17.1% had controlled BP. Awareness and control were less common in upper-middle-income countries, whereas treatment was lowest in low-income countries.[68]
- In a cohort study of Korean patients from 2009 to 2013 with health insurance claims for hypertension (N=38 520), those with poor adherence to antihypertensive medication (defined as <50% of days of follow-up covered by a medication prescription fill) had an adjusted risk ratio for stroke of 1.27 (95% CI, 1.17–1.38) compared with those with high adherence (>80% of days covered by prescription fill).[69]
- According to national prescription data in Denmark, the use of antihypertensive medications increased from 184 to 379 defined daily doses per 1000 inhabitants per day. Over this time period, increases were present for ACE inhibitors (from 29 to 105 defined daily doses), angiotensin II receptor blockers (from 13 to 73 defined daily doses), β-blockers (from 17 to 34 defined daily doses), and calcium channel blockers (from 34 to 82 defined daily doses).[70]
- Among 3358 blacks taking antihypertensive medication in the JHS, 25.4% of participants reported not taking ≥1 of their prescribed antihypertensive medications within the 24 hours before their baseline study visit in 2000 to 2004. This percentage was 28.7% at examination 2 (2005–2008) and 28.5% at examination 3 (2009–2012). Nonadherence was associated with higher likelihood of having SBP ≥140 mm Hg or DBP ≥90 mm Hg (prevalence ratio, 1.26 [95% CI, 1.16–1.37]).[71]
- In an analysis of 1590 healthcare providers who completed the DocStyles survey, a web-based survey of healthcare providers, 86.3% reported using a prescribing strategy to increase their patients' adherence to antihypertensive medications. The most common strategies were prescribing once-daily regimens (69.4%), prescribing medications covered by the patient's insurance (61.8%), and using longer fills (59.9%).[72]
- In HCHS/SOL, the prevalence of awareness, treatment, and control of hypertension among males was lowest in those of Central American background (57%, 39%, and 12%, respectively) and highest among those of Cuban background (78%, 65%, and 40%, respectively). Among females, those of South American background had the lowest prevalence of awareness (72%) and treatment (64%), whereas hypertension control was lowest among females of Central American background (32%). Only Hispanic females reporting mixed/other background had a hypertension control rate that exceeded 50%.[73]

Mortality (See Table 8-1)

- Using data from the NVSS, in 2017,[74] there were 90 098 deaths primarily attributable to HBP (Table 8-1). The 2017 age-adjusted death rate primarily attributable to HBP was 23.0 per 100 000. Age-adjusted death rates attributable to HBP (per 100 000) in 2017 were 23.0 for NH white males, 54.1 for NH black males, 21.8 for Hispanic males, 16.4 for NH Asian/Pacific Islander males, 30.1 for NH American Indian/Alaska Native males, 18.6 for NH white females, 37.8 for NH black females, 16.9 for Hispanic females, 14.7 for NH Asian/Pacific Islander females, and 19.7 for NH American Indian/Alaska Native females (unpublished NHLBI tabulation using CDC WONDER[75]).
- From 2007 to 2017, the death rate attributable to HBP increased 25.7%, and the actual number of deaths attributable to HBP rose 56.1%. During this 10-year period, in NH whites, the HBP age-adjusted death rate increased 34.0%, whereas the actual number of deaths attributable to HBP increased 54.9%. In NH blacks, the HBP death rate increased 1.8%, whereas the actual number of deaths attributable to HBP increased 37.3%. In Hispanics, the HBP death rate increased 17.7%, and the actual number of deaths attributable to HBP increased 105.0% (unpublished NHLBI tabulation using CDC WONDER[75]).
- When any mention of HBP was present, the overall age-adjusted death rate in 2017 was 120.6 per 100 000. Death rates were 132.9 for NH white males, 224.9 for NH black males, 91.3 for NH Asian or Pacific Islander males, 167.3 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 120.8 for Hispanic males. In females, rates were 99.8 for NH white females, 155.3 for NH black females, 69.5 for NH Asian or Pacific Islander females, 114.8 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 88.6 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER[75]).
- The elimination of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females.[76] The elimination of hypertension

is projected to have a larger impact on CVD mortality than the elimination of all other risk factors among females and all except smoking among males.[76]

- Among US adults meeting the eligibility criteria for SPRINT, SBP treatment to a treatment goal of <120 mm Hg versus <140 mm Hg has been projected to prevent ≈107 500 deaths per year (95% CI, 93 300–121 200).[77]
- In a cohort of 63 910 adult participants in the Spanish Ambulatory Blood Pressure Registry conducted from 2004 to 2014, masked hypertension had the largest HR for all-cause mortality versus sustained normotension (2.83 [95% CI, 2.12–3.79]), compared with 1.80 (95% CI, 1.41–2.31) for sustained hypertension and 1.79 (95% CI, 1.38–2.32) for white-coat hypertension.[78]

Complications

- In a meta-analysis that included 95 772 US females and 30 555 US males, each 10-mm Hg higher SBP was associated with an effect size (eg, RR or HR) for CVD of 1.25 (95% CI, 1.18–1.32) among females and 1.15 (95% CI, 1.11–1.19) among males. Among 65 806 females and 92 515 males in this meta-analysis, the RR for CVD mortality associated with 10-mm Hg higher SBP was 1.16 (95% CI, 1.10–1.23) among females and 1.17 (95% CI, 1.12–1.22) among males.[79]
- In a study of >1 million adults with hypertension, the lifetime risk of CVD at 30 years of age was 63.3% compared with 46.1% for those without hypertension. Those with hypertension developed CVD 5.0 years earlier than their counterparts without hypertension.[80] The largest lifetime risk differences between people with versus without hypertension were for angina, MI, and stroke. At 60 years of age, the lifetime risk for CVD was 60.2% for those with hypertension and 44.6% for their counterparts without hypertension.
- In a sample of 4851 adults 18 to 30 years of age at baseline from the CARDIA cohort, for those who developed hypertension before 40 years of age, incident CVD rates were 3.15 (95% CI, 2.47–4.02) for those with stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg) per 1000 person-years and 8.04 (95% CI, 6.45–10.03) for those with stage 2 hypertension (≥140/90 mm Hg or taking antihypertensive medication) per 1000 person-years over the median follow-up of ≈19 years.[81]
- In a cohort of older US adults, both isolated systolic hypertension and systolic-diastolic hypertension were associated with an increased risk for HF (multivariable-adjusted HR, 1.86 [95% CI, 1.51–2.30] and HR, 1.73 [95% CI, 1.24–2.42], respectively) compared with participants without hypertension.[82]
- In a meta-analysis of 12 prospective studies (N=2 170 265), participants with a history of hypertension were more likely to develop kidney cancer (RR, 1.67 [95% CI, 1.46–1.90]).[83]
- Among 17 312 participants with hypertension, nondipping BP was associated with an HR for CVD of 1.40 (95% CI, 1.20–1.63).[84]
- In the JHS, a cohort composed exclusively of blacks, masked hypertension was associated with an HR for CVD of 2.49 (95% CI, 1.26–4.93).[85]
- A meta-analysis (23 cohorts with 20 445 participants) showed that white- coat hypertension is associated with an increased risk for CVD among untreated individuals (adjusted HR, 1.38 [95% CI, 1.15–1.65]) but not among treated individuals (HR, 1.16 [95% CI, 0.91–1.49]).[86]
- Among adults with established CKD, apparent treatment-resistant hypertension has been associated with increased risk for CVD (HR, 1.38 [95% CI, 1.22–1.56]), renal outcomes including a 50% decline in eGFR or ESRD (HR, 1.28 [95% CI, 1.11–1.46]), HF (HR, 1.66 [95% CI, 1.38–2.00]), and all-cause mortality (HR, 1.24 [95% CI, 1.06–1.45]).[9]
- In an international case-control study (n=13 447 cases of stroke and n=13 472 control subjects), a previous history of hypertension or SBP/DBP ≥140/90 mm Hg was associated with an OR for stroke of 2.98 (95% CI, 2.72–3.28). The PAR for stroke accounted for by hypertension was 47.9%.[87]
- Among adults 45 years of age without HF, HF-free survival was shorter among those with versus without hypertension, respectively, in males (30.4 versus 34.3 years), females (33.5 versus 37.6 years), blacks (33.2 versus 37.3 years), and whites (31.9 versus 36.3 years).[88]
- In prospective follow-up of the REGARDS, MESA, and JHS cohorts (N=31 856), 63.0% (95% CI, 54.9%–71.1%) of the 2584 incident CVD events occurred in participants with SBP <140 and DBP <90 mm Hg.[89]
- Over a median follow-up of 18.8 years in 4851 adults from the CARDIA cohort, among those who developed hypertension before 40 years of age, incident CVD rates were 2.74 (95% CI, 1.78–4.20) for those with elevated BP or prehypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg) per 1000 person-years compared with 1.37 (95% CI, 1.07–1.75), 2.74 (95% CI, 1.78–4.20) among those who retained normal BP through 40 years of age.[81]
- Higher SBP explains ≈50% of the excess stroke risk among blacks compared with whites.[90]

Healthcare Utilization: Hospital Discharges/Ambulatory Care Visits (See Table 8-1)

- Beginning in 2016, a code for hypertensive crisis (*ICD-10-CM* I16) was added to the HCUP inpatient database. For 2016, hypertensive crisis is included in the total number of inpatient hospital stays for HBP. From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis was 292 000 and 486 000, respectively. The number of discharges with any listing of HBP increased from 13 851 000 to 16 676 000 (Table 8-1).
- In 2016, there were 63 000 principal diagnosis discharges for essential hypertension (HCUP,[91] unpublished NHLBI tabulation).
- In 2016, there were 11 612 000 all-listed discharges for essential hypertension (HCUP,[91] unpublished NHLBI tabulation).
- In 2016, 32 779 000 of 883 725 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,[92] unpublished NHLBI tabulation). A total of 1 016 000 of 145 591 000 ED visits in 2016 and 3 743 000 of 125 721 000 hospital outpatient visits in 2011 were for essential hypertension (NHAMCS,[93] unpublished NHLBI tabulation).
- Among REGARDS study participants ≥65 years of age with hypertension, compared with those without apparent treatment-resistant hypertension, participants with apparent treatment-resistant hypertension and uncontrolled BP had more primary care visits (2.77 versus 2.27 per year) and more cardiologist visits (0.50 versus 0.35 per year). In this same study, there were no statistically significant differences in laboratory testing for end-organ damage or secondary causes of hypertension among participants with apparent treatment-resistant hypertension and uncontrolled BP (72.4%), apparent treatment-resistant hypertension and controlled BP (76.5%), or hypertension but no apparent treatment-resistant hypertension (71.8%).[94]

Cost (See Table 8-1)

- The estimated direct and indirect cost of HBP for 2014 to 2015 (annual average) was $55.9 billion (Table 8-1).
- From 2003 to 2014, the annual mean additional medical cost for a person with hypertension was $1920 compared with a person without hypertension, according to data from MEPS.[95]
- Using data from MEPS for 2011 to 2014, among individuals with a diagnosis code for hypertension who were ≥18 years of age (N=26 049), the mean annual costs of hypertension ranged from $3914 (95% CI, $3456–$4372) for those with no comorbidities to $13 920 (95% CI, $13 166–$14 674) for those with ≥3 comorbidities.[96]
- Adjusted to 2012 US dollars, the monetary savings and QALYs gained with lifetime treatment were $7387 and 1.14 for white males, $7796 and 0.89 for white females, $8400 and 1.66 for black males, and $10 249 and 1.79 for black females, respectively.[97]
- Projections show that by 2035, the total direct costs of HBP could increase to an estimated $220.9 billion (based on methodology described in Heidenreich et al[98]).[99]
- According to IMS Health's National Prescription Audit, the number of prescriptions for antihypertensive medication increased from 614 million to 653 million between 2010 and 2014. The 653 million antihypertensive prescriptions filled in 2014 cost $28.81 billion.[100]

Global Burden (See Chart 8-6)

- In 2010, HBP was 1 of the 5 leading risk factors for the burden of disease (years of life lost and DALYs) in all regions with the exception of Western sub-Saharan Africa.[101]
- In a meta-analysis of population-studies conducted in Africa, the prevalence of hypertension was 55.2% among adults ≥55 years of age.[102]
- In a systematic review, a higher percentage of hypertension guidelines developed in high-income countries used high-quality systematic reviews of relevant evidence than did those developed in low- and middle-income countries (63.5% versus 10%).[103]
- On the basis of data from 135 population-based studies (N=968 419 adults from 90 countries), it was estimated that 31.1% (95% CI, 30.0%–32.2%) of the world adult population had hypertension in 2010. The prevalence was 28.5% (95% CI, 27.3%–29.7%) in high-income countries and 31.5% (95% CI, 30.2%–32.9%) in low-middle-income countries. It was also estimated that 1.39 billion adults worldwide had hypertension in 2010 (349 million in high-income countries and 1.04 billion in low- and middle-income countries).[104]
- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195

countries and territories. Age-standardized mortality rates attributable to high SBP are generally lower in high-income countries (Chart 8-6).[105]

- In 2015, the prevalence of SBP ≥140 mm Hg was estimated to be 20 526 per 100 000. This represents an increase from 17 307 per 100 000 in 1990.[106] Also, the prevalence of SBP 110 to 115 mm Hg or higher increased from 73 119 per 100 000 to 81 373 per 100 000 between 1990 and 2015. There were 3.47 billion adults worldwide with SBP of 110 to 115 mm Hg or higher in 2015. Of this group, 874 million had SBP ≥140 mm Hg.[106]
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP ≥140 mm Hg.[106] In addition, 10.7 million deaths and 211 million DALYs in 2015 could be attributed to SBP of 110 to 115 mm Hg or higher.[106]
- Between 1990 and 2015, the number of deaths related to SBP ≥140 mm Hg did not increase in high-income countries (from 2.197 to 1.956 million deaths) but did increase in high-middle-income (from 1.288 to 2.176 million deaths), middle-income (from 1.044 to 2.253 million deaths), low-middle-income (from 0.512 to 1.151 million deaths), and low-income (from 0.146 to 0.293 million deaths) countries.[106]
- Among ≈1.7 million participants from the Chinese mainland 35 to 75 years of age from 2014 to 2017, the age- and sex-standardized prevalence of hypertension was 37.2%.[107]
- In a meta-analysis of 25 studies (N=54 196 participants 2–19 years of age) conducted in Africa, the pooled prevalence of SBP or DBP ≥95th percentile was 5.5% and the pooled prevalence of SBP or DBP ≥90th percentile was 12.7%. The prevalence of SBP/DBP ≥95th percentile was 30.8% among children with obesity versus 5.5% among normal-weight children.[108]
- Among 12 971 Turkish adults who completed the Chronic Diseases and Risk Factors Survey, a nationwide study, the age-adjusted prevalence of hypertension in 2011 was 27.1%; 65% of participants were aware they had hypertension, 59% were treated, and 30% had SBP/DBP <140/90 mm Hg.[109]

Table 8-1. HBP in the United States

Population Group	Prevalence, 2013–2016, Age ≥20 y	Mortality,* 2017, All Ages	Hospital Discharges,† 2016, All Ages	Estimated Cost, 2014–2015
Both sexes	116 400 000 (46.0%)	90 098	486 000	$55.9 Billion
Males	58 700 000 (49.0%)	43 127 (47.9%)‡	246 000	…
Females	57 700 000 (42.8%)	46 971 (52.1%)‡	240 000	…
NH white males	48.2%	29 086	…	…
NH white females	41.3%	33 396	…	…
NH black males	58.6%	8690	…	…
NH black females	56.0%	8387	…	…
Hispanic males	47.4%	3478	…	…
Hispanic females	40.8%	3282	…	…
NH Asian males	46.4%	1269§	…	…
NH Asian females	36.4%	1538§	…	…
NH American Indian/Alaska Native	…	568	…	…

Hypertension is defined in terms of NHANES (National Health and Nutrition Examination Survey) blood pressure measurements and health interviews. A subject was considered to have hypertension if systolic blood pressure (SBP) was ≥130 mm Hg or diastolic blood pressure (DBP) was ≥80 mm Hg, if the subject said "yes" to taking antihypertensive medication, or if the subject was told on 2 occasions that he or she had hypertension. A previous publication that used NHANES 2011 to 2014 data estimated there were 103.3 million noninstitutionalized US adults with hypertension.[4] The number of US adults with hypertension in this table includes both noninstitutionalized and institutionalized US individuals. Also, the previous study did not include individuals who reported having been told on 2 occasions that they had hypertension as having hypertension unless they met another criterion (SBP was ≥130 mm Hg or DBP was ≥80 mm Hg, if the subject said "yes" to taking antihypertensive medication). Ellipses (…) indicate data not available; HBP, high blood pressure; and NH, non-Hispanic.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian, and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†Beginning in 2016, a code for hypertensive crisis (*International Classification of Diseases, 10th Revision, Clinical Modification* I16) was added to the Healthcare Cost and Utilization Project (HCUP) inpatient database and is included in the total number of hospital discharges for HBP.

‡These percentages represent the portion of total HBP mortality that is for males vs females.

§Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES (2013–2016).[5] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System, 2017.[74] These data represent underlying cause of death only. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Unpublished NHLBI tabulation using HCUP 2016.[91] Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey[110] include estimated direct costs for 2014 to 2015 (annual average); indirect costs calculated by NHLBI for 2014 to 2015 (annual average).

Table 8-2. Hypertension Awareness, Treatment, and Control: NHANES 1999 to 2004, 2005 to 2010, and 2011 to 2016 Age-Adjusted Percent With Hypertension in US Adults by Sex and Race/Ethnicity

	Awareness, %			Treatment, %			Control, %		
	1999–2004	2005–2010	2011–2016	1999–2004	2005–2010	2011–2016	1999–2004	2005–2010	2011–2016
Overall	51.8	60.2	63.7	40.3	50.7	52.8	14.1	22.4	24.6
NH white males	46.7	55.8	61.2	35.0	45.7	48.9	13.3	20.4	24.8
NH white females	58.7	65.5	68.9	47.4	57.8	60.6	16.8	26.0	28.6
NH black males	47.6	59.1	62.3	35.5	46.5	48.4	11.2	18.0	17.2
NH black females	67.6	74.5	74.7	55.5	65.9	64.6	19.0	28.7	26.4
Mexican American males*	30.8	37.8	43.8	18.5	27.1	30.3	6.5	11.7	11.6
Mexican American females*	51.6	56.7	66.2	39.0	47.2	53.2	11.7	20.0	27.0

Values are percentages. Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A subject was considered to have hypertension if systolic blood pressure was ≥130 mm Hg or diastolic blood pressure was ≥80 mm Hg, or if the subject said "yes" to taking antihypertensive medication. NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used. Total includes race/ethnicity groups not shown (other Hispanic, other race, and multiracial).

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES (1999–2004, 2005–2010, 2011–2016).[5]

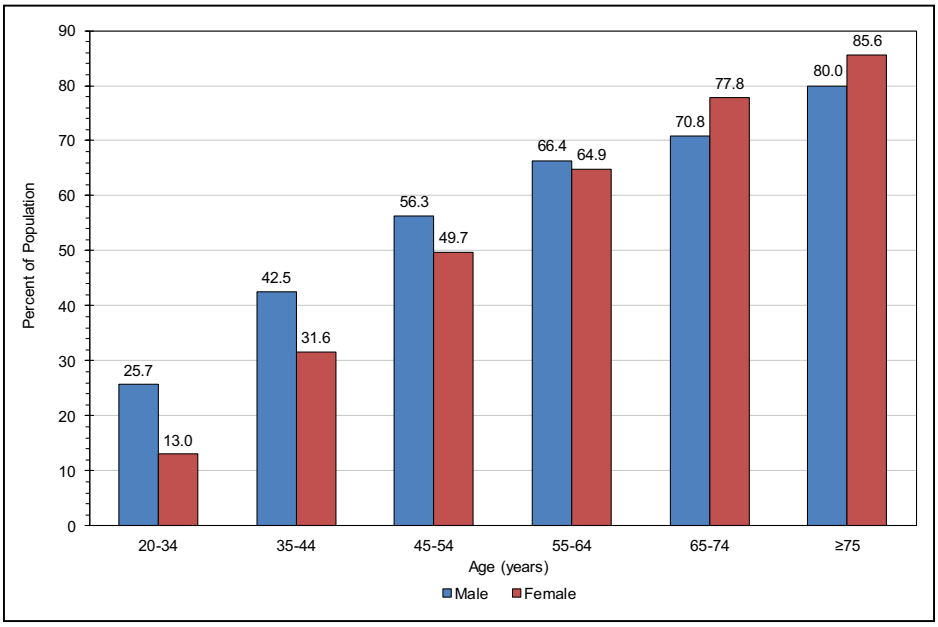

Chart 8-1. Prevalence of hypertension in US adults ≥20 years of age by sex and age (NHANES, 2013–2016).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[5]

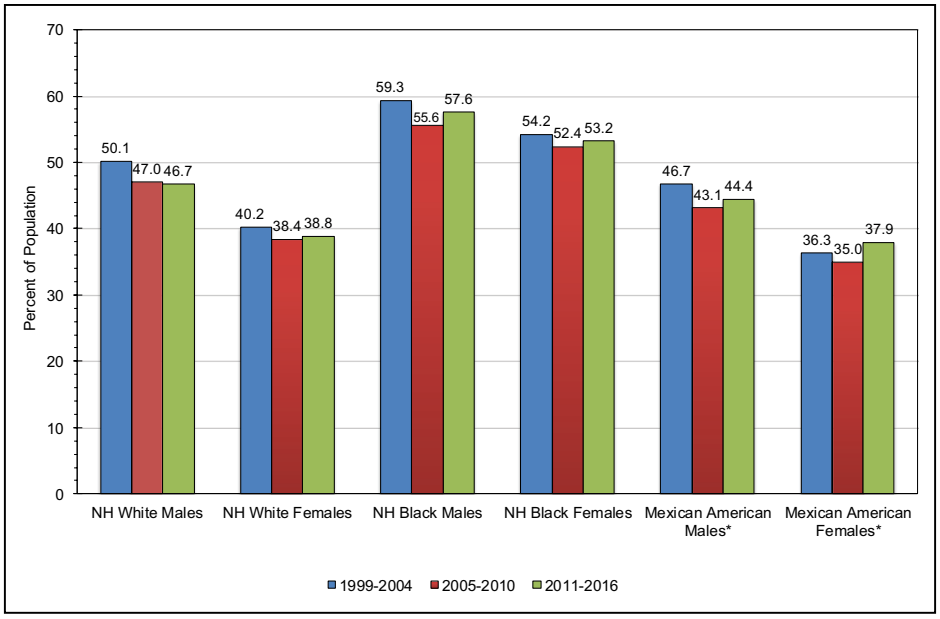

Chart 8-2. Age-adjusted prevalence trends for hypertension in US adults ≥20 years of age by race/ethnicity, sex, and survey year (NHANES, 1999–2004, 2005–2010, and 2010–2016).

Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

*The category of Mexican Americans was consistently collected in all NHANES years, but the combined category of Hispanics was only used starting in 2007. Consequently, for long-term trend data, the category Mexican American is used.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 1999 to 2016.[5]

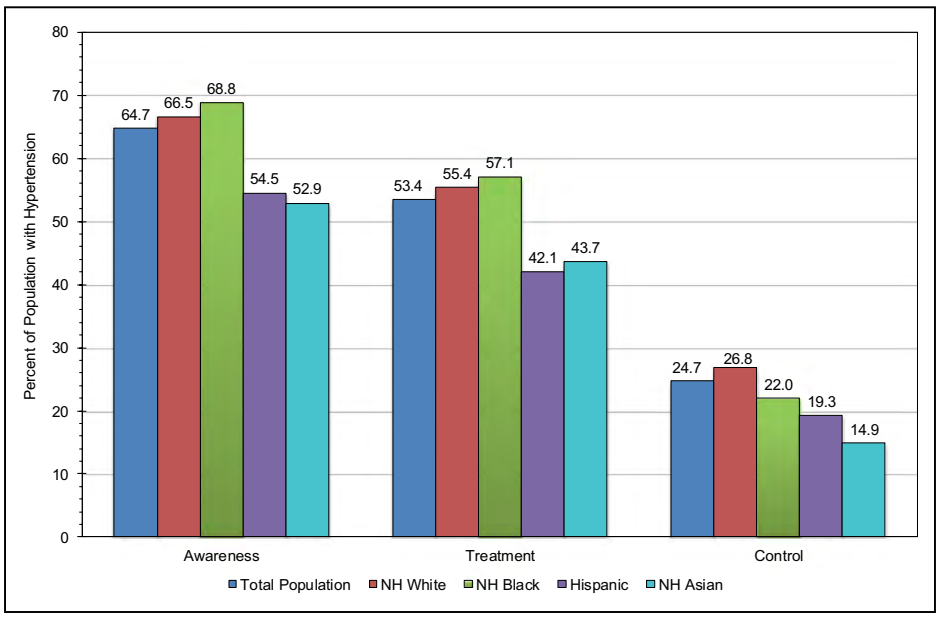

Chart 8-3. Extent of awareness, treatment, and control of HBP by race/ethnicity, United States (NHANES, 2013–2016).

Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES 2013 to 2016.[5]

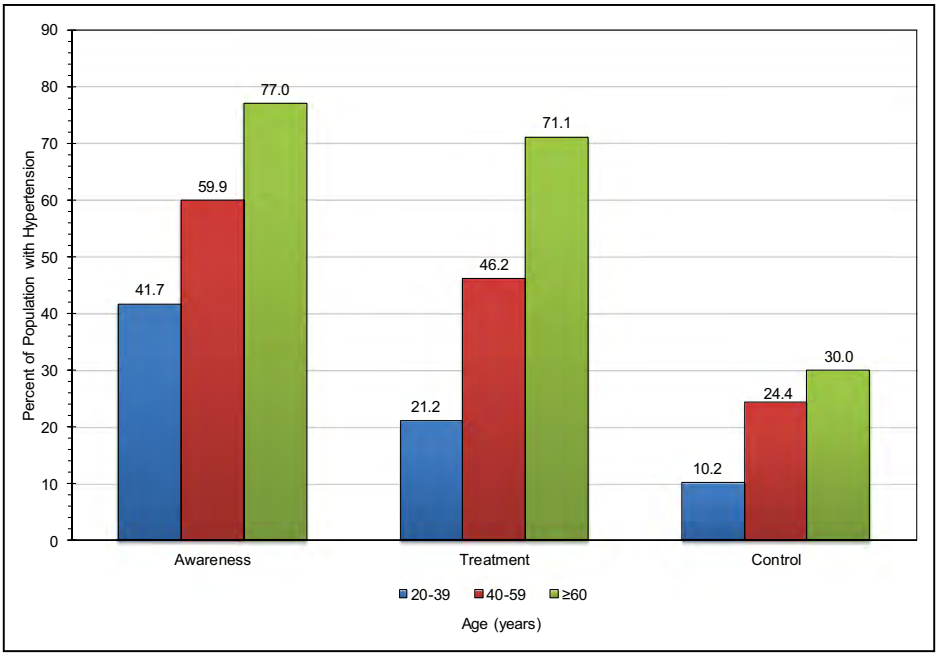

Chart 8-4. Extent of awareness, treatment, and control of HBP by age, United States (NHANES, 2013–2016).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES 2013 to 2016.[5]

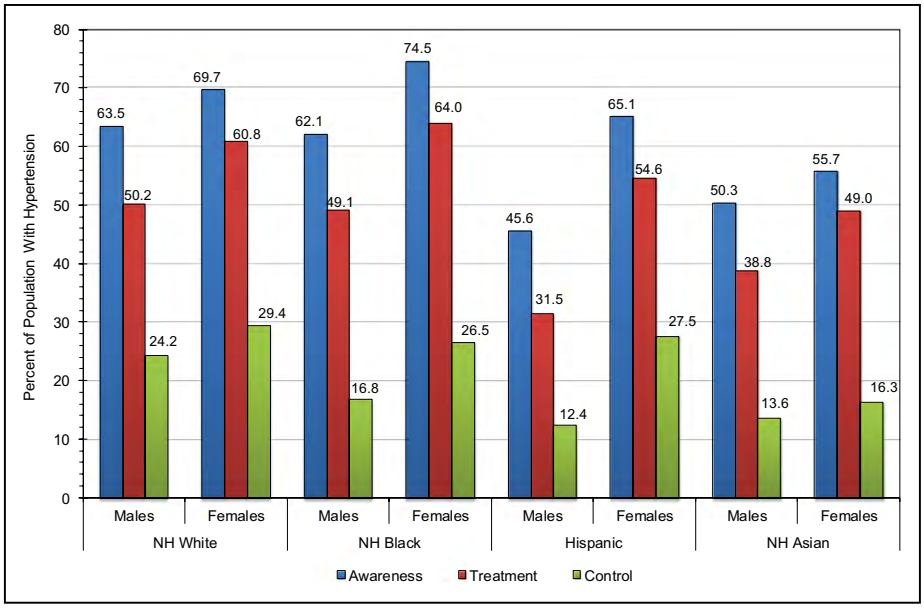

Chart 8-5. Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex, United States (NHANES, 2013–2016).
Hypertension is defined in terms of NHANES blood pressure measurements and health interviews. A person was considered to have hypertension if he or she had systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, if he or she said "yes" to taking antihypertensive medication, or if the person was told on 2 occasions that he or she had hypertension.
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[5]

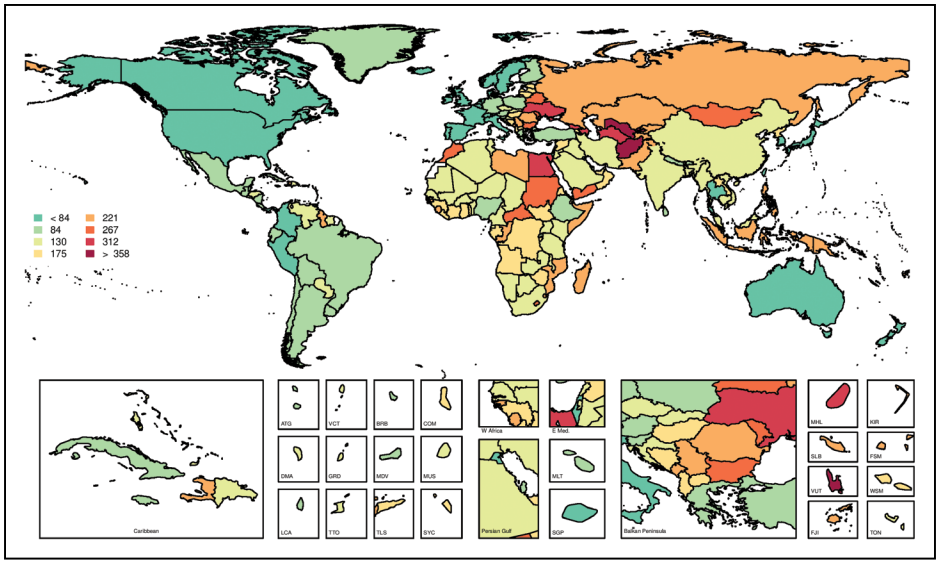

Chart 8-6. Age-standardized global mortality rates attributable to high systolic blood pressure (SBP) per 100 000, both sexes, 2017.
Age-standardized mortality rates attributable to high SBP are generally lower in high-income countries.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[105] Printed with permission.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, et al; and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206–1252. doi: 10.1161/01.HYP.0000107251.49515.c2
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
4. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation.* 2018;137:109–118. doi: 10.1161/CIRCULATIONAHA.117.032582
5. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
6. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Behavioral Risk Factor Surveillance System (BRFSS). BRFSS prevalence & trends data [online] (2017). Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed April 1, 2019.
7. Melgarejo JD, Maestre GE, Thijs L, Asayama K, Boggia J, Casiglia E, Hansen TW, Imai Y, Jacobs L, Jeppesen J, et al; on behalf of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. Prevalence, treatment, and control rates of conventional and ambulatory hypertension across 10 populations in 3 continents. *Hypertension.* 2017;70:50–58. doi: 10.1161/HYPERTENSIONAHA.117.09188
8. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *Am J Hypertens.* 2015;28:355–361. doi: 10.1093/ajh/hpu151
9. Thomas G, Xie D, Chen HY, Anderson AH, Appel LJ, Bodana S, Brecklin CS, Drawz P, Flack JM, Miller ER 3rd, et al; CRIC Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic Renal Insufficiency Cohort Study. *Hypertension.* 2016;67:387–396. doi: 10.1161/HYPERTENSIONAHA.115.06487
10. Armario P, Calhoun DA, Oliveras A, Blanch P, Vinyoles E, Banegas JR, Gorostidi M, Segura J, Ruilope LM, Dudenbostel T, et al. Prevalence and clinical characteristics of refractory hypertension. *J Am Heart Assoc.* 2017;6:e007365. doi: 10.1161/JAHA.117.007365
11. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control [published correction appears in *N Engl J Med.* 2017;377:2506]. *N Engl J Med.* 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939
12. Bress AP, Tanner RM, Hess R, Colantonio LD, Shimbo D, Muntner P. Generalizability of SPRINT results to the U.S. adult population. *J Am Coll Cardiol.* 2016;67:463–472. doi: 10.1016/j.jacc.2015.10.037
13. Xu Y, Chen X, Wang K. Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis. *J Am Soc Hypertens.* 2017;11:530–540. doi: 10.1016/j.jash.2017.06.004
14. Franklin SS, Thijs L, Asayama K, Li Y, Hansen TW, Boggia J, Jacobs L, Zhang Z, Kikuya M, Björklund-Bodegård K, et al; and the IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol.* 2016;68:2033–2043. doi: 10.1016/j.jacc.2016.08.035
15. Bromfield SG, Ngameni CA, Colantonio LD, Bowling CB, Shimbo D, Reynolds K, Safford MM, Banach M, Toth PP, Muntner P. Blood pressure, antihypertensive polypharmacy, frailty, and risk for serious fall injuries among older treated adults with hypertension. *Hypertension.* 2017;70:259–266. doi: 10.1161/HYPERTENSIONAHA.116.09390
16. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr.* 2015;169:272–279. doi: 10.1001/jamapediatrics.2014.3216
17. Ning H, Labarthe DR, Shay CM, Daniels SR, Hou L, Van Horn L, Lloyd-Jones DM. Status of cardiovascular health in US children up to 11

years of age: the National Health and Nutrition Examination Surveys 2003-2010. *Circ Cardiovasc Qual Outcomes.* 2015;8:164–171. doi: 10.1161/CIRCOUTCOMES.114.001274
18. Li L, Pérez A, Wu LT, Ranjit N, Brown HS, Kelder SH. Cardiometabolic risk factors among severely obese children and adolescents in the United States, 1999-2012. *Child Obes.* 2016;12:12–19. doi: 10.1089/chi.2015.0136
19. Lubrano R, Paoli S, Spiga S, Falsaperla R, Vitaliti G, Gentile I, Elli M. Impact of ambulatory blood pressure monitoring on the diagnosis of hypertension in children. *J Am Soc Hypertens.* 2015;9:780–784. doi: 10.1016/j.jash.2015.07.016
20. Koebnick C, Mohan Y, Li X, Porter AH, Daley MF, Luo G, Kuizon BD. Failure to confirm high blood pressures in pediatric care-quantifying the risks of misclassification. *J Clin Hypertens (Greenwich).* 2018;20:174–182. doi: 10.1111/jch.13159
21. Brown AGM, Houser RF, Mattei J, Mozaffarian D, Lichtenstein AH, Folta SC. Hypertension among US-born and foreign-born non-Hispanic Blacks: National Health and Nutrition Examination Survey 2003-2014 data. *J Hypertens.* 2017;35:2380–2387. doi: 10.1097/HJH.0000000000001489
22. National Center for Health Statistics. National Health Interview Survey, 2014. public-use data files. Centers for Disease Control and Prevention website. http://www.cdc.gov/nchs/nhis/nhis_2014_data_release.htm. Accessed April 1, 2019.
23. Young DR, Fischer H, Arterburn D, Bessesen D, Cromwell L, Daley MF, Desai J, Ferrara A, Fitzpatrick SL, Horberg MA, et al. Associations of overweight/obesity and socioeconomic status with hypertension prevalence across racial and ethnic groups. *J Clin Hypertens (Greenwich).* 2018;20:532–540. doi: 10.1111/jch.13217
24. Thomas SJ, Booth JN 3rd, Bromfield SG, Seals SR, Spruill TM, Ogedegbe G, Kidambi S, Shimbo D, Calhoun D, Muntner P. Clinic and ambulatory blood pressure in a population-based sample of African Americans: the Jackson Heart Study. *J Am Soc Hypertens.* 2017;11:204–212.e5. doi: 10.1016/j.jash.2017.02.001
25. Thomas SJ, Booth JN, Dai C, Li X, Allen N, Calhoun D, Carson AP, Gidding S, Lewis CE, Shikany JM, et al. Cumulative incidence of hypertension by 55 years of age in blacks and whites: the CARDIA study. *J Am Heart Assoc.* 2018;7:e007988. doi: 10.1161/JAHA.117.007988
26. Chen V, Ning H, Allen N, Kershaw K, Khan S, Lloyd-Jones DM, Wilkins JT. Lifetime risks for hypertension by contemporary guidelines in African American and white men and women. *JAMA Cardiol.* 2019;4:455–459. doi: 10.1001/jamacardio.2019.0529
27. Gao J, Sun H, Liang X, Gao M, Zhao H, Qi Y, Wang Y, Liu Y, Li J, Zhu Y, et al. Ideal cardiovascular health behaviors and factors prevent the development of hypertension in prehypertensive subjects. *Clin Exp Hypertens.* 2015;37:650–655. doi: 10.3109/10641963.2015.1047938
28. Liu J, Sui X, Lavie CJ, Zhou H, Park YM, Cai B, Liu J, Blair SN. Effects of cardiorespiratory fitness on blood pressure trajectory with aging in a cohort of healthy men. *J Am Coll Cardiol.* 2014;64:1245–1253. doi: 10.1016/j.jacc.2014.06.1184
29. Zhang Y, Moran AE. Trends in the prevalence, awareness, treatment, and control of hypertension among young adults in the United States, 1999 to 2014. *Hypertension.* 2017;70:736–742. doi: 10.1161/HYPERTENSIONAHA.117.09801
30. Xi B, Zhang T, Zhang M, Liu F, Zong X, Zhao M, Wang Y. Trends in elevated blood pressure among US children and adolescents: 1999-2012. *Am J Hypertens.* 2016;29:217–225. doi: 10.1093/ajh/hpv091
31. Yang Q, Zhong Y, Merritt R, Cogswell ME. Trends in high blood pressure among United States adolescents across body weight category between 1988 and 2012. *J Pediatr.* 2016;169:166–173.e3. doi: 10.1016/j.jpeds.2015.10.007
32. Roulet C, Bovet P, Brauchli T, Simeoni U, Xi B, Santschi V, Paradis G, Chiolero A. Secular trends in blood pressure in children: a systematic review. *J Clin Hypertens (Greenwich).* 2017;19:488–497. doi: 10.1111/jch.12955
33. Egeland GM, Skurtveit S, Staff AC, Eide GE, Daltveit AK, Klungsoyr K, Trogstad L, Magnus PM, Brantsaeter AL, Haugen M. Pregnancy-related risk factors are associated with a significant burden of treated hypertension within 10 years of delivery: findings from a population-based Norwegian cohort. *J Am Heart Assoc.* 2018;7:e008318. doi: 10.1161/JAHA.117.008318
34. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, Rich-Edwards JW. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med.* 2018;169:224–232. doi: 10.7326/M17-2740
35. Howard G, Cushman M, Moy CS, Oparil S, Muntner P, Lackland DT, Manly JJ, Flaherty ML, Judd SE, Wadley VG, et al. Association of clinical and social factors with excess hypertension risk in black compared with white US adults. *JAMA.* 2018;320:1338–1348. doi: 10.1001/jama.2018.13467
36. Jackson SL, Cogswell ME, Zhao L, Terry AL, Wang CY, Wright J, Coleman King SM, Bowman B, Chen TC, Merritt R, et al. Association between urinary sodium and potassium excretion and blood pressure among adults in the United States: National Health and Nutrition Examination Survey, 2014. *Circulation.* 2018;137:237–246. doi: 10.1161/CIRCULATIONAHA.117.029193
37. Jayalath VH, de Souza RJ, Ha V, Mirrahimi A, Blanco-Mejia S, Di Buono M, Jenkins AL, Leiter LA, Wolever TM, Beyene J, et al. Sugar-sweetened beverage consumption and incident hypertension: a systematic review and meta-analysis of prospective cohorts. *Am J Clin Nutr.* 2015;102:914–921. doi: 10.3945/ajcn.115.107243
38. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Andriolo V, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of hypertension: a systematic review and dose-response meta-analysis of prospective studies [published correction appears in *Adv Nutr*. 2018;9:163–164]. *Adv Nutr.* 2017;8:793–803. doi: 10.3945/an.117.017178
39. Diaz KM, Booth JN 3rd, Seals SR, Abdalla M, Dubbert PM, Sims M, Ladapo JA, Redmond N, Muntner P, Shimbo D. Physical activity and incident hypertension in African Americans: the Jackson Heart Study. *Hypertension.* 2017;69:421–427. doi: 10.1161/HYPERTENSIONAHA.116.08398
40. Liu X, Zhang D, Liu Y, Sun X, Han C, Wang B, Ren Y, Zhou J, Zhao Y, Shi Y, et al. Dose-response association between physical activity and incident hypertension: a systematic review and meta-analysis of cohort studies. *Hypertension.* 2017;69:813–820. doi: 10.1161/HYPERTENSIONAHA.116.08994
41. Shen Y, Liu H, Dai T, Guan Y, Tu J, Nie H. Association between restless legs syndrome and hypertension: a meta-analysis of nine population-based studies. *Neurol Sci.* 2018;39:235–242. doi: 10.1007/s10072-017-3182-4
42. Ramos AR, Weng J, Wallace DM, Petrov MR, Wohlgemuth WK, Sotres-Alvarez D, Loredo JS, Reid KJ, Zee PC, Mossavar-Rahmani Y, et al. Sleep patterns and hypertension using actigraphy in the Hispanic Community Health Study/Study of Latinos. *Chest.* 2018;153:87–93. doi: 10.1016/j.chest.2017.09.028
43. Johnson DA, Thomas SJ, Abdalla M, Guo N, Yano Y, Rueschman M, Tanner RM, Mittleman MA, Calhoun DA, Wilson JG, et al. Association between sleep apnea and blood pressure control among blacks. *Circulation.* 2019;139:1275–1284. doi: 10.1161/CIRCULATIONAHA.118.036675
44. Tanner RM, Shimbo D, Irvin MR, Spruill TM, Bromfield SG, Seals SR, Young BA, Muntner P. Chronic kidney disease and incident apparent treatment-resistant hypertension among blacks: data from the Jackson Heart Study. *J Clin Hypertens (Greenwich).* 2017;19:1117–1124. doi: 10.1111/jch.13065
45. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: a meta-analysis. *J Hypertens.* 2015;33:221–229. doi: 10.1097/HJH.0000000000000428
46. Kershaw KN, Robinson WR, Gordon-Larsen P, Hicken MT, Goff DC Jr, Carnethon MR, Kiefe CI, Sidney S, Diez Roux AV. Association of changes in neighborhood-level racial residential segregation with changes in blood pressure among black adults: the CARDIA Study. *JAMA Intern Med.* 2017;177:996–1002. doi: 10.1001/jamainternmed.2017.1226
47. Dolezsar CM, McGrath JJ, Herzig AJM, Miller SB. Perceived racial discrimination and hypertension: a comprehensive systematic review. *Health Psychol.* 2014;33:20–34. doi: 10.1037/a0033718
48. Shallcross AJ, Butler M, Tanner RM, Bress AP, Muntner P, Shimbo D, Ogedegbe G, Sims M, Spruill TM. Psychosocial correlates of apparent treatment-resistant hypertension in the Jackson Heart Study [published correction appears in *J Hum Hypertens*. 2017;31:486]. *J Hum Hypertens.* 2017;31:474–478. doi: 10.1038/jhh.2016.100
49. Mayne SL, Moore KA, Powell-Wiley TM, Evenson KR, Block R, Kershaw KN. Longitudinal associations of neighborhood crime and perceived safety with blood pressure: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Hypertens.* 2018;31:1024–1032. doi: 10.1093/ajh/hpy066
50. Sun D, Liu J, Xiao L, Liu Y, Wang Z, Li C, Jin Y, Zhao Q, Wen S. Recent development of risk-prediction models for incident hypertension: an updated systematic review. *PLoS One.* 2017;12:e0187240. doi: 10.1371/journal.pone.0187240
51. Ye C, Fu T, Hao S, Zhang Y, Wang O, Jin B, Xia M, Liu M, Zhou X, Wu Q, et al. Prediction of incident hypertension within the next year: prospective study using statewide electronic health records and machine learning. *J Med Internet Res.* 2018;20:e22. doi: 10.2196/jmir.9268
52. Hardy ST, Holliday KM, Chakladar S, Engeda JC, Allen NB, Heiss G, Lloyd-Jones DM, Schreiner PJ, Shay CM, Lin D, et al. Heterogeneity in blood pressure transitions over the life course: age-specific emergence of racial/ethnic and sex disparities in the United States. *JAMA Cardiol.* 2017;2:653–661. doi: 10.1001/jamacardio.2017.0652

53. Liu C, Kraja AT, Smith JA, Brody JA, Franceschini N, Bis JC, Rice K, Morrison AC, Lu Y, Weiss S, et al; CHD Exome+ Consortium; ExomeBP Consortium; GoT2DGenes Consortium; T2D-GENES Consortium; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia; CKDGen Consortium. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet.* 2016;48:1162–1170. doi: 10.1038/ng.3660
54. Surendran P, Drenos F, Young R, Warren H, Cook JP, Manning AK, Grarup N, Sim X, Barnes DR, Witkowska K, et al; CHARGE-Heart Failure Consortium; EchoGen Consortium; METASTROKE Consortium; GIANT Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study; Wellcome Trust Case Control Consortium; Understanding Society Scientific Group; EPIC-CVD Consortium; CHARGE+ Exome Chip Blood Pressure Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; ExomeBP Consortium; CHD Exome+ Consortium. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat Genet.* 2016;48:1151–1161. doi: 10.1038/ng.3654
55. Ehret GB, Ferreira T, Chasman DI, Jackson AU, Schmidt EM, Johnson T, Thorleifsson G, Luan J, Donnelly LA, Kanoni S, et al; CHARGE-EchoGen Consortium; CHARGE-HF Consortium; Wellcome Trust Case Control Consortium. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet.* 2016;48:1171–1184. doi: 10.1038/ng.3667
56. Hoffmann TJ, Ehret GB, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, Iribarren C, Chakravarti A, Risch N. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet.* 2017;49:54–64. doi: 10.1038/ng.3715
57. Yu B, Pulit SL, Hwang SJ, Brody JA, Amin N, Auer PL, Bis JC, Boerwinkle E, Burke GL, Chakravarti A, et al; on behalf of the CHARGE Consortium and the National Heart, Lung, and Blood Institute GO ESP. Rare exome sequence variants in CLCN6 reduce blood pressure levels and hypertension risk. *Circ Cardiovasc Genet.* 2016;9:64–70. doi: 10.1161/CIRCGENETICS.115.001215
58. Tragante V, Barnes MR, Ganesh SK, Lanktree MB, Guo W, Franceschini N, Smith EN, Johnson T, Holmes MV, Padmanabhan S, et al. Gene-centric meta-analysis in 87,736 individuals of European ancestry identifies multiple blood-pressure-related loci. *Am J Hum Genet.* 2014;94:349–360. doi: 10.1016/j.ajhg.2013.12.016
59. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B, Ntalla I, Surendran P, Liu C, Cook JP, et al; International Consortium of Blood Pressure (ICBP) 1000G Analyses; BIOS Consortium; Lifelines Cohort Study; Understanding Society Scientific group; CHD Exome+ Consortium; ExomeBP Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE) BP Exome Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; UK Biobank CardioMetabolic Consortium BP working group. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk [published correction appears in *Nat Genet.* 2017;49:1558]. *Nat Genet.* 2017;49:403–415. doi: 10.1038/ng.3768
60. He KY, Li X, Kelly TN, Liang J, Cade BE, Assimes TL, Becker LC, Beitelshees AL, Bress AP, Chang YC, et al; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, TOPMed Blood Pressure Working Group. Leveraging linkage evidence to identify low-frequency and rare variants on 16p13 associated with blood pressure using TOPMed whole genome sequencing data. *Hum Genet.* 2019;138:199–210. doi: 10.1007/s00439-019-01975-0
61. Basson J, Sung YJ, Fuentes LL, Schwander K, Cupples LA, Rao DC. Influence of smoking status and intensity on discovery of blood pressure loci through gene-smoking interactions. *Genet Epidemiol.* 2015;39:480–488. doi: 10.1002/gepi.21904
62. Sung YJ, de Las Fuentes L, Schwander KL, Simino J, Rao DC. Gene-smoking interactions identify several novel blood pressure loci in the Framingham Heart Study. *Am J Hypertens.* 2015;28:343–354. doi: 10.1093/ajh/hpu149
63. Li C, He J, Chen J, Zhao J, Gu D, Hixson JE, Rao DC, Jaquish CE, Gu CC, Chen J, et al. Genome-wide gene-sodium interaction analyses on blood pressure: the Genetic Epidemiology Network of Salt-Sensitivity Study. *Hypertension.* 2016;68:348–355. doi: 10.1161/HYPERTENSIONAHA.115.06765
64. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol.* 2016;12:110–122. doi: 10.1038/nrneph.2015.176
65. Ostchega Y, Zhang G, Kit BK, Nwankwo T. Factors associated with home blood pressure monitoring among US adults: National Health and Nutrition Examination Survey, 2011-2014. *Am J Hypertens.* 2017;30:1126–1132. doi: 10.1093/ajh/hpx101
66. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med.* 2011;365:1876–1885. doi: 10.1056/NEJMoa1010112
67. Ostchega Y, Zhang G, Hughes JP, Nwankwo T. Factors associated with hypertension control in US adults using 2017 ACC/AHA guidelines: National Health and Nutrition Examination Survey 1999-2016. *Am J Hypertens.* 2018;31:886–894. doi: 10.1093/ajh/hpy047
68. Yang F, Qian D, Hu D; Healthy Aging and Development Study Group, Nanjing Medical University; Data Mining Group of Biomedical Big Data, Nanjing Medical University. Prevalence, awareness, treatment, and control of hypertension in the older population: results from the multiple national studies on ageing. *J Am Soc Hypertens.* 2016;10:140–148. doi: 10.1016/j.jash.2015.11.016
69. Lee HJ, Jang SI, Park EC. Effect of adherence to antihypertensive medication on stroke incidence in patients with hypertension: a population-based retrospective cohort study. *BMJ Open.* 2017;7:e014486. doi: 10.1136/bmjopen-2016-014486
70. Sundbøll J, Adelborg K, Mansfield KE, Tomlinson LA, Schmidt M. Seventeen-year nationwide trends in antihypertensive drug use in Denmark. *Am J Cardiol.* 2017;120:2193–2200. doi: 10.1016/j.amjcard.2017.08.042
71. Butler MJ, Tanner RM, Muntner P, Shimbo D, Bress AP, Shallcross AJ, Sims M, Ogedegbe G, Spruill TM. Adherence to antihypertensive medications and associations with blood pressure among African Americans with hypertension in the Jackson Heart Study. *J Am Soc Hypertens.* 2017;11:581–588.e5. doi: 10.1016/j.jash.2017.06.011
72. Chang TE, Ritchey MD, Ayala C, Durthaler JM, Loustalot F. Use of strategies to improve antihypertensive medication adherence within United States outpatient health care practices, DocStyles 2015-2016. *J Clin Hypertens (Greenwich).* 2018;20:225–232. doi: 10.1111/jch.13188
73. Sorlie PD, Allison MA, Avilés-Santa ML, Cai J, Daviglus ML, Howard AG, Kaplan R, Lavange LM, Raij L, Schneiderman N, et al. Prevalence of hypertension, awareness, treatment, and control in the Hispanic Community Health Study/Study of Latinos. *Am J Hypertens.* 2014;27:793–800. doi: 10.1093/ajh/hpu003
74. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
75. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999-2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019
76. Patel SA, Winkel M, Ali MK, Narayan KM, Mehta NK. Cardiovascular mortality associated with 5 leading risk factors: national and state preventable fractions estimated from survey data. *Ann Intern Med.* 2015;163:245–253. doi: 10.7326/M14-1753
77. Bress AP, Kramer H, Khatib R, Beddhu S, Cheung AK, Hess R, Bansal VK, Cao G, Yee J, Moran AE, et al. Potential deaths averted and serious adverse events incurred from adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) intensive blood pressure regimen in the United States: projections from NHANES (National Health and Nutrition Examination Survey). *Circulation.* 2017;135:1617–1628. doi: 10.1161/CIRCULATIONAHA.116.025322
78. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ, Ruiz-Hurtado G, Segura J, Rodríguez-Artalejo F, Williams B. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med.* 2018;378:1509–1520. doi: 10.1056/NEJMoa1712231
79. Wei YC, George NI, Chang CW, Hicks KA. Assessing sex differences in the risk of cardiovascular disease and mortality per increment in systolic blood pressure: a systematic review and meta-analysis of follow-up studies in the United States. *PLoS One.* 2017;12:e0170218. doi: 10.1371/journal.pone.0170218
80. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet.* 2014;383:1899–1911. doi: 10.1016/S0140-6736(14)60685-1
81. Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, Gidding SS, Bress AP, Greenland P, Muntner P, et al. Association of blood pressure classification in young adults using the 2017 American College of Cardiology/American Heart Association blood pressure guideline with cardiovascular events later in life. *JAMA.* 2018;320:1774–1782. doi: 10.1001/jama.2018.13551

82. Tsimploulis A, Sheriff HM, Lam PH, Dooley DJ, Anker MS, Papademetriou V, Fletcher RD, Faselis C, Fonarow GC, Deedwania P, et al. Systolic-diastolic hypertension versus isolated systolic hypertension and incident heart failure in older adults: insights from the Cardiovascular Health Study [published correction appears in *Int J Cardiol*. 2017;238:181]. *Int J Cardiol*. 2017;235:11–16. doi: 10.1016/j.ijcard.2017.02.139
83. Hidayat K, Du X, Zou SY, Shi BM. Blood pressure and kidney cancer risk: meta-analysis of prospective studies. *J Hypertens*. 2017;35:1333–1344. doi: 10.1097/HJH.0000000000001286
84. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, et al; for the ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) meta-analysis. *Hypertension*. 2016;67:693–700. doi: 10.1161/HYPERTENSIONAHA.115.06981
85. Booth JN 3rd, Diaz KM, Seals SR, Sims M, Ravenell J, Muntner P, Shimbo D. Masked hypertension and cardiovascular disease events in a prospective cohort of blacks: the Jackson Heart Study. *Hypertension*. 2016;68:501–510. doi: 10.1161/HYPERTENSIONAHA.116.07553
86. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, Huang H, Zeng J, Hu Y, Xu D. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. *J Hypertens*. 2017;35:677–688. doi: 10.1097/HJH.0000000000001226
87. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, et al; INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388:761–775. doi: 10.1016/S0140-6736(16)30506-2
88. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, obesity, diabetes, and heart failure-free survival: the Cardiovascular Disease Lifetime Risk Pooling Project. *JACC Heart Fail*. 2016;4:911–919. doi: 10.1016/j.jchf.2016.08.001
89. Tajeu GS, Booth JN 3rd, Colantonio LD, Gottesman RF, Howard G, Lackland DT, O'Brien EC, Oparil S, Ravenell J, Safford MM, et al. Incident cardiovascular disease among adults with blood pressure <140/90 mm Hg. *Circulation*. 2017;136:798–812. doi: 10.1161/CIRCULATIONAHA.117.027362
90. Howard G, Safford MM, Moy CS, Howard VJ, Kleindorfer DO, Unverzagt FW, Soliman EZ, Flaherty ML, McClure LA, Lackland DT, et al. Racial differences in the incidence of cardiovascular risk factors in older black and white adults. *J Am Geriatr Soc*. 2017;65:83–90. doi: 10.1111/jgs.14472
91. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP). http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
92. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
93. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
94. Vemulapalli S, Deng L, Patel MR, Kilgore ML, Jones WS, Curtis LH, Irvin MR, Svetkey LP, Shimbo D, Calhoun DA, et al. National patterns in intensity and frequency of outpatient care for apparent treatment-resistant hypertension. *Am Heart J*. 2017;186:29–39. doi: 10.1016/j.ahj.2017.01.008
95. Kirkland EB, Heincelman M, Bishu KG, Schumann SO, Schreiner A, Axon RN, Mauldin PD, Moran WP. Trends in healthcare expenditures among US adults with hypertension: national estimates, 2003–2014. *J Am Heart Assoc*. 2018;7:e008731. doi: 10.1161/JAHA.118.008731
96. Park C, Fang J, Hawkins NA, Wang G. Comorbidity status and annual total medical expenditures in U.S. hypertensive adults. *Am J Prev Med*. 2017;53(suppl 2):S172–S181. doi: 10.1016/j.amepre.2017.07.014
97. Tajeu GS, Mennemeyer S, Menachemi N, Weech-Maldonado R, Kilgore M. Cost-effectiveness of antihypertensive medication: exploring race and sex differences using data from the REasons for Geographic and Racial Differences in Stroke Study. *Med Care*. 2017;55:552–560. doi: 10.1097/MLR.0000000000000719
98. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, et al; on behalf of the American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944. doi: 10.1161/CIR.0b013e31820a55f5
99. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001.
100. Ritchey M, Tsipas S, Loustalot F, Wozniak G. Use of pharmacy sales data to assess changes in prescription- and payment-related factors that promote adherence to medications commonly used to treat hypertension, 2009 and 2014. *PLoS One*. 2016;11:e0159366. doi: 10.1371/journal.pone.0159366
101. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010 [published corrections appear in *Lancet*. 2013;381:1276 and *Lancet*. 2013;381:628]. *Lancet*. 2012;380:2224–2260. doi: 10.1016/S0140-6736(12)61766-8
102. Kaze AD, Schutte AE, Erqou S, Kengne AP, Echouffo-Tcheugui JB. Prevalence of hypertension in older people in Africa: a systematic review and meta-analysis. *J Hypertens*. 2017;35:1345–1352. doi: 10.1097/HJH.0000000000001345
103. Owolabi M, Olowoyo P, Miranda JJ, Akinyemi R, Feng W, Yaria J, Makanjuola T, Yaya S, Kaczorowski J, Thabane L, et al; for the COUNCIL Initiative. Gaps in hypertension guidelines in low- and middle-income versus high-income countries: a systematic review. *Hypertension*. 2016;68:1328–1337. doi: 10.1161/HYPERTENSIONAHA.116.08290
104. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–450. doi: 10.1161/CIRCULATIONAHA.115.018912
105. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
106. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015 [published correction appears in *JAMA*. 2017;317:648]. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043
107. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, Cheng X, Mu L, Zhang H, Liu J, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project) [published correction appears in *Lancet*. 2017;390:2548]. *Lancet*. 2017;390:2549–2558. doi: 10.1016/S0140-6736(17)32478-9
108. Noubiap JJ, Essouma M, Bigna JJ, Jingi AM, Aminde LN, Nansseu JR. Prevalence of elevated blood pressure in children and adolescents in Africa: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2:e375–e386. doi: 10.1016/S2468-2667(17)30123-8
109. Dastan I, Erem A, Cetinkaya V. Awareness, treatment, control of hypertension, and associated factors: results from a Turkish national study. *Clin Exp Hypertens*. 2018;40:90–98. doi: 10.1080/10641963.2017.1334797
110. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States, 1996–2015. Agency for Healthcare Research and Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed June 17, 2019.

9. DIABETES MELLITUS

ICD-9 250; ICD-10 E10 to E11. See Tables 9-1 and 9-2 and Charts 9-1 through 9-10

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DM is a heterogeneous mix of health conditions characterized by glucose dysregulation. In the United States, the most common forms are type 2 DM, which affects 90% to 95% of those with DM,[1] and type 1 DM, which constitutes 5% to 10% of DM.[2] DM is diagnosed based on FPG ≥126 mg/dL, 2-hour postchallenge glucose ≥200 mg/dL during an oral glucose tolerance test, random glucose ≥200 mg/dL with presentation of hyperglycemia symptoms, or HbA_{1c} ≥6.5%.[3] DM is a major risk factor for CVD, including CHD and stroke.[4] The AHA has identified untreated FPG levels of <100 mg/dL for children and adults as 1 of the 7 components of ideal CVH.[5]

Abbreviations Used in Chapter 9

ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	albumin-to-creatinine ratio
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities
ASCEND	A Study of Cardiovascular Events in Diabetes
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
CVH	cardiovascular health
DM	diabetes mellitus
ED	emergency department
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
EXAMINE	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
FHS	Framingham Heart Study
FPG	fasting plasma glucose

(*Continued*)

Abbreviations Used in Chapter 9 Continued

GBD	Global Burden of Disease
GRS	genetic risk score
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HDL	high-density lipoprotein
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IDF	International Diabetes Federation
IHD	ischemic heart disease
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IRR	incidence rate ratio
JHS	Jackson Heart Study
LDL-C	low-density lipoprotein cholesterol
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	major adverse cardiovascular events
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity
PAF	population attributable fraction
PWV	pulse-wave velocity
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SEARCH	SEARCH for Diabetes in Youth
SSB	sugar-sweetened beverage
TC	total cholesterol
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TIMI	Thrombolysis in Myocardial Infarction
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
UI	uncertainty interval
USRDS	United States Renal Data System
VTE	venous thromboembolism
WC	waist circumference

Prevalence

Youth

- Approximately 193 000 people <20 years of age were diagnosed with DM in 2015.[1]
- During 2001 to 2009, the prevalence of type 1 DM increased 30% from 1.48 per 1000 youths to 1.93 per 1000 youths.[6]
  - Among youths with type 1 DM, 22.1% are overweight and 12.6% are obese.[7]
- Type 2 DM, a disease usually diagnosed in adults ≥40 years of age, can be diagnosed among people <20 years of age. Between 2001 and 2009, the prevalence of type 2 DM in youths increased by 30.5%.[6]
  - Among youths with type 2 DM, 10.4% are overweight and 79.4% are obese.[7]
- Among US adolescents 12 to 19 years of age in 2005 to 2014, the prevalence of DM was 0.8% (95% CI, 0.6%–1.1%). Of those with DM, 28.5% (95% CI, 16.4%–44.8%) were undiagnosed.[8]
- Among US adolescents 12 to 19 years of age in 2005 to 2014, the prevalence of prediabetes was 17.7% (95% CI, 15.8%–19.8%).[8] Males were more likely to have prediabetes than females (22.0% [95% CI, 19.5%–24.7%] versus 13.2% [95% CI, 10.4%–16.7%]). Also, the prevalence of prediabetes was higher in NH blacks (21.0% [95% CI, 17.7%–24.7%]) and Hispanics (22.9% [95% CI, 19.9%–26.3%]) than in NH white participants (15.1% [95% CI, 12.3%–18.6%]).[8]

Adults
(See Table 9-1 and Charts 9-1 through 9-5)

- On the basis of data from NHANES 2013 to 2016,[9] an estimated 26 million adults have diagnosed DM, 9.4 million adults (3.7%) have undiagnosed DM, and 91.8 million adults (37.6%) have prediabetes. The prevalence of prediabetes and DM differs by sex and race/ethnicity (Table 9-1).
- After adjustment for population age differences, NHANES 2013 to 2016[9] data for people ≥20 years of age indicate that the prevalence of diagnosed DM was 9.4% in NH white males and 7.3% in NH white females, 14.7% in NH black males and 13.4% in NH black females, 15.1% in Hispanic males and 14.1% in Hispanic females, and 12.8% in NH Asian males and 9.9% in NH Asian females (Table 9-1 and Chart 9-1).
- On the basis of 2015 data from the Indian Health Service, the age-adjusted prevalence of diagnosed DM among American Indians/Alaska Natives was 14.9% for males and 15.3% for females.[1]
- On the basis of NHANES 2013 to 2016[9] data, the age-adjusted prevalence of diagnosed DM in adults ≥20 years of age varies by race/ethnicity and years of education. NH white adults with more than a high school education had the lowest prevalence (7.6%), and Hispanic adults with a high school education had the highest prevalence (17.7%; Chart 9-2).
- In the prospective, multicenter, population-based HCHS/SOL, 16 415 adults of Hispanic/Latino descent 18 to 74 years of age were enrolled from 4 US metropolitan areas from 2008 to 2011. The prevalence of DM varied for adults with different Hispanic backgrounds. DM prevalence ranged from 10.2% in South Americans to 13.4% in Cubans, 17.7% in Central Americans, 18.0% in Dominicans and Puerto Ricans, and 18.3% in Mexicans.[10]
- Among foreign-born participants of the US NHANES 1999 to 2012, the prevalence of DM increased with duration of time spent in the United States and was 6.1%, 9.3%, 11.1%, and 20.0% among those in the United States for <1, 1 to 9, 10 to 19, and ≥20 years, respectively.[11]
- Using NHANES 2011 to 2014 data, NH blacks (OR, 2.53 [95% CI, 1.71–3.73]), Asians (OR, 6.16 [95% CI, 3.76–10.08]), and Hispanics (OR, 1.88 [95% CI, 1.19–2.99]) were more likely to have undiagnosed DM than NH whites.[12]
- The prevalence of diagnosed DM in adults was higher for both males and females in the NHANES 2013 to 2016 data than in the NHANES 1988 to 1994 data. Males had a higher prevalence of both diagnosed DM and undiagnosed DM than females in 2013 to 2016. Prevalence of diagnosed and undiagnosed DM increased for both males and females between study periods (Chart 9-3). During this time period, 2 DM diagnostic changes occurred: the threshold definition for diagnosed DM was lowered from ≥140 mg/dL to ≥126 mg/dL in 1997,[13] and HbA_{1c} ≥6.5% was added as a diagnostic test in 2010.[3]
- Geographic variations in DM prevalence have been reported in the United States.
  - Across counties in the United States during 1999 to 2012, the prevalence of diagnosed DM ranged from 5.6% to 20.4%, the prevalence of undiagnosed DM ranged from 3.2% to 6.8%, and the prevalence of total DM ranged from 8.8% to 26.4%.[14] The prevalence of diagnosed DM was highest in the Deep South, near the Texas-Mexico border, and in counties with Native American reservations and was lowest in counties in the upper Midwest and parts of Alaska and New England.
  - Using state-level data from BRFSS[15] 2017, Mississippi had the highest age-adjusted

prevalence of diagnosed DM (12.9%) and Montana had the lowest prevalence (6.7%). The age-adjusted prevalence of diagnosed DM was higher among the US territories of Guam (15.8%) and Puerto Rico (15.0%; Chart 9-4).[15]

— Using data from the REGARDS study, the median (range) predicted prevalence of DM was 14% (10%–20%) among whites and 31% (28%–41%) among blacks.[16] DM was most prevalent in the west and central Southeast among whites (Louisiana, Arkansas, Mississippi, Alabama, Tennessee, and southern Kentucky, as well as parts of North Carolina and South Carolina).

- The age-adjusted prevalence of diagnosed DM and undiagnosed DM increased from 5.0% and 3.5%, respectively, in 1999 to 2000 to 7.8% and 4.4%, respectively, in 2009 to 2010.[17] The prevalence of diagnosed DM increased among NH blacks and whites over this time period.
- The prevalence of diagnosed DM in adults was higher for NH black, NH white, and Hispanic adults in NHANES 1999 to 2010 than in NHANES 1988 to 1994. Prevalence of undiagnosed DM increased slightly between studies (Chart 9-5).[18]

Incidence

Youth

- During 2011 to 2012, an estimated 17 900 people <20 years of age in the United States were diagnosed with incident type 1 DM, and 5300 individuals 10 to 19 years of age were newly diagnosed with type 2 DM annually.[1]
- In the SEARCH study, the incidence rate of type 1 DM increased by 1.4% annually (from 19.5 to 21.7 cases per 100 000 youths per year in 2003 to 2012).[19] The increase was larger for males than for females and for Hispanics and Asian or Pacific Islanders than for other ethnic groups. Also, the incidence of type 2 DM increased by 7.1% annually (from 9.0 to 12.5 cases per 100 000 youths per year from 2003 to 2012). The annual increase was larger among females than males and among NH blacks, Hispanics, Asian or Pacific Islanders, and Native Americans compared with NH whites.
- Projecting disease burden for the US population <20 years of age by 2050, the number of youths with type 1 DM is expected to increase from 166 018 to 203 382, and the number with type 2 DM will increase from 20 203 to 30 111. Less conservative modeling projects the number of youths with type 1 DM at 587 488 and those with type 2 DM at 84 131 by 2050.[20]

Adults (See Table 9-1)

- Approximately 1.5 million US adults ≥18 years of age were diagnosed with incident DM in 2015 (Table 9-1).[1]
- In the CARDIA study, the risk of DM was higher for black females than white females (HR, 2.86 [95% CI, 2.19–3.72]) and for black males than white males (HR, 1.67 [95% CI, 1.28–2.17]) after adjustment for age and field center.[21]

Risk Factors for Developing DM

- In MESA, the incidence rate of DM per 1000 person-years associated with having 0, 1, 2, 3, 4, and 5 to 6 ideal CVH factors was 21.8, 18.6, 13.0, 11.2, 4.7, and 3.6, respectively.[22] Lower DM risk was associated with more ideal CVH factors for Asians, Hispanics, NH blacks, and NH whites. Ideal CVH factors included TC, BP, dietary intake, tobacco use, PA, and BMI.
- In CARDIA, black males and females were more likely to develop DM than white males and females (for males: HR, 1.67 [95% CI, 1.28–2.17]; for females: HR 2.86, [95% CI, 2.19–3.72]) in sex-stratified analyses. Adjustment for FPG, BMI, WC, SBP, use of antihypertensive medications, triglycerides to HDL ratio, and parental history of DM explained the higher incidence of DM observed for black adults compared with white adults, respectively, over 30 years of follow-up.[21]
- In a meta-analysis, each 1-SD higher BMI in childhood was associated with an increased risk for developing DM as an adult (pooled OR, 1.23 [95% CI, 1.10–1.37] for children ≤6 years of age; 1.78 [95% CI, 1.51–2.10] for children 7 to 11 years of age; and 1.70 [95% CI, 1.30–2.22] for those 12 to 18 years of age).[23]
- Compared with birth weight of 3.63 to 4.5 kg, low birth weight (<2.72 kg) increased the risk of type 2 DM (OR, 2.15 [95% CI, 1.54–3.00]), with 47% of this association mediated by insulin resistance.[24]
- Of the 20.9 million new cases of DM predicted to occur over 10 years in the United States, 1.8 million could be attributable to consumption of SSBs. A meta-analysis showed that each 1 serving per day higher consumption of SSBs was associated with an 18% increased risk for DM.[25]
- In a meta-analysis, 600 to 3999, 4000 to 7999, and ≥8000 MET min/wk of PA versus <600 MET min/wk were associated with a decreased risk for developing DM of 0.86 (95% CI, 0.82–0.90), 0.75 (95% CI, 0.70–0.80), and 0.72 (95% CI, 0.68–0.77), respectively.[26]
- In the CARDIA study, higher cardiorespiratory fitness was associated with lower risk for incident

prediabetes/DM (difference of 1 MET: HR, 0.99898 [95% CI, 0.99861–0.99940]; *P*<0.01), which persisted after adjustment for covariates.[27]

- Systematic reviews have found an association between sedentary time and DM even after adjustment for PA.[28,29] For example, Biswas et al[28] analyzed 5 studies and found that higher sedentary time was associated with elevated risk of DM (RR, 1.91 [95% CI, 1.64–2.22]).
- A systematic review found higher type 2 DM risk or prevalence was associated with living in an urban versus rural area (OR, 1.40 [95% CI, 1.22–1.61]), whereas higher neighborhood walkability was associated with lower risk or prevalence (OR, 0.79 [95% CI, 0.72–0.87]).[30]
- In NHANES 2007 to 2014, the prevalence of gestational DM was 7.6%, with 19.7% having a subsequent diagnosis of DM. Age-standardized prevalence of gestational DM was highest among Hispanic females (9.3%) and lower among NH white adults (7.0%) and NH black adults (6.9%).[31]
- In the Nurses' Health Study II, the risk of DM was increased for females with a history of gestational hypertension (HR, 1.65 [95% CI, 1.42–1.91]) or preeclampsia (HR, 1.75 [95% CI, 1.58–1.93]) during first pregnancy compared with females with normotension.[32]

Risk Prediction

- Several risk prediction algorithms for type 2 DM have been developed.[33–36] In 2017, an updated version of the QDiabetes risk prediction algorithm was published. The best performing model explained 63.3% of the variation in the time of diagnosis of type 2 DM, with a C statistic of 0.89.[37]
- Risk prediction algorithms for CVD among individuals with DM have also been developed.[38,39] Recent analyses of the performance of these risk scores found moderate performance, with C statistics ranging from 0.66 to 0.73.[38–40] The QRISK3 score has been reported to have C statistics of 0.86 to 0.87.[36]
- The TIMI risk score for secondary prevention performed moderately well among adults with type 2 DM and high CVD risk. The C statistic was 0.71 (95% CI, 0.69–0.73) for CVD death and 0.66 (95% CI, 0.64–0.67) for a composite end point of CVD death, MI, or stroke.[39]

Family History and Genetics

- DM is heritable; twin or family studies have demonstrated a range of heritability estimates from 30% to 70% depending on age of onset.[41,42] In the FHS, having a parent or sibling with DM conferred a 3.4 times increased risk of DM, which increased to 6.1 if both parents were affected.[43] On the basis of data from NHANES 2009 to 2014, individuals with DM had an adjusted prevalence ratio for family history of DM of 4.27 (95% CI, 3.57–5.12) compared with individuals without DM or prediabetes.[44]
- There are monogenic forms of DM, such as maturity-onset DM of the young. In the TODAY study of overweight and obese children and adolescents with type 2 DM, 4.5% of individuals were found to have monogenic DM.[45]
- The majority of DM is a complex disease characterized by multiple genetic variants with gene-gene and gene-environment interactions. Genome-wide genetic studies of common DM conducted in large sample sizes through meta-analyses have identified >100 genetic variants associated with DM, with the most consistent being a common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene.[46–49]
- Other risk loci for DM identified from GWASs include variants in the genes *SLC30A8* and *HHEX* (related to β-cell development or function) and in the *NAT2* (N-acetyltransferase 2) gene, associated with insulin sensitivity.[48,50]
- GWASs in non-European ethnicities have also identified significant risk loci for DM, including variants in the gene *KCNQ1* (identified from a GWAS in Japanese individuals and replicated in other ethnicities).[48,51] Transethnic analyses have identified genetic variants that are specific to certain ethnicities, for example, within the *PEPD* gene (specific to East Asian ancestry) and *KLF14* gene (specific to European ancestry).[46,47]
- Lifestyle appears to overcome risk conferred by a polygenic risk score composed of a combination of these common variants. In a study of the UK Biobank, genetic composition and combined health behaviors had a log-additive effect on the risk of developing DM, but ideal lifestyle returned the risk of incident DM toward the referent (low genetic risk) group in both the intermediate- and high-genetic-risk groups.[52]
- Genetic variants associated with traits that are risk factors for DM have themselves been shown to associate with DM. For example, in a genome-wide study in the UK Biobank, polygenic risk scores associated with body fat distribution were associated with a higher risk of DM.[53] However, the utility of clinical genetic testing for common type 2 DM is currently unclear.
- In the ACCORD trial, 2 genetic markers were identified with excess CVD mortality in the intensive treatment arm. A GRS has been developed that includes these genetic markers and was found to

be associated with the effect of intensive glycemic treatment of cardiovascular outcomes.[54]
- Novel genes that harbor rare variants associated with common DM have been identified, with the strongest being for a variant in the gene *CCND2* (encoding a protein that helps regulate the cell cycle) that reduces the risk of DM by half.[55]
- Inactivation of rare variants in the *ANGPTL4* (angiopoietin-like 4) gene, which leads to loss of the gene's ability to inhibit lipoprotein lipase, has been associated with reduced DM risk.[56]
- Type 1 DM is also heritable. Early genetic studies identified the role of the *MHC* (major histocompatibility complex) gene in this disease, with the greatest contributor being the human leukocyte antigen region, estimated to contribute to ≈50% of the genetic risk.[57]
- A GRS composed of 9 type 1 DM–associated risk variants has been shown to be able to discriminate type 1 DM from type 2 DM (AUC 0.87), which could be clinically useful given the increasing prevalence of obesity in young adults.[58]
- There may exist shared genetic architectures of DM-related diseases. For example, there are shared genes between polycystic ovarian syndrome and DM; another study found that a DM-associated GRS was also associated with FPG levels in pregnancy[59]; and a recent GWAS in latent autoimmune DM in adults found overlap of many genetic signals with type 1 and type 2 DM.[60]
- The risk of complications from DM is also heritable. For example, diabetic kidney disease shows familial clustering, with diabetic siblings of patients with diabetic kidney disease having a 2-fold increased risk of also developing diabetic kidney disease.[61] Genetic variants have also been identified that appear to increase the risk of CAD or dyslipidemia in patients with DM[62,63] or be protective against diabetic retinopathy in some groups.[64]

Prevention

- Among adults without DM in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of ≥150 min/wk and 58.6% met the weight loss or maintenance goal for DM prevention. Adults with prediabetes were less likely to meet the PA and weight goals than adults with normal glucose levels.[65]
- In 2015, 33.9% of US adults ≥18 years of age had prediabetes, defined as FPG 100 to 125 mg/dL or HbA_{1c} 5.7% to 6.4%.[1] The prevalence of prediabetes increased with age and was higher for males (36.6%) than females (29.3%).[1]
- In NHANES 2011 to 2014 data, among adults with prediabetes, 36.6% had hypertension, 51.2% had dyslipidemia, 24.3% smoked, 7.7% had albuminuria, and 4.6% had reduced eGFR.[66]
- Among adults ≥20 years of age with overweight or obesity from 4 integrated health systems in the United States, 47.2% had prediabetes in 2012 to 2013.[67]
- In the Diabetes Prevention Program of adults with prediabetes (defined as 2-hour postchallenge glucose of 140–199 mg/dL), the absolute risk reduction for DM was 20% for those adherent to the lifestyle modification intervention and 9% for those adherent to the metformin intervention compared with placebo over a median 3-year follow-up. Metformin was effective among those with higher predicted risk at baseline, whereas lifestyle intervention was effective regardless of baseline predicted risk.[68]

Awareness, Treatment, and Control (See Chart 9-6)

- On the basis of NHANES 2013 to 2016 data for adults with DM, 20.9% had their DM treated and controlled, 45.2% had their DM treated but uncontrolled, 9.2% were aware they had DM but were not treated, and 24.7% were undiagnosed and not treated (Chart 9-6).
- The awareness of prediabetes is low, with only 11.6% of adults with prediabetes reporting being told they have prediabetes by a healthcare professional.[1]
- From 2004 through 2011 in the TODAY study, less than half of children (41.1% of Hispanic and 31.5% of NH black children) with recent-onset type 2 DM maintained durable glycemic control with metformin monotherapy, which is a higher rate of treatment failure than observed in adult cohorts.[69]
- In a pooled analysis of ARIC, MESA, and JHS, 41.8%, 32.1%, and 41.9% of participants were at target levels for BP, LDL-C, and HbA_{1c}, respectively; 41.1%, 26.5%, and 7.2% were at target levels for any 1, 2, or all 3 factors, respectively. Having 1, 2, and 3 factors at goal was associated with 36%, 52%, and 62%, respectively, lower risk of CVD events compared with participants with no risk factors at goal.[70]
- In NHANES 2007 to 2010 data, 52.5% of adults with DM had an HbA_{1c} <7.0%, 51.1% achieved a BP <130/80 mm Hg, 56.2% had an LDL-C <100 mg/dL, and 18.8% had reached all 3 treatment targets. Compared with NH whites, Mexican Americans were less likely to meet HbA_{1c} and LDL-C goals, and NH blacks were less likely to meet BP and LDL-C goals.[71] Additionally, 22.3% of adults with DM reported being current smokers.[72]

- In NHANES 2011 to 2016, 50.4% of adults with DM who were taking antihypertensive medications did not meet BP treatment goals according to both the 2017 Hypertension Clinical Practice Guidelines and the American Diabetes Association standards of medical care.[73]
- In NHANES 2011 to 2016, 83.4% of adults with DM had an HbA_{1c} test in the past year. Testing rates were higher for individuals with health insurance (86.6%) than for those without health insurance (55.9%).[74]
- Using data from BRFSS 2013, individuals with private insurance were more likely than those without insurance to have had HbA_{1c} testing (OR, 2.60 [95% CI, 2.02–3.35]), a foot examination (OR, 1.72 [95% CI, 1.32–2.25]), or an eye examination (OR, 2.01 [95% CI, 1.56–2.58]) in the past year.[75]
- In the SEARCH study (Washington and South Carolina sites), the prevalence of food insecurity among individuals with type 1 DM was 19.5%. Youth and young adults from food-insecure households were more likely to have an HbA_{1c} >9.0% (OR, 2.37 [95% CI, 1.10–5.09]).[76]
- Among young adults with type 2 DM in the SEARCH study, those who transferred from pediatric care to an adult care provider or no care provider were more likely to have an HbA_{1c} >9% (OR, 4.5 [95% CI, 1.8–11.2] for transfer to adult care provider and OR, 4.6 [95% CI, 1.4–14.6] for transfer to no care provider).[77]
- Among HCHS/SOL study participants with DM, 43.0% had HbA_{1c} <7.0%, 48.7% had BP <130/80 mm Hg, 36.6% had LDL-C <100 mg/dL, and 8.4% had reached all 3 treatment targets.[78]
  - HCHS/SOL participants in the lowest versus highest tertile of sedentary time were more likely to have controlled their HbA_{1c} to <7% (OR, 1.76 [95% CI, 1.10–2.82]) and their triglycerides to <150 mg/dL (OR, 2.16 [95% CI, 1.36–3.46]).[79]
- According to NHANES 2007 to 2012, 17% of US adults with DM met the criteria for major depression or subsyndromal symptomatic depression. This represents 3.7 million US adults with these conditions.[80]
- From NHANES 2003 to 2012 data, 52% of adults with DM were taking cholesterol-lowering medications.[81]
- In the AHA's GWTG Program, patients with ACS and DM were less likely to have LDL-C checked or a statin prescribed than patients with ACS but without DM.[82]
- In the IMPROVE-IT trial, adults with DM randomized to ezetimibe plus statin versus placebo plus statin had a lower risk of the composite end point of CVD death, CHD, and stroke (HR, 0.85 [95% CI, 0.78–0.94]).[83]
- In MEPS, 70% (95% CI, 68%–71%), 67% (95% CI, 66%–69%), and 68% (95% CI, 66%–71%) of US adults with DM received appropriate DM care (HbA_{1c} measurement, foot examination, and an eye examination) in 2002, 2007, and 2013, respectively[84]; however, only 39.6% of adults with DM reported receiving dilated eye examinations annually.[85]
- Among Medicare Advantage patients with DM from 2006 to 2013, use of metformin increased from 47.6% to 53.5%, use of dipeptidyl peptidase 4 inhibitors increased from 0.5% to 14.9%, insulin use increased from 17.1% to 23.0%, use of sulfonylureas decreased from 38.8% to 30.8%, and thiazolidinedione use decreased from 28.5% to 5.6%.[86]
- The ASCEND trial used a factorial design to examine the effect of aspirin and omega-3 fatty acid supplementation on CVD risk among individuals with DM and no history of CVD. Over a mean follow-up of 7.4 years, the CVD event rate was lower among those in the aspirin group than those in the placebo group (RR, 0.88 [95% CI, 0.79–0.97]), but there was also a higher rate of major bleeding events (RR, 1.29 [95% CI, 1.09–1.52]), such that the absolute benefits were largely counterbalanced by the increased bleeding risk.[87] Furthermore, omega-3 fatty acid supplementation did not reduce CVD risk compared with placebo (RR, 0.97 [95% CI, 0.87–1.08]).[88]
- The Steno-2 study of 7.8 years of intensified, multifactorial treatment for individuals in Denmark with type 2 DM and microalbuminuria found that 21.2 years after the start of the study, the intensive treatment intervention group had decreased mortality (HR, 0.55 [95% CI, 0.36–0.83]), decreased rate of CVD events (HR, 0.55 [95% CI, 0.39–0.77]), decreased rate of macroalbuminuria (HR, 0.52 [95% CI, 0.32–0.84)], and decreased rate of HF hospitalizations (HR, 0.30 [95% CI, 0.14–0.64]) compared with the conventional therapy group.[89,90]

Mortality (See Table 9-1)

- DM was listed as the underlying cause of mortality for 83 564 people (46 302 males and 37 262 females) in the United States in 2017 (Table 9-1).[91]
- The 2017 overall age-adjusted death rate attributable to DM was 21.5 per 100 000. For males, the age-adjusted death rates per 100 000 population were 24.0 for NH whites, 46.6 for NH blacks, 31.3

for Hispanics, 20.1 for NH Asian/Pacific Islanders, and 55.0 for NH American Indian/Alaska Natives. For females, the age-adjusted death rates per 100 000 population were 14.6 for NH whites, 32.8 for NH blacks, 20.9 for Hispanics, 13.7 for NH Asian/Pacific Islanders, and 38.3 for NH American Indian/Alaska Natives (unpublished NHLBI tabulation using CDC WONDER[92]).

- In a study of NHIS 1997 to 2009 participants followed up through 2011, DM was the underlying cause for 3.3% of deaths and a contributing cause for 10.8% of deaths. The PAF for death associated with DM was 11.5%. Although DM was more often cited as an underlying and contributing cause of death for NH blacks and Hispanics than for NH whites, the PAF was similar in each racial/ethnic group.[93]
- In a collaborative meta-analysis of 980 793 individuals from 68 prospective studies, DM was associated with all-cause mortality among both males (RR, 1.59 [95% CI, 1.54–1.65]) and females (RR, 2.00 [95% CI, 1.90–2.11]).[94]
- Among NHIS participants enrolled in 2000 to 2009 and followed up through 2011, males and females with diagnosed DM had 1.56 and 1.69 times as high risk of all-cause mortality as those without diagnosed DM (HR, 1.56 [95% CI, 1.49–1.64] and 1.69 [95% CI, 1.61–1.78], respectively).[95]
- In the Swedish National Diabetes Register, there was a significant decline in all-cause mortality from 1998 to 2014 among individuals with type 1 DM (HR, 0.71 [95% CI, 0.66–0.78]), but this decline was not statistically different from the decline observed among individuals without DM (HR, 0.77 [95% CI, 0.72–0.83]). In contrast, the decline in all-cause mortality from 1998 to 2014 among individuals with type 2 DM (HR, 0.79 [95% CI, 0.78–0.80]) was less than the decline observed among individuals without DM (HR, 0.69 [95% CI, 0.68–0.70]).[96]
- In the Swedish National Diabetes Register, compared with individuals without DM, the adjusted HR for all-cause mortality for individuals with type 1 DM who met all risk factor targets was 1.31 (95% CI, 0.93–1.85), whereas the HR for individuals with type 1 DM who met no risk factor targets was 7.33 (95% CI, 5.08–10.57).[97] Individuals with type 2 DM who met all risk factor targets (HbA_{1c}, LDL-C, BP, urine ACR, and nonsmoker) had similar risks of death, MI, and stroke as those without DM.[98]
- The association of new-onset type 2 DM and all-cause mortality exhibited a U-shaped relationship by BMI, with the strongest associations observed among those with BMI ≥40 kg/m^2 (HR, 1.37 [95% CI, 1.11–1.71] for short-term mortality risk within 5 years and HR, 2.00 [95% CI, 1.58–2.54] for long-term mortality risk >5 years).[99]
- In the NHIS from 1985 to 2014, there was a decrease in major CVD deaths, with 25% greater percentage reduction among adults with DM than among adults without DM.[100]
- The leading cause of death among patients with type 1 DM is CVD, which accounted for 22% of deaths among those in the Allegheny County, PA, type 1 DM registry, followed by renal (20%) and infectious (18%) causes.[101]
- Age at diagnosis is an important factor in mortality rates among individuals with type 1 DM. In the Swedish National Diabetes Register, those who developed type 1 DM before 10 years of age experienced a loss of 17.7 life-years (95% CI, 14.5–20.4) for females and 14.2 life-years (95% CI, 12.1–18.2) for males compared with those without type 1 DM.[102]

Complications (See Chart 9-7)

Microvascular Complications

- Among those ≤21 years of age with newly diagnosed DM in a US managed care network, 20% of youth with type 1 DM and 7.2% of youth with type 2 DM developed diabetic retinopathy over a median follow-up of 3 years.[103]
- Among American Indian and Alaska Native individuals with DM using primary care clinics of the US Indian Health Service, tribal, and urban Indian healthcare facilities, 17.7% had nonproliferative diabetic retinopathy, 2.3% had proliferative diabetic retinopathy, and 2.3% had diabetic macular edema.[104]
- On the basis of analyses of data from the NIS, the USRDS, and the US NVSS, between 1995 and 2015 (Chart 9-7), substantial declines have been observed in the age-standardized rates of hospitalization for lower-extremity amputation (32.4% decline), incident DM-related ESRD (39.0% decline), and mortality attributable to hyperglycemic crisis (34.2% decline) among those with diagnosed DM.[105]
- Among adults with DM in NHANES 2007 to 2012, the overall age-adjusted prevalence of CKD was 40.2% in 2007 to 2008, 36.9% in 2009 to 2010, and 37.6% in 2011 to 2012.[106] The prevalence of CKD was 58.7% in US adults with DM ≥65 years of age, 25.7% in those <65 years of age, 43.5% in NH blacks and Mexican Americans, and 38.7% in NH whites.
- Using the Kidney Disease Improving Global Outcomes classification for CKD among adults

with type 2 DM in NHANES 2007 to 2014, the prevalence of stage 3a CKD (mildly to moderately decreased kidney function) was 10.4% (95% CI, 9.1%–11.7%), stage 3b CKD (moderately to severely decreased) was 5.4% (95% CI, 4.5%–6.4%), stage 4 CKD (severely decreased) was 1.8% (95% CI, 1.3%–2.4%), and stage 5 CKD (kidney failure) was 0.4% (95% CI, 0.2%–0.7%).[107]

- The prevalence of any diabetic kidney disease, defined as persistent albuminuria, persistent reduced eGFR, or both, did not significantly change from the period 1988 to 1994 (28.4% [95% CI, 23.8%–32.9%]) to 2009 to 2014 (26.2% [95% CI, 22.6%–29.9%]). Persistence was calculated based on elevated values obtained during both the mobile examination and home collection sample on a subset of NHANES participants. However, the prevalence of albuminuria decreased from 20.8% (95% CI, 16.3%–25.3%) to 15.9% (95% CI, 12.7%–19.0%) and the prevalence of reduced eGFR increased from 9.2% (95% CI, 6.2%–12.2%) to 14.1% (95% CI, 11.3%–17.0%) over this time period.[108]

CVD Complications

- Among NHIS participants enrolled in 2000 to 2009 and followed up through 2011, DM was associated with increased risk for CVD mortality for both males and females.[95]
- In the TECOS trial of adults with type 2 DM and ASCVD, females with DM had a lower risk of MI (HR, 0.70 [95% CI, 0.55–0.90]) and stroke (HR, 0.52 [95% CI, 0.38–0.71]) than males with DM.[109]
- On the basis of analyses of data from the NHIS, between 1995 and 2015, the rate of hospitalizations for IHD declined 67.8% and the rate of hospitalization for stroke declined 37.9% among patients with DM (Chart 9-7).[110]
- The HRs of CHD events comparing participants with DM only, DM and prevalent CHD, and neither DM nor prevalent CHD with those with prevalent CHD were 0.65 (95% CI, 0.54–0.77), 1.54 (95% CI, 1.30–1.83), and 0.41 (95% CI, 0.35–0.47), respectively, after adjustment for demographics and risk factors.[111] Compared with participants who had prevalent CHD, the HR of CHD events for participants with severe DM was 0.88 (95% CI, 0.72–1.09).
- A 1-SD increase in glucose variability increased the risk of CVD (HR, 1.11 [95% CI, 1.01–1.23] for coefficient of variation and HR, 1.14 [95% CI, 1.04–1.25] for average real variability) in the Veterans Affairs Diabetes Trial after adjustment for risk factors and mean glucose.[112]
- In a prospective cohort study of individuals with childhood-onset type 1 DM, a 1% increase in HbA_{1c} was associated with a 1.26-fold increase in incident CVD (95% CI, 1.07–1.45).[113]
- In a meta-analysis of 19 studies, DM was not associated with an increased risk for VTE (pooled RR, 1.10 [95% CI, 0.94–1.29]).[114]
- Compared with those with normal glucose, carotid-femoral PWV was 95.8 cm/s (95% CI, 69.4–122.1 cm/s) and 21.3 cm/s (95% CI, –0.8 to 43.4 cm/s) higher for participants with DM and prediabetes, respectively.[115] A similar pattern was present for brachial-ankle PWV.
- In MESA, 63% of participants with DM had a CAC score >0 compared with 48% of those without DM.[116]
- In CARDIA, a longer duration of DM was associated with CAC presence (per 5-year longer duration: HR, 1.15 [95% CI, 1.06–1.25]) and worse cardiac function, including early diastolic relaxation and higher diastolic filling pressure.[117]
- In a nationwide Danish registry, the adjusted IRRs for AF comparing people with and without DM were 2.34 (95% CI, 1.52–3.60), 1.52 (95% CI, 1.47–1.56), 1.20 (95% CI, 1.18–1.23), and 0.99 (95% CI; 0.97–1.01) for adults 18 to 39, 40 to 64, 65 to 74, and 75 to 100 years of age, respectively.[118]
- In an analysis of NHANES 2001 to 2010, the prevalence of AP among participants with CHD was similar for adults with and without DM (49% and 46%, respectively).[119]
- DM increases the risk of HF and adversely affects outcomes among patients with HF.
  - DM alone qualifies for the most recent ACC/AHA diagnostic criteria for stages A and B HF, a classification of patients without HF but at notably high risk for its development.[120]
  - In a meta-analysis of 10 prospective cohort studies, the HR for HF per 1-mmol/L (≈18 mg/dL) increase in FPG level was 1.11 (95% CI, 1.04–1.17), which suggests an independent and continuous positive association between FPG and HF.[121]
  - Post hoc analysis of data from the EVEREST randomized trial of patients hospitalized with decompensated systolic HF demonstrated that DM increased the risk of the composite outcome of cardiovascular mortality and HF hospitalization (HR, 1.17 [95% CI, 1.04–1.31]) over a median 9.9 months of follow-up.[122]
  - The association between glycemia and outcomes has been mixed in patients with HF, and there is insufficient evidence to recommend specific glucose treatment goals in patients hospitalized with HF.[123]

Hypoglycemia

- Hypoglycemia is a major factor that limits glycemic control in DM. In 2010, among Medicare beneficiaries with DM, hospitalizations for hypoglycemia and hyperglycemia occurred at a rate of 612 and 367 per 100 000 person-years, respectively.[124]
- In the Veterans Affairs Diabetes Trial, severe hypoglycemia within the prior 3 months was associated with an increased risk of a CVD event (HR, 1.9 [95% CI, 1.06–3.52]), CVD mortality (HR 3.7 [95% CI 1.3–10.4]), and all-cause mortality (HR, 2.4 [95% CI, 1.1–5.1)].[125]
- In the LEADER trial, patients with type 2 DM who experienced a severe hypoglycemic event had an increased risk of MACE (HR, 2.2 [95% CI, 1.6–3.0]) and CVD death (HR, 3.7 [95% CI, 2.6–5.4]).[126] Similarly, in the EXAMINE trial, severe hypoglycemia was associated with an increased risk of MACE (HR, 2.42 [95% CI, 1.27–4.60]).[127]
- In ARIC, severe hypoglycemia was associated with an increased risk of CHD (HR, 2.02 [95% CI, 1.27–3.20]), all-cause mortality (HR, 1.73 [95% CI, 1.38–2.17]), cardiovascular mortality (HR, 1.64 [95% CI, 1.15–2.34]), and cancer mortality (HR, 2.49 [95% CI, 1.46–4.24]).[128]
- In a post hoc analysis of the TECOS trial of adults with type 2 DM and ASCVD, nonfatal MI and nonfatal stroke increased the risk of severe hypoglycemia (HR, 2.31 [95% CI, 1.39–3.82] for MI and HR, 2.07 [95% CI, 1.01–4.23] for stroke) after adjustment for clinical factors.[129]
- Severe hypoglycemia is more common with increasing age, with use of insulin or sulfonylureas, and in those with impaired renal function, type 1 DM, and prior severe hypoglycemia.[130] Higher rates of hypoglycemia have also been reported in NH blacks compared with NH whites.[131]
- Using data from the Optum Labs Data Warehouse, 6419 index hospitalizations for hypoglycemia were identified among individuals with DM from 2009 to 2014. The 30-day readmission after these index hospitalizations was 10%, with the majority of these readmissions being for other primary causes and only 12% for recurrent hypoglycemia.[132]

Healthcare Utilization (See Table 9-1)

- In 2016, there were 580 000 principal diagnosis discharges for DM (HCUP,[133] unpublished NHLBI tabulation; Table 9-1).
- Among Medicare beneficiaries with type 2 DM enrolled in Medicare Advantage prescription drug plans hospitalized between 2012 and 2014, there was a 17.1% 30-day readmission rate.[134] Using data from the Optum Labs Data Warehouse, individuals with type 2 DM hospitalized between 2009 and 2014 had a 10.8% 30-day readmission rate.[135]
- According to the 2014 NIS, the rate of hospitalization among adults with DM was 327.2 per 1000 people with DM for any cause (7.2 million discharges), 70.4 per 1000 people with DM for major CVD (1.5 million discharges), 5.0 per 1000 people with DM for lower-extremity amputation (108 000 discharges), and 7.7 per 1000 people with DM for diabetic ketoacidosis (168 000 discharges).[1]
- According to the 2014 NEDS, the rate of ED visits was 648.9 per 1000 people with DM for any cause (14.2 million visits), 11.2 per 1000 people with DM for hypoglycemia (245 000 visits), and 9.5 per 1000 people with DM for hyperglycemia (207 000 visits).[1]
- Among participants in the ARIC study without a prior diagnosis of DM, hospitalization rates were 163 (95% CI, 158–169), 217 (95% CI, 206–228), and 254 (95% CI, 226–281) per 1000 person-years with HbA_{1c} <5.7%, 5.7% to <6.5%, and ≥6.5%, respectively. Among those with diagnosed DM, the hospitalization rates were 340 (95% CI, 297–384) and 504 (95% CI, 462–547) for participants with HbA_{1c} <7.0% and ≥7.0%, respectively.[136]

Cost (See Table 9-1)

- In 2017, the cost of DM was estimated at $327 billion, up 26% from 2012, accounting for 1 in 4 healthcare dollars.[137] Of these costs, $237 billion were direct medical costs and $90 billion resulted from reduced productivity. Medical costs for patients with DM were 2.3 times higher than for people without DM, with an average medical expenditure of $16 752 per year for people with DM, of which $9601 was attributed to DM.[137]
- Informal care is estimated to cost $1192 to $1321 annually per person with DM.[138]
- Using 2001 to 2013 MarketScan data, the per capita total excess medical expenditure for individuals with DM in the first 10 years after diagnosis is $50 445.[139]
- In 2014, the cost for DM-related preventable hospitalizations was $5.9 billion. Between 2001 and 2014, this cost increased annually by 1.6%, of which 25% was attributable to an increase in the cost per hospitalization and 75% was attributable to an increase in the number of hospitalizations.[140] The DM-related preventable hospitalization rate has decreased slightly[140] or stayed stable.[141]
- A systematic review estimated that CVD costs account for 20% to 49% of the total direct costs of DM care.[142]

Global Burden of DM (See Table 9-2 and Charts 9-8 through 9-10)

- The GBD 2017 Study used bayesian meta-regression tools and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[143]
  - The prevalence of DM increased 129.7% for males and 120.9% for females between 1990 and 2017. Overall, 245.5 million males and 230.5 million females worldwide have DM (Table 9-2).
  - Age-standardized mortality rates attributable to high FPG are generally lower in high income countries (Chart 9-8).
  - Age-standardized mortality attributable to DM is highest in Oceania, Southern and sub-Saharan Africa, Southeast Asia, and parts of Central and Tropical Latin America (Chart 9-9).
  - The age-standardized prevalence of DM is highest in Oceania (Chart 9–10).
- According to the IDF Atlas, the global prevalence of DM was 451 million (95% CI, 367–585 million) for adults 18 to 99 years of age in 2017 and is projected to increase to 693 million (95% CI, 522–903 million) by 2045.[144] The IDF Atlas global prevalence estimate did not include all ages and used a different methodology than the GBD prevalence estimate reported here.
- The global economic burden of DM was $1.3 trillion in 2015. It is estimated to increase to $2.1 to 2.5 trillion by 2030.[145]

Table 9-1. DM in the United States

Population Group	Prevalence of Diagnosed DM, 2013–2016: Age ≥20 y	Prevalence of Undiagnosed DM, 2013–2016: Age ≥20 y	Prevalence of Prediabetes, 2013–2016: Age ≥20 y	Incidence of Diagnosed DM, 2015: Age ≥18 y*	Mortality, 2017: All Ages†	Hospital Discharges, 2016: All Ages	Cost, 2017‡
Both sexes	26 000 000 (9.8%)	9 400 000 (3.7%)	91 800 000 (37.6%)	1 500 000	83 564	580 000	$327 Billion
Males	13 700 000 (10.9%)	5 500 000 (4.6%)	51 700 000 (44.0%)	…	46 302 (55.4%)§	319 000	…
Females	12 300 000 (8.9%)	3 900 000 (2.8%)	40 100 000 (31.3%)	…	37 262 (44.6%)§	261 000	…
NH white males	9.4%	4.7%	43.7%	…	31 343	…	…
NH white females	7.3%	2.6%	32.2%	…	23 773	…	…
NH black males	14.7%	1.7%	31.9%	…	7494	…	…
NH black females	13.4%	3.3%	24.0%	…	7304	…	…
Hispanic males	15.1%	6.3%	48.1%	…	5054	…	…
Hispanic females	14.1%	4.0%	31.7%	…	4162	…	…
NH Asian males	12.8%	6.1%	47.1%	…	1612	…	…
NH Asian females	9.9%	2.1%	29.4%	…	1435	…	…
NH American Indian or Alaska Native	…	…	…	…	1114	…	…

Undiagnosed DM is defined as those whose fasting glucose is ≥126 mg/dL but who did not report being told by a healthcare provider that they had DM. Prediabetes is a fasting blood glucose of 100 to <126 mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance. DM indicates diabetes mellitus; ellipses (…), data not available; and NH, non-Hispanic.

*Centers for Disease Control and Prevention, National Diabetes Statistics Report, 2017.[1]

†Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

‡American Diabetes Association.[2]

§These percentages represent the portion of total DM mortality that is for males vs females.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed DM: unpublished National Heart Lung and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey, 2013 to 2016.[9] Percentages for sex and racial/ethnic groups are age adjusted for Americans ≥20 years of age. Mortality: unpublished NHLBI tabulation using National Vital Statistics System, 2017.[91] These data represent DM as the underlying cause of death only. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Healthcare Cost and Utilization Project, 2016.[133]

Table 9-2. Global Prevalence and Mortality of DM, 2017

	Both Sexes Combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	1.4 (1.3 to 1.4)	476.0 (436.6 to 522.8)	0.7 (0.6 to 0.7)	245.5 (225.2 to 269.4)	0.7 (0.7 to 0.7)	230.5 (211.2 to 252.8)
Percent change total number 1990 to 2017	125.5 (116.9 to 132.4)	125.4 (116.9 to 135.6)	141.9 (133.3 to 151.1)	129.7 (121.0 to 140.3)	112.2 (101.5 to 120.7)	120.9 (112.2 to 130.9)
Percent change total number 2007 to 2017	34.7 (32.2 to 37.3)	29.6 (24.7 to 35.0)	35.7 (32.8 to 38.8)	29.3 (24.3 to 35.0)	33.8 (30.1 to 37.5)	29.8 (24.6 to 35.4)
Rate per 100 000	17.5 (17.1 to 17.9)	5886.9 (5403.6 to 6458.5)	18.6 (18.1 to 19.0)	6261.0 (5750.2 to 6867.1)	16.6 (16.1 to 17.2)	5527.6 (5062.4 to 6058.0)
Percent change rate 1990 to 2017	11.6 (7.4 to 14.9)	24.2 (19.6 to 29.5)	17.0 (13.1 to 21.2)	26.4 (21.6 to 31.8)	6.4 (1.1 to 10.7)	22.0 (17.3 to 27.2)
Percent change rate 2007 to 2017	1.2 (–0.7 to 3.1)	3.9 (0.0 to 8.2)	1.0 (–1.1 to 3.3)	4.0 (–0.2 to 8.4)	0.9 (–1.8 to 3.7)	3.8 (–0.4 to 8.0)

DM indicates diabetes mellitus; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[143] Printed with permission. Copyright © 2018, University of Washington.

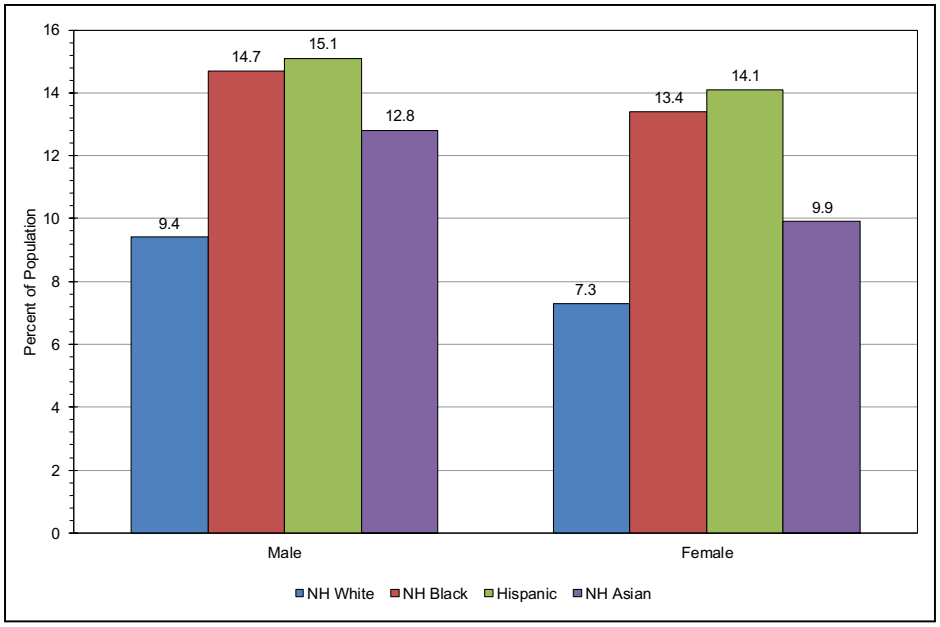

Chart 9-1. Age-adjusted prevalence of diagnosed diabetes mellitus in US adults ≥20 years of age by race/ethnicity and sex (NHANES, 2013–2016).
NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[9]

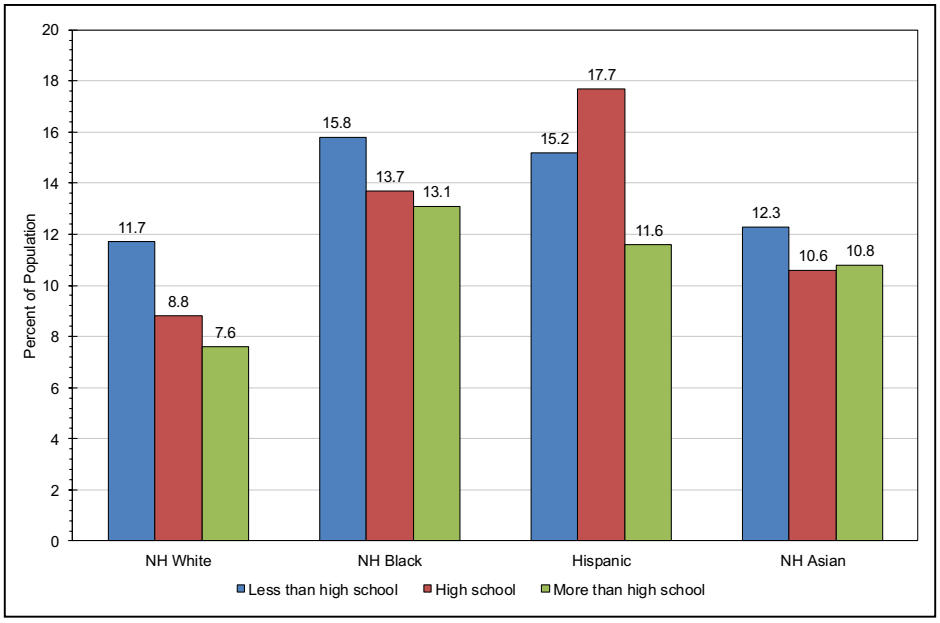

Chart 9-2. Age-adjusted prevalence of diagnosed diabetes mellitus in US adults ≥20 years of age by race/ethnicity and years of education (NHANES, 2013–2016).

NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[9]

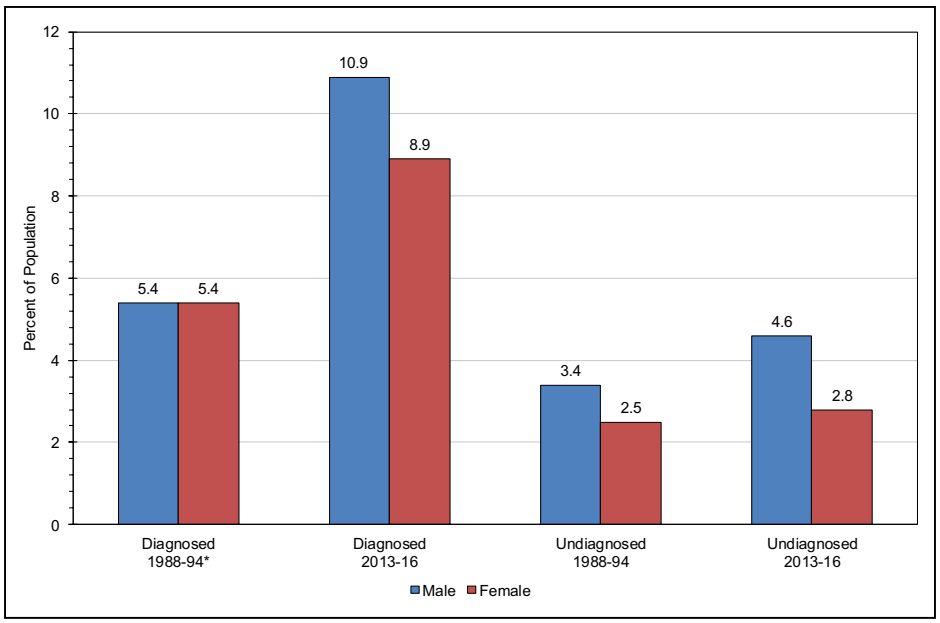

Chart 9-3. Trends in diabetes mellitus prevalence in US adults ≥20 years of age by sex (NHANES, 1988–1994 and 2013–2016).

The definition of diabetes mellitus changed in 1997 (from glucose ≥140 mg/dL to ≥126 mg/dL).

NHANES indicates National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 1988 to 1994 and 2013 to 2016.[9]

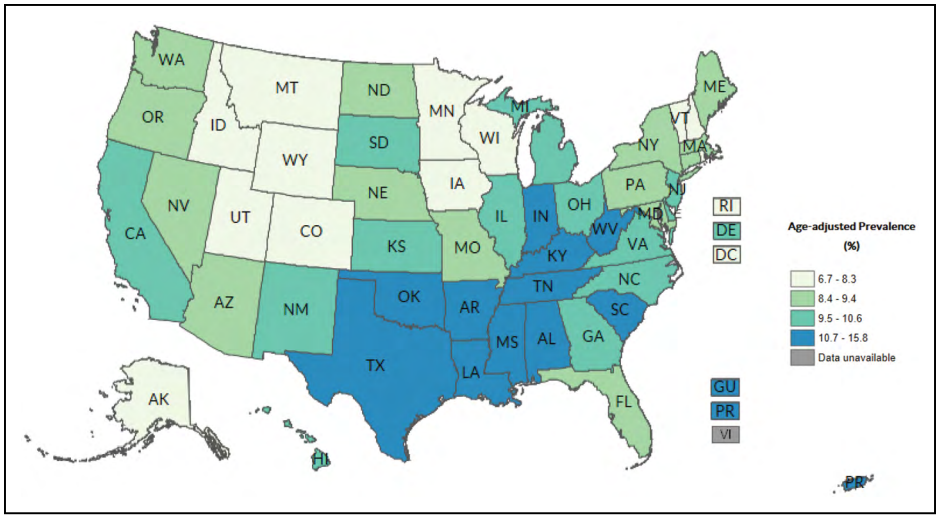

Chart 9-4. Age-adjusted percentage of adults with diagnosed diabetes mellitus, US states and territories, 2017.
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Source: Reprinted from Behavioral Risk Factor Surveillance System Prevalence and Trends Data.[15]

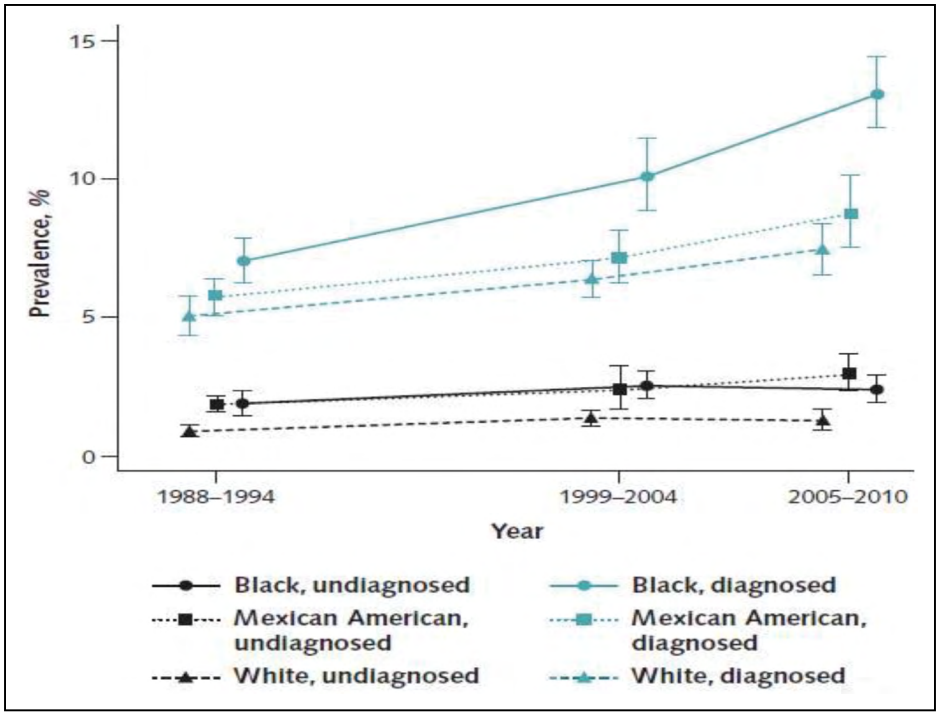

Chart 9-5. Trends in the prevalence of diagnosed and undiagnosed diabetes mellitus (calibrated hemoglobin A_{1c} levels >6.5%), by racial/ethnic group, 1988 to 1994, 1999 to 2004, and 2005 to 2010.
Data from US adults ≥20 years of age in NHANES 1988 to 1994, 1999 to 2004, and 2005 to 2010.
NHANES indicates National Health and Nutrition Examination Survey.
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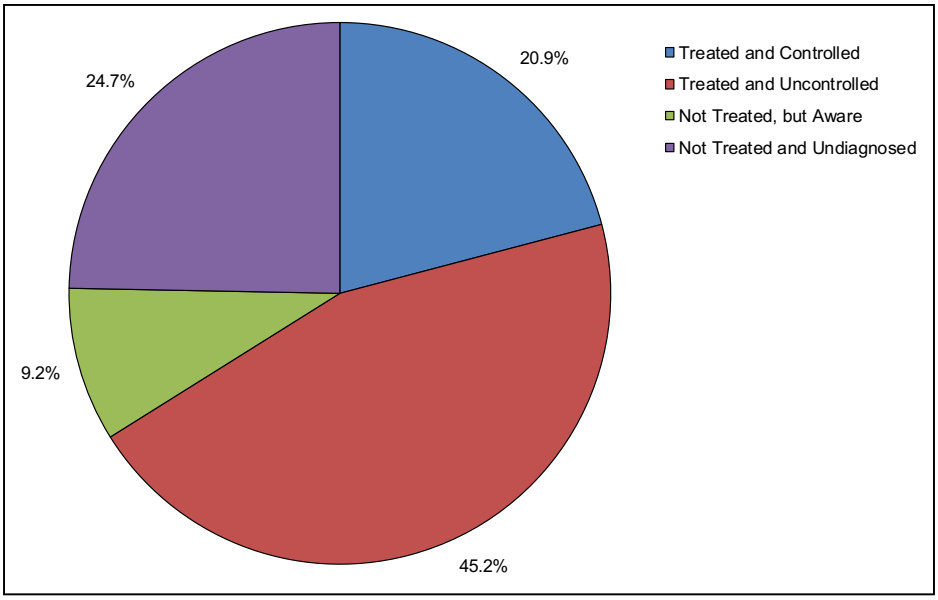

Chart 9-6. Awareness, treatment, and control of diabetes mellitus in US adults ≥20 years of age (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[9]

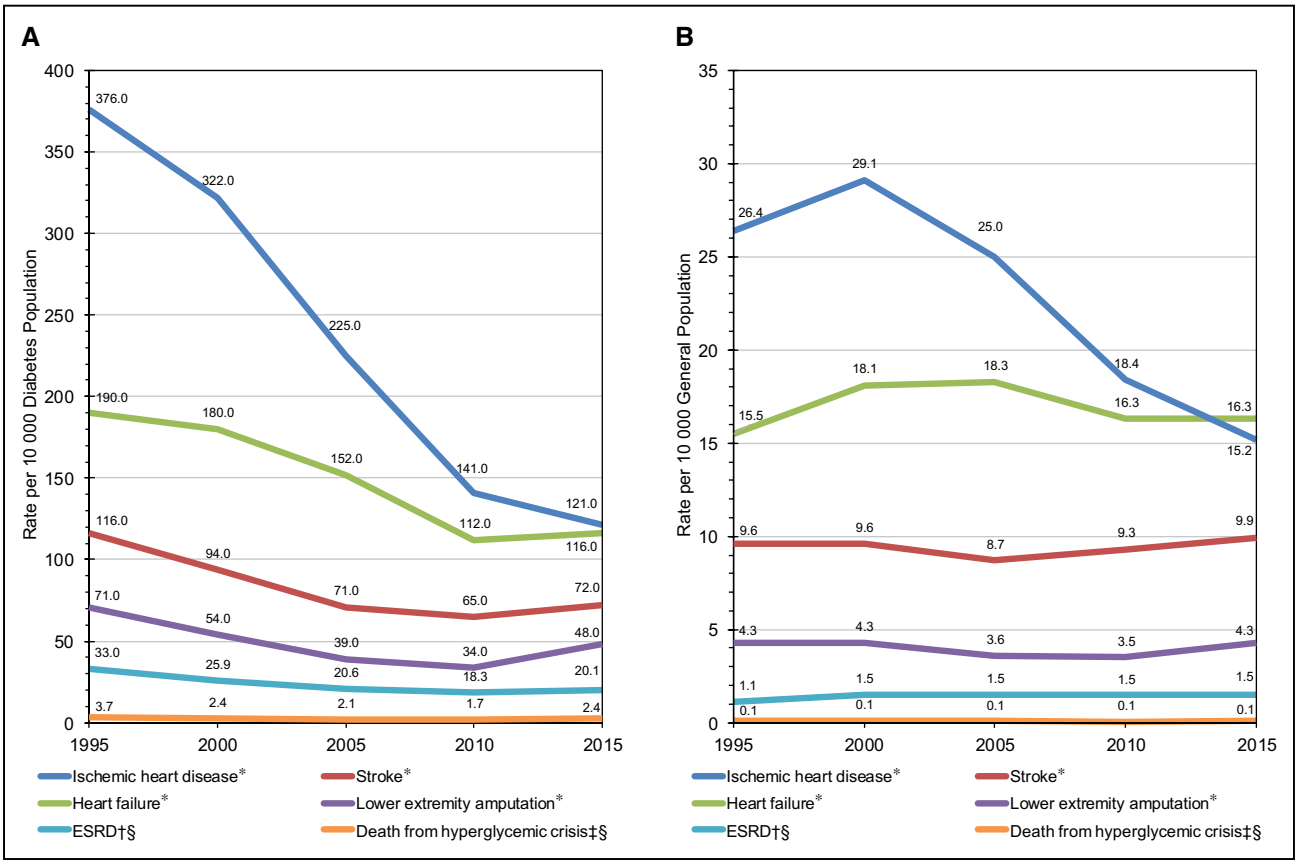

Chart 9-7. Trends in age-standardized rates of complications among US adults ≥18 years of age from 1995 to 2015.
Data in (**A**) include the population with diabetes and (**B**) include the general population (with or without diabetes).
Age adjustment is to the 2000 US standard population using age groups <45, 45 to 64, 65 to 74, and ≥75 years of age.
ESRD indicates end-stage renal disease.
*Hospitalization rates; data from the National Inpatient Sample of the Agency for Healthcare Research and Quality.
†DM-related ESRD; data from the United States Renal Data System.
‡Data from the Centers for Disease Control and Prevention's National Vital Statistics System.
§Hyperglycemic crisis and ESRD rates are for all ages.
Source: Centers for Disease Control and Prevention Diabetes Atlas[105] using data sources listed in the symbol notes.

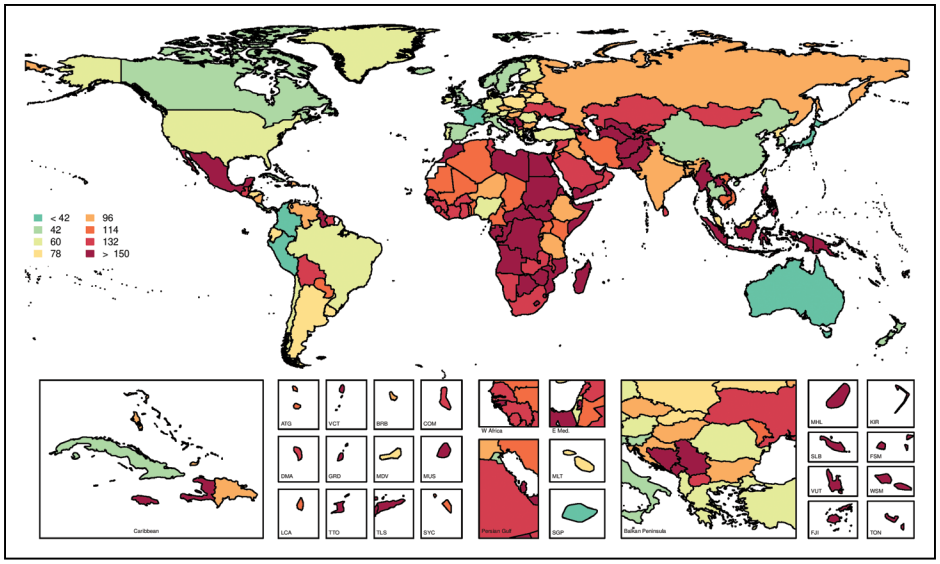

Chart 9-8. Age-standardized global mortality rates attributable to high fasting plasma glucose (FPG) per 100 000, both sexes, 2017.
Age-standardized mortality rates attributable to high FPG are generally lower in high-income countries.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[143] Printed with permission.

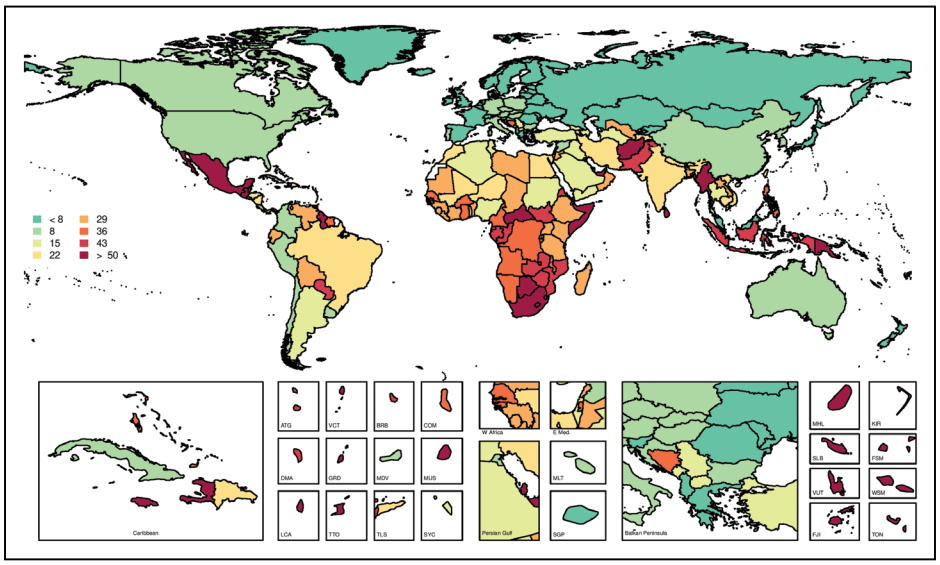

Chart 9-9. Age-standardized global mortality rates attributable to diabetes mellitus (DM) per 100 000, both sexes, 2017.
Age-standardized mortality attributable to DM is highest in Oceania, Southern and sub-Saharan Africa, Southeast Asia, and parts of Central and Tropical Latin America.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[143] Printed with permission.

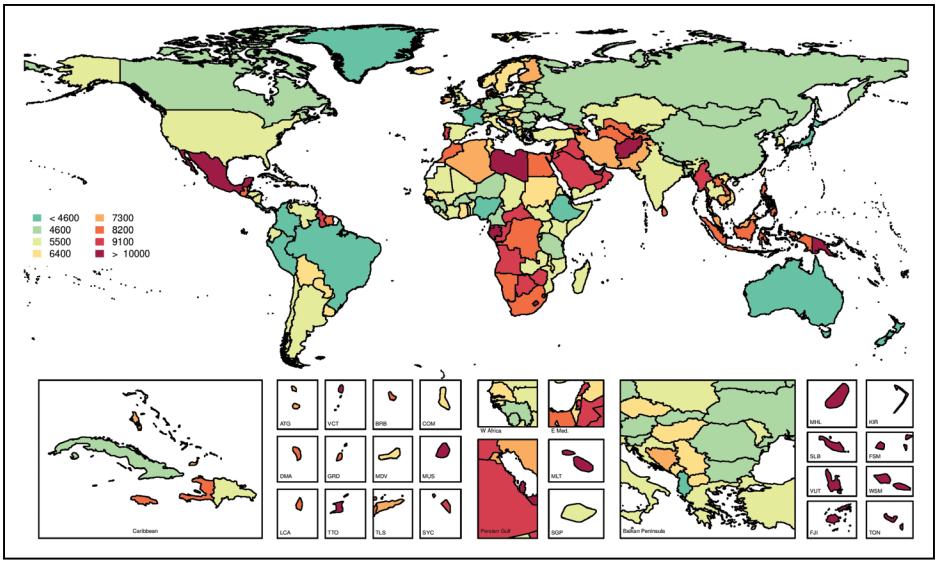

Chart 9-10. Age-standardized global prevalence rates of diabetes mellitus (DM) per 100 000, both sexes, 2017.
The age-standardized prevalence of DM is highest in Oceania.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
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REFERENCES

1. National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. National Diabetes Statistics Report, 2017: Estimates of Diabetes and Its Burden in the United States. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2017.
2. Menke A, Orchard TJ, Imperatore G, Bullard KM, Mayer-Davis E, Cowie CC. The prevalence of type 1 diabetes in the United States. *Epidemiology.* 2013;24:773–774. doi: 10.1097/EDE.0b013e31829ef01a
3. American Diabetes Association. Standards of medical care in diabetes: 2010 [published correction appears in *Diabetes Care*. 2010;33:692]. *Diabetes Care*. 2010;33(suppl 1):S11–S61. doi: 10.2337/dc10-S011
4. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies [published correction appears in *Lancet*. 2010;376:958]. *Lancet.* 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9
5. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
6. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, et al; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA.* 2014;311:1778–1786. doi: 10.1001/jama.2014.3201
7. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, Dabelea D, Hamman R, Waitzfelder B, Kahn HS; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. *Pediatr Diabetes.* 2010;11:4–11. doi: 10.1111/j.1399-5448.2009.00519.x
8. Menke A, Casagrande S, Cowie CC. Prevalence of diabetes in adolescents aged 12 to 19 years in the United States, 2005-2014. *JAMA.* 2016;316:344–345. doi: 10.1001/jama.2016.8544
9. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
10. Schneiderman N, Llabre M, Cowie CC, Barnhart J, Carnethon M, Gallo LC, Giachello AL, Heiss G, Kaplan RC, LaVange LM, et al. Prevalence of diabetes among Hispanics/Latinos from diverse backgrounds: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes Care.* 2014;37:2233–2239. doi: 10.2337/dc13-2939
11. Tsujimoto T, Kajio H, Sugiyama T. Obesity, diabetes, and length of time in the United States: analysis of National Health and Nutrition Examination Survey 1999 to 2012. *Medicine (Baltimore).* 2016;95:e4578. doi: 10.1097/MD.0000000000004578
12. Kim EJ, Kim T, Conigliaro J, Liebschutz JM, Paasche-Orlow MK, Hanchate AD. Racial and ethnic disparities in diagnosis of chronic medical conditions in the USA. *J Gen Intern Med.* 2018;33:1116–1123. doi: 10.1007/s11606-018-4471-1
13. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1197.
14. Dwyer-Lindgren L, Mackenbach JP, van Lenthe FJ, Flaxman AD, Mokdad AH. Diagnosed and undiagnosed diabetes prevalence by county in the U.S., 1999-2012. *Diabetes Care.* 2016;39:1556–1562. doi: 10.2337/dc16-0678
15. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Behavioral Risk Factor Surveillance System (BRFSS). BRFSS prevalence & trends data [online] (2016). Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed May 6, 2019.
16. Loop MS, Howard G, de Los Campos G, Al-Hamdan MZ, Safford MM, Levitan EB, McClure LA. Heat Maps of hypertension, diabetes mellitus, and smoking in the continental United States. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003350. doi: 10.1161/CIRCOUTCOMES.116.003350
17. Zhang N, Yang X, Zhu X, Zhao B, Huang T, Ji Q. Type 2 diabetes mellitus unawareness, prevalence, trends and risk factors: National Health and Nutrition Examination Survey (NHANES) 1999-2010. *J Int Med Res.* 2017;45:594–609. doi: 10.1177/0300060517693178
18. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Ann Intern Med.* 2014;160:517–525. doi: 10.7326/M13-2411

19. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, et al; SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med*. 2017;376:1419–1429. doi: 10.1056/NEJMoa1610187
20. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, Lawrence JM, Liese AD, Liu LL, Mayer-Davis EJ, et al; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care*. 2012;35:2515–2520. doi: 10.2337/dc12-0669
21. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. *JAMA*. 2017;318:2457–2465. doi: 10.1001/jama.2017.19546
22. Joseph JJ, Echouffo-Tcheugui JB, Carnethon MR, Bertoni AG, Shay CM, Ahmed HM, Blumenthal RS, Cushman M, Golden SH. The association of ideal cardiovascular health with incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. *Diabetologia*. 2016;59:1893–1903. doi: 10.1007/s00125-016-4003-7
23. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev*. 2016;17:56–67. doi: 10.1111/obr.12316
24. Song Y, Huang YT, Song Y, Hevener AL, Ryckman KK, Qi L, LeBlanc ES, Kazlauskaite R, Brennan KM, Liu S. Birthweight, mediating biomarkers and the development of type 2 diabetes later in life: a prospective study of multi-ethnic women. *Diabetologia*. 2015;58:1220–1230. doi: 10.1007/s00125-014-3479-2
25. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *Br J Sports Med*. 2016;50:496–504. doi: 10.1136/bjsports-2016-h3576rep
26. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, Veerman JL, Delwiche K, Iannarone ML, Moyer ML, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*. 2016;354:i3857. doi: 10.1136/bmj.i3857
27. Chow LS, Odegaard AO, Bosch TA, Bantle AE, Wang Q, Hughes J, Carnethon M, Ingram KH, Durant N, Lewis CE, et al. Twenty year fitness trends in young adults and incidence of prediabetes and diabetes: the CARDIA study. *Diabetologia*. 2016;59:1659–1665. doi: 10.1007/s00125-016-3969-5
28. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis [published correction appears in *Ann Intern Med*. 2015;163:400]. *Ann Intern Med*. 2015;162:123–132. doi: 10.7326/M14-1651
29. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, Edwards P, Woodcock J, Brage S, Wijndaele K. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol*. 2018;33:811–829. doi: 10.1007/s10654-018-0380-1
30. den Braver NR, Lakerveld J, Rutters F, Schoonmade LJ, Brug J, Beulens JWJ. Built environmental characteristics and diabetes: a systematic review and meta-analysis. *BMC Med*. 2018;16:12. doi: 10.1186/s12916-017-0997-z
31. Casagrande SS, Linder B, Cowie CC. Prevalence of gestational diabetes and subsequent type 2 diabetes among U.S. women. *Diabetes Res Clin Pract*. 2018;141:200–208. doi: 10.1016/j.diabres.2018.05.010
32. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, Rich-Edwards JW. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med*. 2018;169:224–232. doi: 10.7326/M17-2740
33. Bang H, Edwards AM, Bomback AS, Ballantyne CM, Brillon D, Callahan MA, Teutsch SM, Mushlin AI, Kern LM. Development and validation of a patient self-assessment score for diabetes risk. *Ann Intern Med*. 2009;151:775–783. doi: 10.7326/0003-4819-151-11-200912010-00005
34. Buijsse B, Simmons RK, Griffin SJ, Schulze MB. Risk assessment tools for identifying individuals at risk of developing type 2 diabetes. *Epidemiol Rev*. 2011;33:46–62. doi: 10.1093/epirev/mxq019
35. Chen L, Magliano DJ, Balkau B, Colagiuri S, Zimmet PZ, Tonkin AM, Mitchell P, Phillips PJ, Shaw JE. AUSDRISK: an Australian type 2 diabetes risk assessment tool based on demographic, lifestyle and simple anthropometric measures [published correction appears in *Med J Aust*. 2010;192:274]. *Med J Aust*. 2010;192:197–202.
36. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099. doi: 10.1136/bmj.j2099
37. Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. *BMJ*. 2017;359:j5019. doi: 10.1136/bmj.j5019
38. Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, et al; Scottish Diabetes Research Network Epidemiology Group. Performance of cardiovascular disease risk scores in people diagnosed with type 2 diabetes: external validation using data from the National Scottish Diabetes Register. *Diabetes Care*. 2018;41:2010–2018. doi: 10.2337/dc18-0578
39. Bergmark BA, Bhatt DL, Braunwald E, Morrow DA, Steg PG, Gurmu Y, Cahn A, Mosenzon O, Raz I, Bohula E, et al. Risk assessment in patients with diabetes with the TIMI risk score for atherothrombotic disease. *Diabetes Care*. 2018;41:577–585. doi: 10.2337/dc17-1736
40. Chowdhury MZI, Yeasmin F, Rabi DM, Ronksley PE, Turin TC. Prognostic tools for cardiovascular disease in patients with type 2 diabetes: a systematic review and meta-analysis of C-statistics. *J Diabetes Complications*. 2019;33:98–111. doi: 10.1016/j.jdiacomp.2018.10.010
41. Almgren P, Lehtovirta M, Isomaa B, Sarelin L, Taskinen MR, Lyssenko V, Tuomi T, Groop L; Botnia Study Group. Heritability and familiality of type 2 diabetes and related quantitative traits in the Botnia Study. *Diabetologia*. 2011;54:2811–2819. doi: 10.1007/s00125-011-2267-5
42. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance: a population-based twin study. *Diabetologia*. 1999;42:139–145. doi: 10.1007/s001250051131
43. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes*. 2000;49:2201–2207. doi: 10.2337/diabetes.49.12.2201
44. Moonesinghe R, Beckles GLA, Liu T, Khoury MJ. The contribution of family history to the burden of diagnosed diabetes, undiagnosed diabetes, and prediabetes in the United States: analysis of the National Health and Nutrition Examination Survey, 2009-2014. *Genet Med*. 2018;20:1159–1166. doi: 10.1038/gim.2017.238
45. Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefsen S, White NH, Pollin TI. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. *Genet Med*. 2018;20:583–590. doi: 10.1038/gim.2017.150
46. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segrè AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, et al; Wellcome Trust Case Control Consortium; Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) Investigators; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Asian Genetic Epidemiology Network–Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012;44:981–990. doi: 10.1038/ng.2383
47. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium, South Asian Type 2 Diabetes (SAT2D) Consortium, Mexican American Type 2 Diabetes (MAT2D) Consortium and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortium. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet*. 2014;46:234–244. doi: 10.1038/ng.2897
48. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature*. 2007;445:881–885. doi: 10.1038/nature05616
49. Woo HJ, Reifman J. Genetic interaction effects reveal lipid-metabolic and inflammatory pathways underlying common metabolic disease risks. *BMC Med Genomics*. 2018;11:54. doi: 10.1186/s12920-018-0373-7
50. Knowles JW, Xie W, Zhang Z, Chennamsetty I, Chennemsetty I, Assimes TL, Paananen J, Hansson O, Pankow J, Goodarzi MO, et al; RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease) Consortium; EUGENE2 (European Network on Functional Genomics of Type 2 Diabetes) Study; GUARDIAN (Genetics UndeRlying DIAbetes in HispaNics) Consortium; SAPPHIRe (Stanford Asian and Pacific Program for

Hypertension and Insulin Resistance) Study. Identification and validation of N-acetyltransferase 2 as an insulin sensitivity gene [published correction appears in *J Clin Invest*. 2016;126:403]. *J Clin Invest.* 2015;125:1739–1751. doi: 10.1172/JCI74692
51. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet.* 2008;40:1092–1097. doi: 10.1038/ng.207
52. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank Study. *JAMA Cardiol.* 2018;3:693–702. doi: 10.1001/jamacardio.2018.1717
53. Lotta LA, Wittemans LBL, Zuber V, Stewart ID, Sharp SJ, Luan J, Day FR, Li C, Bowker N, Cai L, et al. Association of genetic variants related to gluteofemoral vs abdominal fat distribution with type 2 diabetes, coronary disease, and cardiovascular risk factors. *JAMA.* 2018;320:2553–2563. doi: 10.1001/jama.2018.19329
54. Shah HS, Gao H, Morieri ML, Skupien J, Marvel S, Paré G, Mannino GC, Buranasupkajorn P, Mendonca C, Hastings T, et al. Genetic predictors of cardiovascular mortality during intensive glycemic control in type 2 diabetes: findings from the ACCORD clinical trial. *Diabetes Care.* 2016;39:1915–1924. doi: 10.2337/dc16-0285
55. Steinthorsdottir V, Thorleifsson G, Sulem P, Helgason H, Grarup N, Sigurdsson A, Helgadottir HT, Johannsdottir H, Magnusson OT, Gudjonsson SA, et al. Identification of low-frequency and rare sequence variants associated with elevated or reduced risk of type 2 diabetes. *Nat Genet.* 2014;46:294–298. doi: 10.1038/ng.2882
56. Gusarova V, O'Dushlaine C, Teslovich TM, Benotti PN, Mirshahi T, Gottesman O, Van Hout CV, Murray MF, Mahajan A, Nielsen JB, et al. Genetic inactivation of ANGPTL4 improves glucose homeostasis and is associated with reduced risk of diabetes. *Nat Commun.* 2018;9:2252. doi: 10.1038/s41467-018-04611-z
57. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. *Lancet.* 2016;387:2331–2339. doi: 10.1016/S0140-6736(16)30582-7
58. Oram RA, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care.* 2016;39:337–344. doi: 10.2337/dc15-1111
59. Moen GH, LeBlanc M, Sommer C, Prasad RB, Lekva T, Normann KR, Qvigstad E, Groop L, Birkeland KI, Evans DM, et al. Genetic determinants of glucose levels in pregnancy: genetic risk scores analysis and GWAS in the Norwegian STORK cohort. *Eur J Endocrinol.* 2018;179:363–372. doi: 10.1530/EJE-18-0478
60. Cousminer DL, Ahlqvist E, Mishra R, Andersen MK, Chesi A, Hawa MI, Davis A, Hodge KM, Bradfield JP, Zhou K, et al; Bone Mineral Density in Childhood Study. First genome-wide association study of latent autoimmune diabetes in adults reveals novel insights linking immune and metabolic diabetes. *Diabetes Care.* 2018;41:2396–2403. doi: 10.2337/dc18-1032
61. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am J Kidney Dis.* 2004;43:796–800. doi: 10.1053/j.ajkd.2003.12.043
62. Qi L, Qi Q, Prudente S, Mendonca C, Andreozzi F, di Pietro N, Sturma M, Novelli V, Mannino GC, Formoso G, et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA.* 2013;310:821–828. doi: 10.1001/jama.2013.276305
63. Słomiński B, Ławrynowicz U, Ryba-Stanisławowska M, Skrzypkowska M, Myśliwska J, Myśliwiec M. CCR5-Δ32 polymorphism is a genetic risk factor associated with dyslipidemia in patients with type 1 diabetes. *Cytokine.* 2018;114:81-85. doi: 10.1016/j.cyto.2018.11.005
64. Cao M, Tian Z, Zhang L, Liu R, Guan Q, Jiang J. Genetic association of AKR1B1 gene polymorphism rs759853 with diabetic retinopathy risk: a meta-analysis. *Gene.* 2018;676:73–78. doi: 10.1016/j.gene.2018.07.014
65. Siegel KR, Bullard KM, Imperatore G, Ali MK, Albright A, Mercado CI, Li R, Gregg EW. Prevalence of major behavioral risk factors for type 2 diabetes. *Diabetes Care.* 2018;41:1032–1039. doi: 10.2337/dc17-1775
66. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. *Lancet Diabetes Endocrinol.* 2018;6:392–403. doi: 10.1016/S2213-8587(18)30027-5
67. Nichols GA, Horberg M, Koebnick C, Young DR, Waitzfelder B, Sherwood NE, Daley MF, Ferrara A. Cardiometabolic risk factors among 1.3 million adults with overweight or obesity, but not diabetes, in 10 geographically diverse regions of the United States, 2012-2013. *Prev Chronic Dis.* 2017;14:E22. doi: 10.5888/pcd14.160438
68. Herman WH, Pan Q, Edelstein SL, Mather KJ, Perreault L, Barrett-Connor E, Dabelea DM, Horton E, Kahn SE, Knowler WC, et al; Diabetes Prevention Program Research Group. Impact of lifestyle and metformin interventions on the risk of progression to diabetes and regression to normal glucose regulation in overweight or obese people with impaired glucose regulation [published corrections appear in *Diabetes Care*. 2018;41:913 and *Diabetes Care*. 2019;42:701]. *Diabetes Care.* 2017;40:1668–1677. doi: 10.2337/dc17-1116
69. Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, Arslanian S, Cuttler L, Nathan DM, Tollefsen S, Wilfley D, et al; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med.* 2012;366:2247–2256. doi: 10.1056/NEJMoa1109333
70. Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, Correa A, Folsom AR, Kachroo S, Mukherjee J, et al;. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care.* 2016;39:668–676. doi: 10.2337/dc15-2439
71. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care.* 2013;36:2271–2279. doi: 10.2337/dc12-2258
72. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010 [published correction appears in *N Engl J Med*. 2013;369:587]. *N Engl J Med.* 2013;368:1613–1624. doi: 10.1056/NEJMsa1213829
73. Muntner P, Whelton PK, Woodward M, Carey RM. A comparison of the 2017 American College of Cardiology/American Heart Association blood pressure guideline and the 2017 American Diabetes Association diabetes and hypertension position statement for U.S. adults with diabetes. *Diabetes Care.* 2018;41:2322–2329. doi: 10.2337/dc18-1307
74. Twarog JP, Charyalu AM, Subhani MR, Shrestha P, Peraj E. Differences in HbA1C% screening among U.S. adults diagnosed with diabetes: findings from the National Health and Nutrition Examination Survey (NHANES). *Prim Care Diabetes.* 2018;12:533–536. doi: 10.1016/j.pcd.2018.07.006
75. Doucette ED, Salas J, Wang J, Scherrer JF. Insurance coverage and diabetes quality indicators among patients with diabetes in the US general population. *Prim Care Diabetes.* 2017;11:515–521. doi: 10.1016/j.pcd.2017.05.007
76. Mendoza JA, Haaland W, D'Agostino RB, Martini L, Pihoker C, Frongillo EA, Mayer-Davis EJ, Liu LL, Dabelea D, Lawrence JM, et al. Food insecurity is associated with high risk glycemic control and higher health care utilization among youth and young adults with type 1 diabetes. *Diabetes Res Clin Pract.* 2018;138:128–137. doi: 10.1016/j.diabres.2018.01.035
77. Agarwal S, Raymond JK, Isom S, Lawrence JM, Klingensmith G, Pihoker C, Corathers S, Saydah S, D'Agostino RB Jr, Dabelea D. Transfer from paediatric to adult care for young adults with type 2 diabetes: the SEARCH for Diabetes in Youth Study. *Diabet Med.* 2018;35:504–512. doi: 10.1111/dme.13589
78. Casagrande SS, Aviles-Santa L, Corsino L, Daviglus ML, Gallo LC, Espinoza Giacinto RA, Llabre MM, Reina SA, Savage PJ, Schneiderman N, et al. Hemoglobin A1C, blood pressure, and LDL-cholesterol control among Hispanic/Latino adults with diabetes: results from the Hispanic Community Health STUDY/Study of Latinos (HCHS/SOL). *Endocr Pract.* 2017;23:1232–1253. doi: 10.4158/EP171765.OR
79. Wang X, Strizich G, Hua S, Sotres-Alvarez D, Buelna C, Gallo LC, Gellman MD, Mossavar-Rahmani Y, O'Brien MJ, Stoutenberg M, et al. Objectively measured sedentary time and cardiovascular risk factor control in US Hispanics/Latinos with diabetes mellitus: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *J Am Heart Assoc.* 2017;6:e004324. doi: 10.1161/JAHA.116.004324
80. Albertorio-Diaz JR, Eberhardt MS, Oquendo M, Mesa-Frias M, He Y, Jonas B, Kang K. Depressive states among adults with diabetes: findings from the National Health and Nutrition Examination Survey, 2007-2012. *Diabetes Res Clin Pract.* 2017;127:80–88. doi: 10.1016/j.diabres.2017.02.031
81. Mercado CI, Gregg E, Gillespie C, Loustalot F. Trends in lipid profiles and descriptive characteristics of U.S. adults with and without diabetes and cholesterol-lowering medication use: National Health and Nutrition Examination Survey, 2003–2012, United States. *PLoS One.* 2018;13:e0193756. doi: 10.1371/journal.pone.0193756

82. Deedwania P, Acharya T, Kotak K, Fonarow GC, Cannon CP, Laskey WK, Peacock WF, Pan W, Bhatt DL; GWTG Steering Committee and Investigators. Compliance with guideline-directed therapy in diabetic patients admitted with acute coronary syndrome: findings from the American Heart Association's Get With The Guidelines-Coronary Artery Disease (GWTG-CAD) program. *Am Heart J.* 2017;187:78–87. doi: 10.1016/j.ahj.2017.02.025
83. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, Park JG, White JA, Bohula EA, Braunwald E; on behalf of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation.* 2018;137:1571–1582. doi: 10.1161/CIRCULATIONAHA.117.030950
84. Levine DM, Linder JA, Landon BE. The quality of outpatient care delivered to adults in the United States, 2002 to 2013. *JAMA Intern Med.* 2016;176:1778–1790. doi: 10.1001/jamainternmed.2016.6217
85. Tran EMT, Bhattacharya J, Pershing S. Self-reported receipt of dilated fundus examinations among patients with diabetes: Medicare Expenditure Panel Survey, 2002-2013. *Am J Ophthalmol.* 2017;179:18–24. doi: 10.1016/j.ajo.2017.04.009
86. Lipska KJ, Yao X, Herrin J, McCoy RG, Ross JS, Steinman MA, Inzucchi SE, Gill TM, Krumholz HM, Shah ND. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. *Diabetes Care.* 2017;40:468–475. doi: 10.2337/dc16-0985
87. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med.* 2018;379:1529–1539. doi: 10.1056/NEJMoa1804988
88. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med.* 2018;379:1540–1550. doi: 10.1056/NEJMoa1804989
89. Gæde P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, Pedersen O. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. *Diabetologia.* 2016;59:2298–2307. doi: 10.1007/s00125-016-4065-6
90. Oellgaard J, Gæde P, Rossing P, Rørth R, Køber L, Parving HH, Pedersen O. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study. *Diabetologia.* 2018;61:1724–1733. doi: 10.1007/s00125-018-4642-y
91. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death microdata files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
92. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999–2017. CDC WONDER Online Database [database online]. Released December 2018. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019
93. Stokes A, Preston SH. Deaths attributable to diabetes in the United States: comparison of data sources and estimation approaches. *PLoS One.* 2017;12:e0170219. doi: 10.1371/journal.pone.0170219
94. Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. *Lancet Diabetes Endocrinol.* 2018;6:538–546. doi: 10.1016/S2213-8587(18)30079-2
95. Liu L, Simon B, Shi J, Mallhi AK, Eisen HJ. Impact of diabetes mellitus on risk of cardiovascular disease and all-cause mortality: evidence on health outcomes and antidiabetic treatment in United States adults. *World J Diabetes.* 2016;7:449–461. doi: 10.4239/wjd.v7.i18.449
96. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med.* 2017;376:1407–1418. doi: 10.1056/NEJMoa1608664
97. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Range of risk factor levels: control, mortality, and cardiovascular outcomes in type 1 diabetes mellitus. *Circulation.* 2017;135:1522–1531. doi: 10.1161/CIRCULATIONAHA.116.025961
98. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2018;379:633–644. doi: 10.1056/NEJMoa1800256
99. Edqvist J, Rawshani A, Adiels M, Björck L, Lind M, Svensson AM, Gudbjörnsdottir S, Sattar N, Rosengren A. BMI and mortality in patients with new-onset type 2 diabetes: a comparison with age- and sex-matched control subjects from the general population. *Diabetes Care.* 2018;41:485–493. doi: 10.2337/dc17-1309
100. Cheng YJ, Imperatore G, Geiss LS, Saydah SH, Albright AL, Ali MK, Gregg EW. Trends and disparities in cardiovascular mortality among U.S. adults with and without self-reported diabetes, 1988-2015. *Diabetes Care.* 2018;41:2306–2315. doi: 10.2337/dc18-0831
101. Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes.* 2010;59:3216–3222. doi: 10.2337/db10-0862
102. Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson AM, Eliasson B, Gudbjörnsdottir S. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet.* 2018;392:477–486. doi: 10.1016/S0140-6736(18)31506-X
103. Wang SY, Andrews CA, Herman WH, Gardner TW, Stein JD. Incidence and risk factors for developing diabetic retinopathy among youths with type 1 or type 2 diabetes throughout the United States. *Ophthalmology.* 2017;124:424–430. doi: 10.1016/j.ophtha.2016.10.031
104. Bursell SE, Fonda SJ, Lewis DG, Horton MB. Prevalence of diabetic retinopathy and diabetic macular edema in a primary care-based teleophthalmology program for American Indians and Alaskan Natives. *PLoS One.* 2018;13:e0198551. doi: 10.1371/journal.pone.0198551
105. Centers for Disease Control and Prevention. US Diabetes Surveillance System Diabetes Atlas. https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html. Accessed May 28, 2019.
106. Wu B, Bell K, Stanford A, Kern DM, Tunceli O, Vupputuri S, Kalsekar I, Willey V. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns: NHANES 2007-2012. *BMJ Open Diabetes Res Care.* 2016;4:e000154. doi: 10.1136/bmjdrc-2015-000154
107. Wang T, Xi Y, Lubwama R, Hannanchi H, Iglay K, Koro C. Chronic kidney disease among US adults with type 2 diabetes and cardiovascular diseases: a national estimate of prevalence by KDIGO 2012 classification. *Diabetes Metab Syndr.* 2019;13:612–615. doi: 10.1016/j.dsx.2018.11.026
108. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA.* 2016;316:602–610. doi: 10.1001/jama.2016.10924
109. Alfredsson J, Green JB, Stevens SR, Reed SD, Armstrong PW, Angelyn Bethel M, Engel SS, McGuire DK, Van de Werf F, Hramiak I, et al. Sex differences in management and outcomes of patients with type 2 diabetes and cardiovascular disease: a report from TECOS. *Diabetes Obes Metab.* 2018;20:2379–2388. doi: 10.1111/dom.13377
110. US Diabetes Surveillance System, Division of Diabetes Translation. Diabetes data and statistics. Centers for Disease Control and Prevention website. 2018. https://www.cdc.gov/diabetes/data. Accessed March 29, 2019.
111. Mondesir FL, Brown TM, Muntner P, Durant RW, Carson AP, Safford MM, Levitan EB. Diabetes, diabetes severity, and coronary heart disease risk equivalence: REasons for Geographic and Racial Differences in Stroke (REGARDS). *Am Heart J.* 2016;181:43–51. doi: 10.1016/j.ahj.2016.08.002
112. Zhou JJ, Schwenke DC, Bahn G, Reaven P; VADT Investigators. Glycemic variation and cardiovascular risk in the Veterans Affairs Diabetes Trial. *Diabetes Care.* 2018;41:2187–2194. doi: 10.2337/dc18-0548
113. Miller RG, Anderson SJ, Costacou T, Sekikawa A, Orchard TJ. Hemoglobin A1c level and cardiovascular disease incidence in persons with type 1 diabetes: an application of joint modeling of longitudinal and time-to-event data in the Pittsburgh Epidemiology of Diabetes Complications Study. *Am J Epidemiol.* 2018;187:1520–1529. doi: 10.1093/aje/kwx386
114. Bell EJ, Folsom AR, Lutsey PL, Selvin E, Zakai NA, Cushman M, Alonso A. Diabetes mellitus and venous thromboembolism: a systematic review and meta-analysis. *Diabetes Res Clin Pract.* 2016;111:10–18. doi: 10.1016/j.diabres.2015.10.019
115. Loehr LR, Meyer ML, Poon AK, Selvin E, Palta P, Tanaka H, Pankow JS, Wright JD, Griswold ME, Wagenknecht LE, et al. Prediabetes and diabetes are associated with arterial stiffness in older adults: the ARIC Study. *Am J Hypertens.* 2016;29:1038–1045. doi: 10.1093/ajh/hpw036

116. Bertoni AG, Kramer H, Watson K, Post WS. Diabetes and clinical and subclinical CVD. *Glob Heart.* 2016;11:337–342. doi: 10.1016/j.gheart.2016.07.005
117. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Gidding SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA Study. *Diabetes Care.* 2018;41:731–738. doi: 10.2337/dc17-2233
118. Pallisgaard JL, Schjerning AM, Lindhardt TB, Procida K, Hansen ML, Torp-Pedersen C, Gislason GH. Risk of atrial fibrillation in diabetes mellitus: a nationwide cohort study. *Eur J Prev Cardiol.* 2016;23:621–627. doi: 10.1177/2047487315599892
119. Hui G, Koch B, Calara F, Wong ND. Angina in coronary artery disease patients with and without diabetes: US National Health and Nutrition Examination Survey 2001-2010. *Clin Cardiol.* 2016;39:30–36. doi: 10.1002/clc.22488
120. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation [published correction appears in *Circulation*. 2010;121:e258]. *Circulation.* 2009;119:e391–e479. doi: 10.1161/CIRCULATIONAHA.109.192065
121. Khan H, Kunutsor SK, Kauhanen J, Kurl S, Gorodeski EZ, Adler AI, Butler J, Laukkanen JA. Fasting plasma glucose and incident heart failure risk: a population-based cohort study and new meta-analysis. *J Card Fail.* 2014;20:584–592. doi: 10.1016/j.cardfail.2014.05.011
122. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, Nodari S, Konstam M, Swedberg K, Maggioni AP, et al; EVEREST Investigators. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail.* 2013;15:194–202. doi: 10.1093/eurjhf/hfs153
123. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, Jessup M, Kosiborod M, Pritchett AM, Ramasubbu K, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; and Council on Quality and Outcomes Research. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation.* 2016;134:e535–e578. doi: 10.1161/CIR.0000000000000450
124. Lipska KJ, Ross JS, Wang Y, Inzucchi SE, Minges K, Karter AJ, Huang ES, Desai MM, Gill TM, Krumholz HM. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med.* 2014;174:1116–1124. doi: 10.1001/jamainternmed.2014.1824
125. Davis SN, Duckworth W, Emanuele N, Hayward RA, Wiitala WL, Thottapurathu L, Reda DJ, Reaven PD; Investigators of the Veterans Affairs Diabetes Trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the Veterans Affairs Diabetes Trial. *Diabetes Care.* 2019;42:157–163. doi: 10.2337/dc18-1144
126. Zinman B, Marso SP, Christiansen E, Calanna S, Rasmussen S, Buse JB; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Hypoglycemia, cardiovascular outcomes, and death: the LEADER experience. *Diabetes Care.* 2018;41:1783–1791. doi: 10.2337/dc17-2677
127. Heller SR, Bergenstal RM, White WB, Kupfer S, Bakris GL, Cushman WC, Mehta CR, Nissen SE, Wilson CA, Zannad F, et al; EXAMINE Investigators. Relationship of glycated haemoglobin and reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial [published correction appears in *Diabetes Obes Metab*. 2017;19:1333]. *Diabetes Obes Metab.* 2017;19:664–671. doi: 10.1111/dom.12871
128. Lee AK, Warren B, Lee CJ, McEvoy JW, Matsushita K, Huang ES, Sharrett AR, Coresh J, Selvin E. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care.* 2018;41:104–111. doi: 10.2337/dc17-1669
129. Standl E, Stevens SR, Armstrong PW, Buse JB, Chan JCN, Green JB, Lachin JM, Scheen A, Travert F, Van de Werf F, et al. Increased risk of severe hypoglycemic events before and after cardiovascular outcomes in TECOS suggests an at-risk type 2 diabetes frail patient phenotype. *Diabetes Care.* 2018;41:596–603. doi: 10.2337/dc17-1778
130. Schroeder EB, Xu S, Goodrich GK, Nichols GA, O'Connor PJ, Steiner JF. Predicting the 6-month risk of severe hypoglycemia among adults with diabetes: development and external validation of a prediction model. *J Diabetes Complications.* 2017;31:1158–1163. doi: 10.1016/j.jdiacomp.2017.04.004
131. Karter AJ, Lipska KJ, O'Connor PJ, Liu JY, Moffet HH, Schroeder EB, Lawrence JM, Nichols GA, Newton KM, Pathak RD, et al; SUPREME-DM Study Group. High rates of severe hypoglycemia among African American patients with diabetes: the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. *J Diabetes Complications.* 2017;31:869–873. doi: 10.1016/j.jdiacomp.2017.02.009
132. McCoy RG, Herrin J, Lipska KJ, Shah ND. Recurrent hospitalizations for severe hypoglycemia and hyperglycemia among U.S. adults with diabetes. *J Diabetes Complications.* 2018;32:693–701. doi: 10.1016/j.jdiacomp.2018.04.007
133. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). HCUPnet, 1996–2016. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
134. Collins J, Abbass IM, Harvey R, Suehs B, Uribe C, Bouchard J, Prewitt T, DeLuzio T, Allen E. Predictors of all-cause 30 day readmission among Medicare patients with type 2 diabetes. *Curr Med Res Opin.* 2017;33:1517–1523. doi: 10.1080/03007995.2017.1330258
135. McCoy RG, Lipska KJ, Herrin J, Jeffery MM, Krumholz HM, Shah ND. Hospital readmissions among commercially insured and Medicare Advantage beneficiaries with diabetes and the impact of severe hypoglycemic and hyperglycemic events. *J Gen Intern Med.* 2017;32:1097–1105. doi: 10.1007/s11606-017-4095-x
136. Schneider AL, Kalyani RR, Golden S, Stearns SC, Wruck L, Yeh HC, Coresh J, Selvin E. Diabetes and prediabetes and risk of hospitalization: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care.* 2016;39:772–779. doi: 10.2337/dc15-1335
137. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41:917–928. doi: 10.2337/dci18-0007
138. Joo H, Zhang P, Wang G. Cost of informal care for patients with cardiovascular disease or diabetes: current evidence and research challenges. *Qual Life Res.* 2017;26:1379–1386. doi: 10.1007/s11136-016-1478-0
139. Shrestha SS, Zhang P, Hora IA, Gregg EW. Trajectory of excess medical expenditures 10 years before and after diabetes diagnosis among U.S. adults aged 25-64 years, 2001-2013. *Diabetes Care.* 2019;42:62–68. doi: 10.2337/dc17-2683
140. Shrestha SS, Zhang P, Hora I, Geiss LS, Luman ET, Gregg EW. Factors contributing to increases in diabetes-related preventable hospitalization costs among U.S. adults during 2001-2014. *Diabetes Care.* 2019;42:77–84. doi: 10.2337/dc18-1078
141. Rubens M, Saxena A, Ramamoorthy V, Khera R, Hong J, Veledar E, Nasir K. Trends in diabetes-related preventable hospitalizations in the U.S., 2005-2014. *Diabetes Care.* 2018;41:e72–e73. doi: 10.2337/dc17-1942
142. Einarson TR, Acs A, Ludwig C, Panton UH. Economic burden of cardiovascular disease in type 2 diabetes: a systematic review. *Value Health.* 2018;21:881–890. doi: 10.1016/j.jval.2017.12.019
143. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
144. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* 2018;138:271–281. doi: 10.1016/j.diabres.2018.02.023
145. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, Davies J, Vollmer S. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care*. 2018;41:963–970. doi: 10.2337/dc17-1962

10. METABOLIC SYNDROME

See Charts 10-1 through 10-7

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Definition

- MetS is a multicomponent risk factor for CVD and type 2 DM that reflects the clustering of individual cardiometabolic risk factors related to abdominal obesity and insulin resistance. MetS is a useful entity for communicating the nature of lifestyle-related cardiometabolic risk to both patients and clinicians. Although multiple definitions for MetS have been proposed, the IDF, NHLBI, AHA, and others recommended a harmonized definition for MetS based on the presence of any 3 of the following 5 risk factors[1]:
  - FPG ≥100 mg/dL or undergoing drug treatment for elevated glucose
  - HDL-C <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
  - Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
  - WC >102 cm in males or >88 cm in females for people of most ancestries living in the United States. Ethnicity- and country-specific thresholds can be used for diagnosis in other groups,

Abbreviations Used in Chapter 10

AF	atrial fibrillation
AHA	American Heart Association
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes
ARIC	Atherosclerosis Risk in Communities
ATP III	Adult Treatment Panel III
BioSHaRE	Biobank Standardization and Harmonization for Research Excellence in the European Union
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
Carbs	carbohydrates
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHRIS	Collaborative Health Research in South Tyrol Study
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DESIR	Data from an Epidemiological Study on the Insulin Resistance Syndrome
DILGOM	Dietary, Lifestyle, and Genetics Determinants of Obesity and Metabolic Syndrome
DM	diabetes mellitus
EGCUT	Estonian Genome Center of the University of Tartu
FPG	fasting plasma glucose
GFR	glomerular filtration rate
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
HUNT2	Nord-Trøndelag Health Study
IDF	International Diabetes Federation
IL	interleukin
IMT	intima-media thickness
JHS	Jackson Heart Study
KORA	Cooperative Health Research in the Region of Augsburg
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular

(*Continued*)

Abbreviations Used in Chapter 10 Continued

MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MetS	metabolic syndrome
MHO	metabolically healthy obesity
MI	myocardial infarction
MICROS	Microisolates in South Tyrol Study
MORGAM	MONICA [Monitoring Trends and Determinants in Cardiovascular Disease], Risk, Genetics, Archiving and Monograph Project
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NCDS	National Child Development Study
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH-AARP	National Institutes of Health–American Association of Retired Persons
NIPPON DATA	National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged
NL	The Netherlands
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAD	peripheral artery disease
PAR	population attributable risk
PREMA	Prediction of Metabolic Syndrome in Adolescence
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RENIS-T6	Renal Iohexol-Clearance Survey in Tromsø 6
RR	relative risk
RV	right ventricular
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
SNP	single-nucleotide polymorphism
SSB	sugar-sweetened beverage
VTE	venous thromboembolism
WC	waist circumference
WHO	World Health Organization

particularly Asians and individuals of non-European ancestry who have predominantly resided outside the United States.
  - SBP ≥130 mm Hg or DBP ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension
- Several adverse health conditions are related to MetS but are not part of its clinical definition. These include NAFLD, sexual/reproductive dysfunction (erectile dysfunction in males and polycystic ovarian syndrome in females), OSA, certain forms of cancer, and possibly osteoarthritis, as well as a general proinflammatory and prothrombotic state.[2]
- Type 2 DM, defined as FPG ≥126 mg/dL, random or 2-hour postchallenge glucose ≥200 mg/dL, HbA_{1c} ≥6.5%, or taking hypoglycemic medication, is a separate clinical diagnosis distinct from MetS; however, many of those with type 2 DM will also have MetS.

Prevalence

Youth
(See Chart 10-1)

- On the basis of NHANES 1999 to 2014, the prevalence of MetS in adolescents 12 to 19 years of age in the United States varied by geographic region. MetS prevalence was lower in the Northeast (6.25% [95% CI, 4.14%–8.36%]) and West (6.31% [95% CI, 4.73%–7.89%]) regions and higher in the South (7.57% [95% CI, 5.80%–9.33%]) and Midwest (11.42% [95% CI, 8.11%–14.72%]). Prevalence was higher in adolescent males versus females across all regions (Chart 10-1).[3]
- In HCHS/SOL Youth, the prevalence of MetS among children 10 to 16 years of age varied according to the clinical definition used, with only 1 participant being classified as having MetS by all 3 clinical definitions.[4]
- Although MetS categorization is generally unstable at younger ages, a single grouping of cardiometabolic risk factors (ie, abdominal obesity, insulin resistance, dyslipidemia, and elevated BP) was identified in a confirmatory factor analysis and shown to be present across the age spectrum from children to adults.[5] However, a separate confirmatory factor analysis in HCHS/SOL Youth showed that SBP and FPG did not cluster with other MetS components.[4]
- Uncertainty remains concerning the definition of the obesity component of MetS in the pediatric population because it is age dependent. Therefore, use of BMI percentiles[6] and waist-height ratio[7] has been recommended. Using CDC and FitnessGram standards for pediatric obesity, the prevalence of MetS in obese youth ranges from 19% to 35%.[6]

Adults
(See Chart 10-2)

The following estimates include many who also have DM, in addition to those with MetS without DM:

- On the basis of NHANES 2007 to 2014, the overall prevalence of MetS was 34.3% and was similar for males (35.3%) and females (33.3%).[8] The prevalence of MetS increased with age, from 19.3% among people 20 to 39 years of age to 37.7% for people 40 to 59 years of age and 54.9% among people ≥60 years of age.
- In a meta-analysis of 26 609 young adults (18–30 years of age) across 34 studies, the prevalence of MetS was 4.8% to 7% depending on the definition used.[9]
- In HCHS/SOL, the overall prevalence of MetS among Hispanics/Latinos living in the United States was 34% among males and 36% among females (Chart 10-2).[10] MetS prevalence increased with age, with the highest prevalence in females 70 to 74 years of age (Chart 10-2). In males and females, the lowest prevalence of MetS was observed among South Americans (27%). In males, the highest prevalence was observed in Cubans (35%), and in females, the highest prevalence was observed among Puerto Ricans (41%; Chart 10-2).
- Among blacks in the JHS, the overall prevalence of MetS was 34%, and it was higher in females than in males (40% versus 27%, respectively).[11]
- The prevalence of MetS has been noted to be high in individuals with certain conditions, including schizophrenia spectrum disorders[12]; use of atypical antipsychotic drugs[13]; prior solid organ transplants[14,15]; prior hematopoietic cell transplantation[16,17]; HIV infection[18]; prior treatment for blood cancers[17,19]; systemic inflammatory disorders such as psoriasis,[20] systemic lupus erythematosus,[21] and rheumatoid arthritis[22]; multiple sclerosis[23]; well-controlled type 1 DM[24]; hypopituitarism[25]; prior gestational DM[26]; prior pregnancy-induced hypertension[27]; cerebral palsy[28]; war-related bilateral lower-limb amputation[29] or spinal cord injury[30] in veterans; and select professions, including law enforcement[31] and firefighters.[32]

Secular Trends

Youth
(See Chart 10-3)

- In NHANES 1999 to 2012, the prevalence of MetS decreased among youth 12 to 19 years of age. This was most evident when considering a MetS severity *Z* score (slope=–0.015; *P*=0.030). During

this period, levels of HDL-C increased and triglycerides decreased along with decreased consumption of carbohydrates and increased unsaturated fat intake (Chart 10-3).[33]

Adults (See Charts 10-4 through 10-6)

- Secular trends in MetS differ based on the definition used. Using the harmonized MetS criteria, the prevalence of MetS increased from 25.3% in NHANES 1988 to 1994 to 34.2% in NHANES 2007 to 2012.[34] Although the prevalence of MetS increased for each race-sex group from NHANES 1999 to 2006 to NHANES 2007 to 2012, NH black males had the greatest increase (55%) across the entire study period from NHANES 1998 to 1994 to NHANES 2007 to 2012, whereas Mexican American females had the smallest (2% increase; Chart 10-4). In contrast, using ATP III criteria, the prevalence of MetS was stable overall in NHANES 2003 to 2014.[35] Additionally, the prevalence of MetS remained stable in both men and women in NHANES 2007 to 2014 (Chart 10-5).
- The prevalence of MetS is affected by changes in the prevalence of its individual components. In NHANES 2007 to 2014, elevated triglycerides and elevated FPG decreased, whereas low HDL remained stable for males and females (Chart 10-5). In contrast, abdominal adiposity increased for females, and elevated BP increased overall (Chart 10-5).[8,35]
- In the ARIC study (1987–1998), prevalence of MetS increased from 33% to 50% over the mean 10-year follow-up, with differences by age and sex.[36] The prevalence of MetS was lower in black males than in white males at all time points and for all ages across the study. Black females had higher prevalence of MetS than white females at baseline and subsequent time points for all ages except for those >60 years of age (Chart 10-6).

Risk Factors

Youth

- In the PREMA Study, independent predictors of MetS from childhood to adolescence were low birth weight, small head circumference, and a parent with overweight or obesity.[37] When all 3 of these predictors were present, the sensitivity and specificity of identifying MetS was 91% and 98%, respectively, in both the derivation and validation cohorts.
- In an RCT of an intervention to promote longer duration of exclusive breastfeeding in mother-child pairs, the risk of childhood MetS after 11.5 years of follow-up was increased among boys in the intervention group (OR, 1.49 [95% CI, 1.01–2.22]) but not girls (OR, 0.94 [95% CI, 0.63–1.42]) in the intervention group compared with control groups.[38]
- In NHANES 2007 to 2010, higher exposure to secondhand smoke was associated with prevalent MetS (OR, 5.4 [95% CI, 1.7–16.9]) among adolescents 12 to 19 years of age. Additionally, higher secondhand smoke exposure interacted with low exposure to certain nutrients (vitamin E and omega-3 PUFAs) to increase the odds of MetS.[39]
- Daily intake of added sugar >186 g/d was associated with prevalent MetS (OR, 8.4 [95% CI, 4.7–12.1]) among adolescents 12 to 19 years of age in NHANES 2005 to 2012.[40]

Adults

- There is a bidirectional association between MetS and depression. In prospective studies, depression increases the risk of MetS (OR, 1.49 [95% CI, 1.19–1.87]), and MetS increases the risk of depression (OR, 1.52 [95% CI, 1.20–1.91]).[41]
- In prospective or retrospective cohort studies, numerous factors have been reported as being directly associated with incident MetS, defined by 1 of the major definitions, including age,[42] inability to understand or read food labels,[43] smoking,[44,45] parental smoking,[46] low levels of PA,[47] and physical fitness.[48]
- Dietary habits are also associated with incident MetS, including a Western diet[49] and consumption or intake of soft drinks,[50] diet soda,[51] energy-dense beverages,[52] SSBs,[53] fructose,[54] magnesium,[55,56] energy,[57] carbohydrates,[58] total fat,[59] meats (total, red, and processed but not white meat),[60] and fried foods.[51] Additionally, skipping breakfast[61] and a problematic relationship to eating and food[62] are risk factors.
- Other risk factors for incident MetS include parental history of DM,[59] pediatric MetS,[59] obesity or BMI,[63,64] childhood obesity,[65] childhood MetS,[66] intra-abdominal fat,[67] gain in weight or BMI,[57] weight fluctuation,[68] and heart rate.[69]
- Blood biomarkers associated with incident MetS include homeostasis model assessment,[70] fasting insulin,[71] 2-hour insulin,[71] proinsulin,[71] oxidized LDL-C,[72,73] HDL particle concentration,[74] LDL particle concentration,[74,75] lipoprotein-associated phospholipase A2,[76] uric acid,[77–79] γ-glutamyltransferase,[80,81] alanine transaminase,[80] plasminogen activator inhibitor-1,[73] fibroblast growth factor 21,[82] aldosterone,[83] leptin,[84] ferritin,[85] CRP,[86] adipocyte–fatty acid binding protein,[87] testosterone and sex hormone–binding globulin,[88,89] matrix metalloproteinase 9,[90] serum free triiodothyronine,[91] active periodontitis,[92,93] use of protease inhibitors in

HIV-infected patients,[94] and urinary bisphenol A levels.[95]

- In a pooled population of 117 020 patients from 20 studies who were followed up for a median of 5 years (range, 3–14.7 years), NAFLD was associated with an increased risk of incident MetS when using alanine aminotransferase (RR, 1.80 [95% CI, 1.72–1.89] for highest versus lowest quartile or quintile), γ-glutamyltransferase (RR, 1.98 [95% CI, 1.89–2.07] for highest versus lowest quartile or quintile), or ultrasonography (RR, 3.22 [95% CI, 3.05–3.41]) to assess NAFLD.[80]
- In a meta-analysis that included 76 699 participants and 13 871 incident cases of MetS, there was a negative linear relationship between leisure-time PA and development of MetS.[96] For every increase of 10 MET h/wk (approximately equal to 150 minutes of moderate PA per week), risk of MetS was reduced by 10% (RR, 0.90 [95% CI, 0.86–0.94]).
- Prior studies have reported higher MetS incidence among individuals with lower educational attainment, lower SES,[97,98] more experiences of everyday discrimination,[99] and long-term work stress.[100]
- The following factors have been reported as being inversely associated with incident MetS, defined by 1 of the major definitions, in prospective or retrospective cohort studies: muscular strength,[101] increased PA or physical fitness,[102,103] aerobic training,[104] cardiorespiratory fitness (eg, maximal oxygen uptake),[105] and living at geographically higher elevation.[106]
- Dietary habits are also inversely associated with incident MetS, including alcohol use,[107] fiber intake,[108,109] consumption of fruits and vegetables,[110] white fish intake,[111] Mediterranean diet,[112,113] dairy consumption (particularly yogurt and low-fat dairy products),[51,114] consumption of fermented milk with *Lactobacillus plantarum*,[115] consumption of animal or fat protein,[116] hot tea consumption (but not sugar-sweetened iced tea),[117] coffee consumption,[118] vitamin D intake,[119] intake of tree nuts,[120] walnut intake,[121] avocado intake,[122] intake of long-chain omega-3 PUFAs,[123] potassium intake,[124] and ability to interpret nutrition labels.[43]
- Blood biomarkers that are inversely associated with incident MetS include insulin sensitivity,[71] ratio of aspartate aminotransferase to alanine aminotransferase,[125] total testosterone,[67,71,126] serum 25-hydroxyvitamin D,[127] sex hormone–binding globulin,[67,71,126] and Δ5-desaturase activity.[128]
- In cross-sectional studies, prevalent MetS is associated with a high-salt diet[129]; a high dietary inflammatory index[130]; stress[131]; proinflammatory cytokines such as IL-6 and tumor necrosis factor-α[73]; low cardiorespiratory fitness[132]; sarcopenia in middle aged and older nonobese adults[133]; cancer antigen 19-9[132,134]; erythrocyte parameters[135] such as hemoglobin level and red blood cell distribution width; excessive dietary calcium (>1200 mg/d) in males[136]; inadequate energy intake among patients undergoing dialysis[137]; blood parameters such as hemoglobin, platelet, and white blood cell counts[138]; and OSA.[139]
- In cross-sectional studies, increased standing,[140] "weekend warrior" and regular PA patterns,[141] handgrip strength,[142] a vegetarian diet,[143] subclinical hypothyroidism in males,[144] muscle mass to visceral fat ratio in college students,[145] marijuana use,[146] total antioxidant capacity from diet and dietary supplements,[147] organic food consumption,[148] anti-inflammatory cytokines (IL-10),[73] ghrelin,[73] adiponectin,[73] and antioxidant factors (paraoxonase-1)[73] were inversely associated with prevalent MetS. In NHANES 2003 to 2008, high neighborhood racial/ethnic diversity[149] was associated with a lower MetS prevalence (OR, 0.71 [95% CI, 0.52–0.96]) after adjustment for neighborhood-level poverty and individual factors.

Subclinical Disease (See Chart 10-6)

- In the ARIC study (1987–1998), using a sex- and race/ethnicity-specific MetS severity score, 76% of ARIC participants progressed over a mean 10-year follow-up, with faster progression observed in younger participants and in females (Chart 10-6).[36]
- Isolated MetS, which could be considered an earlier form of overt MetS, has been defined as those with ≥3 MetS components but without overt hypertension and DM. In a population-based random sample of 2042 residents of Olmsted County, MN, those with isolated MetS had a higher incidence of hypertension, DM, diastolic dysfunction, and reduced renal function (GFR <60 mL/min) compared with healthy control subjects ($P<0.05$).[150]

Genetics and Family History

- Several pleiotropic variants of genes of apolipoproteins (*APOE*, *APOC1*, *APOC3*, and *APOA5*), Wnt signaling pathway (*TCF7L2*), lipoproteins (*LPL*, *CETP*), mitochondrial proteins (*TOMM40*), gene transcription regulation (*PROX1*), cell proliferation (*DUSP9*), cAMP signaling (*ADCY5*), and oxidative LDL metabolism (*COLEC12*), as well as expression of liver-specific genes (*HNF1A*), have been identified across various racial/ethnic populations that could explain some of the correlated architecture of MetS traits.[151–154]

- The minor G allele of the atrial natriuretic peptide genetic variant rs5068, which is associated with higher levels of circulating atrial natriuretic peptide, has been associated with lower prevalence of MetS in whites and blacks.[155]
- SNPs of inflammatory genes (encoding IL-6, IL-1β, and IL-10) and plasma fatty acids, as well as interactions among these SNPs, are differentially associated with odds of MetS.[156]

Prevention and Awareness of MetS

- Identification and treatment of MetS aligns with the AHA 2020 Impact Goal,[156a] with emphasis on PA, healthy diet, and healthy weight for attainment of ideal BP, serum cholesterol, and FPG levels. Monitoring the prevalence of MetS is a secondary metric in the 2020 Impact Goal. Identification of MetS represents a call to action for the healthcare provider and patient to address underlying lifestyle-related risk factors. A multidisciplinary team of healthcare professionals is desirable to adequately address these multiple issues in patients with MetS.[3]
- Despite the high prevalence of MetS, the public's recognition of MetS is limited.[4] Communicating with patients about MetS and its clinical assessment may increase risk perception and motivation toward a healthier behavior.[5]

Morbidity and Mortality

Adults

- MetS is associated with CVD morbidity and mortality. A meta-analysis of 87 studies comprising 951 083 subjects showed MetS increased the risk of CVD (summary RR, 2.35 [95% CI, 2.02–2.73]), with significant increased risks (RRs ranging from 1.6 to 2.9) for all-cause mortality, CVD mortality, MI, and stroke, even for those with MetS without DM.[157]
- The cardiovascular risk associated with MetS varies on the basis of the combination of MetS components present. Of all possible ways to have 3 MetS components, the combination of central obesity, elevated BP, and hyperglycemia conferred the greatest risk for CVD (HR, 2.36 [95% CI, 1.54–3.61]) and mortality (HR, 3.09 [95% CI, 1.93–4.94]) in the Framingham Offspring Study.[64]
- In a meta-analysis of 20 prospective cohort studies that included 57 202 adults ≥60 years of age, MetS was associated with increased risk of all-cause mortality (RR, 1.20 [95% CI, 1.05–1.38] for males and RR, 1.22 [95% CI, 1.02–1.44] for females) and CVD mortality (RR, 1.29 [95% CI, 1.09–1.53] for males and RR, 1.20 [95% CI, 0.91–1.60] for females).[158] There was significant heterogeneity across the studies (all-cause mortality, I^2=55.9%, P=0.001; CVD mortality, I^2=58.1%, P=0.008). In subgroup analyses, the association of MetS with CVD and all-cause mortality varied by geographic location, sample size, definition of MetS, and adjustment for frailty.
- The impact of MetS on mortality has been shown to be modified by objective sleep duration.[159] In data from the Penn State Adult Cohort, a prospective population-based study of sleep disorders, objectively measured short sleep duration (<6 hours) was associated with increased all-cause mortality (HR, 1.99 [95% CI, 1.53–2.59]) and CVD mortality (HR, 2.10 [95% CI, 1.39–3.16]), whereas sleep ≥6 hours was not associated with increased all-cause mortality (HR, 1.29 [95% CI, 0.89–1.87]) or CVD mortality (HR, 1.49 [95% CI, 0.75–2.97]) among participants with MetS.
- In the INTERHEART case-control study of 26 903 subjects from 52 countries, MetS was associated with an increased risk of MI, both according to the WHO (OR, 2.69 [95% CI, 2.45–2.95]) and the IDF (OR, 2.20 [95% CI, 2.03–2.38]) definitions, with a PAR of 14.5% (95% CI, 12.7%–16.3%) and 16.8% (95% CI, 14.8%–18.8%), respectively, and associations that were similar across all regions and ethnic groups. In addition, the presence of ≥3 risk factors with above-threshold values was associated with increased risk of MI (OR, 1.50 [95% CI, 1.24–1.81]) compared with having <3 risk factors with above-threshold values. Similar results were observed when the IDF definition was used.[160]
- In the Three-City Study, among 7612 participants ≥65 years of age who were followed up for 5.2 years, MetS was associated with increased total CHD (HR, 1.78 [95% CI, 1.39–2.28]) and fatal CHD (HR, 2.40 [95% CI, 1.41–4.09]); however, MetS was not associated with CHD beyond its individual risk components.[161]
- Among 3414 patients with stable CVD and atherogenic dyslipidemia who were treated intensively with statins in the AIM-HIGH trial, neither the presence of MetS or the number of MetS components was associated with cardiovascular outcomes, including coronary events, ischemic stroke, nonfatal MI, CAD death, or the composite end point.[162]
- Using the 36 cohorts represented in the MORGAM Project, the risk of CVD in MetS declined with greater age in females but not males.[163]
- It is estimated that 13.3% to 44% of the excess CVD mortality in the United States, compared with other countries such as Japan, is explained by MetS or MetS–related existing CVD.[164]

- MetS is associated with risk of stroke.[165] In a meta-analysis of 16 studies including 116 496 participants who were initially free of CVD, those with MetS had an increased risk of stroke (pooled RR, 1.70 [95% CI, 1.49–1.95]) compared with those without MetS. The magnitude of the effect was stronger among females (RR, 1.83 [95% CI, 1.31–2.56]) than males (RR, 1.47 [95% CI, 1.22–1.78]). Finally, those with MetS had the highest risk for ischemic stroke (RR, 2.12 [95% CI, 1.46–3.08]) rather than hemorrhagic stroke (RR, 1.48 [95% CI, 0.98–2.24]).
- In the ARIC study, among 13 168 participants with a median follow-up of 23.6 years, MetS was independently associated with an increased risk of SCD (adjusted HR, 1.70 [95% CI, 1.37–2.12]; $P<0.001$).[166] The risk of SCD varied according to the number of MetS components (HR, 1.31 per 1 additional component of the MetS [95% CI, 1.19–1.44]; $P<0.001$), independent of race or sex.

Complications

Youth

- Among 771 participants 6 to 19 years of age from the NHLBI's Lipid Research Clinics Princeton Prevalence Study and the Princeton Follow-up Study, the risk of CVD was substantially higher among those with MetS than among those without MetS (OR, 14.6 [95% CI, 4.8–45.3]) who were followed up for 25 years.[167]
- In an International Childhood Cardiovascular Cohort Consortium that included 5803 participants in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, and Minnesota Insulin Study) with a mean follow-up period of 22.3 years, childhood MetS and overweight were associated with a >2.4-fold risk for adult MetS from 5 years of age onward.[66] The risk for type 2 DM was increased beginning at 8 years of age (RR, 2.6 [95% CI, 1.4–6.8]) based on international cutoff values for definition of childhood MetS. Risk of carotid IMT was increased beginning at 11 years of age (RR, 2.44 [95% CI, 1.55–3.55]) using the same definition.
- Among 1757 youths from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, those with MetS in youth and adulthood were at 3.4 times increased risk of high carotid IMT and 12.2 times increased risk of type 2 DM in adulthood as those without MetS at either time. Adults whose MetS had resolved after their youth did not have an increased risk of having high IMT or type 2 DM.[63]
- In the Princeton Lipid Research Cohort Study, MetS severity scores during childhood were lowest among those who never developed CVD and were proportionally higher progressing from those who developed early CVD (mean 38 years of age) to those who developed CVD later in life (mean 50 years of age).[168] MetS severity score was also strongly associated with early onset of DM.[169]
- MetS score, based on the number of components of MetS, was associated with biomarkers of inflammation, endothelial damage, and CVD risk in a separate cohort of 677 prepubertal children.[170]

Adults

MetS and Subclinical CVD

- MetS has also been associated with incident AF,[171] recurrent AF after ablation,[172] HF,[173] and PAD.[174]
- In MESA, among 6603 people 45 to 84 years of age (1686 [25%] with MetS without DM and 881 [13%] with DM), subclinical atherosclerosis assessed by CAC was more severe in people with MetS and DM than in those without these conditions, and the extent of CAC was a strong predictor of CHD and CVD events in these groups.[175] There appears to be a synergistic relationship between MetS, NAFLD, and prevalence of CAC,[176,177] as well as a synergistic relationship with smoking.[178] Furthermore, the progression of CAC was greater in people with MetS and DM than in those without, and progression of CAC predicted future CVD event risk both in those with MetS and in those with DM.[179] In MESA, the prevalence of thoracic calcification was 33% for people with MetS compared with 38% for those with DM (with and without MetS) and 24% of those with neither DM nor MetS.[180]
- In the DESIR cohort, MetS was associated with an unfavorable hemodynamic profile, including increased brachial central pulse pressure and increased pulse-pressure amplification, compared with similar individuals with isolated hypertension but without MetS.[181] In MESA, MetS was associated with major and minor electrocardiographic abnormalities, although this varied by sex.[182] MetS is associated with reduced heart rate variability and altered cardiac autonomic modulation in adolescents.[183]
- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.[184] Furthermore, individuals with both MetS and DM have demonstrated increased microvascular and macrovascular dysfunction.[185] MetS is associated with increased thrombosis, including increased resistance to aspirin[186] and clopidogrel loading.[187]
- In a meta-analysis of 8 population-based studies that included 19 696 patients (22.2% with

MetS), MetS was associated with higher carotid IMT (standard mean difference 0.28±0.06 [95% CI, 0.16–0.40]; *P*=0.00003) and higher prevalence of carotid plaques than in individuals without MetS (pooled OR, 1.61 [95% CI, 1.29–2.01]; *P*<0.0001).[188]

- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomography, MetS has been shown to be closely related to increased epicardial adipose tissues,[189] regional neck fat distribution,[190] increased visceral fat in other locations,[191] increased ascending aortic diameter,[192] high-risk coronary plaque features including increased necrotic core,[193] impaired coronary flow reserve,[194] abnormal indices of LV strain,[195,196] LV diastolic dysfunction,[197] LV dyssynchrony,[198] and subclinical RV dysfunction.[199]

MetS and Non-CVD Complications

- In data from ARIC and JHS, MetS was associated with an increased risk of DM (HR, 4.36 [95% CI, 3.83–4.97]), although the association was attenuated after adjustment for the individual components of the MetS.[200] However, use of a continuous sex- and race-specific MetS severity *Z* score was associated with an increased risk of DM independent of individual MetS components, with increases in this score over time conferring additional risk for DM.
- In RENIS-T6, MetS was associated with a mean 0.30 mL/min per year (95% CI, 0.02–0.58 mL/min per year) faster decline in GFR than in individuals without MetS.[201]
- MetS is also associated with cancer (in particular, breast, endometrial, prostate, pancreatic, hepatic, colorectal, and renal),[202,203] as well as gastroenteropancreatic neuroendocrine tumors.[204] MetS is linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.[203,205] In a meta-analysis of 24 studies that included 132 589 males with prostate cancer (17.4% with MetS), MetS was associated with worse oncological outcomes, including biochemical recurrence and more aggressive tumor features.[206] Among 94 555 females free of cancer at baseline in the prospective NIH-AARP cohort, MetS was associated with increased risk of breast cancer mortality (HR, 1.73 [95% CI, 1.09–2.75]), particularly among postmenopausal females (HR, 2.07 [95% CI, 1.32–3.25]).[207]
- In data obtained from HCUP, hospitalized patients with a diagnosis of MetS and cancer had significantly increased odds of adverse health outcomes, including increased postsurgical complications (OR, 1.20 [95% CI, 1.03–1.39] and OR, 1.22 [95% CI, 1.09–1.37] for breast and prostate cancer, respectively).[208]
- In 25 038 black and white participants from the REGARDS study, MetS was associated with increased risk of cancer-related mortality (HR, 1.22 [95% CI, 1.03–1.45]).[202] For those with all 5 MetS components present, the risk of cancer mortality was 59% higher than for those without a MetS component present (HR, 1.59 [95% CI, 1.01–2.51]).
- In NHANES III, MetS was associated with total cancer mortality (HR, 1.33 [95% CI, 1.04–1.70]) and breast cancer mortality (HR, 2.1 [95% CI, 1.09–4.11]).[209]
- MetS was associated with a higher incidence of hepatocellular carcinoma in males (RR, 1.75 [95% CI, 1.28–2.38]) but not in females (RR, 1.18 [95% CI, 0.76–1.84]).[210]
- NAFLD, a spectrum of liver disease that ranges from isolated fatty liver to fatty liver plus inflammation (nonalcoholic steatohepatitis), is hypothesized to represent the hepatic manifestation of MetS. On the basis of data from NHANES 2011 to 2014, the overall prevalence of NAFLD among US adults was 21.9%.[211] The global prevalence of NAFLD is estimated at 25.2%.[212] In a prospective study of 4401 Japanese adults 21 to 80 years of age who were free of NAFLD at baseline, the presence of MetS increased the risk for NAFLD in both males (OR, 4.00 [95% CI, 2.63–6.08]) and females (OR, 11.20 [95% CI, 4.85–25.87]).[213] In cross-sectional studies, an increase in the number of MetS components was associated with underlying nonalcoholic steatohepatitis and advanced fibrosis in NAFLD.[211,214]
- MetS is also associated with erectile dysfunction.[215] In MESA, the prevalence of erectile dysfunction among participants 55 to 65 years of age with MetS was 16% compared with 10% in their counterparts without MetS (*P*<0.001).[215]
- MetS has been associated with cirrhosis[216] and cognitive decline,[217] and possibly with VTE[218] and incident asthma.[219]
- Among 725 Chinese adults ≥90 years of age, MetS was associated with prevalent disability in activities of daily living (OR, 1.65 [95% CI, 1.10–3.21]) and instrumental activities of daily living (OR, 2.09 [95% CI, 1.17–4.32]).[220]

Cost and Healthcare Utilization

- MetS is associated with increased healthcare use and healthcare-related costs among individuals with and without DM. Overall, healthcare costs increase by ≈24% for each additional MetS component present.[221]
- The presence of MetS increases the risk for postoperative complications, including prolonged hospital stay and risk for blood transfusion, surgical

site infection, and respiratory failure, across various surgical populations.[208,222,223]

Global Burden of MetS (See Chart 10-7)

- MetS is becoming hyperendemic around the world. Published evidence has described the prevalence of MetS in Canada,[224] Latin America,[225] India,[226–230] Bangladesh,[231] Iran,[232,233] Nigeria,[234] South Africa,[235] Ecuador,[236] Nigeria,[237] and Vietnam,[238] as well as many other countries.
- On the basis of data from NIPPON DATA (1990–2005), the age-adjusted prevalence of MetS in a Japanese population was 19.3%.[164] In a partially representative Chinese population, the 2009 age-adjusted prevalence of MetS in China was 21.3%,[239] whereas in northwest China, the prevalence for 2010 was 15.1%,[240] and in 2018, the prevalence in Chinese adults in Hong Kong was 14.1%.[241]
- In a report from BioSHaRE, which harmonizes modern data from 10 different population-based cohorts in 7 European countries, the age-adjusted prevalence of MetS in obese subjects ranged from 24% to 65% in females and from ≈43% to ≈78% in males. In the obese population, the prevalence of MetS far exceeded the prevalence of MHO, which had a prevalence of 7% to 28% in females and 2% to 19% in males. The prevalence of MetS varied considerably by European country in the BioSHaRE consortium (Chart 10-7).[242]
- The prevalence of MetS has been reported to be low (14.6%) in a population-representative study in France (the French Nutrition and Health Survey, 2006–2007) compared with other industrialized countries.[243]
- In a systematic review of 10 Brazilian studies, the weighted mean prevalence of MetS in Brazil was 29.6%.[244]
- In a meta-analysis of 10 191 subjects across 6 studies, the prevalence of MetS in Argentina was 27.5% (95% CI, 21.3%–34.1%), and prevalence was higher in males than in females (29.4% versus 27.4%; P=0.02).[245]
- In a report from a representative survey of the northern state of Nuevo León, Mexico, the prevalence of MetS in adults (≥16 years of age) for 2011 to 2012 was 54.8%. In obese adults, the prevalence reached 73.8%. The prevalence in adult North Mexican females (60.4%) was higher than in adult North Mexican males (48.9%).[246] Among older Mexican adults (≥65 years of age), the prevalence was 72.9% (75.7% in males; 70.4% in females).[247]
- MetS is highly prevalent in modern indigenous populations, notably in Brazil and Australia. The prevalence of MetS was estimated to be 41.5% in indigenous groups in Brazil,[244,246] 33.0% in Australian Aborigines, and 50.3% in Torres Strait Islanders.[248]
- In a meta-analysis of cross-sectional studies that assessed the prevalence of MetS in Middle Eastern countries, the pooled prevalence estimate for MetS was 25% (95% CI, 0.252–0.257). Prevalence ranged from a low of 2.2% up to 60% depending on the time frame, country studied, and definition of MetS used. There was high heterogeneity among the 59 included studies.[249]

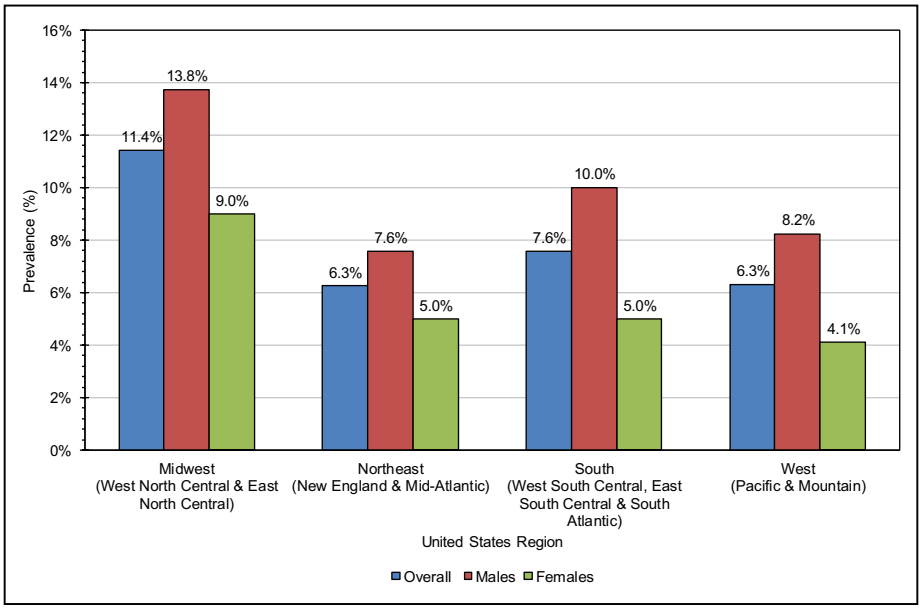

Chart 10-1. Prevalence of metabolic syndrome by sex and US region among adolescents 12 to 19 years of age (NHANES, 1999–2014).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Data derived from DeBoer et al.[3]

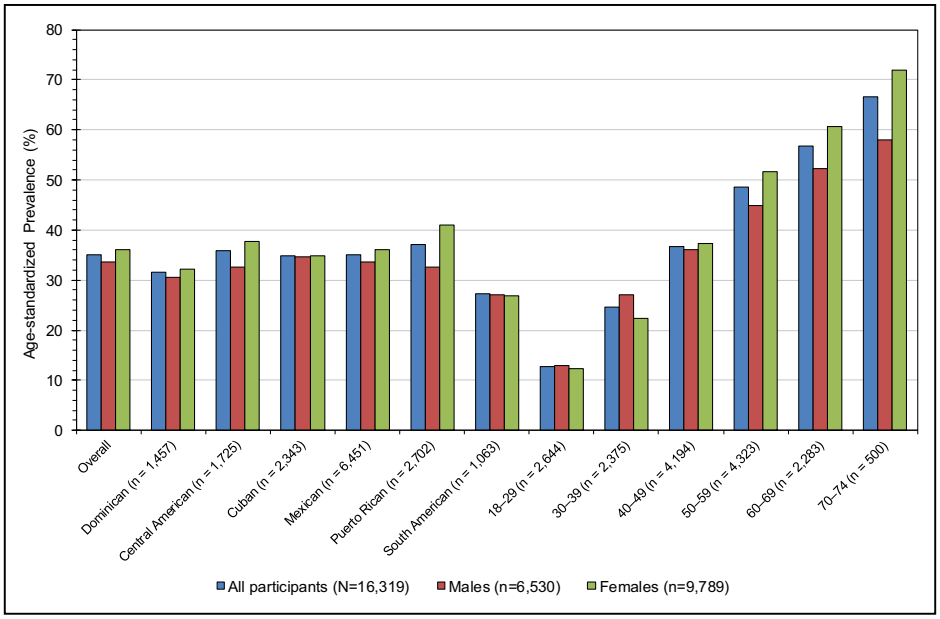

Chart 10-2. Age-standardized prevalence of metabolic syndrome by age and sex in Hispanics/Latinos in HCHS/SOL, United States, 2008 to 2011.
Values were weighted for survey design and nonresponse and were age standardized to the population described by the 2010 US census.
HCHS/SOL indicates Hispanic Community Health Study/Study of Latinos.
Source: Data derived from Heiss et al.[10]

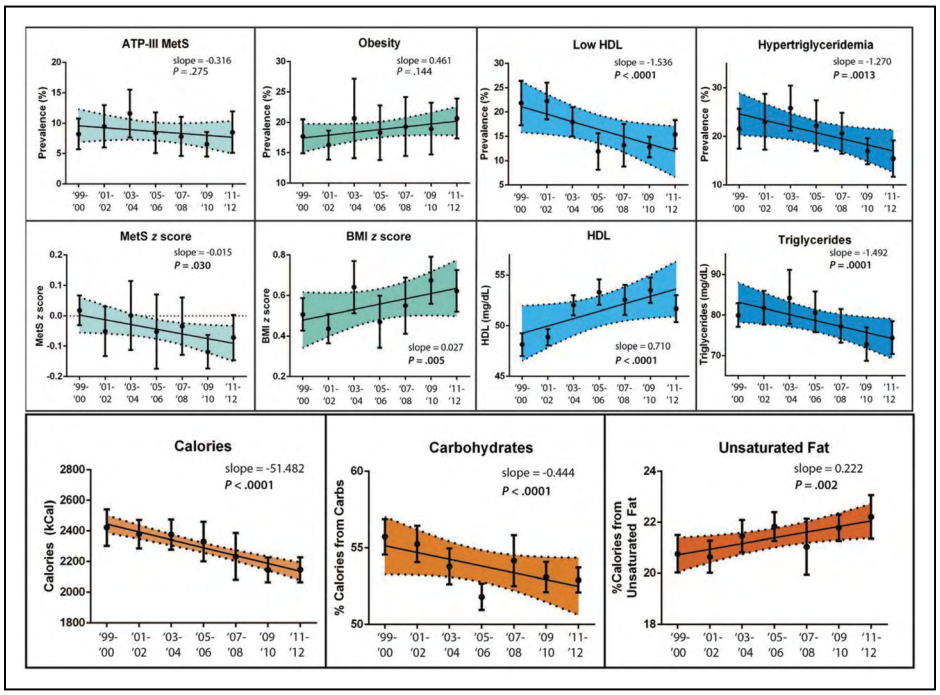

Chart 10-3. Prevalence of MetS in US youth (NHANES, 1999–2012).
ATP III indicates Adult Treatment Panel III; BMI, body mass index; Carbs, carbohydrates; HDL, high-density lipoprotein; MetS, metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.
Source: Reproduced with permission from Lee et al.[33] Copyright © 2016, by the American Academy of Pediatrics.

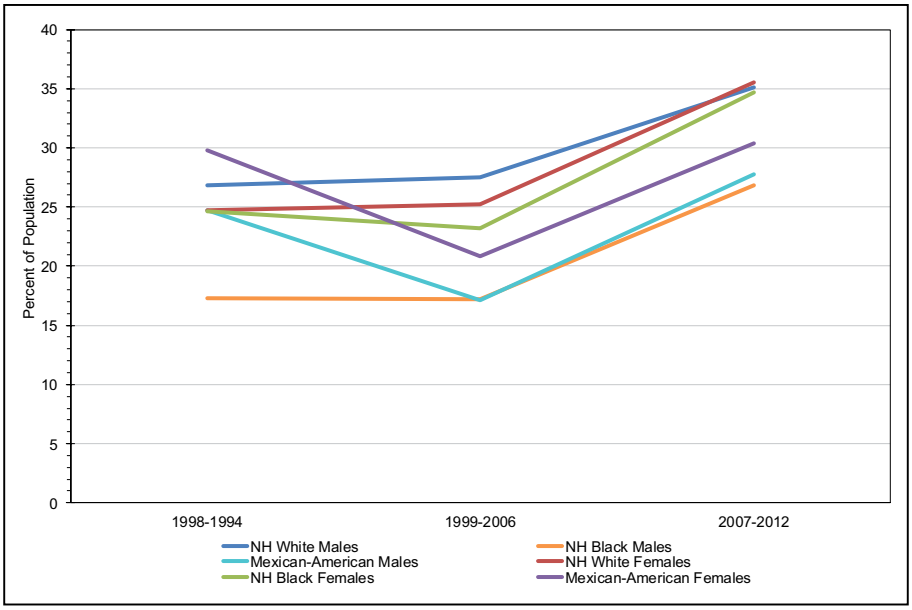

Chart 10-4. Prevalence of metabolic syndrome among US adults (NHANES, 1998–2012).
Metabolic syndrome was defined using the criteria agreed to jointly by the International Diabetes Federation; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity. NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.
Source: Data derived from Moore et al.[34]

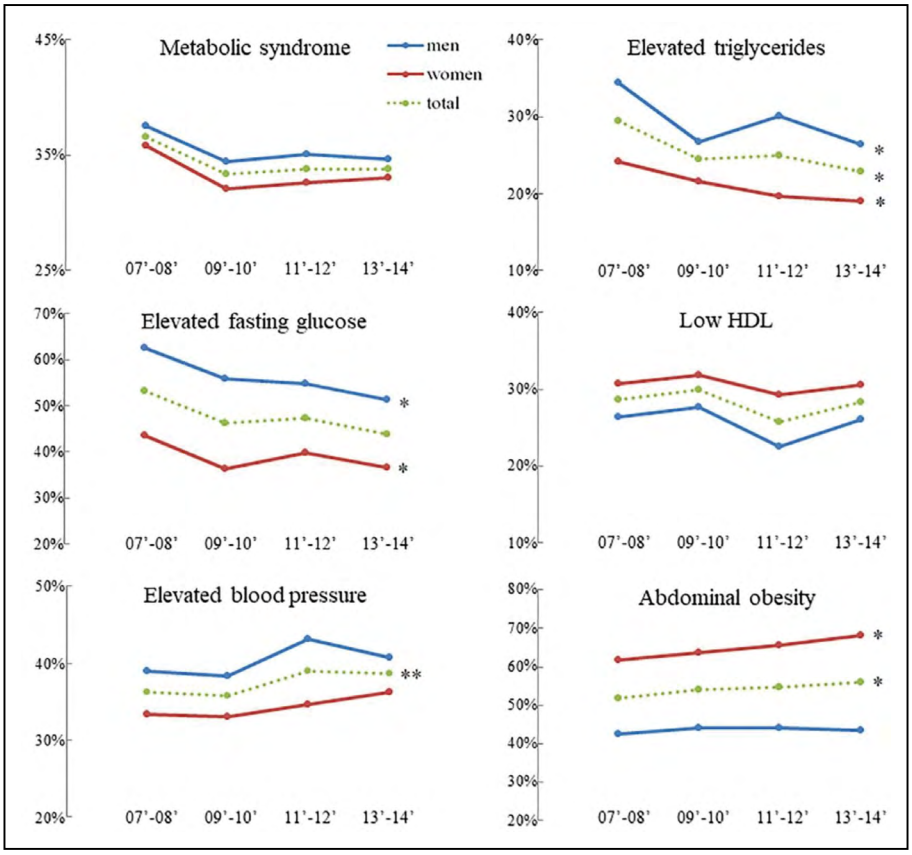

Chart 10-5. Sex-stratified trends in the age-adjusted weighted prevalence of metabolic syndrome and its components among US adults (NHANES, 2007–2014).
HDL indicates high-density lipoprotein; and NHANES, National Health and Nutrition Examination Survey.
**P* for trend <0.05.
***P* for trend=0.05, after adjustment for age, sex, and race, as appropriate.
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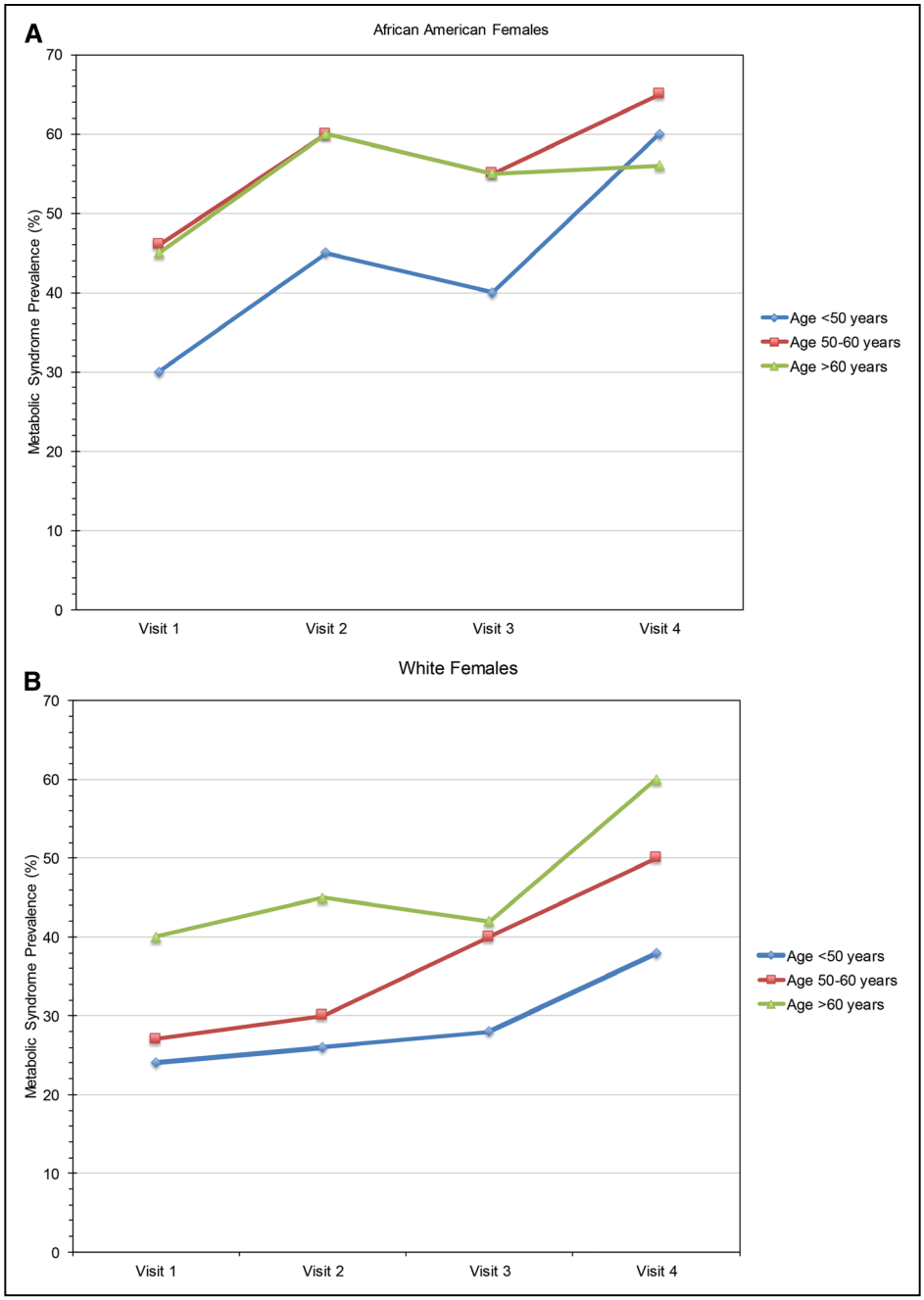

Chart 10-6. Ten-year progression of metabolic syndrome in the ARIC study, stratified by age, sex, and race/ethnicity, United States, 1987 to 1998.
A, African-American females; (**B**) white females; (**C**) white males; (**D**) African-American males.
Data obtained from visit 1 (1987–1989), visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998).
ARIC indicates Atherosclerosis Risk in Communities.
Source: Data derived from Vishnu et al.[36]

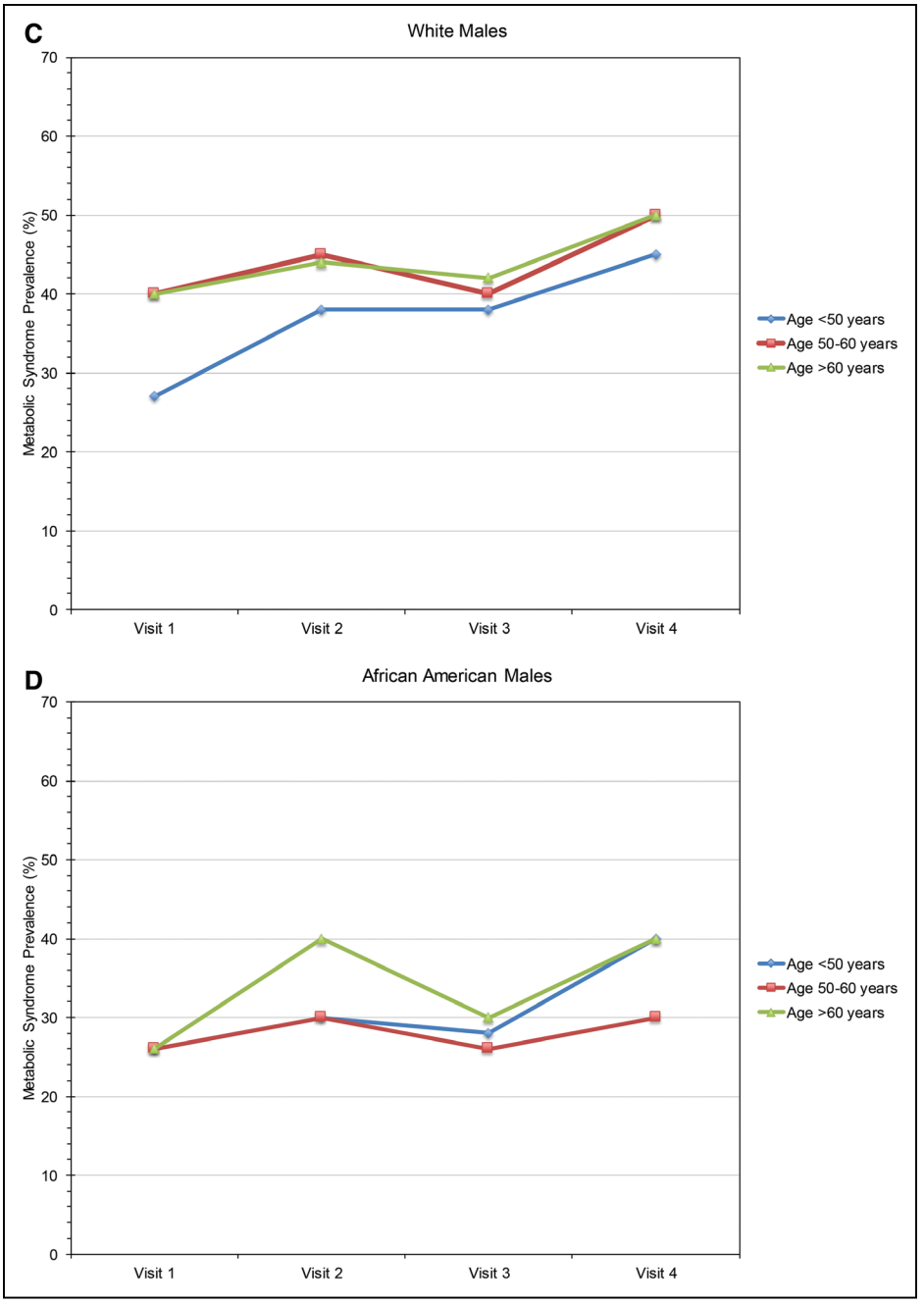

Chart 10-6. (**Continued**)

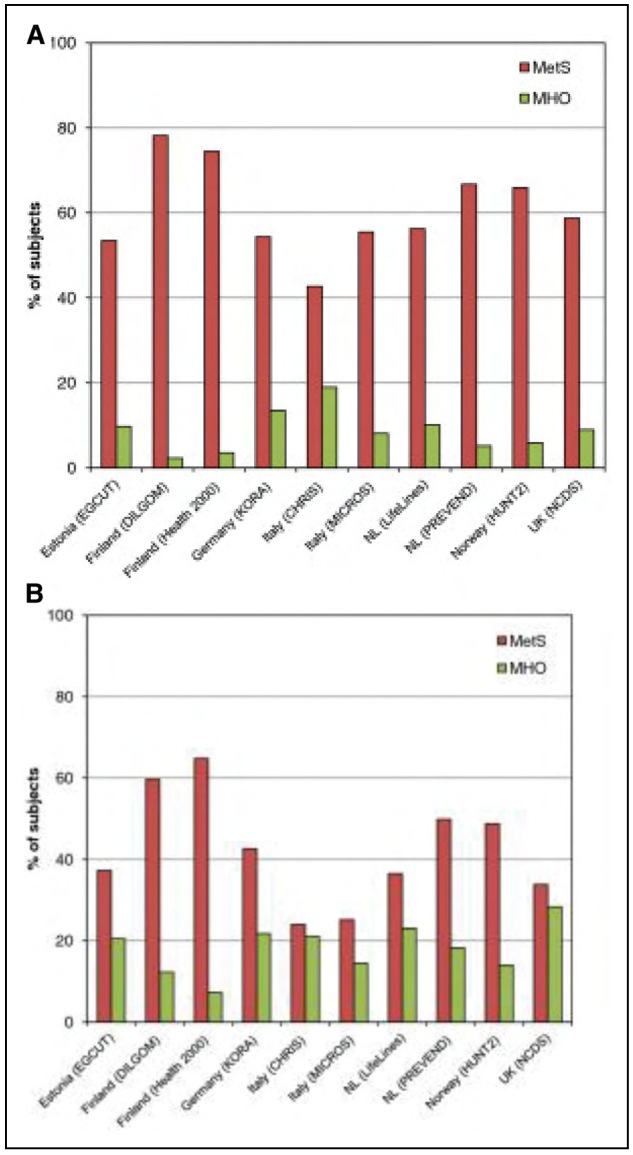

Chart 10-7. Age-standardized prevalence of MetS and MHO among obese (body mass index ≥30 kg/m^2) people in different European cohorts, 1995 to 2012 (global data).

Data are shown for males (**A**) and females (**B**). CHRIS indicates Collaborative Health Research in South Tyrol Study; DILGOM, Dietary, Lifestyle, and Genetics Determinants of Obesity and Metabolic Syndrome; EGCUT, Estonian Genome Center of the University of Tartu; HUNT2, Nord-Trøndelag Health Study; KORA, Cooperative Health Research in the Region of Augsburg; MetS, metabolic syndrome; MHO, metabolically healthy obesity; MICROS, Microisolates in South Tyrol Study; NCDS, National Child Development Study; NL, the Netherlands; and PREVEND, Prevention of Renal and Vascular End-Stage Disease. Source: Reprinted from van Vliet-Ostaptchouk et al.[242]

REFERENCES

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644
2. Mendrick DL, Diehl AM, Topor LS, Dietert RR, Will Y, La Merrill MA, Bouret S, Varma V, Hastings KL, Schug TT, et al. Metabolic syndrome and associated diseases: from the bench to the clinic. *Toxicol Sci.* 2018;162:36–42. doi: 10.1093/toxsci/kfx233
3. DeBoer MD, Filipp SL, Gurka MJ. Geographical variation in the prevalence of obesity and metabolic syndrome among US adolescents. *Pediatr Obes.* 2019;14:e12483. doi: 10.1111/ijpo.12483
4. Reina SA, Llabre MM, Vidot DC, Isasi CR, Perreira K, Carnethon M, Parrinello CM, Gallo LC, Ayala GX, Delamater A. Metabolic syndrome in Hispanic youth: results from the Hispanic Community Children's Health Study/Study of Latino Youth. *Metab Syndr Relat Disord.* 2017;15:400–406. doi: 10.1089/met.2017.0054
5. Viitasalo A, Lakka TA, Laaksonen DE, Savonen K, Lakka HM, Hassinen M, Komulainen P, Tompuri T, Kurl S, Laukkanen JA, et al. Validation of metabolic syndrome score by confirmatory factor analysis in children and adults and prediction of cardiometabolic outcomes in adults. *Diabetologia.* 2014;57:940–949. doi: 10.1007/s00125-014-3172-5
6. Laurson KR, Welk GJ, Eisenmann JC. Diagnostic performance of BMI percentiles to identify adolescents with metabolic syndrome. *Pediatrics.* 2014;133:e330–e338. doi: 10.1542/peds.2013-1308
7. Khoury M, Manlhiot C, McCrindle BW. Role of the waist/height ratio in the cardiometabolic risk assessment of children classified by body mass index. *J Am Coll Cardiol.* 2013;62:742–751. doi: 10.1016/j.jacc.2013.01.026
8. Shin D, Kongpakpaisarn K, Bohra C. Trends in the prevalence of metabolic syndrome and its components in the United States 2007-2014. *Int J Cardiol.* 2018;259:216–219. doi: 10.1016/j.ijcard.2018.01.139
9. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. *Prev Med Rep.* 2017;7:211–215. doi: 10.1016/j.pmedr.2017.07.004
10. Heiss G, Snyder ML, Teng Y, Schneiderman N, Llabre MM, Cowie C, Carnethon M, Kaplan R, Giachello A, Gallo L, et al. Prevalence of metabolic syndrome among Hispanics/Latinos of diverse background: the Hispanic Community Health Study/Study of Latinos. *Diabetes Care.* 2014;37:2391–2399. doi: 10.2337/dc13-2505
11. Khan RJ, Gebreab SY, Sims M, Riestra P, Xu R, Davis SK. Prevalence, associated factors and heritabilities of metabolic syndrome and its individual components in African Americans: the Jackson Heart Study. *BMJ Open.* 2015;5:e008675. doi: 10.1136/bmjopen-2015-008675
12. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry.* 2014;71:1350–1363. doi: 10.1001/jamapsychiatry.2014.1314
13. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K, Jara B. Metabolic syndrome and obesity among users of second generation antipsychotics: a global challenge for modern psychopharmacology. *Pharmacol Res.* 2015;101:74–85. doi: 10.1016/j.phrs.2015.07.022
14. Sorice GP, Di Pizio L, Sun VA, Schirò T, Muscogiuri G, Mezza T, Cefalo CM, Prioletta A, Pontecorvi A, Giaccari A. Metabolic syndrome in transplant patients: an updating point of view. *Minerva Endocrinol.* 2012;37:211–220.
15. Thoefner LB, Rostved AA, Pommergaard HC, Rasmussen A. Risk factors for metabolic syndrome after liver transplantation: a systematic review and meta-analysis. *Transplant Rev (Orlando).* 2018;32:69–77. doi: 10.1016/j.trre.2017.03.004
16. DeFilipp Z, Duarte RF, Snowden JA, Majhail NS, Greenfield DM, Miranda JL, Arat M, Baker KS, Burns LJ, Duncan CN, et al. Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT. *Bone Marrow Transplant.* 2017;52:173–182. doi: 10.1038/bmt.2016.203
17. Bielorai B, Pinhas-Hamiel O. Type 2 diabetes mellitus, the metabolic syndrome, and its components in adult survivors of acute lymphoblastic leukemia and hematopoietic stem cell transplantations. *Curr Diab Rep.* 2018;18:32. doi: 10.1007/s11892-018-0998-0
18. Calza L, Colangeli V, Magistrelli E, Rossi N, Rosselli Del Turco E, Bussini L, Borderi M, Viale P. Prevalence of metabolic syndrome in HIV-infected patients naive to antiretroviral therapy or receiving a first-line treatment. *HIV Clin Trials.* 2017;18:110–117. doi: 10.1080/15284336.2017.1311502
19. Oudin C, Berbis J, Bertrand Y, Vercasson C, Thomas F, Chastagner P, Ducassou S, Kanold J, Tabone MD, Paillard C, et al. Prevalence and characteristics of metabolic syndrome in adults from the French Childhood Leukemia Survivors' Cohort: a comparison with controls from the French population. *Haematologica.* 2018;103:645–654. doi: 10.3324/haematol.2017.176123
20. Rodríguez-Zúñiga MJM, García-Perdomo HA. Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome. *J Am Acad Dermatol.* 2017;77:657–666.e8. doi: 10.1016/j.jaad.2017.04.1133
21. Sun C, Qin W, Zhang YH, Wu Y, Li Q, Liu M, He CD. Prevalence and risk of metabolic syndrome in patients with systemic lupus erythematosus: a meta-analysis. *Int J Rheum Dis.* 2017;20:917–928. doi: 10.1111/1756-185X.13153
22. Gomes KWP, Luz AJP, Felipe MRB, Beltrão LA, Sampaio AXC, Rodrigues CEM. Prevalence of metabolic syndrome in rheumatoid arthritis patients from Northeastern Brazil: association with disease activity. *Mod Rheumatol.* 2018;28:258–263. doi: 10.1080/14397595.2017.1316813
23. Sicras-Mainar A, Ruíz-Beato E, Navarro-Artieda R, Maurino J. Comorbidity and metabolic syndrome in patients with multiple sclerosis from Asturias and Catalonia, Spain. *BMC Neurol.* 2017;17:134. doi: 10.1186/s12883-017-0914-2
24. Chillarón JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism.* 2014;63:181–187. doi: 10.1016/j.metabol.2013.10.002
25. Verhelst J, Mattsson AF, Luger A, Thunander M, Góth MI, Koltowska-Häggström M, Abs R. Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol.* 2011;165:881–889. doi: 10.1530/EJE-11-0599
26. Noctor E, Crowe C, Carmody LA, Kirwan B, O'Dea A, Glynn LG, McGuire BE, O'Shea PM, Dunne FP. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. *Acta Diabetol.* 2015;52:153–160. doi: 10.1007/s00592-014-0621-z
27. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP, Passos MT, Dos Santos LF, Famá EAB, Nishida SK, Sass N. Pregnancy as an early stress test for cardiovascular and kidney disease diagnosis. *Pregnancy Hypertens.* 2018;12:169–173. doi: 10.1016/j.preghy.2017.11.008
28. Heyn PC, Tagawa A, Pan Z, Thomas S, Carollo JJ. Prevalence of metabolic syndrome and cardiovascular disease risk factors in adults with cerebral palsy. *Dev Med Child Neurol.* 2019;61:477–483. doi: 10.1111/dmcn.14148
29. Ejtahed HS, Soroush MR, Hasani-Ranjbar S, Angoorani P, Mousavi B, Masumi M, Edjtehadi F, Soveid M. Prevalence of metabolic syndrome and health-related quality of life in war-related bilateral lower limb amputees. *J Diabetes Metab Disord.* 2017;16:17. doi: 10.1186/s40200-017-0298-2
30. Gater DR Jr, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med.* 2019;42:86–93. doi: 10.1080/10790268.2017.1423266
31. Zimmerman FH. Cardiovascular disease and risk factors in law enforcement personnel: a comprehensive review. *Cardiol Rev.* 2012;20:159–166. doi: 10.1097/CRD.0b013e318248d631
32. Li K, Lipsey T, Leach HJ, Nelson TL. Cardiac health and fitness of Colorado male/female firefighters. *Occup Med (Lond).* 2017;67:268–273. doi: 10.1093/occmed/kqx033
33. Lee AM, Gurka MJ, DeBoer MD. Trends in metabolic syndrome severity and lifestyle factors among adolescents [published correction appears in *Pediatrics.* 2016;138:e20161255]. *Pediatrics.* 2016;137:e20153177. doi: 10.1542/peds.2015-3177
34. Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Prev Chronic Dis.* 2017;14:E24. doi: 10.5888/pcd14.160287
35. Palmer MK, Toth PP. Trends in lipids, obesity, metabolic syndrome, and diabetes mellitus in the United States: an NHANES analysis

(2003-2004 to 2013-2014). *Obesity (Silver Spring).* 2019;27:309–314. doi: 10.1002/oby.22370
36. Vishnu A, Gurka MJ, DeBoer MD. The severity of the metabolic syndrome increases over time within individuals, independent of baseline metabolic syndrome status and medication use: the Atherosclerosis Risk in Communities Study. *Atherosclerosis.* 2015;243:278–285. doi: 10.1016/j.atherosclerosis.2015.09.025
37. Efstathiou SP, Skeva II, Zorbala E, Georgiou E, Mountokalakis TD. Metabolic syndrome in adolescence: can it be predicted from natal and parental profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) study. *Circulation.* 2012;125:902–910. doi: 10.1161/CIRCULATIONAHA.111.034546
38. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Thompson J, et al. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. *Circulation.* 2014;129:321–329. doi: 10.1161/CIRCULATIONAHA.113.005160
39. Moore BF, Clark ML, Bachand A, Reynolds SJ, Nelson TL, Peel JL. Interactions between diet and exposure to secondhand smoke on metabolic syndrome among children: NHANES 2007-2010. *J Clin Endocrinol Metab.* 2016;101:52–58. doi: 10.1210/jc.2015-2477
40. Rodríguez LA, Madsen KA, Cotterman C, Lustig RH. Added sugar intake and metabolic syndrome in US adolescents: cross-sectional analysis of the National Health and Nutrition Examination Survey 2005-2012. *Public Health Nutr.* 2016;19:2424–2434. doi: 10.1017/S1368980016000057
41. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care.* 2012;35:1171–1180. doi: 10.2337/dc11-2055
42. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *J Am Coll Cardiol.* 2013;62:697–703. doi: 10.1016/j.jacc.2013.05.064
43. Kang HT, Shim JY, Lee YJ, Linton JA, Park BJ, Lee HR. Reading nutrition labels is associated with a lower risk of metabolic syndrome in Korean adults: the 2007-2008 Korean NHANES. *Nutr Metab Cardiovasc Dis.* 2013;23:876–882. doi: 10.1016/j.numecd.2012.06.007
44. Cheng E, Burrows R, Correa P, Güichapani CG, Blanco E, Gahagan S. Light smoking is associated with metabolic syndrome risk factors in Chilean young adults. *Acta Diabetol.* 2019;56:473–479. doi: 10.1007/s00592-018-1264-2
45. Kim BJ, Kang JG, Han JM, Kim JH, Lee SJ, Seo DC, Lee SH, Kim BS, Kang JH. Association of self-reported and cotinine-verified smoking status with incidence of metabolic syndrome in 47 379 Korean adults. *J Diabetes.* 2019;11:402–409. doi: 10.1111/1753-0407.12868
46. Juonala M, Magnussen CG, Venn A, Gall S, Kähönen M, Laitinen T, Taittonen L, Lehtimäki T, Jokinen E, Sun C, et al. Parental smoking in childhood and brachial artery flow-mediated dilatation in young adults: the Cardiovascular Risk in Young Finns study and the Childhood Determinants of Adult Health study. *Arterioscler Thromb Vasc Biol.* 2012;32:1024–1031. doi: 10.1161/ATVBAHA.111.243261
47. Wilsgaard T, Jacobsen BK. Lifestyle factors and incident metabolic syndrome: the Tromsø Study 1979-2001. *Diabetes Res Clin Pract.* 2007;78:217–224. doi: 10.1016/j.diabres.2007.03.006
48. Ferreira I, Henry RM, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD; Amsterdam Growth and Health Longitudinal Study. The metabolic syndrome, cardiopulmonary fitness, and subcutaneous trunk fat as independent determinants of arterial stiffness: the Amsterdam Growth and Health Longitudinal Study. *Arch Intern Med.* 2005;165:875–882. doi: 10.1001/archinte.165.8.875
49. Drake I, Sonestedt E, Ericson U, Wallström P, Orho-Melander M. A Western dietary pattern is prospectively associated with cardio-metabolic traits and incidence of the metabolic syndrome. *Br J Nutr.* 2018;119:1168–1176. doi: 10.1017/S000711451800079X
50. Narain A, Kwok CS, Mamas MA. Soft drink intake and the risk of metabolic syndrome: a systematic review and meta-analysis. *Int J Clin Pract.* 2017;71. doi: 10.1111/ijcp.12927
51. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation.* 2008;117:754–761. doi: 10.1161/CIRCULATIONAHA.107.716159
52. Appelhans BM, Baylin A, Huang MH, Li H, Janssen I, Kazlauskaite R, Avery EF, Kravitz HM. Beverage intake and metabolic syndrome risk over 14 years: the Study of Women's Health Across the Nation. *J Acad Nutr Diet.* 2017;117:554–562. doi: 10.1016/j.jand.2016.10.011
53. Shin S, Kim SA, Ha J, Lim K. Sugar-sweetened beverage consumption in relation to obesity and metabolic syndrome among Korean adults: a cross-sectional study from the 2012–2016 Korean National Health and Nutrition Examination Survey (KNHANES). *Nutrients*. 2018;10:E1467. doi: 10.3390/nu10101467
54. Kelishadi R, Mansourian M, Heidari-Beni M. Association of fructose consumption and components of metabolic syndrome in human studies: a systematic review and meta-analysis. *Nutrition.* 2014;30:503–510. doi: 10.1016/j.nut.2013.08.014
55. He K, Liu K, Daviglus ML, Morris SJ, Loria CM, Van Horn L, Jacobs DR Jr, Savage PJ. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation.* 2006;113:1675–1682. doi: 10.1161/CIRCULATIONAHA.105.588327
56. Song Y, Ridker PM, Manson JE, Cook NR, Buring JE, Liu S. Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care.* 2005;28:1438–1444. doi: 10.2337/diacare.28.6.1438
57. Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD. Development of fatness, fitness, and lifestyle from adolescence to the age of 36 years: determinants of the metabolic syndrome in young adults: the Amsterdam Growth and Health Longitudinal Study. *Arch Intern Med.* 2005;165:42–48. doi: 10.1001/archinte.165.1.42
58. Kwon YJ, Lee HS, Lee JW. Association of carbohydrate and fat intake with metabolic syndrome. *Clin Nutr.* 2018;37:746–751. doi: 10.1016/j.clnu.2017.06.022
59. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr.* 2008;152:201–206. doi: 10.1016/j.jpeds.2007.09.010
60. Kim Y, Je Y. Meat consumption and risk of metabolic syndrome: results from the Korean population and a meta-analysis of observational studies. *Nutrients*. 2018;10: E390. doi: 10.3390/nu10040390
61. Deshmukh-Taskar P, Nicklas TA, Radcliffe JD, O'Neil CE, Liu Y. The relationship of breakfast skipping and type of breakfast consumed with overweight/obesity, abdominal obesity, other cardiometabolic risk factors and the metabolic syndrome in young adults: the National Health and Nutrition Examination Survey (NHANES): 1999-2006. *Public Health Nutr.* 2013;16:2073–2082. doi: 10.1017/S1368980012004296
62. Yoon C, Jacobs DR, Duprez DA, Neumark-Sztainer D, Steffen LM, Mason SM. Problematic eating behaviors and attitudes predict long-term incident metabolic syndrome and diabetes: the Coronary Artery Risk Development in Young Adults Study. *Int J Eat Disord*. 2019;52:304-308. doi: 10.1002/eat.23020
63. Magnussen CG, Koskinen J, Juonala M, Chen W, Srinivasan SR, Sabin MA, Thomson R, Schmidt MD, Nguyen QM, Xu JH, et al. A diagnosis of the metabolic syndrome in youth that resolves by adult life is associated with a normalization of high carotid intima-media thickness and type 2 diabetes mellitus risk: the Bogalusa Heart and Cardiovascular Risk in Young Finns studies. *J Am Coll Cardiol.* 2012;60:1631–1639. doi: 10.1016/j.jacc.2012.05.056
64. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB Sr. Trajectories of entering the metabolic syndrome: the Framingham Heart Study. *Circulation*. 2009;120:1943–1950. doi: 10.1161/CIRCULATIONAHA.109.855817
65. Kim J, Lee I, Lim S. Overweight or obesity in children aged 0 to 6 and the risk of adult metabolic syndrome: a systematic review and meta-analysis. *J Clin Nurs.* 2017;26:3869–3880. doi: 10.1111/jocn.13802
66. Koskinen J, Magnussen CG, Sinaiko A, Woo J, Urbina E, Jacobs DR Jr, Steinberger J, Prineas R, Sabin MA, Burns T, et al. Childhood age and associations between childhood metabolic syndrome and adult risk for metabolic syndrome, type 2 diabetes mellitus and carotid intima media thickness: the International Childhood Cardiovascular Cohort Consortium. *J Am Heart Assoc*. 2017;6:e005632. doi: 10.1161/JAHA.117.005632
67. Tong J, Boyko EJ, Utzschneider KM, McNeely MJ, Hayashi T, Carr DB, Wallace TM, Zraika S, Gerchman F, Leonetti DL, et al. Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese-Americans. *Diabetologia.* 2007;50:1156–1160. doi: 10.1007/s00125-007-0651-y
68. Vergnaud AC, Bertrais S, Oppert JM, Maillard-Teyssier L, Galan P, Hercberg S, Czernichow S. Weight fluctuations and risk for metabolic syndrome in an adult cohort. *Int J Obes (Lond).* 2008;32:315–321. doi: 10.1038/sj.ijo.0803739
69. Tomiyama H, Yamada J, Koji Y, Yambe M, Motobe K, Shiina K, Yamamoto Y, Yamashina A. Heart rate elevation precedes the development of

metabolic syndrome in Japanese men: a prospective study. *Hypertens Res.* 2007;30:417–426. doi: 10.1291/hypres.30.417
70. Bonora BM, Marescotti M, Marcuzzo G, Avogaro A, Fadini GP. Synergistic interactions among metabolic syndrome components and homeostasis model assessment of insulin resistance in a middle-aged general population over time. *Metab Syndr Relat Disord.* 2015;13:171–178. doi: 10.1089/met.2014.0163
71. Palaniappan L, Carnethon MR, Wang Y, Hanley AJ, Fortmann SP, Haffner SM, Wagenknecht L; Insulin Resistance Atherosclerosis Study. Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. *Diabetes Care.* 2004;27:788–793. doi: 10.2337/diacare.27.3.788
72. Calcaterra V, De Giuseppe R, Biino G, Mantelli M, Marchini S, Bendotti G, Madè A, Avanzini MA, Montalbano C, Cossellu G, et al. Relation between circulating oxidized-LDL and metabolic syndrome in children with obesity: the role of hypertriglyceridemic waist phenotype. *J Pediatr Endocrinol Metab.* 2017;30:1257–1263. doi: 10.1515/jpem-2017-0239
73. Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. *Int J Med Sci.* 2016;13:25–38. doi: 10.7150/ijms.13800
74. Mani P, Ren HY, Neeland IJ, McGuire DK, Ayers CR, Khera A, Rohatgi A. The association between HDL particle concentration and incident metabolic syndrome in the multi-ethnic Dallas Heart Study. *Diabetes Metab Syndr.* 2017;11(suppl 1):S175–S179. doi: 10.1016/j.dsx.2016.12.028
75. Tehrani DM, Zhao Y, Blaha MJ, Mora S, Mackey RH, Michos ED, Budoff MJ, Cromwell W, Otvos JD, Rosenblit PD, et al. Discordance of low-density lipoprotein and high-density lipoprotein cholesterol particle versus cholesterol concentration for the prediction of cardiovascular disease in patients with metabolic syndrome and diabetes mellitus (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol.* 2016;117:1921–1927. doi: 10.1016/j.amjcard.2016.03.040
76. Acevedo M, Varleta P, Kramer V, Valentino G, Quiroga T, Prieto C, Parada J, Adasme M, Briones L, Navarrete C. Comparison of lipoprotein-associated phospholipase A2 and high sensitive C-reactive protein as determinants of metabolic syndrome in subjects without coronary heart disease: in search of the best predictor. *Int J Endocrinol.* 2015;2015:934681. doi: 10.1155/2015/934681
77. Chen YY, Kao TW, Yang HF, Chou CW, Wu CJ, Lai CH, Sun YS, Wang CC, Chen WL. The association of uric acid with the risk of metabolic syndrome, arterial hypertension or diabetes in young subjects: an observational study. *Clin Chim Acta.* 2018;478:68–73. doi: 10.1016/j.cca.2017.12.038
78. Kawamoto R, Ninomiya D, Kasai Y, Senzaki K, Kusunoki T, Ohtsuka N, Kumagi T. Baseline and changes in serum uric acid independently predict 11-year incidence of metabolic syndrome among community-dwelling women. *J Endocrinol Invest.* 2018;41:959–968. doi: 10.1007/s40618-017-0822-8
79. Lee YB, Jun JE, Lee SE, Ahn J, Kim G, Jee JH, Bae JC, Jin SM, Kim JH. Utility of serum albumin for predicting incident metabolic syndrome according to hyperuricemia. *Diabetes Metab J.* 2018;42:529–537. doi: 10.4093/dmj.2018.0012
80. Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, Roverato A, Guaraldi G, Lonardo A. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome: evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol.* 2016;31:936–944. doi: 10.1111/jgh.13264
81. Lin CM, Hsieh CH, Lee CH, Pei D, Lin JD, Wu CZ, Liang YJ, Hung YJ, Chen YL. Predictive value of serum gamma-glutamyltranspeptidase for future cardiometabolic dysregulation in adolescents: a 10-year longitudinal study [published correction appears in *Sci Rep.* 2018;8:16934]. *Sci Rep.* 2017;7:9636. doi: 10.1038/s41598-017-09719-8
82. Lakhani I, Gong M, Wong WT, Bazoukis G, Lampropoulos K, Wong SH, Wu WKK, Wong MCS, Ong KL, Liu T, et al; International Health Informatics Study (IHIS) Network. Fibroblast growth factor 21 in cardio-metabolic disorders: a systematic review and meta-analysis. *Metabolism.* 2018;83:11–17. doi: 10.1016/j.metabol.2018.01.017
83. Ingelsson E, Pencina MJ, Tofler GH, Benjamin EJ, Lanier KJ, Jacques PF, Fox CS, Meigs JB, Levy D, Larson MG, et al. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. *Circulation.* 2007;116:984–992. doi: 10.1161/CIRCULATIONAHA.107.708537
84. Galletti F, Barbato A, Versiero M, Iacone R, Russo O, Barba G, Siani A, Cappuccio FP, Farinaro E, della Valle E, et al. Circulating leptin levels predict the development of metabolic syndrome in middle-aged men: an 8-year follow-up study. *J Hypertens.* 2007;25:1671–1677. doi: 10.1097/HJH.0b013e3281afa09e
85. Iwanaga S, Sakano N, Taketa K, Takahashi N, Wang DH, Takahashi H, Kubo M, Miyatake N, Ogino K. Comparison of serum ferritin and oxidative stress biomarkers between Japanese workers with and without metabolic syndrome. *Obes Res Clin Pract.* 2014;8:e201–e298. doi: 10.1016/j.orcp.2013.01.003
86. Mazidi M, Toth PP, Banach M. C-reactive protein is associated with prevalence of the metabolic syndrome, hypertension, and diabetes mellitus in US adults. *Angiology.* 2018;69:438–442. doi: 10.1177/0003319717729288
87. Xu A, Tso AW, Cheung BM, Wang Y, Wat NM, Fong CH, Yeung DC, Janus ED, Sham PC, Lam KS. Circulating adipocyte-fatty acid binding protein levels predict the development of the metabolic syndrome: a 5-year prospective study. *Circulation.* 2007;115:1537–1543. doi: 10.1161/CIRCULATIONAHA.106.647503
88. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, Liu S. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med.* 2009;361:1152–1163. doi: 10.1056/NEJMoa0804381
89. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. *Diabetes Care.* 2010;33:1618–1624. doi: 10.2337/dc09-1788
90. Yadav SS, Mandal RK, Singh MK, Verma A, Dwivedi P, Sethi R, Usman K, Khattri S. High serum level of matrix metalloproteinase 9 and promoter polymorphism - 1562 C:T as a new risk factor for metabolic syndrome. *DNA Cell Biol.* 2014;33:816–822. doi: 10.1089/dna.2014.2511
91. Gu Y, Wang Y, Zhang Q, Liu L, Meng G, Yao Z, Wu H, Xia Y, Bao X, Shi H, et al. The association between thyroid function and incidence of metabolic syndrome in euthyroid subjects: Tianjin chronic low-grade systemic inflammation and health cohort study. *Clin Endocrinol (Oxf).* 2018;88:735–743. doi: 10.1111/cen.13576
92. Daudt LD, Musskopf ML, Mendez M, Remonti LLR, Leitão CB, Gross JL, Weidlich P, Oppermann RV. Association between metabolic syndrome and periodontitis: a systematic review and meta-analysis. *Braz Oral Res.* 2018;32:e35. doi: 10.1590/1807-3107bor-2018.vol32.0035
93. Kim OS, Shin MH, Kweon SS, Lee YH, Kim OJ, Kim YJ, Chung HJ. The severity of periodontitis and metabolic syndrome in Korean population: the Dong-gu study. *J Periodontal Res.* 2018;53:362–368. doi: 10.1111/jre.12521
94. Echecopar-Sabogal J, D'Angelo-Piaggio L, Chanamé-Baca DM, Ugarte-Gil C. Association between the use of protease inhibitors in highly active antiretroviral therapy and incidence of diabetes mellitus and/or metabolic syndrome in HIV-infected patients: a systematic review and meta-analysis. *Int J STD AIDS.* 2018;29:443–452. doi: 10.1177/0956462417732226
95. Teppala S, Madhavan S, Shankar A. Bisphenol A and metabolic syndrome: results from NHANES. *Int J Endocrinol.* 2012;2012:598180. doi: 10.1155/2012/598180
96. Zhang D, Liu X, Liu Y, Sun X, Wang B, Ren Y, Zhao Y, Zhou J, Han C, Yin L, et al. Leisure-time physical activity and incident metabolic syndrome: a systematic review and dose-response meta-analysis of cohort studies. *Metabolism.* 2017;75:36–44. doi: 10.1016/j.metabol.2017.08.001
97. Chichlowska KL, Rose KM, Diez-Roux AV, Golden SH, McNeill AM, Heiss G. Life course socioeconomic conditions and metabolic syndrome in adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol.* 2009;19:875–883. doi: 10.1016/j.annepidem.2009.07.094
98. Wu HF, Tam T, Jin L, Lao XQ, Chung RY, Su XF, Zee B. Age, gender, and socioeconomic gradients in metabolic syndrome: biomarker evidence from a large sample in Taiwan, 2005–2013. *Ann Epidemiol.* 2017;27:315–322.e2. doi: 10.1016/j.annepidem.2017.04.003
99. Beatty Moody DL, Chang Y, Brown C, Bromberger JT, Matthews KA. Everyday discrimination and metabolic syndrome incidence in a racially/ethnically diverse sample: Study of Women's Health Across the Nation. *Psychosom Med.* 2018;80:114–121. doi: 10.1097/PSY.0000000000000516
100. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ.* 2006;332:521–525. doi: 10.1136/bmj.38693.435301.80
101. Jurca R, Lamonte MJ, Barlow CE, Kampert JB, Church TS, Blair SN. Association of muscular strength with incidence of metabolic syndrome

in men. *Med Sci Sports Exerc*. 2005;37:1849–1855. doi: 10.1249/01.mss.0000175865.17614.74
102. Wannamethee SG, Shaper AG, Whincup PH. Modifiable lifestyle factors and the metabolic syndrome in older men: effects of lifestyle changes. *J Am Geriatr Soc*. 2006;54:1909–1914. doi: 10.1111/j.1532-5415.2006.00974.x
103. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4:e002014. doi: 10.1161/JAHA.115.002014
104. Bateman LA, Slentz CA, Willis LH, Shields AT, Piner LW, Bales CW, Houmard JA, Kraus WE. Comparison of aerobic versus resistance exercise training effects on metabolic syndrome (from the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise - STRRIDE-AT/RT). *Am J Cardiol*. 2011;108:838–844. doi: 10.1016/j.amjcard.2011.04.037
105. Kelley E, Imboden MT, Harber MP, Finch H, Kaminsky LA, Whaley MH. Cardiorespiratory fitness is inversely associated with clustering of metabolic syndrome risk factors: the Ball State Adult Fitness Program Longitudinal Lifestyle Study. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:155–164. doi: 10.1016/j.mayocpiqo.2018.03.001
106. Lopez-Pascual A, Bes-Rastrollo M, Sayón-Orea C, Perez-Cornago A, Díaz-Gutiérrez J, Pons JJ, Martínez-González MA, González-Muniesa P, Martínez JA. Living at a geographically higher elevation is associated with lower risk of metabolic syndrome: prospective analysis of the SUN cohort. *Front Physiol*. 2016;7:658. doi: 10.3389/fphys.2016.00658
107. Stoutenberg M, Lee DC, Sui X, Hooker S, Horigian V, Perrino T, Blair S. Prospective study of alcohol consumption and the incidence of the metabolic syndrome in US men. *Br J Nutr*. 2013;110:901–910. doi: 10.1017/S0007114512005764
108. Grooms KN, Ommerborn MJ, Pham DQ, Djousse L, Clark CR. Dietary fiber intake and cardiometabolic risks among US adults, NHANES 1999–2010. *Am J Med*. 2013;126:1059–1067.e1-4. doi: 10.1016/j.amjmed.2013.07.023
109. Wei B, Liu Y, Lin X, Fang Y, Cui J, Wan J. Dietary fiber intake and risk of metabolic syndrome: a meta-analysis of observational studies. *Clin Nutr*. 2018;37:1935-1942. doi: 10.1016/j.clnu.2017.10.019
110. Shin JY, Kim JY, Kang HT, Han KH, Shim JY. Effect of fruits and vegetables on metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Int J Food Sci Nutr*. 2015;66:416–425. doi: 10.3109/09637486.2015.1025716
111. Vázquez C, Botella-Carretero JI, Corella D, Fiol M, Lage M, Lurbe E, Richart C, Fernández-Real JM, Fuentes F, Ordóñez A, et al; WISH-CARE Study Investigators. White fish reduces cardiovascular risk factors in patients with metabolic syndrome: the WISH-CARE study, a multicenter randomized clinical trial. *Nutr Metab Cardiovasc Dis*. 2014;24:328–335. doi: 10.1016/j.numecd.2013.09.018
112. Echeverria G, McGee EE, Urquiaga I, Jimenez P, D'Acuna S, Villarroel L, Velasco N, Leighton F, Rigotti A. Inverse associations between a locally validated Mediterranean Diet index, overweight/obesity, and metabolic syndrome in Chilean adults. *Nutrients*. 2017;9:E862. doi: 10.3390/nu9080862
113. Carlos S, De La Fuente-Arrillaga C, Bes-Rastrollo M, Razquin C, Rico-Campà A, Martínez-González MA, Ruiz-Canela M. Mediterranean diet and health outcomes in the SUN cohort. *Nutrients*. 2018;10:439.
114. Babio N, Becerra-Tomás N, Martínez-González MÁ, Corella D, Estruch R, Ros E, Sayón-Orea C, Fitó M, Serra-Majem L, Arós F, et al; PREDIMED Investigators. Consumption of yogurt, low-fat milk, and other low-fat dairy products is associated with lower risk of metabolic syndrome incidence in an elderly Mediterranean population. *J Nutr*. 2015;145:2308–2316. doi: 10.3945/jn.115.214593
115. Barreto FM, Colado Simão AN, Morimoto HK, Batisti Lozovoy MA, Dichi I, Helena da Silva Miglioranza L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition*. 2014;30:939–942. doi: 10.1016/j.nut.2013.12.004
116. Hill AM, Harris Jackson KA, Roussell MA, West SG, Kris-Etherton PM. Type and amount of dietary protein in the treatment of metabolic syndrome: a randomized controlled trial. *Am J Clin Nutr*. 2015;102:757–770. doi: 10.3945/ajcn.114.104026
117. Vernarelli JA, Lambert JD. Tea consumption is inversely associated with weight status and other markers for metabolic syndrome in US adults. *Eur J Nutr*. 2013;52:1039–1048. doi: 10.1007/s00394-012-0410-9
118. Shang F, Li X, Jiang X. Coffee consumption and risk of the metabolic syndrome: a meta-analysis. *Diabetes Metab*. 2016;42:80–87. doi: 10.1016/j.diabet.2015.09.001
119. Maki KC, Fulgoni VL 3rd, Keast DR, Rains TM, Park KM, Rubin MR. Vitamin D intake and status are associated with lower prevalence of metabolic syndrome in U.S. adults: National Health and Nutrition Examination Surveys 2003-2006. *Metab Syndr Relat Disord*. 2012;10:363–372. doi: 10.1089/met.2012.0020
120. O'Neil CE, Fulgoni VL 3rd, Nicklas TA. Tree nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. adults: NHANES 2005-2010. *Nutr J*. 2015;14:64. doi: 10.1186/s12937-015-0052-x
121. Hosseinpour-Niazi S, Hosseini S, Mirmiran P, Azizi F. Prospective study of nut consumption and incidence of metabolic syndrome: Tehran Lipid and Glucose Study. *Nutrients*. 2017;9:E1056. doi: 10.3390/nu9101056
122. Fulgoni VL 3rd, Dreher M, Davenport AJ. Avocado consumption is associated with better diet quality and nutrient intake, and lower metabolic syndrome risk in US adults: results from the National Health and Nutrition Examination Survey (NHANES) 2001-2008. *Nutr J*. 2013;12:1. doi: 10.1186/1475-2891-12-1
123. Kim YS, Xun P, He K. Fish consumption, long-chain omega-3 polyunsaturated fatty acid intake and risk of metabolic syndrome: a meta-analysis. *Nutrients*. 2015;7:2085–2100. doi: 10.3390/nu7042085
124. Shin D, Joh HK, Kim KH, Park SM. Benefits of potassium intake on metabolic syndrome: the fourth Korean National Health and Nutrition Examination Survey (KNHANES IV). *Atherosclerosis*. 2013;230:80–85. doi: 10.1016/j.atherosclerosis.2013.06.025
125. Yadav D, Choi E, Ahn SV, Baik SK, Cho YZ, Koh SB, Huh JH, Chang Y, Sung KC, Kim JY. Incremental predictive value of serum AST-to-ALT ratio for incident metabolic syndrome: the ARIRANG Study. *PLoS One*. 2016;11:e0161304. doi: 10.1371/journal.pone.0161304
126. Liu S, Sun Q. Sex differences, endogenous sex-hormone hormones, sex-hormone binding globulin, and exogenous disruptors in diabetes and related metabolic outcomes. *J Diabetes*. 2018;10:428–441. doi: 10.1111/1753-0407.12517
127. Al-Khalidi B, Kimball SM, Rotondi MA, Ardern CI. Standardized serum 25-hydroxyvitamin D concentrations are inversely associated with cardiometabolic disease in U.S. adults: a cross-sectional analysis of NHANES, 2001-2010 [published correction appears in *Nutr J*. 2017;16:32]. *Nutr J*. 2017;16:16. doi: 10.1186/s12937-017-0237-6
128. Mayneris-Perxachs J, Guerendiain M, Castellote AI, Estruch R, Covas MI, Fitó M, Salas-Salvadó J, Martínez-González MA, Aros F, Lamuela-Raventós RM, et al; for PREDIMED Study Investigators. Plasma fatty acid composition, estimated desaturase activities, and their relation with the metabolic syndrome in a population at high risk of cardiovascular disease. *Clin Nutr*. 2014;33:90–97. doi: 10.1016/j.clnu.2013.03.001
129. Oh SW, Han KH, Han SY, Koo HS, Kim S, Chin HJ. Association of sodium excretion with metabolic syndrome, insulin resistance, and body fat. *Medicine (Baltimore)*. 2015;94:e1650. doi: 10.1097/MD.0000000000001650
130. Kim H-Y, Lee J, Kim J. Association between dietary inflammatory index and metabolic syndrome in the general Korean population. *Nutrients*. 2018;10:E648. doi: 10.3390/nu10050648
131. Janczura M, Bochenek G, Nowobilski R, Dropinski J, Kotula-Horowitz K, Laskowicz B, Stanisz A, Lelakowski J, Domagala T. The relationship of metabolic syndrome with stress, coronary heart disease and pulmonary function: an occupational cohort-based study [published correction appears in *PLoS One*. 2015;10:e0139408]. *PLoS One*. 2015;10:e0133750. doi: 10.1371/journal.pone.0133750
132. Edwards MK, Loprinzi PD. High amounts of sitting, low cardiorespiratory fitness, and low physical activity levels: 3 key ingredients in the recipe for influencing metabolic syndrome prevalence. *Am J Health Promot*. 2018;32:587–594. doi: 10.1177/0890117116684889
133. Zhang H, Lin S, Gao T, Zhong F, Cai J, Sun Y, Ma A. Association between sarcopenia and metabolic syndrome in middle-aged and older non-obese adults: a systematic review and meta-analysis. *Nutrients*. 2018;10: E364. doi: 10.3390/nu10030364
134. Du R, Cheng D, Lin L, Sun J, Peng K, Xu Y, Xu M, Chen Y, Bi Y, Wang W, et al. Association between serum CA 19-9 and metabolic syndrome: a cross-sectional study. *J Diabetes*. 2017;9:1040–1047. doi: 10.1111/1753-0407.12523
135. Huang LL, Dou DM, Liu N, Wang XX, Fu LY, Wu X, Wang P. Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross sectional study. *BMJ Open*. 2018;8:e019792. doi: 10.1136/bmjopen-2017-019792

136. Kim MK, Chon SJ, Noe EB, Roh YH, Yun BH, Cho S, Choi YS, Lee BS, Seo SK. Associations of dietary calcium intake with metabolic syndrome and bone mineral density among the Korean population: KNHANES 2008-2011. *Osteoporos Int*. 2017;28:299–308. doi: 10.1007/s00198-016-3717-1
137. Duong TV, Wong TC, Chen HH, Chen TW, Chen TH, Hsu YH, Peng SJ, Kuo KL, Liu HC, Lin ET, et al. Inadequate dietary energy intake associates with higher prevalence of metabolic syndrome in different groups of hemodialysis patients: a clinical observational study in multiple dialysis centers. *BMC Nephrol.* 2018;19:236. doi: 10.1186/s12882-018-1041-z
138. Ahmadzadeh J, Mansorian B, Attari MM, Mohebbi I, Naz-Avar R, Moghadam K, Ghareh-Bagh SAK. The association between hematological parameters and metabolic syndrome in Iranian men: a single center large-scale study. *Diabetes Metab Syndr.* 2018;12:17–21. doi: 10.1016/j.dsx.2017.07.044
139. Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, Ji Q. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. *BMC Pulm Med.* 2015;15:105. doi: 10.1186/s12890-015-0102-3
140. Shuval K, Barlow CE, Finley CE, Gabriel KP, Schmidt MD, DeFina LF. Standing, obesity, and metabolic syndrome: findings from the Cooper Center Longitudinal Study. *Mayo Clin Proc.* 2015;90:1524–1532. doi: 10.1016/j.mayocp.2015.07.022
141. Xiao J, Chu M, Shen H, Ren W, Li Z, Hua T, Xu H, Liang Y, Gao Y, Zhuang X. Relationship of "weekend warrior" and regular physical activity patterns with metabolic syndrome and its associated diseases among Chinese rural adults. *J Sports Sci.* 2018;36:1963–1971. doi: 10.1080/02640414.2018.1428883
142. Yi DW, Khang AR, Lee HW, Son SM, Kang YH. Relative handgrip strength as a marker of metabolic syndrome: the Korea National Health and Nutrition Examination Survey (KNHANES) VI (2014-2015). *Diabetes Metab Syndr Obes.* 2018;11:227–240. doi: 10.2147/DMSO.S166875
143. Sabaté J, Wien M. A perspective on vegetarian dietary patterns and risk of metabolic syndrome. *Br J Nutr.* 2015;113 (suppl 2):S136–S143. doi: 10.1017/S0007114514004139
144. Benseñor IM, Goulart AC, Molina Mdel C, de Miranda ÉJ, Santos IS, Lotufo PA. Thyrotropin levels, insulin resistance, and metabolic syndrome: a cross-sectional analysis in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Metab Syndr Relat Disord.* 2015;13:362–369. doi: 10.1089/met.2015.0045
145. Ramírez-Vélez R, Garcia-Hermoso A, Prieto-Benavides DH, Correa-Bautista JE, Quino-Ávila AC, Rubio-Barreto CM, González-Ruíz K, Carrillo HA, Correa-Rodríguez M, González-Jiménez E, et al. Muscle mass to visceral fat ratio is an important predictor of the metabolic syndrome in college students. *Br J Nutr*. 2018:1-10. doi: 10.1017/S0007114518003392
146. Vidot DC, Prado G, Hlaing WM, Florez HJ, Arheart KL, Messiah SE. Metabolic syndrome among marijuana users in the United States: an analysis of National Health and Nutrition Examination Survey data. *Am J Med.* 2016;129:173–179. doi: 10.1016/j.amjmed.2015.10.019
147. Kim S, Song Y, Lee JE, Jun S, Shin S, Wie GA, Cho YH, Joung H. Total antioxidant capacity from dietary supplement decreases the likelihood of having metabolic syndrome in Korean adults. *Nutrients*. 2017;9:E1055. doi: 10.3390/nu9101055
148. Baudry J, Lelong H, Adriouch S, Julia C, Allès B, Hercberg S, Touvier M, Lairon D, Galan P, Kesse-Guyot E. Association between organic food consumption and metabolic syndrome: cross-sectional results from the NutriNet-Santé study. *Eur J Nutr.* 2018;57:2477–2488. doi: 10.1007/s00394-017-1520-1
149. Li K, Wen M, Fan JX. Neighborhood racial diversity and metabolic syndrome: 2003-2008 National Health and Nutrition Examination Survey. *J Immigr Minor Health.* 2019;21:151–160. doi: 10.1007/s10903-018-0728-3
150. Patel PA, Scott CG, Rodeheffer RJ, Chen HH. The natural history of patients with isolated metabolic syndrome. *Mayo Clin Proc.* 2016;91:623–633. doi: 10.1016/j.mayocp.2016.02.026
151. Lin E, Kuo PH, Liu YL, Yang AC, Tsai SJ. Detection of susceptibility loci on APOA5 and COLEC12 associated with metabolic syndrome using a genome-wide association study in a Taiwanese population. *Oncotarget.* 2017;8:93349–93359. doi: 10.18632/oncotarget.20967
152. Morjane I, Kefi R, Charoute H, Lakbakbi El Yaagoubi F, Hechmi M, Saile R, Abdelhak S, Barakat A. Association study of HNF1A polymorphisms with metabolic syndrome in the Moroccan population. *Diabetes Metab Syndr.* 2017;11 (suppl 2):S853–S857. doi: 10.1016/j.dsx.2017.07.005
153. Lakbakbi El Yaagoubi F, Charoute H, Morjane I, Sefri H, Rouba H, Ainahi A, Kandil M, Benrahma H, Barakat A. Association analysis of genetic variants with metabolic syndrome components in the Moroccan population. *Curr Res Transl Med*. 2017;65:121–125. doi: 10.1016/j.retram.2017.08.001
154. Carty CL, Bhattacharjee S, Haessler J, Cheng I, Hindorff LA, Aroda V, Carlson CS, Hsu CN, Wilkens L, Liu S, et al. Analysis of metabolic syndrome components in >15000 African Americans identifies pleiotropic variants: results from the Population Architecture Using Genomics and Epidemiology study. *Circ Cardiovasc Genet.* 2014;7:505–513. doi: 10.1161/CIRCGENETICS.113.000386
155. Cannone V, Cefalu' AB, Noto D, Scott CG, Bailey KR, Cavera G, Pagano M, Sapienza M, Averna MR, Burnett JC Jr. The atrial natriuretic peptide genetic variant rs5068 is associated with a favorable cardiometabolic phenotype in a Mediterranean population. *Diabetes Care.* 2013;36:2850–2856. doi: 10.2337/dc12-2337
156. Maintinguer Norde M, Oki E, Ferreira Carioca AA, Teixeira Damasceno NR, Fisberg RM, Lobo Marchioni DM, Rogero MM. Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study. *Clin Nutr.* 2018;37:659–666. doi: 10.1016/j.clnu.2017.02.009
156a. American Heart Association. 2013 Statistical Fact Sheet: 2020 Impact Goal. https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319831.pdf. Accessed November 4, 2019.
157. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;56:1113–1132. doi: 10.1016/j.jacc.2010.05.034
158. Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. *Medicine (Baltimore).* 2017;96:e8491. doi: 10.1097/MD.0000000000008491
159. Fernandez-Mendoza J, He F, LaGrotte C, Vgontzas AN, Liao D, Bixler EO. Impact of the metabolic syndrome on mortality is modified by objective short sleep duration [published correction appears in *J Am Heart Assoc*. 2017;6: e002182]. *J Am Heart Assoc*. 2017;6:e005479. doi: 10.1161/JAHA.117.005479
160. Mente A, Yusuf S, Islam S, McQueen MJ, Tanomsup S, Onen CL, Rangarajan S, Gerstein HC, Anand SS; INTERHEART Investigators. Metabolic syndrome and risk of acute myocardial infarction a case-control study of 26,903 subjects from 52 countries. *J Am Coll Cardiol.* 2010;55:2390–2398. doi: 10.1016/j.jacc.2009.12.053
161. Rachas A, Raffaitin C, Barberger-Gateau P, Helmer C, Ritchie K, Tzourio C, Amouyel P, Ducimetière P, Empana JP. Clinical usefulness of the metabolic syndrome for the risk of coronary heart disease does not exceed the sum of its individual components in older men and women: the Three-City (3C) Study. *Heart.* 2012;98:650–655. doi: 10.1136/heartjnl-2011-301185
162. Lyubarova R, Robinson JG, Miller M, Simmons DL, Xu P, Abramson BL, Elam MB, Brown TM, McBride R, Fleg JL, et al; Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) Investigators. Metabolic syndrome cluster does not provide incremental prognostic information in patients with stable cardiovascular disease: a post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol.* 2017;11:1201–1211. doi: 10.1016/j.jacl.2017.06.017
163. Vishram JK, Borglykke A, Andreasen AH, Jeppesen J, Ibsen H, Jørgensen T, Palmieri L, Giampaoli S, Donfrancesco C, Kee F, et al; MORGAM Project. Impact of age and gender on the prevalence and prognostic importance of the metabolic syndrome and its components in Europeans: the MORGAM Prospective Cohort Project [published correction appears in *PLoS One*. 2015;10:e0128848]. *PLoS One.* 2014;9:e107294. doi: 10.1371/journal.pone.0107294
164. Liu L, Miura K, Fujiyoshi A, Kadota A, Miyagawa N, Nakamura Y, Ohkubo T, Okayama A, Okamura T, Ueshima H. Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. *Am J Cardiol.* 2014;113:84–89. doi: 10.1016/j.amjcard.2013.08.042
165. Li X, Li X, Lin H, Fu X, Lin W, Li M, Zeng X, Gao Q. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. *J Clin Neurosci.* 2017;40:34–38. doi: 10.1016/j.jocn.2017.01.018
166. Hess PL, Al-Khalidi HR, Friedman DJ, Mulder H, Kucharska-Newton A, Rosamond WR, Lopes RD, Gersh BJ, Mark DB, Curtis LH, et al. The metabolic syndrome and risk of sudden cardiac death: the Atherosclerosis Risk in Communities Study. *J Am Heart Assoc*. 2017;6:e006103. doi: 10.1161/JAHA.117.006103
167. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics.* 2007;120:340–345. doi: 10.1542/peds.2006-1699

168. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of metabolic syndrome as a predictor of cardiovascular disease between childhood and adulthood: the Princeton Lipid Research Cohort Study. *J Am Coll Cardiol.* 2015;66:755–757. doi: 10.1016/j.jacc.2015.05.061
169. DeBoer MD, Gurka MJ, Woo JG, Morrison JA. Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study. *Diabetologia.* 2015;58:2745–2752. doi: 10.1007/s00125-015-3759-5
170. Olza J, Aguilera CM, Gil-Campos M, Leis R, Bueno G, Valle M, Cañete R, Tojo R, Moreno LA, Gil Á. A continuous metabolic syndrome score is associated with specific biomarkers of inflammation and CVD risk in prepubertal children. *Ann Nutr Metab.* 2015;66:72–79. doi: 10.1159/000369981
171. Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J.* 2010;159:850–856. doi: 10.1016/j.ahj.2010.02.005
172. Lin KJ, Cho SI, Tiwari N, Bergman M, Kizer JR, Palma EC, Taub CC. Impact of metabolic syndrome on the risk of atrial fibrillation recurrence after catheter ablation: systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2014;39:211–223. doi: 10.1007/s10840-013-9863-x
173. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. *Eur Heart J.* 2015;36:2630–2634. doi: 10.1093/eurheartj/ehv350
174. Vidula H, Liu K, Criqui MH, Szklo M, Allison M, Sibley C, Ouyang P, Tracy RP, Chan C, McDermott MM. Metabolic syndrome and incident peripheral artery disease: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis.* 2015;243:198–203. doi: 10.1016/j.atherosclerosis.2015.08.044
175. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, Szklo M, Barr RG, Wong ND. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care.* 2011;34:2285–2290. doi: 10.2337/dc11-0816
176. Hong HC, Hwang SY, Ryu JY, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. The synergistic impact of nonalcoholic fatty liver disease and metabolic syndrome on subclinical atherosclerosis. *Clin Endocrinol (Oxf).* 2016;84:203–209. doi: 10.1111/cen.12940
177. Al Rifai M, Silverman MG, Nasir K, Budoff MJ, Blankstein R, Szklo M, Katz R, Blumenthal RS, Blaha MJ. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis.* 2015;239:629–633. doi: 10.1016/j.atherosclerosis.2015.02.011
178. Lee YA, Kang SG, Song SW, Rho JS, Kim EK. Association between metabolic syndrome, smoking status and coronary artery calcification. *PLoS One.* 2015;10:e0122430. doi: 10.1371/journal.pone.0122430
179. Wong ND, Nelson JC, Granston T, Bertoni AG, Blumenthal RS, Carr JJ, Guerci A, Jacobs DR Jr, Kronmal R, Liu K, et al. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. *JACC Cardiovasc Imaging.* 2012;5:358–366. doi: 10.1016/j.jcmg.2011.12.015
180. Katz R, Budoff MJ, O'Brien KD, Wong ND, Nasir K. The metabolic syndrome and diabetes mellitus as predictors of thoracic aortic calcification as detected by non-contrast computed tomography in the Multi-Ethnic Study of Atherosclerosis. *Diabet Med.* 2016;33:912–919. doi: 10.1111/dme.12958
181. Safar ME, Balkau B, Lange C, Protogerou AD, Czernichow S, Blacher J, Levy BI, Smulyan H. Hypertension and vascular dynamics in men and women with metabolic syndrome. *J Am Coll Cardiol.* 2013;61:12–19. doi: 10.1016/j.jacc.2012.01.088
182. Ebong IA, Bertoni AG, Soliman EZ, Guo M, Sibley CT, Chen YD, Rotter JI, Chen YC, Goff DC Jr. Electrocardiographic abnormalities associated with the metabolic syndrome and its components: the Multi-Ethnic Study of Atherosclerosis. *Metab Syndr Relat Disord.* 2012;10:92–97. doi: 10.1089/met.2011.0090
183. Rodríguez-Colón SM, He F, Bixler EO, Fernandez-Mendoza J, Vgontzas AN, Calhoun S, Zheng ZJ, Liao D. Metabolic syndrome burden in apparently healthy adolescents is adversely associated with cardiac autonomic modulation: Penn State Children Cohort. *Metabolism.* 2015;64:626–632. doi: 10.1016/j.metabol.2015.01.018
184. Li J, Flammer AJ, Lennon RJ, Nelson RE, Gulati R, Friedman PA, Thomas RJ, Sandhu NP, Hua Q, Lerman LO, et al. Comparison of the effect of the metabolic syndrome and multiple traditional cardiovascular risk factors on vascular function. *Mayo Clin Proc.* 2012;87:968–975. doi: 10.1016/j.mayocp.2012.07.004
185. Walther G, Obert P, Dutheil F, Chapier R, Lesourd B, Naughton G, Courteix D, Vinet A. Metabolic syndrome individuals with and without type 2 diabetes mellitus present generalized vascular dysfunction: cross-sectional study. *Arterioscler Thromb Vasc Biol.* 2015;35:1022–1029. doi: 10.1161/ATVBAHA.114.304591
186. Smith JP, Haddad EV, Taylor MB, Oram D, Blakemore D, Chen Q, Boutaud O, Oates JA. Suboptimal inhibition of platelet cyclooxygenase-1 by aspirin in metabolic syndrome. *Hypertension.* 2012;59:719–725. doi: 10.1161/HYPERTENSIONAHA.111.181404
187. Feldman L, Tubach F, Juliard JM, Himbert D, Ducrocq G, Sorbets E, Triantafyllou K, Kerner A, Abergel H, Huisse MG, et al. Impact of diabetes mellitus and metabolic syndrome on acute and chronic on-clopidogrel platelet reactivity in patients with stable coronary artery disease undergoing drug-eluting stent placement. *Am Heart J.* 2014;168:940–947.e5. doi: 10.1016/j.ahj.2014.08.014
188. Cuspidi C, Sala C, Tadic M, Gherbesi E, Grassi G, Mancia G. Association of metabolic syndrome with carotid thickening and plaque in the general population: a meta-analysis. *J Clin Hypertens (Greenwich).* 2018;20:4–10. doi: 10.1111/jch.13138
189. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, Iacobellis G. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. *Am J Cardiol.* 2013;111:73–78. doi: 10.1016/j.amjcard.2012.08.044
190. Torriani M, Gill CM, Daley S, Oliveira AL, Azevedo DC, Bredella MA. Compartmental neck fat accumulation and its relation to cardiovascular risk and metabolic syndrome. *Am J Clin Nutr.* 2014;100:1244–1251. doi: 10.3945/ajcn.114.088450
191. van der Meer RW, Lamb HJ, Smit JW, de Roos A. MR imaging evaluation of cardiovascular risk in metabolic syndrome. *Radiology.* 2012;264:21–37. doi: 10.1148/radiol.12110772
192. Chun H. Ascending aortic diameter and metabolic syndrome in Korean men. *J Investig Med.* 2017;65:1125–1130. doi: 10.1136/jim-2016-000367
193. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, et al. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. *JACC Cardiovasc Imaging.* 2012;5(suppl):S42–S52. doi: 10.1016/j.jcmg.2012.01.008
194. Di Carli MF, Charytan D, McMahon GT, Ganz P, Dorbala S, Schelbert HR. Coronary circulatory function in patients with the metabolic syndrome. *J Nucl Med.* 2011;52:1369–1377. doi: 10.2967/jnumed.110.082883
195. Almeida AL, Teixido-Tura G, Choi EY, Opdahl A, Fernandes VR, Wu CO, Bluemke DA, Lima JA. Metabolic syndrome, strain, and reduced myocardial function: Multi-Ethnic Study of Atherosclerosis. *Arq Bras Cardiol.* 2014;102:327–335.
196. Canon-Montanez W, Santos ABS, Nunes LA, Pires JCG, Freire CMV, Ribeiro ALP, Mill JG, Bessel M, Duncan BB, Schmidt MI, et al. Central obesity is the key component in the association of metabolic syndrome with left ventricular global longitudinal strain impairment. *Rev Esp Cardiol (Engl Ed).* 2018;71:524–530. doi: 10.1016/j.rec.2017.10.008
197. Aksoy S, Durmuş G, Özcan S, Toprak E, Gurkan U, Oz D, Canga Y, Karatas B, Duman D. Is left ventricular diastolic dysfunction independent from presence of hypertension in metabolic syndrome? An echocardiographic study. *J Cardiol.* 2014;64:194–198. doi: 10.1016/j.jjcc.2014.01.002
198. Crendal E, Walther G, Dutheil F, Courteix D, Lesourd B, Chapier R, Naughton G, Vinet A, Obert P. Left ventricular myocardial dyssynchrony is already present in nondiabetic patients with metabolic syndrome. *Can J Cardiol.* 2014;30:320–324. doi: 10.1016/j.cjca.2013.10.019
199. Tadic M, Cuspidi C, Sljivic A, Andric A, Ivanovic B, Scepanovic R, Ilic I, Jozika L, Marjanovic T, Celic V. Effects of the metabolic syndrome on right heart mechanics and function. *Can J Cardiol.* 2014;30:325–331. doi: 10.1016/j.cjca.2013.12.006
200. Gurka MJ, Golden SH, Musani SK, Sims M, Vishnu A, Guo Y, Cardel M, Pearson TA, DeBoer MD. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk in Communities Study and Jackson Heart Study. *Diabetologia.* 2017;60:1261–1270. doi: 10.1007/s00125-017-4267-6
201. Stefansson VTN, Schei J, Solbu MD, Jenssen TG, Melsom T, Eriksen BO. Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population. *Kidney Int.* 2018;93:1183–1190. doi: 10.1016/j.kint.2017.11.012
202. Akinyemiju T, Moore JX, Judd S, Lakoski S, Goodman M, Safford MM, Pisu M. Metabolic dysregulation and cancer mortality in a

national cohort of blacks and whites. *BMC Cancer.* 2017;17:856. doi: 10.1186/s12885-017-3807-2
203. Micucci C, Valli D, Matacchione G, Catalano A. Current perspectives between metabolic syndrome and cancer. *Oncotarget.* 2016;7:38959–38972. doi: 10.18632/oncotarget.8341
204. Santos AP, Santos AC, Castro C, Raposo L, Pereira SS, Torres I, Henrique R, Cardoso H, Monteiro MP. Visceral obesity and metabolic syndrome are associated with well-differentiated gastroenteropancreatic neuroendocrine tumors. *Cancers (Basel).* 2018;10:E293. doi: 10.3390/cancers10090293
205. Watanabe J, Kakehi E, Kotani K, Kayaba K, Nakamura Y, Ishikawa S. Metabolic syndrome is a risk factor for cancer mortality in the general Japanese population: the Jichi Medical School Cohort Study. *Diabetol Metab Syndr.* 2019;11:3. doi: 10.1186/s13098-018-0398-2
206. Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, Tubaro A, Morgia G, Serni S. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis.* 2017;20:146–155. doi: 10.1038/pcan.2017.1
207. Dibaba DT, Ogunsina K, Braithwaite D, Akinyemiju T. Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype. *Breast Cancer Res Treat.* 2019;174:209–218. doi: 10.1007/s10549-018-5056-8
208. Akinyemiju T, Sakhuja S, Vin-Raviv N. In-hospital mortality and post-surgical complications among cancer patients with metabolic syndrome. *Obes Surg.* 2018;28:683–692. doi: 10.1007/s11695-017-2900-6
209. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL, Zollinger TW. Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. *Int J Cancer.* 2018;143:535–542. doi: 10.1002/ijc.31344
210. Chen Y, Li X, Wu S, Ye W, Lou L. Metabolic syndrome and the incidence of hepatocellular carcinoma: a meta-analysis of cohort studies. *Onco Targets Ther.* 2018;11:6277–6285. doi: 10.2147/OTT.S154848
211. Wong RJ, Liu B, Bhuket T. Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross-sectional analysis of 2011-2014 National Health and Nutrition Examination Survey. *Aliment Pharmacol Ther.* 2017;46:974–980. doi: 10.1111/apt.14327
212. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64:73–84. doi: 10.1002/hep.28431
213. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med.* 2005;143:722–728. doi: 10.7326/0003-4819-143-10-200511150-00009
214. Xu ZJ, Shi JP, Yu DR, Zhu LJ, Jia JD, Fan JG. Evaluating the relationship between metabolic syndrome and liver biopsy-proven non-alcoholic steatohepatitis in China: a multicenter cross-sectional study design. *Adv Ther.* 2016;33:2069–2081. doi: 10.1007/s12325-016-0416-4
215. Besiroglu H, Otunctemur A, Ozbek E. The relationship between metabolic syndrome, its components, and erectile dysfunction: a systematic review and a meta-analysis of observational studies. *J Sex Med.* 2015;12:1309–1318. doi: 10.1111/jsm.12885
216. Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. *Hepatology.* 2018;67:2141–2149. doi: 10.1002/hep.29631
217. Lee EY, Lee SJ, Kim KM, Yun YM, Song BM, Kim JE, Kim HC, Rhee Y, Youm Y, Kim CO. Association of metabolic syndrome and 25-hydroxyvitamin D with cognitive impairment among elderly Koreans. *Geriatr Gerontol Int.* 2017;17:1069–1075. doi: 10.1111/ggi.12826
218. Ageno W, Di Minno MN, Ay C, Jang MJ, Hansen JB, Steffen LM, Vayà A, Rattazzi M, Pabinger I, Oh D, et al. Association between the metabolic syndrome, its individual components, and unprovoked venous thromboembolism: results of a patient-level meta-analysis. *Arterioscler Thromb Vasc Biol.* 2014;34:2478–2485. doi: 10.1161/ATVBAHA.114.304085
219. Brumpton BM, Camargo CA Jr, Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J.* 2013;42:1495–1502. doi: 10.1183/09031936.00046013
220. Yang M, Xu H, Yang L, Jiang J, Dong B. Metabolic syndrome and disability in Chinese nonagenarians and centenarians. *Aging Clin Exp Res.* 2018;30:943–949. doi: 10.1007/s40520-017-0877-6
221. Boudreau DM, Malone DC, Raebel MA, Fishman PA, Nichols GA, Feldstein AC, Boscoe AN, Ben-Joseph RH, Magid DJ, Okamoto LJ. Health care utilization and costs by metabolic syndrome risk factors. *Metab Syndr Relat Disord.* 2009;7:305–314. doi: 10.1089/met.2008.0070
222. Shariq OA, Fruth KM, Hanson KT, Cronin PA, Richards ML, Farley DR, Thompson GB, Habermann EB, McKenzie TJ. Metabolic syndrome is associated with increased postoperative complications and use of hospital resources in patients undergoing laparoscopic adrenalectomy. *Surgery.* 2018;163:167–175. doi: 10.1016/j.surg.2017.06.023
223. Tee MC, Ubl DS, Habermann EB, Nagorney DM, Kendrick ML, Sarr MG, Truty MJ, Que FG, Reid-Lombardo K, Smoot RL, et al. Metabolic syndrome is associated with increased postoperative morbidity and hospital resource utilization in patients undergoing elective pancreatectomy. *J Gastrointest Surg.* 2016;20:189–198. doi: 10.1007/s11605-015-3007-9
224. Leiter LA, Fitchett DH, Gilbert RE, Gupta M, Mancini GB, McFarlane PA, Ross R, Teoh H, Verma S, Anand S, et al; Cardiometabolic Risk Working Group: Executive Committee. Cardiometabolic risk in Canada: a detailed analysis and position paper by the Cardiometabolic Risk Working Group. *Can J Cardiol.* 2011;27:e1–e33. doi: 10.1016/j.cjca.2010.12.054
225. López-Jaramillo P, Sánchez RA, Diaz M, Cobos L, Bryce A, Parra Carrillo JZ, Lizcano F, Lanas F, Sinay I, Sierra ID, et al; Latin America Expert Group. Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome. *J Hypertens.* 2013;31:223–238. doi: 10.1097/HJH.0b013e32835c5444
226. Yadav D, Mahajan S, Subramanian SK, Bisen PS, Chung CH, Prasad GB. Prevalence of metabolic syndrome in type 2 diabetes mellitus using NCEP-ATPIII, IDF and WHO definition and its agreement in Gwalior Chambal region of Central India. *Glob J Health Sci.* 2013;5:142–155. doi: 10.5539/gjhs.v5n6p142
227. Barik A, Das K, Chowdhury A, Rai RK. Metabolic syndrome among rural Indian adults. *Clin Nutr ESPEN.* 2018;23:129–135. doi: 10.1016/j.clnesp.2017.11.002
228. Gupta A, Sachdeva A, Mahajan N, Gupta A, Sareen N, Pandey RM, Ramakrishnan L, Sati HC, Sharma B, Sharma N, et al. Prevalence of pediatric metabolic syndrome and associated risk factors among school-age children of 10-16 years living in District Shimla, Himachal Pradesh, India. *Indian J Endocrinol Metab.* 2018;22:373–378. doi: 10.4103/ijem.IJEM_251_17
229. Lin BY, Genden K, Shen W, Wu PS, Yang WC, Hung HF, Fu CM, Yang KC. The prevalence of obesity and metabolic syndrome in Tibetan immigrants living in high altitude areas in Ladakh, India. *Obes Res Clin Pract.* 2018;12:365–371. doi: 10.1016/j.orcp.2017.03.002
230. Mini GK, Sarma PS, Thankappan KR. Overweight, the major determinant of metabolic syndrome among industrial workers in Kerala, India: results of a cross-sectional study. *Diabetes Metab Syndr.* 2019;13:3025-3030. doi: 10.1016/j.dsx.2018.07.009
231. Chowdhury MZI, Anik AM, Farhana Z, Bristi PD, Abu Al Mamun BM, Uddin MJ, Fatema J, Akter T, Tani TA, Rahman M, et al. Prevalence of metabolic syndrome in Bangladesh: a systematic review and meta-analysis of the studies. *BMC Public Health.* 2018;18:308. doi: 10.1186/s12889-018-5209-z
232. Amirkalali B, Fakhrzadeh H, Sharifi F, Kelishadi R, Zamani F, Asayesh H, Safiri S, Samavat T, Qorbani M. Prevalence of metabolic syndrome and its components in the Iranian adult population: a systematic review and meta-analysis. *Iran Red Crescent Med J.* 2015;17:e24723. doi: 10.5812/ircmj.24723
233. Heshmat R, Hemati Z, Qorbani M, Nabizadeh Asl L, Motlagh ME, Ziaodini H, Taheri M, Ahadi Z, Shafiee G, Aminaei T, et al. Metabolic syndrome and associated factors in Iranian children and adolescents: the CASPIAN-V study. *J Cardiovasc Thorac Res.* 2018;10:214–220. doi: 10.15171/jcvtr.2018.37
234. Oguoma VM, Nwose EU, Richards RS. Prevalence of cardio-metabolic syndrome in Nigeria: a systematic review. *Public Health.* 2015;129:413–423. doi: 10.1016/j.puhe.2015.01.017
235. Peer N, Lombard C, Steyn K, Levitt N. High prevalence of metabolic syndrome in the black population of Cape Town: the Cardiovascular Risk in Black South Africans (CRIBSA) study. *Eur J Prev Cardiol.* 2015;22:1036–1042. doi: 10.1177/2047487314549744
236. Orces CH, Gavilanez EL. The prevalence of metabolic syndrome among older adults in Ecuador: results of the SABE survey. *Diabetes Metab Syndr.* 2017;11 (suppl 2):S555–S560. doi: 10.1016/j.dsx.2017.04.004
237. Raimi TH, Odusan O, Fasanmade OA, Odewabi AO, Ohwovoriole AE. Metabolic syndrome among apparently healthy Nigerians with the harmonized criteria: prevalence and concordance with the International Diabetes Federation (IDF) and Third Report of the National Cholesterol

Education Programme-Adult Treatment Panel III (NCEP-ATP III) criteria. *J Cardiovasc Disease Res*. 2017;8:145–150. doi: 10.5530/jcdr.2017.4.32
238. Binh TQ, Phuong PT, Nhung BT, Tung DD. Metabolic syndrome among a middle-aged population in the Red River Delta region of Vietnam. *BMC Endocr Disord.* 2014;14:77. doi: 10.1186/1472-6823-14-77
239. Xi B, He D, Hu Y, Zhou D. Prevalence of metabolic syndrome and its influencing factors among the Chinese adults: the China Health and Nutrition Survey in 2009. *Prev Med.* 2013;57:867–871. doi: 10.1016/j.ypmed.2013.09.023
240. Zhao Y, Yan H, Yang R, Li Q, Dang S, Wang Y. Prevalence and determinants of metabolic syndrome among adults in a rural area of Northwest China. *PLoS One.* 2014;9:e91578. doi: 10.1371/journal.pone.0091578
241. Ng SM, Su X. Prevalence and correlates of metabolic syndrome in Hong Kong Chinese adults: a random community sample study. *Psychol Health Med.* 2018;23:485–495. doi: 10.1080/13548506.2017.1395057
242. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, Gaye A, Gögele M, Heier M, Hiekkalinna T, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord.* 2014;14:9. doi: 10.1186/1472-6823-14-9
243. Vernay M, Salanave B, de Peretti C, Druet C, Malon A, Deschamps V, Hercberg S, Castetbon K. Metabolic syndrome and socioeconomic status in France: the French Nutrition and Health Survey (ENNS, 2006-2007). *Int J Public Health.* 2013;58:855–864. doi: 10.1007/s00038-013-0501-2
244. de Carvalho Vidigal F, Bressan J, Babio N, Salas-Salvadó J. Prevalence of metabolic syndrome in Brazilian adults: a systematic review. *BMC Public Health.* 2013;13:1198. doi: 10.1186/1471-2458-13-1198
245. Diaz A, Espeche W, March C, Flores R, Parodi R, Genesio MA, Sabio R, Poppe S. Prevalence of metabolic syndrome in Argentina in the last 25 years: systematic review of population observational studies [in Spanish]. *Hipertens Riesgo Vasc.* 2018;35:64–69. doi: 10.1016/j.hipert.2017.08.003
246. Salas R, Bibiloni MdM, Ramos E, Villarreal JZ, Pons A, Tur JA, Sureda A. Metabolic syndrome prevalence among Northern Mexican adult population. *PLoS One.* 2014;9:e105581. doi: 10.1371/journal.pone.0105581
247. Ortiz-Rodríguez MA, Yáñez-Velasco L, Carnevale A, Romero-Hidalgo S, Bernal D, Aguilar-Salinas C, Rojas R, Villa A, Tur JA. Prevalence of metabolic syndrome among elderly Mexicans. *Arch Gerontol Geriatr.* 2017;73:288–293. doi: 10.1016/j.archger.2017.09.001
248. Li M, McCulloch B, McDermott R. Metabolic syndrome and incident coronary heart disease in Australian indigenous populations. *Obesity (Silver Spring).* 2012;20:1308–1312. doi: 10.1038/oby.2011.156
249. Ansarimoghaddam A, Adineh HA, Zareban I, Iranpour S, HosseinZadeh A, Kh F. Prevalence of metabolic syndrome in Middle-East countries: meta-analysis of cross-sectional studies. *Diabetes Metab Syndr.* 2018;12:195–201. doi: 10.1016/j.dsx.2017.11.004

11. KIDNEY DISEASE

ICD-10 N18.0. See Charts 11-1 through 11-10

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Definition (See Chart 11-1)

CKD, defined as reduced GFR (<60 mL·min^{-1}·1.73 m^{-2}), excess urinary albumin excretion (≥30 mg/d or mg/gCr), or both, is a serious health condition and a worldwide public health problem that is associated with poor outcomes and a high cost to the US healthcare system.[1]

- GFR is usually estimated from the serum creatinine level using equations that account for age, sex, and race.
- The spot urine ACR is recommended as a measure of urine albumin excretion.

Abbreviations Used in Chapter 11

ACC	American College of Cardiology
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
Af Am	African American
AHA	American Heart Association
AI/AN	American Indian or Alaska Native
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMS	Centers for Medicare & Medicaid Services
CVA	cerebrovascular accident
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GFR	glomerular filtration rate
GWAS	genome-wide association study
HANDLS	Health Aging in Neighborhoods of Diversity Across the Life Span
HBP	high blood pressure
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HF	heart failure
HR	hazard ratio
HTN	hypertension

(*Continued*)

Abbreviations Used in Chapter 11 Continued

ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IMT	intima-media thickness
JHS	Jackson Heart Study
KDIGO	Kidney Disease: Improving Global Outcomes
LV	left ventricular
MACE	major adverse cardiovascular events
MESA	Multi-Ethnic Study of Atherosclerosis
MR	mitral regurgitation
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NIS	National (Nationwide) Inpatient Sample
OR	odds ratio
OSA	obstructive sleep apnea
PAD	peripheral arterial/artery disease
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PI	Pacific Islander
RR	relative risk
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SES	socioeconomic status
SHARP	Study of Heart and Renal Protection
SNP	single-nucleotide polymorphism
SR	self-report
STS	Society of Thoracic Surgeons
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack
TVT	Transcatheter Valve Therapy
UI	uncertainty interval
USRDS	United States Renal Data System
VA	ventricular arrhythmia
VHD	valvular heart disease
VTE	venous thromboembolism

- CKD is characterized by eGFR category (G1–G5) and albuminuria category (A1–A3), as well as cause of CKD (Chart 11-1).[2]
- ESRD is defined as severe CKD requiring long-term renal replacement treatment such as hemodialysis, peritoneal dialysis, or kidney transplantation.[1] ESRD is an extremely high-risk population for cardiovascular morbidity and mortality.

Prevalence (See Charts 11-1 through 11-3)

- Using data from NHANES 2013 to 2016, the USRDS has estimated the prevalence of CKD by eGFR and albuminuria categories as shown in Chart 11-1. The overall prevalence of CKD (eGFR <60 mL·min^{-1}·1.73 m^{-2} or ACR ≥30 mg/g; shown in yellow, orange, and red in Chart 11-1) in 2013 to 2016 was 14.8%.[1]
- The prevalence of CKD increases substantially with age, as follows[1]:

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  - 6.3% for those 20 to 39 years of age
  - 10.4% for those 40 to 59 years of age
  - 32.2% for those ≥60 years of age
- From 2001 to 2016, the prevalence of ACR ≥30 mg/g was higher but prevalence of eGFR <60 mL·min^{-1}·1.73 m^{-2} was lower among NH blacks than NH whites.[1]
- At the end of 2016, the unadjusted prevalence of ESRD estimated from cases reported to the CMS in the United States was 2161 per million (0.22%).[1]
- The prevalence of ESRD varies regionally across the United States (Chart 11-2), mirroring the prevalence of traditional risk factors such as DM or hypertension.
- ESRD prevalence is highest in Native Hawaiians/Pacific Islanders compared with other races, and prevalence is higher among Hispanics than among NH individuals (Chart 11-3).

Incidence (See Chart 11-3)

- For US adults 30 to 49 years of age, 50 to 64 years of age, and ≥65 years of age without CKD, the residual lifetime incidences of CKD are projected to be 54%, 52%, and 42%, respectively, in the CKD Health Policy Model simulation based on 1999 to 2010 NHANES data.[3]
- The incidence of ESRD is higher among blacks than whites (Chart 11-3),[1] a disparity that persists even after controlling for major ESRD risk factors and that might be explained in part by the higher prevalence of albuminuria and *APOL1* in this population.[4]

Secular Trends (See Chart 11-3)

- According to NHANES data, the prevalence of CKD (eGFR 15–59 mL·min^{-1}·1.73 m^{-2}) in the United States increased slowly over time until 2003 to 2004 because of an aging population and higher prevalence of risk factors, but the prevalence plateaued from 2004 to 2012.[5]
- The prevalence of ESRD increased across most races and ethnicities from 2000 to 2016 primarily because of improved survival, whereas the incidence rate appeared to stabilize or decrease slightly (Chart 11-3).[1]

Risk Factors (See Charts 11-4 and 11-5)

- Many traditional CVD risk factors are also risk factors for CKD, including older age, male sex, hypertension, DM, smoking, and family history of CVD (Chart 11-4). In NHANES 2013 to 2016, the prevalence of CKD was 31% in adults ≥20 years of age with HBP and 37% in adults with DM. Among adults with obesity (BMI >30 kg/m^2), nearly 17% had CKD.[1]
- Even early stages of elevated BP and stage 1 hypertension as defined by the 2017 Hypertension Clinical Practice Guidelines (SBP of 120–139 mm Hg or DBP of 80–89 mm Hg) were associated with incident decreased eGFR (<60 mL·min^{-1}·1.73 m^{-2}) in a meta-analysis of observational cohorts (RR, 1.19 [95% CI, 1.07–1.33] over a mean follow-up of 6.5 years).[6]
- OSA is associated with CKD and CKD progression independent of BMI and other traditional risk factors.[7]
- Zip code–level poverty is associated with ≈25% higher ESRD incidence after accounting for age, sex, and race/ethnicity, and this association appears to be getting stronger over time (2005–2010 versus 1995–2004).[8]
- Importantly, cardiovascular fitness and healthy lifestyles are associated with decreased risk and progression of CKD.[9–11] For example, having more of the AHA's Life's Simple 7 ideal health factors was associated with progressively lower risk of incident CKD in the ARIC study (Chart 11-5).

Social Determinants of CKD

- A recent meta-analysis of 43 studies examining associations between socioeconomic indicators (income, education, and occupation) found that lower SES, particularly income, was associated with a higher prevalence of CKD and faster progression to ESRD.[12] This association was observed in higher- versus lower- or middle-income countries and was more pronounced in the United States relative to Europe.
- In a cross-sectional analysis of 9126 lower-income participants from NHANES 2003 to 2008, food insecurity (ie, the inability to acquire nutritional foods) was associated with a 67% higher odds of age-adjusted prevalent CKD in those with DM and a 37% higher odds of age-adjusted prevalent CKD in those with hypertension. A similar analysis in 1239 participants in the HANDLS study revealed a marginally significant higher odds of CKD in the full cohort, with no evidence of stronger associations in individuals with DM or hypertension.[13]
- In the HCHS/SOL, lower language acculturation was associated with CKD among older subjects (>65 years); however, among subjects with CKD, acculturation measures were not associated with hypertension or DM control.[14]
- In a study of 1620 participants from HANDLS with preserved baseline kidney function, self-reported

experiences of discrimination were associated with lower kidney function assessed via GFR, and associations were particularly pronounced for black females relative to white females, black males, and NH white males.[15]

Genetics/Family History

- Several hundred loci have been implicated in monogenic CKD.[16,17]
- GWASs have revealed several candidate loci for CKD phenotypes, including GFR, albuminuria, kidney injury, and diabetic kidney disease.[18–22]
- Race differences in CKD prevalence might be attributable to differences in genetic risk. The *APOL1* gene has been well studied as a kidney disease locus in individuals of African ancestry.[19] SNPs in *APOL1* that are present in individuals of African ancestry but absent in other racial groups might have been subject to positive selection, conferring protection against trypanosome infection but leading to increased risk of renal disease, potentially through disruption of mitochondrial function.[18]
- Although certain variants of *APOL1* increase risk, this only explains a portion of the disparity in ESRD risk between blacks and nonblacks.[19] For example, eGFR decline was faster even for black subjects with low-risk *APOL1* status (0 or 1 allele) than for whites in CARDIA; this difference was attenuated by adjustment for SES and traditional risk factors.[20]
- Despite associations with kidney risk, *APOL1* does not appear to be associated with overall risk for CVD among blacks with hypertension-attributed CKD,[21] and it is not associated with coronary calcification, carotid IMT, or LV mass among middle-aged black adults in CARDIA.[23]

Awareness

- Awareness of CKD status in NHANES 2013 to 2016 was particularly low, ranging from 2% to 5% for early-stage CKD to 57% for more advanced CKD (eGFR 15–29 mL·min^{-1}·1.73 m^{-2}).[1]

Complications

- In an analysis of GBD 2002 to 2016 data, DALYs attributable to CKD increased by 52.6%, and death attributable to CKD increased by 58.3%. The burden was most pronounced in the Southern United States, with much of the increase in CKD DALYs attributable to increased metabolic risks, aging of the population, and population growth. Age-standardized CKD DALY rates increased by 18.6% over the same time period.[24]

Cost

- In 2016, Medicare spent >$79 billion caring for people with CKD and $35 billion for ESRD, which is 23% of all Medicare fee-for-service spending.[1]

Global Burden of Kidney Disease (See Charts 11-6 and 11-7)

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[25]
  - In 2017, the total estimated prevalence of CKD was 698 million people (95% UI, 649–752 million), a 27% increase since 2007.
  - Age-standardized prevalence of CKD is highest in Eastern Europe, South Asia, sub-Saharan Africa, Latin America, and Oceania (Chart 11-6).
  - Oceania and Mexico had the highest age-standardized mortality rates attributable to CKD in 2017 (Chart 11-7).

Kidney Disease and CVD

Impact of CKD on CVD Outcomes

- CKD is a risk factor for incident and recurrent CHD events, stroke, HF, VTE, and AF and is considered to be a risk-enhancing factor for the purposes of recommending primary prevention therapies such as statins or aggressive BP control.[26–31]
- The association of reduced eGFR with cardiovascular risk is generally similar across age, race, and sex subgroups,[32] although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) versus younger people.[30]
- The addition of eGFR or albuminuria improves CVD prediction beyond traditional risk factors used in risk equations.[30]
- A recent meta-analysis of 21 cohort studies of 27 465 individuals with CKD found that nontraditional risk factors such as serum albumin, phosphate, urate, and hemoglobin are associated with CVD risk in this population.[33]

Prevalence of CVD Among People With CKD (See Charts 11-8 and 11-9)

- People with CKD, as well as those with ESRD, have an extremely high prevalence of comorbid CVDs ranging from IHD and HF to arrhythmias and VTE (Charts 11-8 and 11-9).
- Nearly two-thirds (64.5%) of CKD patients 66 years of age or older have CVD, compared with

approximately one-third (32.4%) of patients without CKD in this age group.[1]
- The prevalence of CVD in ESRD patients differs by treatment modality. Approximately 71% of ESRD patients on hemodialysis have any CVD, whereas 58% of peritoneal dialysis patients and 41% of transplant patients have any CVD (Chart 11-9).

Incidence of CVD Events Among People With CKD

- In 3 community-based cohort studies (JHS, CHS, and MESA), absolute incidence rates for HF, CHD, and stroke for participants with versus without CKD were 22 versus 6.2 (per 1000 person-years) for HF, 24.5 versus 8.4 for CHD, and 13.4 versus 4.8 for stroke.[34]
- Both eGFR and albuminuria appear to more strongly predict HF events than CHD or stroke events.[30]
- GFR predicts stroke risk but is not as strongly associated as albuminuria. In 4 community-based cohorts, lower eGFR (45 versus 95 mL·min^{-1}·1.73 m^{-2}) was associated with an increased risk for ischemic stroke (HR, 1.30 [95% CI, 1.01–1.68]) but not hemorrhagic stroke (HR, 0.92 [95% CI, 0.47–1.81]). Albuminuria (ACR of 300 versus 5 mg/g) was associated with both ischemic and hemorrhagic stroke (HR, 1.62 [95% CI, 1.27–2.07] and 2.57 [95% CI, 1.37–4.83], respectively).[35] In a meta-analysis of 83 studies of >30 000 strokes, there were linear relationships of both eGFR and albuminuria with stroke regardless of stroke subtype.[29] Among people with CKD, proteinuria but not eGFR independently predicted stroke risk.[36]
- In one study of people with CKD 50 to 79 years of age, the ACC/AHA pooled cohort risk equations appeared to be well calibrated (Hosmer-Lemeshow χ^2=2.7, P=0.45), with moderately good discrimination (C index, 0.71 [95% CI, 0.65–0.77]) for ASCVD events.[37]
- Females with CKD appear to have higher risk of incident PAD than males, particularly at younger ages.[38]
- A patient-level pooled analysis of randomized trials explored the effect of CKD on prognosis for females who undergo PCI.[39] Creatinine clearance <45 mL/min was an independent risk factor for 3-year MACE (adjusted HR, 1.56) and all-cause mortality (adjusted HR, 2.67).
- Despite higher overall event rates than NH whites, NH blacks with CKD have similar (or possibly lower) rates of ASCVD events, HF events, and death after adjustment for demographic factors, baseline kidney function, and cardiovascular risk factors.[40] However, the risk of HF associated with CKD might be greater for blacks and Hispanics than for whites.[34]
- Clinically significant bradyarrhythmias appear to be more common than ventricular arrhythmias among hemodialysis patients and are highest in the immediate hours before dialysis sessions.[41]

Prevention and Treatment of CVD in People With CKD

- One potential explanation for the higher CVD event rate in people with CKD is the low uptake of standard therapies. Furthermore, people with advanced CKD and ESRD are often excluded from clinical trials of cardiovascular drugs and devices,[42,43] although recent observational data from large registries can provide insight into the risks and benefits in this population.
- In a nationwide US cohort that included 4726 participants with CKD, only 2366 (50%) self-reported taking statins, whereas an additional 1984 participants (42%) met recommendations for statin treatment according to the 2013 ACC/AHA guideline on treatment of blood cholesterol but did not report using statins.[37]
- Rates of stress testing among Medicare beneficiaries declined from 2008 to 2012, but rates were 5% to 15% higher for those with CKD and ESRD than for those without CKD.[44]
- In a study of >12 000 people undergoing hemodialysis in the USRDS who had AF, only 15% initiated warfarin therapy within 30 days, and 70% discontinued use within 1 year.[45]
- Low eGFR is an indication for reduced dosing of non–vitamin K antagonist oral anticoagulant drugs. Among nearly 15 000 US Air Force patients prescribed non–vitamin K antagonist oral anticoagulant drugs in an administrative database, 1473 had a renal indication for reduced dosing, and 43% of these were potentially overdosed. Potential overdosing was associated with increased risk of major bleeding (HR, 2.9 [95% CI, 1.07–4.46]).[46]
- In a study of 17 910 patients undergoing angiography for stable IHD in Alberta, Canada, those with kidney disease were less likely to be revascularized for angiographically significant (>70%) coronary stenoses (OR, 0.52 [95% CI, 0.35–0.79] for ESRD compared to no CKD; OR, 0.80 [95% CI, 0.71–0.89] for mild-moderate CKD compared to no CKD).[47]
- For patients undergoing TAVR in the United Kingdom, eGFR <45 mL·min^{-1}·1.73 m^{-2} was associated with higher odds of in-hospital (adjusted OR, 1.45 [95% CI, 1.03–2.05]) and longer-term (adjusted OR, 1.36 [95% CI, 1.17–1.58]) mortality compared with higher eGFR.[48] Somewhat higher odds of in-hospital mortality after TAVR were seen for those with ESRD compared with all others in the NIS 2011 to 2014 (adjusted OR, 2.21 [95% CI, 1.81–2.69]).[49]

- For patients with eGFR <60 but >15 mL·min^{-1}·1.73 m^{-2} undergoing TAVR in the TVT registry, approximately one-third will die and 1 in 6 will require dialysis within a year.[50]
- Among patients being treated with hemodialysis who were hospitalized for PAD, the number of endovascular procedures increased nearly 3-fold and the number of surgical procedures dropped by more than two-thirds from 2000 to 2012.[51] Among patients who underwent lower-extremity bypass surgery in the USRDS 2006 to 2011, females with ESRD were less likely than males with ESRD to receive an autogenous vein graft. Among those who received a prosthetic graft, acute graft failure was higher for females.[52]

Mortality Attributable to CVD Among People With CKD (See Chart 11-10)

- CVD is a leading cause of death for people with CKD. Mortality risk depends not only on eGFR but also on category of albuminuria (Chart 11-10). The adjusted RR of all-cause mortality and cardiovascular mortality is highest in those with eGFR 15 to 30 mL·min^{-1}·1.73 m^{-2} and those with ACR >300 mg/g.[2]
- For patients with severe valvular heart disease, CKD is a particularly strong risk factor for mortality. In the Duke University Echocardiography Database (1999–2013), 5-year survival was substantially lower for CKD than for non-CKD patients (42% versus 67% for severe aortic stenosis and 37% versus 65% for severe MR, CKD versus non-CKD, respectively).[53]
- Elevated levels of the alternative glomerular filtration marker cystatin C have been associated with increased risk for CVD and all-cause mortality in studies from a broad range of cohorts.
  - Cystatin C levels predict ASCVD, HF, all-cause mortality, and cardiovascular death in the FHS after accounting for clinical cardiovascular risk factors.[54]
  - Cystatin C–based eGFR was a stronger predictor of HF than creatinine-based eGFR among patients with CKD in the Chronic Renal Insufficiency Cohort study.[55]
  - Strengthened associations with outcomes (relative to creatinine or creatinine-based eGFR) might be explained in part by non-GFR determinants of cystatin C such as chronic inflammation.[56]

Costs of CVD in People With CKD

- In 2015, admissions for CVD accounted for 27% of all inpatient spending for ESRD patients.[1]
- In SHARP, a study of patients in Europe, North America, and Australasia, nonfatal major cardiovascular events were associated with £6133 (95% CI, £5608–£6658) higher costs for ESRD patients on dialysis and £4350 (95% CI, £3819–£4880) for other CKD patients in the year of the event (compared with years before the event).[57]
- Worse preoperative creatinine clearance was associated with higher total costs of CABG from 2000 to 2012 in the STS database ($1250 per 10 mL/min lower clearance).[58]

FOOTNOTE

Disclosure: A portion of the data reported has been supplied by the USRDS.[1] The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73 m²)	G1	Normal to high	≥ 90	54.9	4.2	0.5	59.6
	G2	Mildly decreased	60-89	30.2	2.9	0.3	33.5
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.3	4.7
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.7
	G4	Severely decreased	15-29	0.13	0.10	0.15	0.37
	G5	Kidney failure	< 15	0.01	0.04	0.09	0.13
			Total	89.9	8.5	1.6	100

Chart 11-1. Percentage of NHANES participants within the KDIGO 2012 prognosis of chronic kidney disease by GFR and albuminuria categories, United States, 2013 to 2016.

Green=low risk; Yellow=moderately high risk; Orange=high risk; Red=very high risk.

GFR indicates glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; and NHANES, National Health and Nutrition Examination Survey.

Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 1, Table 1.1,[1] using NHANES 2013 to 2016.

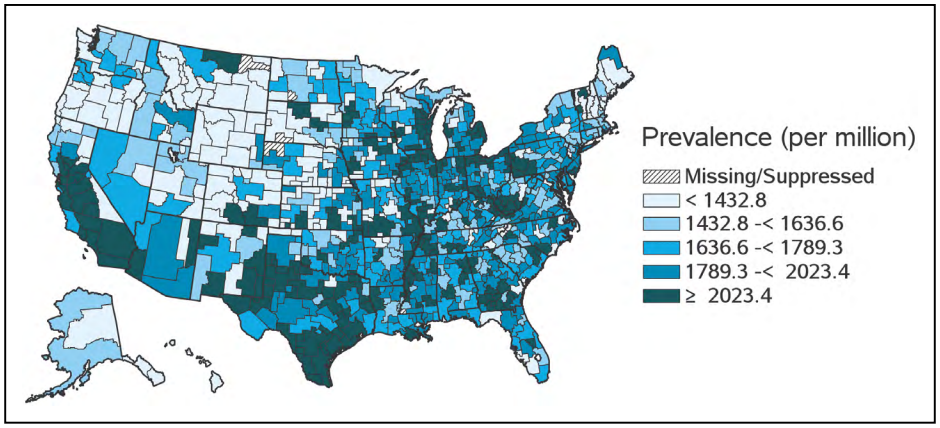

Chart 11-2. Map of the standardized prevalence (per million) of end-stage renal disease by health service area, United States, 2012 to 2016.*
*Standardized for age, sex, and race. The standard population was the US population in 2011. Four health service areas were suppressed because the ratio of crude rate to standardized rate or standardized rate to crude rate was >3. Values for cells with ≤10 patients are suppressed.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 2, Figure 1.10.[1]

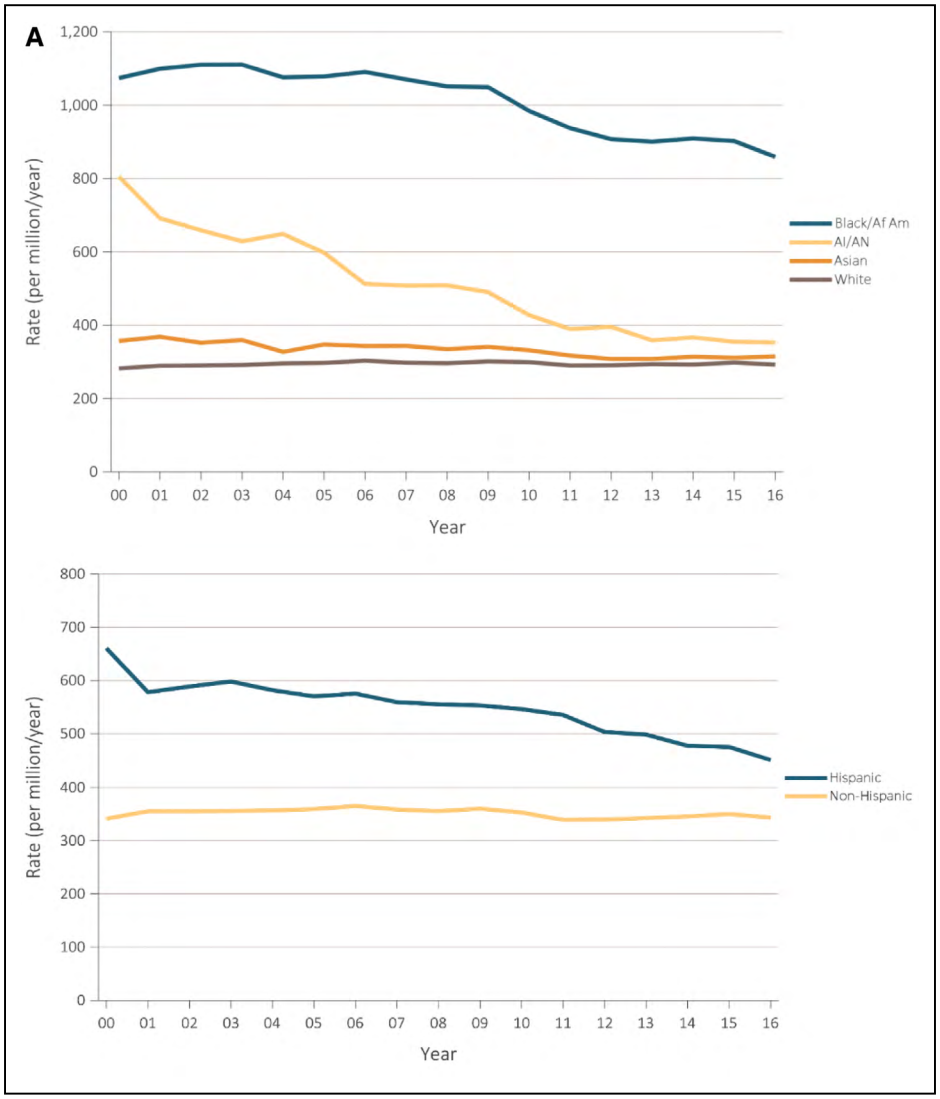

Chart 11-3. Temporal trends in end-stage renal disease, by race and Hispanic ethnicity, United States, 2000 to 2016.
A, Standardized* incidence rate (per million); (**B**) standardized* prevalence of end-stage renal disease.
Af Am indicates African American; AI/AN, American Indian or Alaska Native; NH, non-Hispanic; and PI, Pacific Islander.
*Standardized for age and sex; the ethnicity analysis is further adjusted for race. The standard population was the US population in 2011.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 2, Figures 1.5 to 1.6 and 1.12 to 1.13.[1]

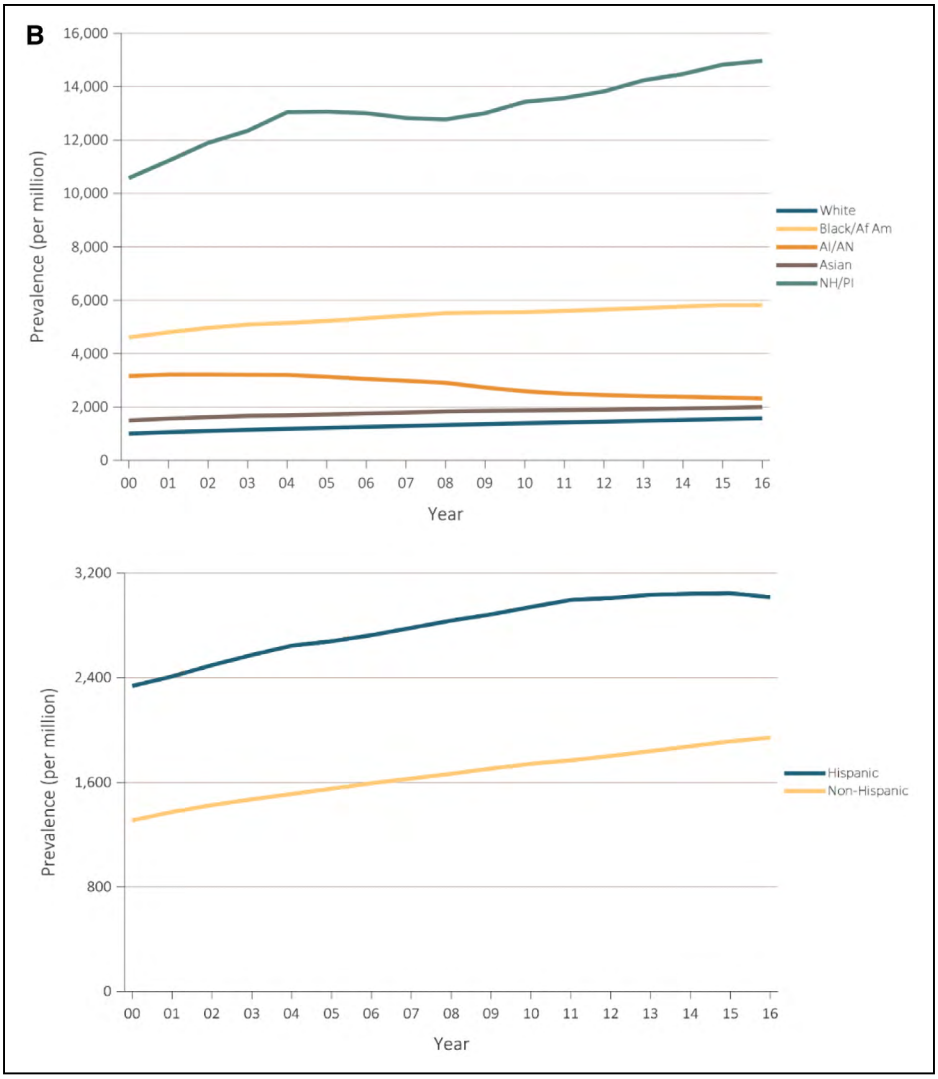

Chart 11-3. (**Continued**)

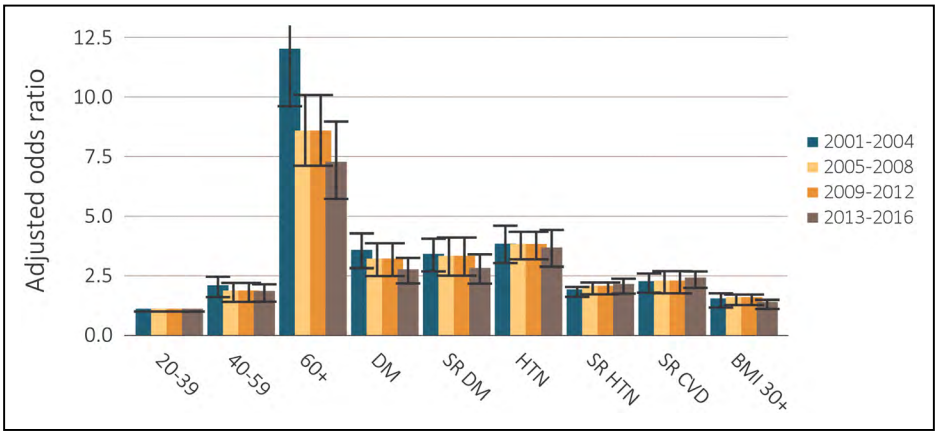

Chart 11-4. Adjusted odds ratios of chronic kidney disease (CKD) in NHANES participants by risk factor, United States, 2001 to 2016.
CKD was defined as presence of estimated glomerular filtration rate (eGFR) <60 mL·min^{-1}·1.73 m^{-2}, urine albumin-to-creatinine ratio (ACR) ≥30 mg/g, and either eGFR <60 mL·min^{-1}·1.73 m^{-2} or ACR ≥30 mg/g for each of the comorbid conditions. Adjusted for age, sex, and race; single-sample estimates of eGFR and ACR; eGFR calculated with the CKD-EPI equation. Whisker lines indicate 95% CIs.
BMI indicates body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; NHANES, National Health and Nutrition Examination Survey; and SR, self-report.
Source: Reprinted from 2018 United States Renal Data System Annual Data Report, volume 1, Figure 1.6,[1] using NHANES 2001 to 2004, 2005 to 2008, 2009 to 2012, and 2013 to 2016.

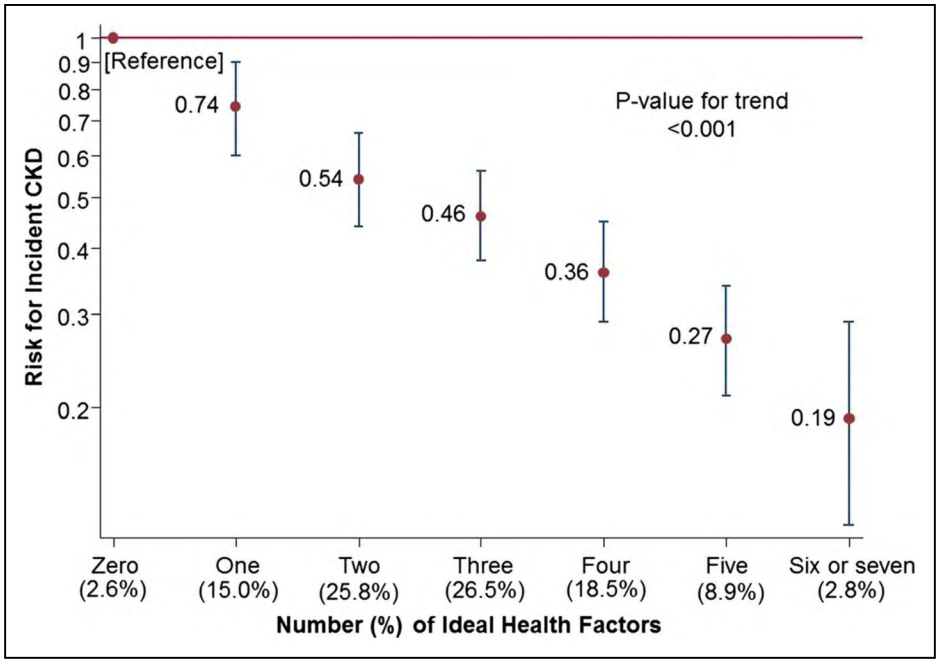

Chart 11-5. Relationship of the AHA's Life's Simple 7 health factors and risk of incident CKD.
Hazard ratio adjusted for age, sex, race, and baseline estimated glomerular filtration rate. Error bars represent the 95% CI.
AHA indicates American Heart Association; and CKD, chronic kidney disease.
Source: Reprinted from Rebholz et al.[11] Copyright © 2016, The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

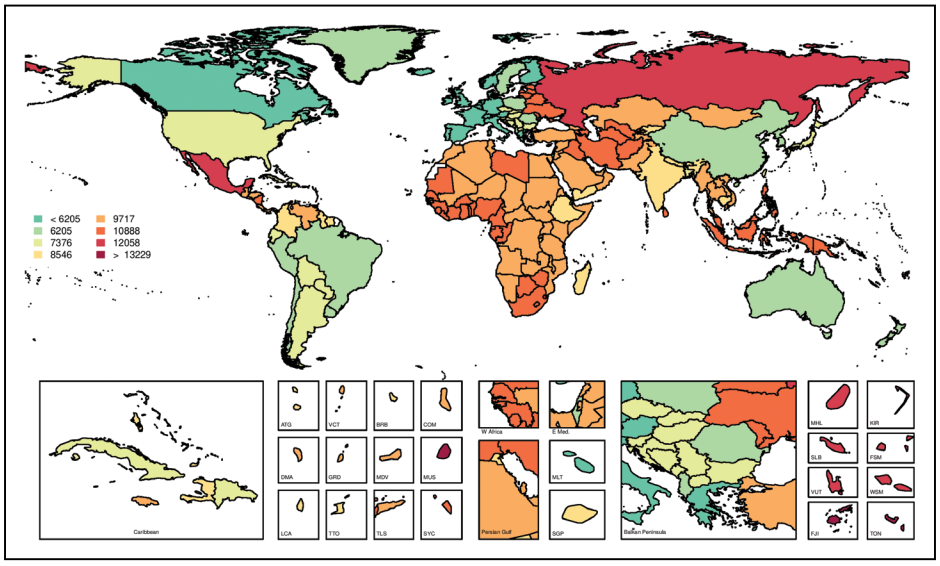

Chart 11-6. Age-standardized global prevalence rates for chronic kidney disease (CKD) per 100 000, both sexes, 2017.
Age-standardized prevalence of CKD is highest in Eastern Europe, South Asia, sub-Saharan Africa, Latin America, and Oceania.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[25] Printed with permission. Copyright © 2018, University of Washington.

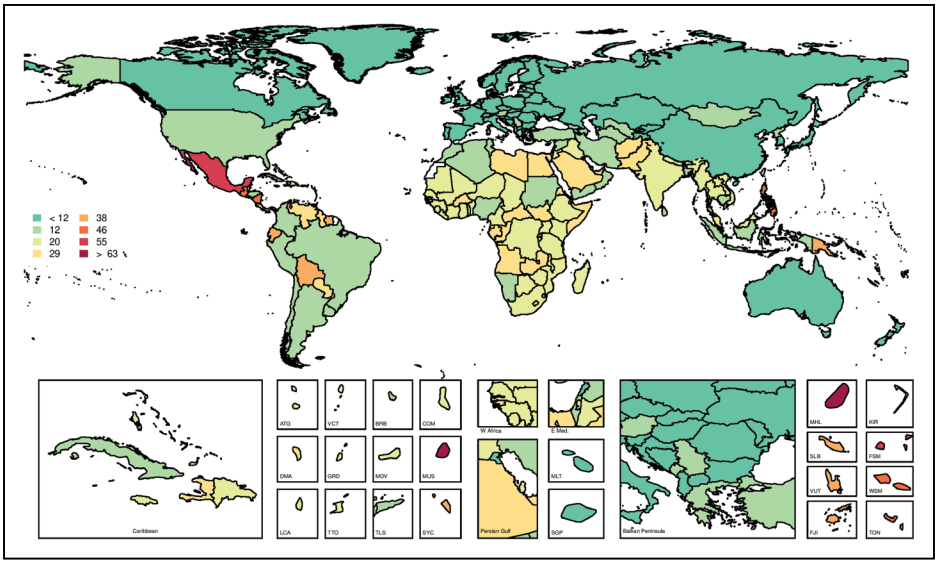

Chart 11-7. Age-standardized global mortality rates for chronic kidney disease (CKD) per 100 000, both sexes, 2017.
Oceania and Mexico have the highest age-standardized mortality rates attributable to CKD in 2017.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[25] Printed with permission. Copyright © 2018, University of Washington.

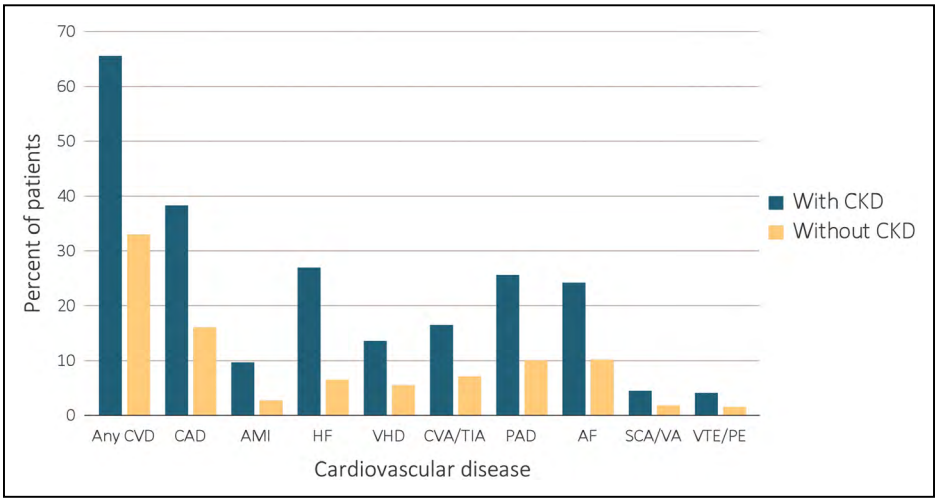

Chart 11-8. Prevalence of CVD in US patients with or without CKD, 2016.
Special analyses, Medicare 5% sample.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VA, ventricular arrhythmia; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: 2018 United States Renal Data System Annual Data Report, volume 1, Figure 4.1[1]

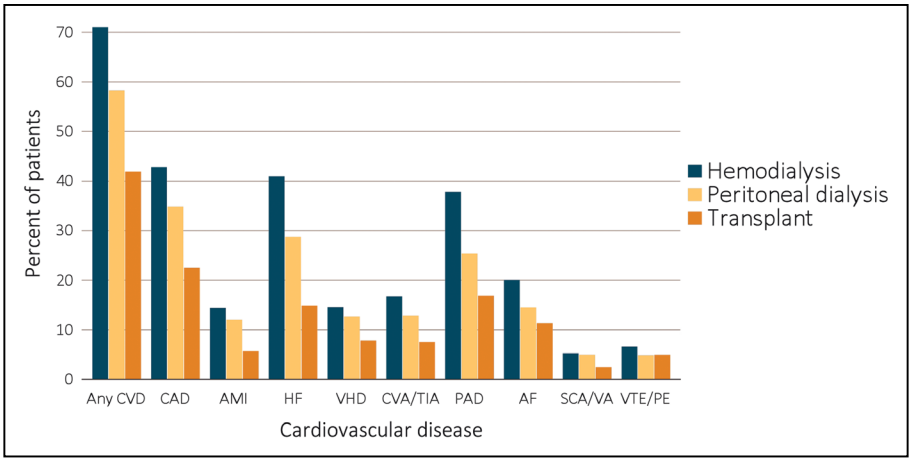

Chart 11-9. Prevalence of CVD in US patients with end-stage renal disease (ESRD) by treatment modality, 2016.
Point prevalent hemodialysis, peritoneal dialysis, and transplant patients ≥22 years of age who were continuously enrolled in Medicare Parts A and B, and with Medicare as primary payer from January 1, 2016, to December 31, 2016, and for whom the ESRD service date was at least 90 days before January 1, 2016.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VA, ventricular arrhythmia; VHD, valvular heart disease; and VTE, venous thromboembolism.
Source: 2018 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.[1]

A

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Chart 11-10. Adjusted relative risk (RR) of clinical outcomes in the US general population according to KDIGO 2012 categories of chronic kidney disease.
A, All-cause mortality and (**B**) cardiovascular mortality, categorized by eGFR and albuminuria category.
Data are derived from categorical meta-analysis of population cohorts. Pooled RRs are expressed relative to the reference (Ref) cell. Colors represent the ranking of the adjusted RRs (green=low risk; yellow=moderate risk; orange=high risk; red=very high risk).
ACR indicates urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and KDIGO, Kidney Disease: Improving Global Outcomes.
Source: Modified from Levey et al[2] with permission from the International Society of Nephrology. Copyright © 2011, International Society of Nephrology.

B

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Chart 11-10. (**Continued**)

REFERENCES

1. United States Renal Data System. 2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
2. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report [published correction appears in *Kidney Int*. 2011;80:1000]. *Kidney Int*. 2011;80:17–28. doi: 10.1038/ki.2010.483
3. Hoerger TJ, Simpson SA, Yarnoff BO, Pavkov ME, Ríos Burrows N, Saydah SH, Williams DE, Zhuo X. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. *Am J Kidney Dis*. 2015;65:403–411. doi: 10.1053/j.ajkd.2014.09.023
4. Lewis EF, Claggett B, Parfrey PS, Burdmann EA, McMurray JJ, Solomon SD, Levey AS, Ivanovich P, Eckardt KU, Kewalramani R, et al. Race and ethnicity influences on cardiovascular and renal events in patients with diabetes mellitus. *Am Heart J*. 2015;170:322–329. doi: 10.1016/j.ahj.2015.05.008
5. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, et al; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med*. 2016;165:473–481. doi: 10.7326/M16-0273
6. Garofalo C, Borrelli S, Pacilio M, Minutolo R, Chiodini P, De Nicola L, Conte G. Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2016;67:89–97. doi: 10.1053/j.ajkd.2015.08.027
7. Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, Arah OA, Ma JZ, Lu JL, Sim JJ, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax*. 2015;70:888–895. doi: 10.1136/thoraxjnl-2015-206970
8. Garrity BH, Kramer H, Vellanki K, Leehey D, Brown J, Shoham DA. Time trends in the association of ESRD incidence with area-level poverty in the US population. *Hemodial Int*. 2016;20:78–83. doi: 10.1111/hdi.12325
9. Kokkinos P, Faselis C, Myers J, Sui X, Zhang J, Tsimploulis A, Chawla L, Palant C. Exercise capacity and risk of chronic kidney disease in US veterans: a cohort study. *Mayo Clin Proc*. 2015;90:461–468. doi: 10.1016/j.mayocp.2015.01.013
10. Ricardo AC, Anderson CA, Yang W, Zhang X, Fischer MJ, Dember LM, Fink JC, Frydrych A, Jensvold NG, Lustigova E, et al; CRIC Study Investigators. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2015;65:412–424. doi: 10.1053/j.ajkd.2014.09.016
11. Rebholz CM, Anderson CA, Grams ME, Bazzano LA, Crews DC, Chang AR, Coresh J, Appel LJ. Relationship of the American Heart Association's Impact Goals (Life's Simple 7) with risk of chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) Cohort Study. *J Am Heart Assoc*. 2016;5:e003192. doi: 10.1161/JAHA.116.003192
12. Zeng X, Liu J, Tao S, Hong HG, Li Y, Fu P. Associations between socioeconomic status and chronic kidney disease: a meta-analysis. *J Epidemiol Community Health*. 2018;72:270–279. doi: 10.1136/jech-2017-209815
13. Crews DC, Kuczmarski MF, Grubbs V, Hedgeman E, Shahinian VB, Evans MK, Zonderman AB, Burrows NR, Williams DE, Saran R, et al; Centers

for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Effect of food insecurity on chronic kidney disease in lower-income Americans. *Am J Nephrol.* 2014;39:27–35. doi: 10.1159/000357595
14. Lora CM, Ricardo AC, Chen J, Cai J, Flessner M, Moncrieft A, Peralta C, Raij L, Rosas SE, Talavera GA, et al. Acculturation and chronic kidney disease in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prev Med Rep.* 2018;10:285–291. doi: 10.1016/j.pmedr.2018.04.001
15. Beydoun MA, Poggi-Burke A, Zonderman AB, Rostant OS, Evans MK, Crews DC. Perceived discrimination and longitudinal change in kidney function among urban adults. *Psychosom Med.* 2017;79:824–834. doi: 10.1097/PSY.0000000000000478
16. Connaughton DM, Kennedy C, Shril S, Mann N, Murray SL, Williams PA, Conlon E, Nakayama M, van der Ven AT, Ityel H, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int.* 2019;95:914–928. doi: 10.1016/j.kint.2018.10.031
17. Mann N, Braun DA, Amann K, Tan W, Shril S, Connaughton DM, Nakayama M, Schneider R, Kitzler TM, van der Ven AT, et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. *J Am Soc Nephrol.* 2019;30:201–215. doi: 10.1681/ASN.2018060575
18. Ma L, Chou JW, Snipes JA, Bharadwaj MS, Craddock AL, Cheng D, Weckerle A, Petrovic S, Hicks PJ, Hemal AK, et al. APOL1 renal-risk variants induce mitochondrial dysfunction. *J Am Soc Nephrol.* 2017;28:1093–1105. doi: 10.1681/ASN.2016050567
19. Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, Appel LJ, Tin A, Coresh J. Race, APOL1 risk, and eGFR decline in the general population. *J Am Soc Nephrol.* 2016;27:2842–2850. doi: 10.1681/ASN.2015070763
20. Peralta CA, Bibbins-Domingo K, Vittinghoff E, Lin F, Fornage M, Kopp JB, Winkler CA. APOL1 genotype and race differences in incident albuminuria and renal function decline. *J Am Soc Nephrol.* 2016;27:887–893. doi: 10.1681/ASN.2015020124
21. Chen TK, Appel LJ, Grams ME, Tin A, Choi MJ, Lipkowitz MS, Winkler CA, Estrella MM. APOL1 risk variants and cardiovascular disease: results from the AASK (African American Study of Kidney Disease and Hypertension). *Arterioscler Thromb Vasc Biol.* 2017;37:1765–1769. doi: 10.1161/ATVBAHA.117.309384
22. Schmitz B, Kleber ME, Lenders M, Delgado GE, Engelbertz C, Huang J, Pavenstädt H, Breithardt G, Brand SM, März W, et al. Genome-wide association study suggests impact of chromosome 10 rs139401390 on kidney function in patients with coronary artery disease. *Sci Rep.* 2019;9:2750. doi: 10.1038/s41598-019-39055-y
23. Gutiérrez OM, Limou S, Lin F, Peralta CA, Kramer HJ, Carr JJ, Bibbins-Domingo K, Winkler CA, Lewis CE, Kopp JB. APOL1 nephropathy risk variants do not associate with subclinical atherosclerosis or left ventricular mass in middle-aged black adults. *Kidney Int.* 2018;93:727–732. doi: 10.1016/j.kint.2017.08.019
24. Bowe B, Xie Y, Li T, Mokdad AH, Xian H, Yan Y, Maddukuri G, Al-Aly Z. Changes in the US burden of chronic kidney disease from 2002 to 2016: an analysis of the Global Burden of Disease study. *JAMA Netw Open.* 2018;1:e184412. doi: 10.1001/jamanetworkopen.2018.4412
25. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
26. Cheung KL, Zakai NA, Folsom AR, Kurella Tamura M, Peralta CA, Judd SE, Callas PW, Cushman M. Measures of kidney disease and the risk of venous thromboembolism in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis.* 2017;70:182–190. doi: 10.1053/j.ajkd.2016.10.039
27. Wanner C, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int.* 2014;85:1303–1309. doi: 10.1038/ki.2014.31
28. Whelton PK, Appel LJ, Sacco RL, Anderson CA, Antman EM, Campbell N, Dunbar SB, Frohlich ED, Hall JE, Jessup M, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations [published correction appears in *Circulation*. 2013;27:e263]. *Circulation*. 2012;126:2880–2889. doi: 10.1161/CIR.0b013e318279acbf
29. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant.* 2015;30:1162–1169. doi: 10.1093/ndt/gfv009
30. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, et al; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol.* 2015;3:514–525. doi: 10.1016/S2213-8587(15)00040-6
31. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2019;139:e1178–e1181]. *Circulation*. 2019;139:e1046–e1081. doi: 10.1161/CIR.0000000000000624
32. Hui X, Matsushita K, Sang Y, Ballew SH, Fülöp T, Coresh J. CKD and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study: interactions with age, sex, and race. *Am J Kidney Dis.* 2013;62:691–702. doi: 10.1053/j.ajkd.2013.04.010
33. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, Brunskill NJ, Gray LJ. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One.* 2018;13:e0192895. doi: 10.1371/journal.pone.0192895
34. Bansal N, Katz R, Robinson-Cohen C, Odden MC, Dalrymple L, Shlipak MG, Sarnak MJ, Siscovick DS, Zelnick L, Psaty BM, et al. Absolute rates of heart failure, coronary heart disease, and stroke in chronic kidney disease: an analysis of 3 community-based cohort studies. *JAMA Cardiol.* 2017;2:314–318. doi: 10.1001/jamacardio.2016.4652
35. Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, Woodward M, Longstreth WT Jr, Psaty BM, Shlipak MG, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke.* 2014;45:1925–1931. doi: 10.1161/STROKEAHA.114.004900
36. Sandsmark DK, Messé SR, Zhang X, Roy J, Nessel L, Lee Hamm L, He J, Horwitz EJ, Jaar BG, Kallem RR, et al; CRIC Study Investigators. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic Renal Insufficiency Cohort study. *Stroke.* 2015;46:2075–2080. doi: 10.1161/STROKEAHA.115.009861
37. Colantonio LD, Baber U, Banach M, Tanner RM, Warnock DG, Gutiérrez OM, Safford MM, Wanner C, Howard G, Muntner P. Contrasting cholesterol management guidelines for adults with CKD. *J Am Soc Nephrol.* 2015;26:1173–1180. doi: 10.1681/ASN.2014040400
38. Wang GJ, Shaw PA, Townsend RR, Anderson AH, Xie D, Wang X, Nessel LC, Mohler ER, Sozio SM, Jaar BG, et al; for the CRIC Study Investigators. Sex differences in the incidence of peripheral artery disease in the Chronic Renal Insufficiency Cohort. *Circ Cardiovasc Qual Outcomes.* 2016;9(suppl 1):S86–S93. doi: 10.1161/CIRCOUTCOMES.115.002180
39. Baber U, Giustino G, Sartori S, Aquino M, Stefanini GG, Steg PG, Windecker S, Leon MB, Wijns W, Serruys PW, et al. Effect of chronic kidney disease in women undergoing percutaneous coronary intervention with drug-eluting stents: a patient-level pooled analysis of randomized controlled trials. *JACC Cardiovasc Interv.* 2016;9:28–38. doi: 10.1016/j.jcin.2015.09.023
40. Lash JP, Ricardo AC, Roy J, Deo R, Fischer M, Flack J, He J, Keane M, Lora C, Ojo A, et al; CRIC Study Investigators. Race/ethnicity and cardiovascular outcomes in adults with CKD: findings from the CRIC (Chronic Renal Insufficiency Cohort) and Hispanic CRIC studies. *Am J Kidney Dis.* 2016;68:545–553. doi: 10.1053/j.ajkd.2016.03.429
41. Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, Pokhariyal S, Charytan DM; MiD Investigators and Committees. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int.* 2018;93:941–951. doi: 10.1016/j.kint.2017.11.019
42. Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, Coca SG. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med.* 2016;176:121–124. doi: 10.1001/jamainternmed.2015.6102
43. Konstantinidis I, Patel S, Camargo M, Patel A, Poojary P, Coca SG, Nadkarni GN. Representation and reporting of kidney disease in cerebrovascular disease: a systematic review of randomized controlled trials. *PLoS One.* 2017;12:e0176145. doi: 10.1371/journal.pone.0176145
44. Herzog CA, Natwick T, Li S, Charytan DM. Comparative utilization and temporal trends in cardiac stress testing in U.S. Medicare beneficiaries with and without chronic kidney disease. *JACC Cardiovasc Imaging.* 2019;12:1420-1426. doi: 10.1016/j.jcmg.2018.04.012

45. Shen JI, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. *Am J Kidney Dis*. 2015;66:677–688. doi: 10.1053/j.ajkd.2015.05.019
46. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol*. 2017;69:2779–2790. doi: 10.1016/j.jacc.2017.03.600
47. Shavadia JS, Southern DA, James MT, Welsh RC, Bainey KR. Kidney function modifies the selection of treatment strategies and long-term survival in stable ischaemic heart disease: insights from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry. *Eur Heart J Qual Care Clin Outcomes*. 2018;4:274–282. doi: 10.1093/ehjqcco/qcx042
48. Ferro CJ, Chue CD, de Belder MA, Moat N, Wendler O, Trivedi U, Ludman P, Townend JN; UK TAVI Steering Group; National Institute for Cardiovascular Outcomes Research. Impact of renal function on survival after transcatheter aortic valve implantation (TAVI): an analysis of the UK TAVI registry. *Heart*. 2015;101:546–552. doi: 10.1136/heartjnl-2014-307041
49. Bhatia N, Agrawal S, Yang S, Yadav K, Agarwal M, Garg L, Agarwal N, Shirani J, Fredi JL. In-hospital outcomes of transcatheter aortic valve implantation in patients with end-stage renal disease on dialysis from a large national database. *Am J Cardiol*. 2017;120:1355–1358. doi: 10.1016/j.amjcard.2017.07.022
50. Hansen JW, Foy A, Yadav P, Gilchrist IC, Kozak M, Stebbins A, Matsouaka R, Vemulapalli S, Wang A, Wang DD, et al. Death and dialysis after transcatheter aortic valve replacement: an analysis of the STS/ACC TVT Registry. *JACC Cardiovasc Interv*. 2017;10:2064–2075. doi: 10.1016/j.jcin.2017.09.001
51. Garimella PS, Balakrishnan P, Correa A, Poojary P, Annapureddy N, Chauhan K, Patel A, Patel S, Konstantinidis I, Chan L, et al. Nationwide trends in hospital outcomes and utilization after lower limb revascularization in patients on hemodialysis. *JACC Cardiovasc Interv*. 2017;10:2101–2110. doi: 10.1016/j.jcin.2017.05.050
52. Arhuidese I, Kernodle A, Nejim B, Locham S, Hicks C, Malas MB. Sex-based outcomes of lower extremity bypass surgery in hemodialysis patients. *J Vasc Surg*. 2018;68:153–160. doi: 10.1016/j.jvs.2017.10.063
53. Samad Z, Sivak JA, Phelan M, Schulte PJ, Patel U, Velazquez EJ. Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. *J Am Heart Assoc*. 2017;6:e006044. doi: 10.1161/JAHA.117.006044
54. Ho JE, Lyass A, Courchesne P, Chen G, Liu C, Yin X, Hwang SJ, Massaro JM, Larson MG, Levy D. Protein biomarkers of cardiovascular disease and mortality in the community. *J Am Heart Assoc*. 2018;7:e008108. doi: 10.1161/JAHA.117.008108
55. He J, Shlipak M, Anderson A, Roy JA, Feldman HI, Kallem RR, Kanthety R, Kusek JW, Ojo A, Rahman M, et al. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) Study. *J Am Heart Assoc*. 2017;6:e005336. doi: 10.1161/JAHA.116.005336
56. Schei J, Stefansson VT, Mathisen UD, Eriksen BO, Solbu MD, Jenssen TG, Melsom T. Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. *Clin J Am Soc Nephrol*. 2016;11:280–286. doi: 10.2215/CJN.07360715
57. Kent S, Schlackow I, Lozano-Kühne J, Reith C, Emberson J, Haynes R, Gray A, Cass A, Baigent C, Landray MJ, et al; SHARP Collaborative Group. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC Nephrol*. 2015;16:65. doi: 10.1186/s12882-015-0054-0
58. LaPar DJ, Rich JB, Isbell JM, Brooks CH, Crosby IK, Yarboro LT, Ghanta RK, Kern JA, Brown M, Quader MA, et al. Preoperative renal function predicts hospital costs and length of stay in coronary artery bypass grafting. *Ann Thorac Surg*. 2016;101:606–612. doi: 10.1016/j.athoracsur.2015.07.079

12. SLEEP

See Charts 12-1 through 12-4

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Sleep can be characterized in many different ways, including quantity of sleep (sleep duration), quality of sleep, or the presence of a sleep disorder, such as insomnia or OSA. All of these characteristics of sleep have been associated with CVD and stroke.

Prevalence (See Charts 12-1 through 12-4)

- The American Academy of Sleep Medicine and the Sleep Research Society published a consensus statement recommending that adults obtain ≥7 hours of sleep per night to promote optimal health.[1] The American Academy of Sleep Medicine and Sleep Research Society also published guidelines for pediatric populations: infants 4 to 12 months old should sleep 12 to 16 hours per day; children 1 to 2 years of age should sleep 11 to 14 hours per day; children 3 to 5 years of age should sleep 10 to 13 hours per day; children 6 to 12 years of age should sleep 9 to 12 hours per day; and adolescents 13 to 18 years of age should sleep 8 to 10 hours per day.[2]
- The CDC analyzed data from the 2014 BRFSS to determine the age-adjusted prevalence of a healthy sleep duration (≥7 hours) in the United States and found that 11.8% of people reported a sleep duration ≤5 hours, 23.0% reported 6 hours, 29.5% reported 7 hours, 27.7% reported 8 hours, 4.4% reported 9 hours, and 3.6% reported ≥10 hours. Overall, 65.2% met the recommended sleep duration of ≥7 hours.[3]
- Analysis of NHANES data (2015–2016) indicated that the proportion of adults getting inadequate sleep (<7 hours) was 19.6%. Younger people were more likely to report sleeping <7 hours, and males were more likely to report sleeping <7 hours at all ages (Chart 12-1).[4]
- The prevalence of inadequate sleep (<7 hours) varied by state or territory: in 2014, the lowest prevalence was seen in South Dakota (28.4%), Colorado (28.5%), and Minnesota (29.2%), and the highest was found in Guam (48.6%), Hawaii (43.6%), and Kentucky (39.4%).[5]
- Prevalence of OSA varies by sex. On the basis of data from the Wisconsin Cohort Study, OSA prevalence estimates among 30- to 70-year-old subjects in the United States in 2007 to 2010 were 33.9% among males and 17.4% among females for AHI ≥5 (mild to severe OSA).[6] Prevalence estimates of moderate to severe OSA (AHI ≥15) were 13.0% for males and 5.6% for females. These estimates are higher than estimates for 1988 to 1994 from the same study, which were 26.4% in males and 13.2% in females for mild to severe OSA.[6]
- In a Canadian study of 100 adult patients with AF (70 males, 30 females) with no history of OSA who underwent home sleep testing, 85% had mild to severe OSA (AHI >5), and it was more common in males (91% versus 70% in females, P=0.006).[7]
- A systematic review estimated the prevalence of OSA in cerebrovascular disease in 3242 patients who had either cerebral infarction, TIA, ischemic stroke, or hemorrhagic stroke and found that the pooled prevalence of OSA defined as AHI >10 events/h was 62% (95% CI, 55%–69%), and the pooled prevalence of severe OSA (AHI >30) was 30% (95% CI, 23%–37%).[8]
- The BRFSS asked respondents, "Over the last 2 weeks, how many days have you had trouble

Abbreviations Used in Chapter 12

AF	atrial fibrillation
AHI	apnea-hypopnea index
AMI	acute myocardial infarction
BMI	body mass index
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
HF	heart failure
HR	hazard ratio
JHS	Jackson Heart Study
MACE	major adverse cardiovascular events
MI	myocardial infarction
NH	non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NSTEMI	non–ST-segment–elevation myocardial infarction
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
STEMI	ST-segment–elevation myocardial infarction
TIA	transient ischemic attack
UA	unstable angina
WHO	World Health Organization

falling asleep or staying asleep or sleeping too much?" and 52% responded zero (never), 27% responded 1 to 6 days, and 21% responded 7 to 14 days (unpublished tabulation using BRFSS,[9] 2017). Females were more likely to report having sleep problems on 7 to 14 of the past 14 days than males at all ages (Chart 12-2).

- Females have a greater risk of insomnia than males. For example, a meta-analysis of 31 studies reported an RR of 1.41 (95% CI, 1.28–1.55) comparing females to males.[10] Furthermore, sex differences increased with age and were largest in those ≥65 years of age.[10]

Children/Adolescents

- National poll data indicated that 63.3% of children 6 to 11 years of age and 56.7% of children 12 to 17 years of age obtained sufficient sleep, whereas 47.2% of children 6 to 11 years of age and 38.5% of children 12 to 17 years of age had excellent sleep quality.[11]
- The estimated prevalence of snoring in pediatric populations (as reported by the parent) is 7.5%, whereas the prevalence of sleep-disordered breathing using diagnostic testing is likely between 1% and 4% (varies depending on definitions and methodologies used).[12]

Adults: Young, Middle-Aged, and Old

- Older adults are more likely to report adequate sleep. Age-specific and age-adjusted percentages of adults who reported adequate sleep (≥7 hours per 24-hour period) were as follows: 67.8% for 18- to 24-year-old adults, 62.1% for 25- to 34-year-old adults, 61.7% for 35- to 44-year-old adults, 62.7% for 45- to 64-year-old adults, and 73.7% for adults ≥65 years of age.[3]
- Prevalence of OSA is higher among older adults. The prevalence of mild to severe OSA (AHI ≥5) was 26.6% for 30- to 49-year-old males and 43.2% for 50- to 70-year-old males, whereas it was 8.7% for 30- to 49-year-old females and 27.8% for 50- to 70-year-old females.[6]

Risk Factors

- Risk factors for short sleep duration include smoking (OR, 0.63 [95% CI, 0.51–0.79] for ex-smokers and OR, 0.68 [95% CI, 0.53–0.85] for never-smokers versus smokers), physical inactivity (OR, 1.48 [95% CI, 1.15–1.86] for no PA versus PA), poor diet (OR, 0.93 [95% CI, 0.91–0.95] per point on nutrient adequacy scale), obesity (OR, 1.39 [95% CI, 1.17–1.65] for BMI ≥30 versus <25 kg/m^2), fair/poor subjective health (OR, 1.93 [95% CI, 1.63–2.32] versus excellent, very good, and good combined), and depressive symptoms (OR, 2.80 [95% CI, 2.01–3.90] for ≥10 versus <10 on the Patient Health Questionnaire).[13]
- Characteristics associated with trouble sleeping include not being married (OR, 1.16 [95% CI, 1.01–1.36], not married versus married), smoking (OR, 0.39 [95% CI, 0.36–0.43] for never-smoker versus current smoker), no alcohol consumption (OR, 0.39 [95% CI, 0.36–0.43] for alcohol consumption versus no consumption), obesity (OR, 1.25 [95% CI, 1.02–1.54] for BMI ≥30 versus <25 kg/m^2), fair/poor subjective health (OR, 1.97 [95% CI, 1.60–2.41] versus excellent/very good/good), and depressive symptoms (OR, 4.71 [95% CI, 3.60–6.17] for ≥10 versus <10 on the Patient Health Questionnaire).[13]
- Predictors of moderate to severe OSA (AHI ≥15) among a sample of 852 blacks were male sex (OR, 2.67 [95% CI, 1.87–3.80]), larger BMI (OR, 2.06 per SD [95% CI, 1.71–2.47]), larger neck circumference (OR, 1.55 per SD [95% CI, 1.18–2.05]), and habitual snoring (OR, 1.94 [95% CI, 1.37–2.75]).[14]
- National data indicate that the following characteristics are associated with increased risk of incident diagnosed insomnia: >45 years of age (HR, 1.69 [95% CI, 1.40–2.03] for 45–64 years of age and HR, 2.11 [95% CI, 1.63–2.73] for ≥65 years) versus 18 to 44 years of age, high school degree (HR, 1.44 [95% CI, 1.18–1.75]) versus college or more, underweight (HR, 1.37 [95% CI, 1.06–1.77]) versus normal weight, greater comorbidities based on Charlson comorbidity index (HR, 1.69 [95% CI, 1.45–1.98] for a score of 1 or 2 and HR, 1.76 [95% CI, 1.32–2.36] for a score ≥3), ever having smoked (HR, 1.45 [95% CI, 1.20–1.76]) versus never having smoked, and physical inactivity (HR, 1.22 [95% CI, 1.06–1.42]) versus PA.[15] The following are associated with reduced risk of incident diagnosed insomnia: male sex (HR, 0.57 [95% CI, 0.48–0.69]) and having never been married (HR, 0.73 [95% CI, 0.59–0.90]) versus being married or cohabitating.[15]

Social Determinants

Race/Ethnicity and Sleep (See Charts 12-3 and 12-4)

- Data from the CDC indicated that the age-adjusted prevalence of healthy sleep duration was lower among Native Hawaiians/Pacific Islanders (53.7%), NH blacks (54.2%), multiracial NH people (53.6%), and American Indians/Alaska Natives (59.6%) compared with NH whites (66.8%), Hispanics (65.5%), and Asians (62.5%).[3]
- The Chicago Area Sleep Study used wrist activity monitoring and showed an adjusted mean sleep duration of 6.7 hours for blacks, 6.8 hours for Asians, 6.9 hours for Hispanic/Latinos, and 7.5

hours for whites.[16] This study also observed lower sleep quality in blacks and Hispanic/Latinos compared with whites.

- In NHANES 2015 to 2016, NH blacks had the highest percentage of respondents reporting sleeping <7 hours per night (32.1%), followed by other Hispanics (26.5%) and Mexican Americans (20.8%), whereas NH whites had the lowest percentage (16.3%) of respondents reporting sleeping <7 hours (Chart 12-3).
- In BRFSS 2017, people of NH other race/ethnicity and NH American Indians/Alaskan Natives had the highest percentages of respondents indicating sleep problems ≥7 of 14 days (32.3% and 24.4%, respectively) whereas NH Asians and Hispanics had the lowest percentages (13.3% and 17.4%, respectively; Chart 12-4).
- In a sample of blacks from the JHS, the prevalence of moderate to severe OSA (AHI ≥15) was 23.6%.[14] In a sample of 14440 Hispanic/Latino adults, the age-adjusted prevalence of moderate to severe OSA (AHI ≥15) was 9.8%.[17]

Other Social Determinants of Sleep

- In addition to race/ethnicity, social characteristics associated with short sleep duration include lower education (OR, 1.47 [95% CI, 1.19–1.78] for less than high school versus greater than high school), not being married (OR, 1.43 [95% CI, 1.25–1.67] for not married versus married), and poverty (OR, 1.54 [95% CI, 1.27–1.85] for poverty/income ratio <1 versus ≥2).[13]
- Among Native Hawaiians and Pacific Islanders from the NHIS, low neighborhood social cohesion was associated with increased odds of short sleep duration (OR, 1.53 [95% CI, 1.10–2.13]). Neighborhood social cohesion was not associated with trouble falling or staying asleep or feeling well rested.[18]
- Data from the WHO's longitudinal Study on Global Ageing and Adult Health from 6 countries (Mexico, Ghana, South Africa, India, China, and Russia) collected in 2007 to 2010 indicated that participants who felt safe in their neighborhoods were less likely to report short sleep in Ghana (OR, 0.44 [95% CI, 0.33–0.58]) and China (OR, 0.72 [95% CI, 0.60–0.87]). Neighborhood safety was also associated with reduced likelihood of insomnia in China (OR, 0.22 [95% CI, 0.13–0.37]), Ghana (OR, 0.52 [95% CI, 0.37–0.71]), Russia (OR, 0.59 [95% CI, 0.43–0.81]), and India (OR, 0.73 [95% CI, 0.62–0.87]).[19]

Family History and Genetics

- Genetic factors may influence sleep either directly by controlling sleep disorders or indirectly through modulation of risk factors such as obesity.
- Heritability of sleep behaviors varies but is estimated to be ≈40%.[20] Genetic studies have identified variants associated with OSA.[21] Data suggest genetic control of interindividual variability in circadian rhythms, with variants in clock genes such as *CRY1* and *CRY2* being of particular interest.[22,23] Several variants have been found to associate with chronotype, insomnia, and sleep duration in the UK Biobank, with evidence for shared genetics between insomnia and cardiometabolic traits.[24–26]

Awareness, Treatment, and Control

- OSA is often undiagnosed. One study examined the prevalence of undiagnosed OSA in surgical patients and found that 661 of 2778 patients (23.8%) screened had high risk of having OSA, and 81% had not been previously diagnosed with OSA. Of these patients, 207 had a home sleep test, and OSA was confirmed in 170 (82.1%).[27]
- A meta-analysis of 8 studies found that all-cause mortality (HR, 0.66 [95% CI, 0.59–0.73]) and cardiovascular mortality (HR, 0.37 [95% CI, 0.16–0.54]) were significantly lower in CPAP-treated patients than in untreated patients.[28]
- An RCT enrolled people 45 to 75 years of age with moderate to severe OSA without excessive daytime sleepiness and who also had coronary or cerebrovascular disease to compare CPAP plus usual care to usual care alone.[29] A total of 2687 patients were included in this secondary prevention trial and followed up for an average of 3.7 years. No statistically significant difference was observed for a composite of primary end points (HR, 1.10 [95% CI, 0.91–1.32]), including death attributable to cardiovascular causes, MI, stroke, or hospitalization for HF, UA, or TIA.
- A retrospective chart review of 75 pediatric patients (7–17 years of age) referred to a sleep clinic for snoring compared 6-month change in BP between 3 groups (25 patients in each): snorers without OSA (AHI <1), with OSA but no treatment (AHI >1), and with OSA with CPAP treatment. SBP was higher at baseline in the 2 OSA groups (P<0.05) but decreased in the CPAP-treated group over 6 months (median change, −5 mm Hg [25th–75th percentile, −19 to 0 mm Hg]), whereas SBP increased in the untreated OSA group (median change, 4 mm Hg [25th–75th percentile: 0 to 10 mm Hg]). DBP did not differ between groups at baseline, nor did the 6-month change in DBP differ between groups.[30]

Mortality

- A meta-analysis of 43 studies indicated that both short sleep (<7 hours per night; RR, 1.13 [95% CI,

1.10–1.17]) and long sleep (>8 hours per night; RR, 1.35 [95% CI, 1.29–1.41]) were associated with a greater risk of all-cause mortality.[31]

- A prospective cohort study found that the association between sleep duration and mortality varied with age.[32] Among adults <65 years of age, short sleep duration (≤5 hours per night) and long sleep duration (≥8 hours per night) were both associated with increased mortality risk (HR, 1.37 [95% CI, 1.09–1.71] and HR, 1.27 [95% CI, 1.08–1.48], respectively). Sleep duration was not significantly associated with mortality in adults ≥65 years of age.
- Data from NHANES 2005 to 2008 indicated that long sleep duration (>8 hours per night) was associated with an increased risk of all-cause mortality in the full sample (HR, 1.90 [95% CI, 1.38–2.60]), among males (HR, 1.48 [95% CI, 1.05–2.09]), among females (HR, 2.32 [95% CI, 1.48–3.61]), and among those ≥65 years of age (HR, 1.80 [95% CI, 1.30–2.50]) but not among those <65 years of age.[13] No statistically significant associations were observed between short sleep (<7 hours per night) and all-cause mortality in this analysis.
- A meta-analysis of 137 prospective cohort studies with a total of 5 134 036 participants found that long sleep duration (cutoff varied by study) was associated with increased mortality risk (RR, 1.39 [95% CI, 1.31–1.47]).[33]
- A meta-analysis of 27 cohort studies found that mild OSA (HR, 1.19 [95% CI, 0.86–1.65]), moderate OSA (HR, 1.28 [95% CI, 0.96–1.69]), and severe OSA (HR, 2.13 [95% CI, 1.68–2.68]) were associated with all-cause mortality in a dose-response fashion. Only severe OSA was associated with cardiovascular mortality (HR, 2.73 [95% CI, 1.94–3.85]).[28]
- A study of US males found that insomnia symptoms were associated with increased risk of all-cause mortality. Specifically, mortality risk was higher for males who reported difficulty initiating sleep (HR, 1.25 [95% CI, 1.04–1.50]) and non-restorative sleep (HR, 1.24 [95% CI, 1.05–1.46]).[34]
- A study among males and females 21 to 75 years of age found that compared with those who never reported insomnia symptoms, those who reported persistent insomnia symptoms at 2 time points ≈5 years apart had an increased risk of all-cause mortality (HR, 1.58 [95% CI, 1.02–2.45]), but those who reported insomnia at only 1 time point did not.[35]

Complications

- Short sleep duration has been associated with several cardiovascular and metabolic health outcomes, including prevalent obesity (OR, 1.55 [95% CI, 1.43–1.68]),[36] incident obesity (OR, 1.45 [95% CI, 1.25–1.67]),[37] incident DM (OR, 1.28 [95% CI, 1.03–1.60]),[38] CHD morbidity or mortality (RR, 1.48 [95% CI, 1.22–1.80]),[39] and stroke (RR, 1.15 [95% CI, 1.00–1.31]).[39]
- Long duration of sleep was also associated with a greater risk of CHD morbidity or mortality (RR, 1.38 [95% CI, 1.15–1.66]), stroke (RR, 1.65 [95% CI, 1.45–1.87]), and total CVD (RR, 1.41 [95% CI, 1.19–1.68]).[39]
- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles).[31] Short sleep (<7 hours per night) was associated with total CVD (RR, 1.14 [95% CI, 1.09–1.20]) and CHD (RR, 1.22 [95% CI, 1.13–1.31]) but not with stroke (RR, 1.09 [95% CI, 0.99–1.19]). Long sleep duration was associated with total CVD (RR, 1.36 [95% CI, 1.26–1.48]), CHD (RR, 1.21 [95% CI, 1.12–1.30]), and stroke (RR, 1.45 [95% CI, 1.30–1.62]).
- Insomnia symptoms have also been associated with incident DM, including difficulty falling asleep (OR, 1.57 [95% CI, 1.25–1.97]) and difficulty staying asleep (OR, 1.84 [95% CI, 1.39–2.43]).[38]
- The deepest stage of non–rapid-eye movement sleep, also called *slow-wave sleep*, is thought to be a restorative stage of sleep. In the Sleep Heart Health Study, which used in-home polysomnography to characterize sleep, it was found that participants with a lower proportion of slow-wave sleep had significantly greater odds of incident hypertension (quartile 1 versus quartile 3; OR, 1.69 [95% CI, 1.21–2.36]).[40]
- A meta-analysis of 15 prospective studies observed a significant association between the presence of OSA and the risk of cerebrovascular disease (HR, 1.94 [95% CI, 1.31–2.89]).[41]
- A prospective observational study enrolled patients with suspected metabolic disorders and possible OSA and examined incident major adverse cardiovascular and cerebrovascular events. A significant elevated risk of major adverse cardiovascular and cerebrovascular events was observed for patients with moderate OSA (HR, 3.85 [95% CI, 1.07–13.88] versus no OSA) and severe OSA (HR, 3.54 [95% CI, 1.03–12.22] versus no OSA). Using CPAP for ≥4 hours per night ≥5 days per week was not significantly associated with major adverse cardiovascular and cerebrovascular events (HR, 1.44 [95% CI, 0.80–2.59] versus less frequent or no CPAP use).[42]
- A meta-analysis analyzed data from 9 cohort studies with 2755 participants that described the association between OSA and MACE after PCI with stenting and found that OSA was associated with a significantly increased risk of MACE (pooled RR, 1.96 [95% CI, 1.36–2.81]).[43]
- Among patients with AMI, the presence of moderate to severe OSA is associated with a greater

likelihood of an NSTEMI versus STEMI (OR, 1.59 [95% CI, 1.07–2.37]), and the prevalence of NSTEMI is highest among those with severe OSA: 18.3% for no OSA, 35.4% for mild OSA, 33.9% for moderate OSA, and 41.6% for severe OSA.[44]

- Central sleep apnea was associated with increased odds of incident AF (OR, 3.00 [95% CI, 1.40–6.44] for central apnea index ≥5 vs <5), but OSA was not associated with incident AF.[45]

Costs

- Analysis of direct and indirect costs related to inadequate sleep in Australia suggested that the approximate cost for a population the size of the United States would be over $585 billion for 2016 to 2017.[46]

Global Burden

- A recent analysis of the global prevalence and burden of OSA estimated that 936 million (95% CI, 903–970 million) men and women 30 to 69 years of age have mild to severe OSA (AHI ≥5), and 425 million (95% CI, 399–450 million) have moderate to severe OSA (AHI ≥15) globally. The prevalence was highest in China, followed by the United States, Brazil, and India.[47]

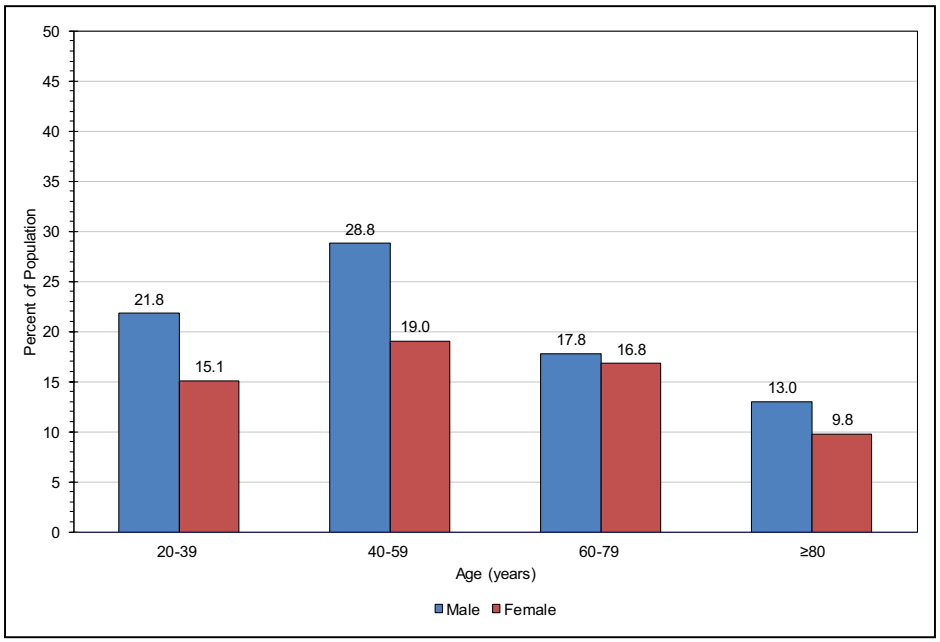

Chart 12-1. Prevalence of inadequate sleep (<7 hours) in US adults by age and sex, 2015 to 2016.
Percentages are adjusted for complex sampling design.
Source: Unpublished tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[4]

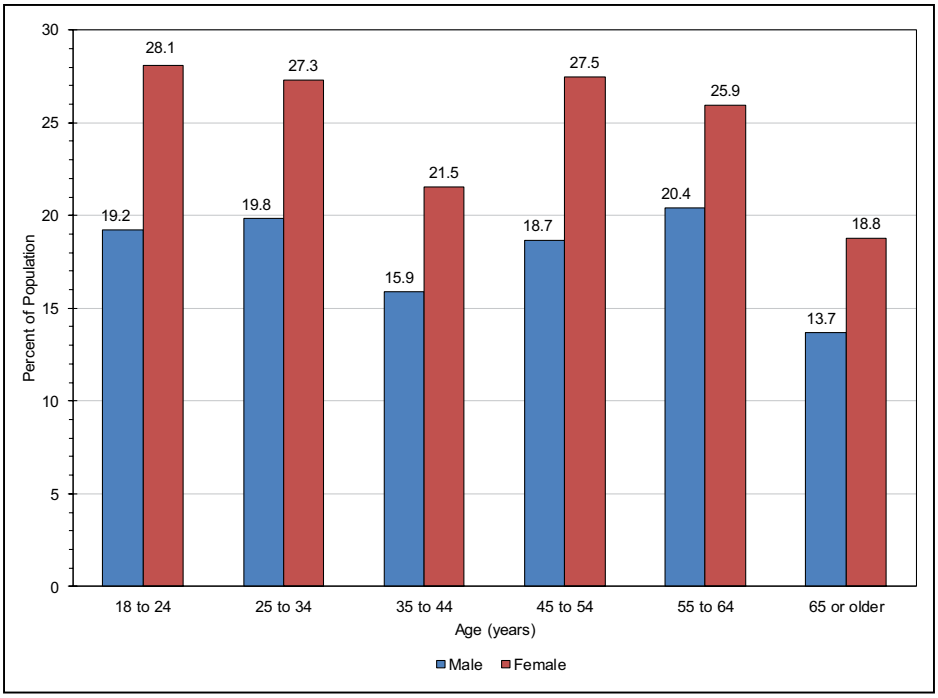

Chart 12-2. Prevalence of reporting sleep problems ≥7 days of 14 days in US adults by sex and age, 2017.
Percentages are adjusted for complex sampling design. Survey question was, "Over the last 2 weeks, how many days have you had trouble falling asleep or staying asleep or sleeping too much?"
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey, 2017.[9]

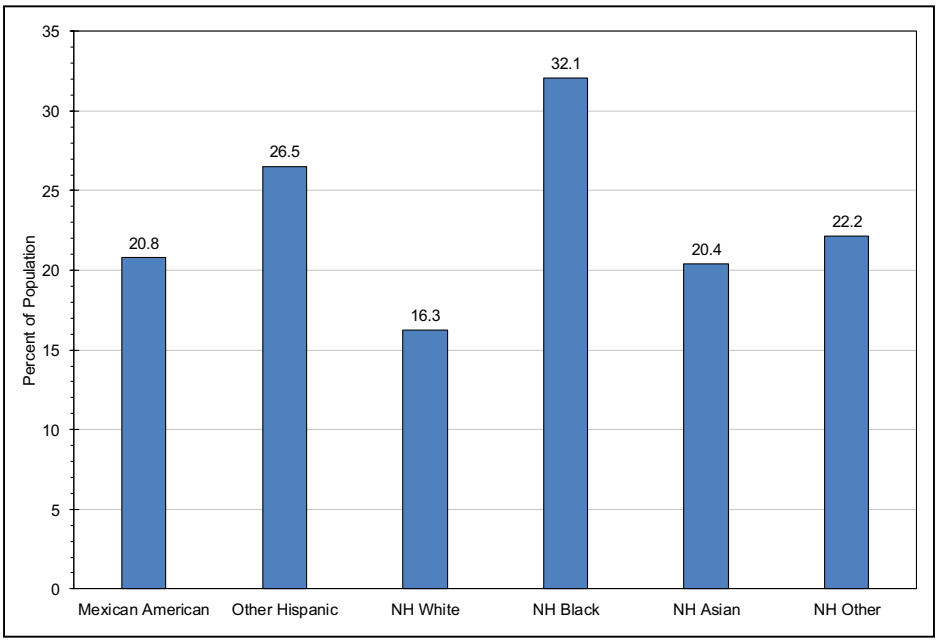

Chart 12-3. Prevalence of inadequate sleep (<7 hours) by race/ethnicity, United States, 2015 to 2016.
Percentages are adjusted for complex sampling design.
NH indicates non-Hispanic.
Source: Unpublished tabulation using National Health and Nutrition Examination Survey, 2015 to 2016.[4]

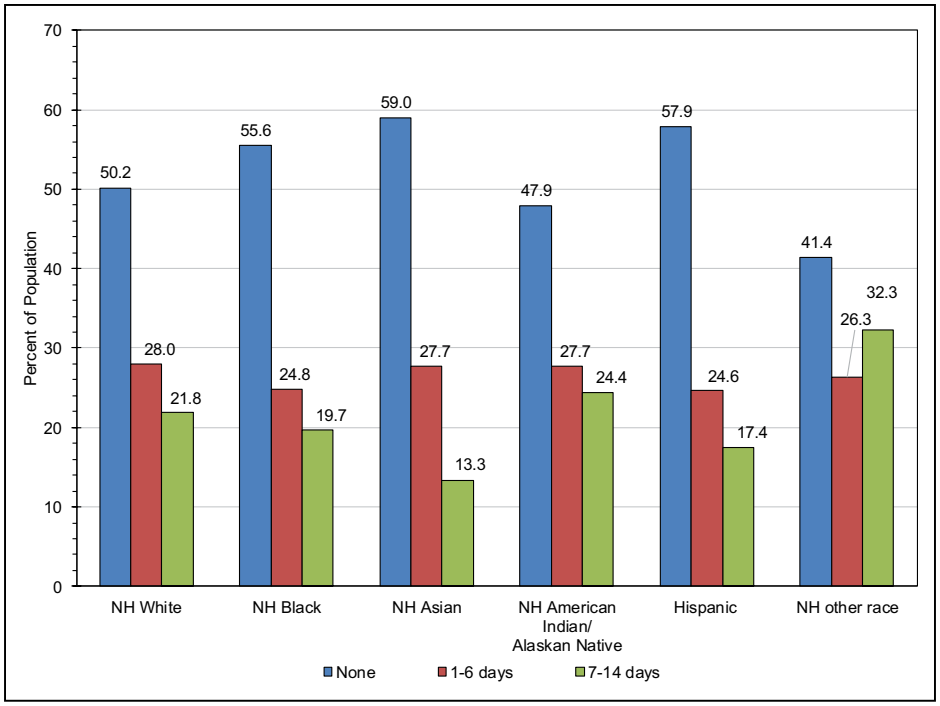

Chart 12-4. Prevalence of reporting sleep problems ≥7 days of 14 days in US adults by race/ethnicity, 2017.
Percentages are adjusted for complex sampling design. Survey question was, "Over the last 2 weeks, how many days have you had trouble falling asleep or staying asleep or sleeping too much?"
NH indicates non-Hispanic.
Source: Unpublished tabulation using Behavioral Risk Factor Surveillance Survey, 2017.[9]

REFERENCES

1. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep.* 2015;38:843–844. doi: 10.5665/sleep.4716
2. Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF, et al. Consensus statement of the American Academy of Sleep Medicine on the recommended amount of sleep for healthy children: methodology and discussion. *J Clin Sleep Med.* 2016;12:1549–1561. doi: 10.5664/jcsm.6288
3. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults: United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2016;65:137–141. doi: 10.15585/mmwr.mm6506a1
4. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/ Accessed April 1, 2019.
5. Gamble S, Mawokomatanda T, Xu F, Chowdhury PP, Pierannunzi C, Flegel D, Garvin W, Town M. Surveillance for certain health behaviors and conditions among states and selected local areas: Behavioral Risk Factor Surveillance System, United States, 2013 and 2014. *MMWR Surveill Summ.* 2017;66:1–144. doi: 10.15585/mmwr.ss6616a1
6. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177:1006–1014. doi: 10.1093/aje/kws342
7. Abumuamar AM, Dorian P, Newman D, Shapiro CM. The prevalence of obstructive sleep apnea in patients with atrial fibrillation. *Clin Cardiol.* 2018;41:601–607. doi: 10.1002/clc.22933
8. Dong R, Dong Z, Liu H, Shi F, Du J. Prevalence, risk factors, outcomes, and treatment of obstructive sleep apnea in patients with cerebrovascular disease: a systematic review. *J Stroke Cerebrovasc Dis.* 2018;27:1471–1480. doi: 10.1016/j.jstrokecerebrovasdis.2017.12.048
9. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Behavioral Risk Factor Surveillance System (BRFSS). BRFSS prevalence & trends data [online] (2017). Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed April 1, 2019.
10. Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. *Sleep.* 2006;29:85–93. doi: 10.1093/sleep/29.1.85
11. Buxton OM, Chang AM, Spilsbury JC, Bos T, Emsellem H, Knutson KL. Sleep in the modern family: protective family routines for child and adolescent sleep. *Sleep Health.* 2015;1:15–27.
12. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc.* 2008;5:242–252. doi: 10.1513/pats.200708-135MG
13. Beydoun HA, Beydoun MA, Chen X, Chang JJ, Gamaldo AA, Eid SM, Zonderman AB. Sex and age differences in the associations between sleep behaviors and all-cause mortality in older adults: results from the National Health and Nutrition Examination Surveys. *Sleep Med.* 2017;36:141–151. doi: 10.1016/j.sleep.2017.05.006
14. Johnson DA, Guo N, Rueschman M, Wang R, Wilson JG, Redline S. Prevalence and correlates of obstructive sleep apnea among African Americans: the Jackson Heart Sleep Study. *Sleep.* 2018;41. doi: 10.1093/sleep/zsy154
15. Chen LJ, Steptoe A, Chen YH, Ku PW, Lin CH. Physical activity, smoking, and the incidence of clinically diagnosed insomnia. *Sleep Med.* 2017;30:189–194. doi: 10.1016/j.sleep.2016.06.040
16. Carnethon MR, De Chavez PJ, Zee PC, Kim KY, Liu K, Goldberger JJ, Ng J, Knutson KL. Disparities in sleep characteristics by race/ethnicity in a population-based sample: Chicago Area Sleep Study. *Sleep Med.* 2016;18:50–55. doi: 10.1016/j.sleep.2015.07.005
17. Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds: the Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med.* 2014;189:335–344. doi: 10.1164/rccm.201309-1735OC
18. Young MC, Gerber MW, Ash T, Horan CM, Taveras EM. Neighborhood social cohesion and sleep outcomes in the Native Hawaiian and Pacific Islander National Health Interview Survey. *Sleep.* 2018;41. doi: 10.1093/sleep/zsy097
19. Hill TD, Trinh HN, Wen M, Hale L. Perceived neighborhood safety and sleep quality: a global analysis of six countries. *Sleep Med.* 2016;18:56–60. doi: 10.1016/j.sleep.2014.12.003

20. Mukherjee S, Saxena R, Palmer LJ. The genetics of obstructive sleep apnoea. *Respirology.* 2018;23:18–27. doi: 10.1111/resp.13212
21. van der Spek A, Luik AI, Kocevska D, Liu C, Brouwer RWW, van Rooij JGJ, van den Hout MCGN, Kraaij R, Hofman A, Uitterlinden AG, et al. Exome-wide meta-analysis identifies rare 3′-UTR variant in ERCC1/CD3EAP associated with symptoms of sleep apnea. *Front Genet.* 2017;8:151. doi: 10.3389/fgene.2017.00151
22. Patke A, Murphy PJ, Onat OE, Krieger AC, Özçelik T, Campbell SS, Young MW. Mutation of the human circadian clock gene CRY1 in familial delayed sleep phase disorder. *Cell.* 2017;169:203–215.e13. doi: 10.1016/j.cell.2017.03.027
23. Hirano A, Shi G, Jones CR, Lipzen A, Pennacchio LA, Xu Y, Hallows WC, McMahon T, Yamazaki M, Ptacek LJ, et al. A Cryptochrome 2 mutation yields advanced sleep phase in humans. *Elife.* 2016;5:e16695. doi: 10.7554/eLife.16695
24. Lane JM, Jones SE, Dashti HS, Wood AR, Aragam KG, van Hees VT, Strand LB, Winsvold BS, Wang H, Bowden J, et al; HUNT All In Sleep. Biological and clinical insights from genetics of insomnia symptoms. *Nat Genet.* 2019;51:387–393. doi: 10.1038/s41588-019-0361-7
25. Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, Rhodes JA, Song Y, Patel K, Anderson SG, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun.* 2019;10:1100. doi: 10.1038/s41467-019-08917-4
26. Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Hu Y, Teder-Laving M, Hayward C, et al. Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. *PLoS Genet.* 2016;12:e1006125. doi: 10.1371/journal.pgen.1006125
27. Finkel KJ, Searleman AC, Tymkew H, Tanaka CY, Saager L, Safer-Zadeh E, Bottros M, Selvidge JA, Jacobsohn E, Pulley D, et al. Prevalence of undiagnosed obstructive sleep apnea among adult surgical patients in an academic medical center. *Sleep Med.* 2009;10:753–758. doi: 10.1016/j.sleep.2008.08.007
28. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. *Sleep Breath.* 2017;21:181–189. doi: 10.1007/s11325-016-1393-1
29. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* 2016;375:919–931. doi: 10.1056/NEJMoa1606599
30. DelRosso LM, King J, Ferri R. Systolic blood pressure elevation in children with obstructive sleep apnea is improved with positive airway pressure use. *J Pediatr.* 2018;195:102–107.e1. doi: 10.1016/j.jpeds.2017.11.043
31. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* 2017;6:e005947. doi: 10.1161/JAHA.117.005947
32. Åkerstedt T, Ghilotti F, Grotta A, Bellavia A, Lagerros YT, Bellocco R. Sleep duration, mortality and the influence of age. *Eur J Epidemiol.* 2017;32:881–891. doi: 10.1007/s10654-017-0297-0
33. Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. *Sleep Med Rev.* 2018;39:25–36. doi: 10.1016/j.smrv.2017.06.011
34. Li Y, Zhang X, Winkelman JW, Redline S, Hu FB, Stampfer M, Ma J, Gao X. Association between insomnia symptoms and mortality: a prospective study of U.S. men. *Circulation.* 2014;129:737–746. doi: 10.1161/CIRCULATIONAHA.113.004500
35. Parthasarathy S, Vasquez MM, Halonen M, Bootzin R, Quan SF, Martinez FD, Guerra S. Persistent insomnia is associated with mortality risk. *Am J Med.* 2015;128:268–275.e2. doi: 10.1016/j.amjmed.2014.10.015
36. Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep.* 2008;31:619–626. doi: 10.1093/sleep/31.5.619
37. Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. *Sleep Med.* 2014;15:1456–1462. doi: 10.1016/j.sleep.2014.07.018
38. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care.* 2010;33:414–420. doi: 10.2337/dc09-1124
39. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J.* 2011;32:1484–1492. doi: 10.1093/eurheartj/ehr007
40. Javaheri S, Zhao YY, Punjabi NM, Quan SF, Gottlieb DJ, Redline S. Slow-wave sleep is associated with incident hypertension: the Sleep Heart Health Study. *Sleep.* 2018;41. doi: 10.1093/sleep/zsx179
41. Wu Z, Chen F, Yu F, Wang Y, Guo Z. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath.* 2018;22:729–742. doi: 10.1007/s11325-017-1604-4
42. Baratta F, Pastori D, Fabiani M, Fabiani V, Ceci F, Lillo R, Lolli V, Brunori M, Pannitteri G, Cravotto E, et al. Severity of OSAS, CPAP and cardiovascular events: a follow-up study. *Eur J Clin Invest.* 2018;48:e12908. doi: 10.1111/eci.12908
43. Wang X, Fan JY, Zhang Y, Nie SP, Wei YX. Association of obstructive sleep apnea with cardiovascular outcomes after percutaneous coronary intervention: a systematic review and meta-analysis. *Medicine (Baltimore).* 2018;97:e0621. doi: 10.1097/MD.0000000000010621
44. Ludka O, Stepanova R, Sert-Kuniyoshi F, Spinar J, Somers VK, Kara T. Differential likelihood of NSTEMI vs STEMI in patients with sleep apnea. *Int J Cardiol.* 2017;248:64–68. doi: 10.1016/j.ijcard.2017.06.034
45. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, Rueschman M, Punjabi NM, Mehra R, Bertisch S, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc.* 2017;6:e004500. doi: 10.1161/JAHA.116.004500
46. Hillman D, Mitchell S, Streatfeild J, Burns C, Bruck D, Pezzullo L. The economic cost of inadequate sleep. *Sleep.* 2018;41. doi: 10.1093/sleep/zsy083
47. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JL, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* 2019;7:687–698. doi: 10.1016/S2213-2600(19)30198-5

13. TOTAL CARDIOVASCULAR DISEASES

ICD-9 390 to 459; ICD-10 I00 to I99. See Tables 13-1 through 13-3 and Charts 13-1 through 13-21

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Prevalence (See Table 13-1 and Chart 13-1)

- On the basis of NHANES 2013 to 2016 data,[1] the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥20 years of age is 48.0% overall (121.5 million in 2016) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.0% overall (24.3 million in 2016; Table 13-1). Chart 13-1 presents the prevalence breakdown of CVD by age and sex, with and without hypertension.
- On the basis of the 2017 NHIS[2]:
  - The age-adjusted prevalence of all types of HD was 10.6%; the corresponding age-adjusted prevalence of HD among whites, blacks, Hispanics, and Asians was 11.0%, 9.7%, 7.4%, and 6.1%, respectively.
  - The age-adjusted prevalence of HD, CAD, hypertension, and stroke was higher in men (11.8%, 7.2%, 26.0%, and 3.3%, respectively) than women (9.5%, 4.2%, 23.1%, and 2.5%, respectively).
  - The population of individuals with a bachelor's degree or higher had lower prevalence of HD, CHD, hypertension, and stroke than individuals with lower levels of education.
  - Unemployed individuals who had previously worked had higher age-adjusted prevalence of HD (14.0%), CAD (7.9%), hypertension (29.4%), and stroke (4.7%) than individuals who were either employed (8.3%, 4.1%, 22.0%, and 1.6%, respectively) or those who were not employed and had never worked (8.9%, 5.2%, 24.5%, and 4.5%, respectively).
- The AHA's 2020 Impact Goals are to improve the CVH of all Americans by 20% while reducing deaths attributable to CVDs and stroke by 20%.[3]

Abbreviations Used in Chapter 13

AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CLRD	chronic lower respiratory disease
CVD	cardiovascular disease
CVH	cardiovascular health
DM	diabetes mellitus
ED	emergency department
FHS	Framingham Heart Study
FPG	fasting plasma glucose
GBD	Global Burden of Disease
HBP	high blood pressure
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IMPACT	International Model for Policy Analysis of Agricultural Commodities and Trade
LDL-C	low-density lipoprotein cholesterol
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
TC	total cholesterol
UI	uncertainty interval

Risk Factors

- A recent study using the GBD methodology examined the burden of CVD among US states and found that a large proportion of CVD is attributable to (in decreasing order of contribution) dietary risks, high SBP, high BMI, high TC level, high FPG level, tobacco smoking, and low levels of PA.[4]
- It is estimated that 47% of all Americans have at least 1 of the 3 well-established key risk factors for CVD, which are HBP, high cholesterol, and smoking.[5]
- In 2005, HBP was the most important single preventable risk factor for cardiovascular mortality in the United States and was responsible for an estimated 395 000 (95% CI, 372 000–414 000) cardiovascular deaths (45% of all cardiovascular deaths). Additional risk factors for cardiovascular mortality were overweight/obesity, physical inactivity, high LDL-C, smoking, high dietary salt, high dietary *trans* fatty acids, and low dietary omega-3 fatty acids.[6]

- When added to traditional CVD risk factors, nontraditional CVD risk factors such as CKD, SBP variability, migraine, severe mental illness, systemic lupus erythematosus, use of corticosteroid or antipsychotic medications, or erectile dysfunction improved CVD prediction by the United Kingdom–based QRISK score.[7]
- In Nurses' Health Study participants, compared with a more typical reproductive lifespan and age at first menarche, early age at menopause (<40 years of age) was associated with a 32% higher CVD risk; extremely early age at menarche (≤10 years of age) was associated with a 22% higher CVD risk.[8]
- People living with HIV are more likely to experience CVD before 60 years of age than uninfected people. Cumulative lifetime CVD risk in people living with HIV (65% for males, 44% for females) is higher than in the general population and similar to that of people living with DM (67% for males, 57% for females).[9]
- Patients living with type 1 DM are at increased risk of early CVD. In participants in the Pittsburgh Epidemiology of Diabetes Complications Study with type 1 DM who were 40 to 44 years of age at baseline, mean absolute 10-year CVD risk was 14.8%. Mean absolute 10-year CVD risk was 6.3% in those 30 to 39 years of age.[10]
- Neighborhood-level socioeconomic deprivation was associated with greater risk of CVD mortality in older males in Britain, independent of individual social class or risk factors.[11] Similar findings have been reported among older adults in the United States.[12]
- Air pollution, as defined by increased ambient exposure to particulate matter (particles with median aerodynamic diameter <2.5 μm), is associated with elevated HBP, poor endothelial function, incident CVD events, and all-cause mortality and accounts in part for the racial differences in all-cause mortality and incident CVD.[13]

Social Determinants and Between-Group Disparities in CVD Risk Factors

- CVD risk factor levels vary among counties and states within the continental United States. Within-state differences in the county prevalence of uncontrolled hypertension were as high as 7.8 percentage points in 2009.[14]
- There are significant state-level variations in poor CVH in the United States that are explained in part by individual and state-level factors such as policies, food, and PA environments.[15]
- Data from the CDC's Vital and Health Statistics 2008 to 2010 showed that smokers with family incomes below the poverty level were more than twice as likely as adults in the highest family income group to be current smokers (29.2% versus 13.9%, respectively).[16]
- The US IMPACT Food Policy Model, a computer simulation model, projected that a national policy combining a 30% fruit and vegetable subsidy targeted to low-income Supplemental Nutrition Assistance Program recipients and a population-wide 10% price reduction in fruits and vegetables in the remaining population could prevent ≈230 000 deaths by 2030 and reduce the socioeconomic disparity in CVD mortality by 6%.[17]
- Analysis of >14 000 middle-aged participants in the ARIC study sponsored by the NHLBI showed that ≈90% of CVD events in black participants, compared with ≈65% in white participants, appeared to be explained by elevated or borderline risk factors. Furthermore, the prevalence of individuals with elevated risk factors was higher among black participants; after accounting for education and known CVD risk factors, the incidence of CVD was identical in black and white participants. Although organizational and social barriers to primary prevention do exist, the primary prevention of elevated risk factors might substantially impact the future incidence of CVD, and these beneficial effects would likely be applicable not only for white but also for black participants.[18]
- A study of nearly 1500 participants in MESA found that Hispanics with hypertension, hypercholesterolemia, or DM who spoke Spanish at home (as a proxy of lower levels of acculturation) or had spent less than half a year in the United States had higher SBP, LDL-C, and FPG, respectively, than Hispanics who were preferential English speakers and who had lived a longer period of time in the United States.[19]
- Findings from >15 000 Hispanics of diverse backgrounds demonstrated that a sizeable proportion of both males and females had major CVD risk factors, with higher prevalence among Puerto Rican subgroups and those with lower SES and a higher level of acculturation.[20]
- Although traditional cardiovascular risk factors are generally similar for males and females, there are several female-specific risk factors, such as disorders of pregnancy, adverse pregnancy outcomes, and menopause.[21]

Genetics and Family History (See Table 13-2)

- A family history of CVD increases risk of CVD, with the largest increase in risk if the family member's CVD was premature (Table 13-2).
- A reported family history of premature parental CHD is associated with incident MI or CHD in

offspring. In FHS, the occurrence of a validated premature atherosclerotic CVD event in either a parent[22] or a sibling[23] was associated with an ≈2-fold elevated risk for CVD, independent of other traditional risk factors. Addition of a family history of premature CVD to a model that contained traditional risk factors provided improved prognostic value in FHS.[22]

- The association of a family history of CVD with increased risk of CVD appears to be present across ethnic subgroups.[24,25]
- Family history is also associated with subtypes of CVD, including HF,[26] stroke,[27] AF,[28] and thoracic aortic disease.[29]
- Estimates of familial clustering of CVD are likely underestimated by self-report; in the multigenerational FHS, only 75% of participants with a documented parental history of a heart attack before 55 years of age reported that history when asked.[30]
- The AHA has published a comprehensive scientific statement on the role of genetics and genomics for the prevention and treatment of CVD.[31]

Prevention (See Chapter 2 for more detailed statistics regarding healthy lifestyle and low risk factor levels.)

- A study of the decrease in US deaths attributable to CHD from 1980 to 2000 suggested that ≈47% of the decrease was attributable to increased use of evidence-based medical therapies for secondary prevention and 44% to changes in risk factors in the population attributable to lifestyle and environmental changes.[32]
- Approximately 80% of CVDs can be prevented through not smoking, eating a healthy diet, engaging in PA, maintaining a healthy weight, and controlling HBP, DM, and elevated lipid levels. The presence of a greater number of optimal CVH metrics is associated with a graded and significantly lower risk of total and CVD mortality.[33]
- During more than 5 million person-years of follow-up combined in the Nurses' Health Studies and Health Professionals Follow-Up Study, regular consumption of peanuts and tree nuts (≥2 times weekly) or walnuts (≥1 time weekly) was associated with a 13% to 19% lower risk of total CVD.[34]
- Seventeen-year mortality data from the NHANES II Mortality Follow-up Study indicated that the RR for fatal CHD was 51% lower for males and 71% lower for females with none of the 3 major risk factors (hypertension, current smoking, and elevated TC [≥240 mg/dL]) than for those with ≥1 risk factor. If all 3 major risk factors had not occurred, it is hypothesized that 64% of all CHD deaths among females and 45% of CHD deaths among males could have been avoided.[35]
- Data from the Cardiovascular Lifetime Risk Pooling Project, which involved 18 cohort studies and combined data on 257 384 people (both black and white males and females), indicate that at 45 years of age, participants with optimal risk factor profiles had a substantially lower lifetime risk of CVD events than those with 1 major risk factor (1.4% versus 39.6% among males; 4.1% versus 20.2% among females). Having ≥2 major risk factors further increased lifetime risk to 49.5% in males and 30.7% in females.[36]
- In another study, FHS investigators conducted follow-up of 2531 males and females who were examined between 40 and 50 years of age and observed their overall rates of survival and survival free of CVD to 85 years of age and beyond. Low levels of the major risk factors in middle age were associated with overall survival and morbidity-free survival to ≥85 years of age.[37]
- In young adults 18 to 30 years of age in the CARDIA study and without clinical risk factors, a Healthy Heart Score combining self-reported information on modifiable lifestyle factors including smoking status, alcohol intake, and healthful dietary pattern predicted risk for early ASCVD (before 55 years of age).[38]
- Data from NHANES 2005 to 2010 showed that only 8.8% of adults complied with ≥6 heart-healthy behaviors. Of the 7 factors studied, healthy diet was the least likely to be achieved (only 22% of adults with a healthy diet).[33]
- In the United States, higher whole grain consumption was associated with lower CVD mortality, independent of other dietary and lifestyle factors. Every serving (28 g/d) of whole grain consumption was associated with a 9% (95% CI, 4%–13%) lower CVD mortality.[39]

Awareness of Warning Signs and Risk Factors for CVD

- Surveys conducted every 3 years since 1997 by the AHA to evaluate trends in females' awareness, knowledge, and perceptions related to CVD found most recently (in 2012) that awareness of HD as the leading cause of death among females was 56%, compared with 30% in 1997 ($P<0.05$). Awareness among black and Hispanic females in 2012 was similar to that of white females in 1997; however, awareness rates in 2012 among black and Hispanic females remained below that of white females. Awareness of heart attack signs remained low for all racial/ethnic and age groups surveyed during the same time.[40]

Mortality
(See Tables 13-1 and 13-3 and Charts 13-2 through 13-18)
ICD-10 I00 to I99 for CVD; C00 to C97 for cancer; C33 to C34 for lung cancer; C50 for breast cancer; J40 to J47 for CLRD; G30 for Alzheimer disease; E10 to E14 for DM; and V01 to X59 and Y85 to Y86 for accidents.

- Deaths attributable to diseases of the heart and CVD in the United States increased steadily during the 1900s to the 1980s and declined into the 2010s (Charts 13-2 and 13-3).
- CHD (42.6%) is the leading cause of CVD death in the United States, followed by stroke (17.0%), HBP (10.5%), HF (9.4%), diseases of the arteries (2.9%), and other minor CVD causes combined (17.6%; Chart 13-4).
- The age-adjusted death rate attributable to CVD decreased from 258.2 per 100 000 population in 2007 to 219.4 per 100 000 in 2017, which amounts to a 15.0% decrease (unpublished NHLBI tabulation using CDC WONDER[41]).
- There was a decrease in life expectancy disparity between white and black males. In 1980, the disparity in life expectancy between the 2 groups was 7 years; however, in 2016, when the life expectancies were 76.4 and 72 years, respectively, the disparity was only 4 years.[42]
- On the basis of these national CVD mortality data, the Million Hearts 2022 Initiative focuses on preventing a combined 1 million heart attacks, strokes, and other cardiovascular events[43]:
  - In 2016, >1000 deaths caused by heart attack, stroke, or other cardiovascular events occurred daily.
  - 2.2 million hospitalizations and 415 480 deaths occurred in 2016.
  - In addition, 33% of the life-changing cardiovascular events occurred in adults 35 to 64 years of age. This age group accounted for 775 000 hospitalization and 75 000 deaths attributable to cardiovascular events.
  - The mortality rate in NH blacks was 211.6 per 100 000, which was the highest compared with all other racial and ethnic groups.
  - There is remarkable geographic variation in the life-changing cardiovascular events, with the highest rates being evident in the Southeastern and Midwestern regions of the United States.
  - The lowest CVD event rates (comprising deaths, hospitalizations, and ED visits) were in Utah (805.7), Wyoming (828.9), and Vermont (840.6), whereas the highest were noted in Washington, DC (2048.2), Tennessee (1551.6), and Kentucky (1510.3).
- On the basis of 2017 mortality data (unpublished NHLBI tabulation using the NVSS[44]):
  - CVD currently claims more lives each year than cancer and chronic lung disease combined (Chart 13-5). In 2017, 365 914 people died of CHD, the most common type of HD.
  - In 2017, 2 813 503 resident deaths were registered in the United States, which exceeds the 2016 figure by 69 255 deaths. Ten leading causes accounted for 74% of all registered deaths. The 10 leading causes of death in 2017 were the same as in 2016; these include HD (No. 1), cancer (No. 2), unintentional injuries (No. 3), CLRDs (No. 4), stroke (No. 5), Alzheimer disease (No. 6), DM (No. 7), influenza and pneumonia (No. 8), kidney disease (No. 9), and suicide (No. 10). Seven of the 10 leading causes of death had an increase in age-adjusted death rates. The age-adjusted rate increased 4.2% for unintentional injuries, 2.3% for Alzheimer disease, 3.7% for suicide, 2.4% for DM, 5.9% for influenza and pneumonia, 0.7% for CLRD, and 0.8% for stroke. The age-adjusted death rates decreased 2.1% for cancer but did not change appreciably for HD or kidney disease.
- HD accounted for 647 457 of the total 859 125 CVD deaths in 2017 (unpublished NHLBI tabulation using NVSS[44]). The number of CVD deaths for both sexes and by age category is shown in Chart 13-6. The number of CVD deaths was 440 460 for males and 418 665 for females (Charts 13-7 and 13-8). The number was 340 026 for NH white males, 54 780 for NH black males, 29 366 for Hispanic males, 11 891 for NH Asian and Pacific Islander males, 326 447 for NH white females, 52 528 for NH black females, 25 309 for Hispanic females, and 11 242 for NH Asian and Pacific Islander females (percentage of total deaths by race/ethnicity is presented in Charts 13-9 through 13-12). Among other causes of death, cancer accounted for 599 108 deaths; chronic lung disease, 160 201; accidents, 169 936; and Alzheimer disease, 121 404 (Chart 13-5).
- The number of CVD deaths for all males and females in the United States declined from 1980 to 2010 but increased in recent years (Chart 13-13). The difference in age-adjusted death rates for HD also narrowed among US racial and ethnic groups between 1999 and 2017. Nonetheless, there was a decrease in the rate of decline in overall age-adjusted HD death rate in recent years, and differences in death rates persisted among major US

racial/ethnic groups. In 1999, there were 337.4 deaths per 100 000 people among NH blacks compared with 156.5 among NH Asians or Pacific Islanders. In 2017, the death rates per 100 000 people for these 2 groups were 208.0 and 85.5, respectively, thus preserving the >2-fold difference in death rates observed in 1999.[42]

- The age-adjusted death rates per 100 000 population for CVD, CHD, and stroke differ by US state (Chart 13-14; Table 13-3) and globally (Charts 13-15 through 13-18).
- CVD death rates also vary among US counties. In 2014, the ratio between counties at the 90th and 10th percentiles was 2.0 for IHD (119.1 versus 235.7 deaths per 100 000 people) and 1.7 for cerebrovascular disease (40.3 versus 68.1 deaths per 100 000 people). For other CVD causes, the ratio ranged from 1.4 (aortic aneurysm: 3.5 versus 5.1 deaths per 100 000 people) to 4.2 (hypertensive HD: 4.3 versus 17.9 deaths per 100 000 people).[45] A region of higher CVD mortality extends from southeastern Oklahoma along the Mississippi River Valley to eastern Kentucky.[45]

Healthcare Utilization: Hospital Discharges/Ambulatory Care Visits (See Table 13-1 and Chart 13-19)

- In the decade between 2005 and 2015, 2 trends were observed in overall access to CVD care attributable to cost. In the first half of this interval (2005 to 2010), there was increased difficulty with accessing medical care because of cost, whereas in the second half (2010 to 2015), the difficulty decreased. In 2015, poor access because of cost affected 1 in every 10 adults in the United States, and regional differences were observed, with the greatest difficulties reported in the South.[42]
- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from 5 899 000 to 4 840 000 (Table 13-1). Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *ICD-9* to *ICD-10*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years. CVD principal diagnosis discharges in 2016 comprised 2 629 000 males and 2 211 000 females (unpublished NHLBI tabulation using HCUP,[46] 2016).
- From 1993 to 2016, the number of hospital discharges for CVD in the United States increased in the first decade and then began to decline in the second decade (Chart 13-19).
- In 2016, there were 72 128 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS,[47] 2016). In 2016, there were 4 774 000 ED visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NHAMCS,[48] 2016).

Operations and Procedures (See Chapter 25 for detailed information.)

- In 2014, an estimated 7 971 000 inpatient cardiovascular operations and procedures were performed in the United States (unpublished NHLBI tabulation of HCUP[46]).

Costs (See Chapter 26 for detailed information.)

- In the United States, 22.2% of adults (53 316 677 people) report any disability. In 2006, 26.7% of resident adult healthcare expenditures were associated with disability care and totaled $397.8 billion.[49] For people with disabilities in the United States, HD, stroke, and hypertension were among the 15 leading conditions that caused those disabilities. Disabilities were defined as difficulty with activities of daily living or instrumental activities of daily living, specific functional limitations (except vision, hearing, or speech), and limitation in ability to do housework or work at a job or business.[32,50] The estimated direct and indirect cost of CVD for 2014 to 2015 was $351.2 billion (MEPS,[51] unpublished NHLBI tabulation).
- In 2016, the AHA estimated that by 2035, 45.1% of the US population would have some form of CVD. Total costs of CVD are expected to reach $1.1 trillion in 2035, with direct medical costs projected to reach $748.7 billion and indirect costs estimated to reach $368 billion.[52]

Global Burden of CVD (See Charts 13-15 through 13-18 and Charts 13-20 and 13-21)

- Death rates for CVD, CHD, stroke, and all CVD in selected countries in 2015 to 2017 are presented in Charts 13-15 through 13-18.
- In 2017, ≈17.8 million (95% UI, 17.5–18.0 million) deaths were attributed to CVD globally, which amounted to an increase of 21.1% (95% UI, 19.7% –22.6%) from 2007. The age-adjusted death rate per 100 000 population was 233.1 (95% UI, 229.7–236.4), which represents a decrease of 10.3% (95% UI, –11.4% to –9.3%) from 2007. Overall, the crude prevalence of CVD was 485.6

million cases (95% UI, 468.0–505.0 million) in 2017, an increase of 28.5% (95% UI, 27.7%–29.4%) compared with 2007. However, the age-adjusted prevalence rate was 6081.6 (95% UI, 5860.8–6320.8) per 100 000, an increase of 0.2% (95% UI, –0.4% to 0.80%) from 2007.[4,53]

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories. CVD mortality and prevalence vary widely among world regions[53]:
  - The highest mortality rates attributable to CVD were in Eastern Europe and Central Asia (Chart 13-20).
  - CVD prevalence is high in the United States, Central Europe, North Africa, and the Middle East. (Chart 13-21).
- CVD is the leading global cause of death and is expected to account for >22.2 million deaths by 2030.[54]
- In 2011, data from the World Economic Forum found that CVD represented 50% of noncommunicable disease deaths.[55] CVD represents 37% of deaths of individuals <70 years of age that are attributable to noncommunicable diseases.[56]
- In 2013, ≈70% of CVD deaths occurred in low- to middle-income countries.[57] In 2016, ≈17.9 million people died of CVD, thus making it the predominant cause of death globally.[56]
- In May 2012, during the World Health Assembly, ministers of health agreed to adopt a global target to reduce premature (30–70 years of age) noncommunicable disease mortality by 25% by 2025.[58] Targets for 6 risk factors (tobacco and alcohol use, salt intake, obesity, and raised BP and glucose) were also agreed on to address this goal. It was projected that if the targets are met, premature deaths attributable to CVDs in 2025 will be reduced by 34%, with 11.4 million and 15.9 million deaths delayed or prevented in those 30 to 69 years of age and ≥70 years of age, respectively.[59]

Table 13-1. CVDs in the United States

Population Group	Total CVD Prevalence,* 2013–2016: Age ≥20 y	Prevalence, 2013–2016: Age ≥20 y†	Mortality, 2017: All Ages‡	Hospital Discharges, 2016: All Ages	Cost, 2014–2015
Both sexes	121 500 000 (48.0%)	24 300 000 (9.0%)	859 125	4 840 000	$351.2 Billion
Males	61 500 000 (51.2%)	12 300 000 (9.6%)	440 460 (51.3%)§	2 629 000	$224.7 Billion
Females	60 000 000 (44.7%)	12 000 000 (8.4%)	418 665 (48.7%)§	2 211 000	$126.5 Billion
NH white males	50.6%	9.7%	340 026	…	…
NH white females	43.4%	8.1%	326 447	…	…
NH black males	60.1%	10.7%	54 780	…	…
NH black females	57.1%	10.5%	52 528	…	…
Hispanic males	49.0%	7.8%	29 366	…	…
Hispanic females	42.6%	8.0%	25 309	…	…
NH Asian males	47.4%	6.5%	11 891‖	…	…
NH Asian females	37.2%	4.6%	11 242‖	…	…
NH American Indian/Alaska Native	…	…	4554	…	…

CVD indicates cardiovascular disease; ellipses (…), data not available; and NH, non-Hispanic.

*Total CVD prevalence includes coronary heart disease, heart failure, stroke, and hypertension.

†Prevalence excluding hypertension.

‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

§These percentages represent the portion of total CVD mortality that is attributable to males vs females.

‖Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey, 2013 to 2016.[1] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2014 US population estimates. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.[44] These data represent underlying cause of death only for *International Classification of Diseases, 10th Revision* codes I00 to I99 (diseases of the circulatory system). Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project.[46] Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey,[51] average annual 2014 to 2015 (direct costs) and mortality data from National Center for Health Statistics, and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).

Table 13-2. ORs for Adult Child MI Conditioned on Combinations of Parental History of MI, 1999 to 2003

	OR (95% CI)
No family history	1.00
One parent with heart attack ≥50 y of age	1.67 (1.55–1.81)
One parent with heart attack <50 y of age	2.36 (1.89–2.95)
Both parents with heart attack ≥50 y of age	2.90 (2.30–3.66)
Both parents with heart attack, one <50 y of age	3.26 (1.72–6.18)
Both parents with heart attack, both <50 y of age	6.56 (1.39–30.95)

Multinational data. MI indicates myocardial infarction; and OR, odds ratio. Data derived from Chow et al.[60]

Table 13-3. Age-Adjusted Death Rates per 100 000 Population for CVD, CHD, and Stroke by State, 2015 to 2017

	CVD			CHD			Stroke		
State	Rank	Death Rate	% Change, 2005–2007 to 2015–2017	Rank	Death Rate	% Change, 2005–2007 to 2015–2017	Rank	Death Rate	% Change, 2005–2007 to 2015–2017
Alabama	51	295.3	−17.4	19	86.6	−31.1	51	51.3	−18.4
Alaska	12	195.0	−15.5	10	77.5	−14.1	25	37.0	−30.3
Arizona	7	188.9	−24.2	26	89.6	−34.9	7	30.4	−27.8
Arkansas	49	287.2	−14.2	52	136.8	−22.1	47	45.4	−26.5
California	16	199.9	−27.9	24	88.8	−39.5	24	36.9	−28.5
Colorado	3	175.7	−22.1	3	66.3	−33.7	20	35.3	−18.2
Connecticut	6	185.8	−21.3	9	76.8	−34.3	3	27.5	−27.0
Delaware	30	218.0	−23.4	32	96.2	−35.5	43	42.4	−7.1
District of Columbia	43	254.8	−23.9	45	110.0	−39.4	28	37.5	−8.2
Florida	17	200.0	−22.6	28	92.9	−35.9	29	37.7	−11.0
Georgia	39	241.5	−23.0	8	75.5	−36.2	46	44.4	−21.9
Hawaii	5	179.0	−20.7	2	65.6	−24.8	23	36.7	−25.5
Idaho	27	210.2	−17.9	18	85.3	−27.9	26	37.4	−31.8
Illinois	32	221.7	−22.3	20	87.0	−37.6	33	38.4	−22.5
Indiana	38	240.2	−20.8	37	101.9	−29.9	37	39.6	−23.3
Iowa	28	213.7	−19.6	40	103.6	−28.9	12	32.8	−30.5
Kansas	33	221.9	−17.1	27	89.6	−27.7	32	38.3	−22.4
Kentucky	44	256.0	−21.0	41	104.4	−32.8	38	40.2	−24.2
Louisiana	48	274.3	−17.3	35	99.5	−31.9	50	46.5	−19.9
Maine	15	198.2	−19.9	13	79.8	−31.2	18	34.9	−26.7
Maryland	34	222.2	−21.2	30	94.7	−35.9	36	39.3	−19.6
Massachusetts	4	177.5	−24.7	6	71.7	−33.8	4	27.6	−30.2
Michigan	42	254.4	−17.0	47	117.4	−26.6	35	38.6	−21.4
Minnesota	2	165.0	−20.2	1	59.9	−31.3	13	32.9	−23.2
Mississippi	52	308.6	−19.1	43	106.4	−33.5	52	51.4	−12.5
Missouri	41	250.7	−19.5	44	108.5	−31.6	39	40.8	−23.3
Montana	23	204.3	−14.2	17	84.7	−16.4	15	34.0	−24.8
Nebraska	19	200.8	−19.0	11	77.5	−24.7	11	32.7	−28.4
Nevada	45	256.4	−18.7	46	112.8	−12.4	22	36.3	−25.5
New Hampshire	9	191.7	−24.0	15	82.4	−36.9	6	28.0	−29.7
New Jersey	26	209.0	−22.4	29	94.1	−36.6	9	30.6	−19.6

(*Continued*)

Table 13-3. Continued

State	CVD			CHD			Stroke		
	Rank	Death Rate	% Change, 2005–2007 to 2015–2017	Rank	Death Rate	% Change, 2005–2007 to 2015–2017	Rank	Death Rate	% Change, 2005–2007 to 2015–2017
New Mexico	13	196.2	–19.5	33	97.1	–22.5	17	34.3	–14.6
New York	31	219.2	–25.3	48	120.4	–36.7	1	25.4	–18.9
North Carolina	29	217.8	–24.1	22	87.8	–33.9	45	43.6	–24.6
North Dakota	11	193.6	–20.8	16	83.7	–35.9	14	33.9	–31.4
Ohio	40	247.3	–18.4	42	104.8	–33.2	40	41.4	–18.3
Oklahoma	50	294.6	–17.5	51	135.7	–28.9	44	42.7	–27.7
Oregon	10	191.8	–22.6	4	66.8	–35.5	34	38.4	–31.5
Pennsylvania	36	228.2	–21.4	34	98.4	–32.8	27	37.4	–20.6
Puerto Rico	1	157.6	–29.2	7	73.5	–36.5	2	26.6	–33.6
Rhode Island	14	198.1	–27.0	39	102.2	–41.0	5	27.8	–28.3
South Carolina	37	237.1	–20.2	23	88.6	–30.8	49	45.6	–24.3
South Dakota	22	204.0	–19.0	38	102.0	–27.6	19	35.3	–25.8
Tennessee	47	266.1	–20.0	50	125.8	–28.6	48	45.6	–24.9
Texas	35	226.5	–21.8	31	95.3	–34.8	41	42.0	–20.8
Utah	20	201.7	–12.7	5	67.4	–21.0	30	37.8	–13.7
Vermont	21	202.1	–15.7	36	101.6	–20.0	10	31.5	–19.7
Virginia	24	205.5	–25.3	14	79.9	–34.0	31	37.9	–29.4
Washington	8	189.1	–23.8	12	78.6	–35.4	21	35.7	–28.8
West Virginia	46	258.1	–22.1	49	124.5	–28.6	42	42.4	–16.4
Wisconsin	25	206.1	–19.5	21	87.3	–27.3	16	34.1	–27.2
Wyoming	18	200.3	–19.2	25	89.1	–23.5	8	30.5	–31.2
Total United States		220.5	–22.1		94.8	–33.9		37.5	–22.5

Rates are most current data available as of April 2019. Rates are per 100 000 people. *International Classification of Diseases, 10th Revision* codes used were I00 to I99 for CVD, I20 to I25 for CHD, and I60 to I69 for stroke. CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System data.[44]

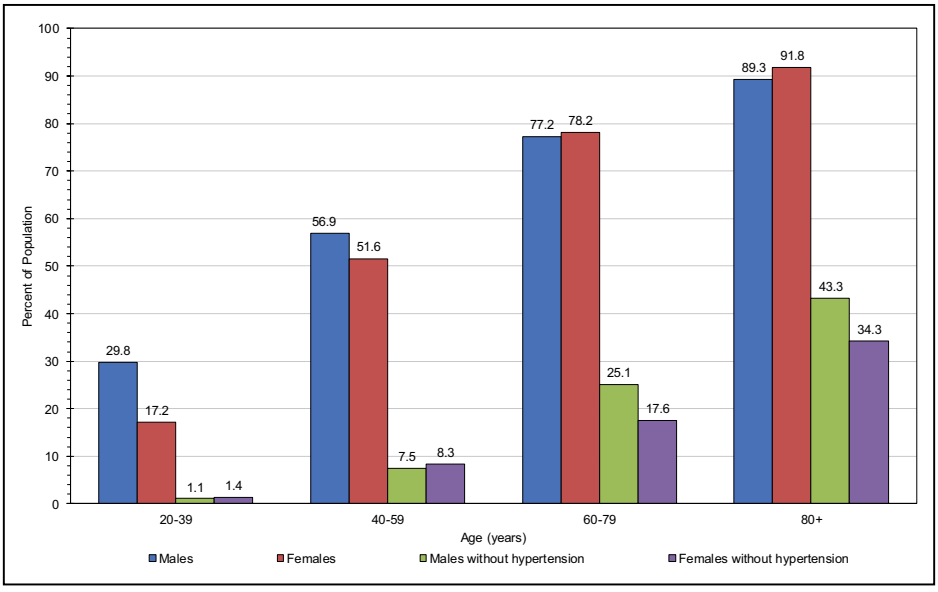


Chart 13-1. Prevalence of cardiovascular disease in US adults ≥20 years of age, by age and sex (NHANES, 2013–2016), with and without hypertension.
These data include coronary heart disease, heart failure, stroke, and with and without hypertension.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[1]

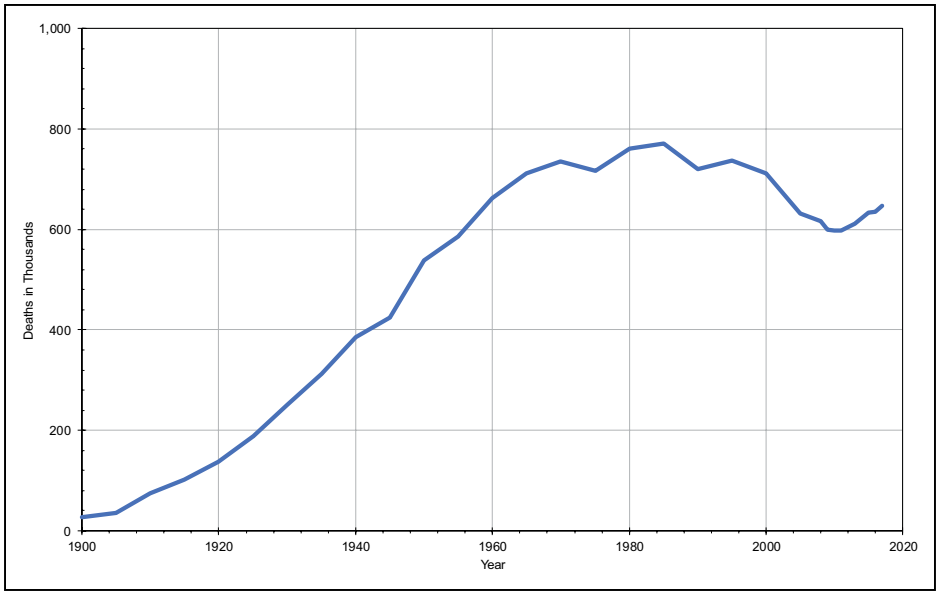


Chart 13-2. Deaths attributable to diseases of the heart, United States, 1900 to 2017.
See Glossary (Chapter 28) for an explanation of "diseases of the heart." In the years 1900 to 1920, the *International Classification of Diseases* codes were 77 to 80; for 1925, 87 to 90; for 1930 to 1945, 90 to 95; for 1950 to 1960, 402 to 404 and 410 to 443; for 1965, 402 to 404 and 410 to 443; for 1970 to 1975, 390 to 398 and 404 to 429; for 1980 to 1995, 390 to 398, 402, and 404 to 429; and for 2000 to 2014, I00 to I09, I11, I13, and I20 to I51. Before 1933, data are for a death registration area and not the entire United States. In 1900, only 10 states were included in the death registration area, and this increased over the years, so part of the increase in numbers of deaths is attributable to an increase in the number of states.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[44]

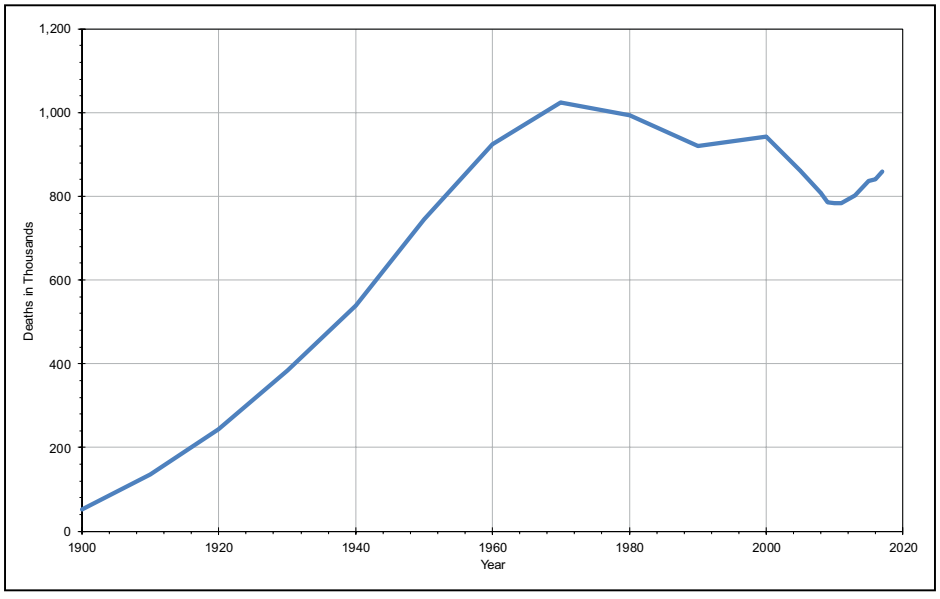


Chart 13-3. Deaths attributable to cardiovascular disease (CVD), United States, 1900 to 2017.
CVD (*International Classification of Diseases, 10th Revision* codes I00–I99) does not include congenital heart disease. Before 1933, data are for a death registration area and not the entire United States.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[44]

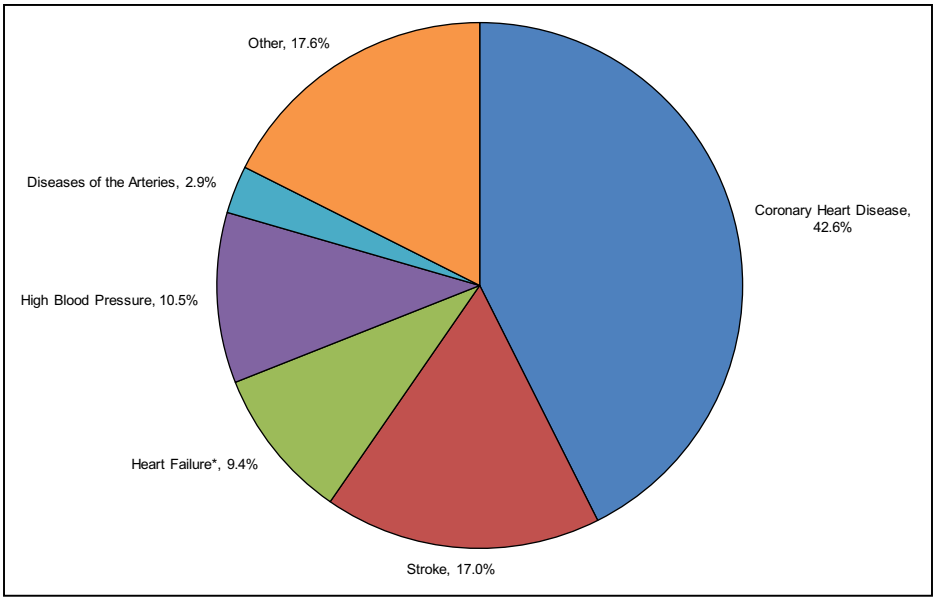
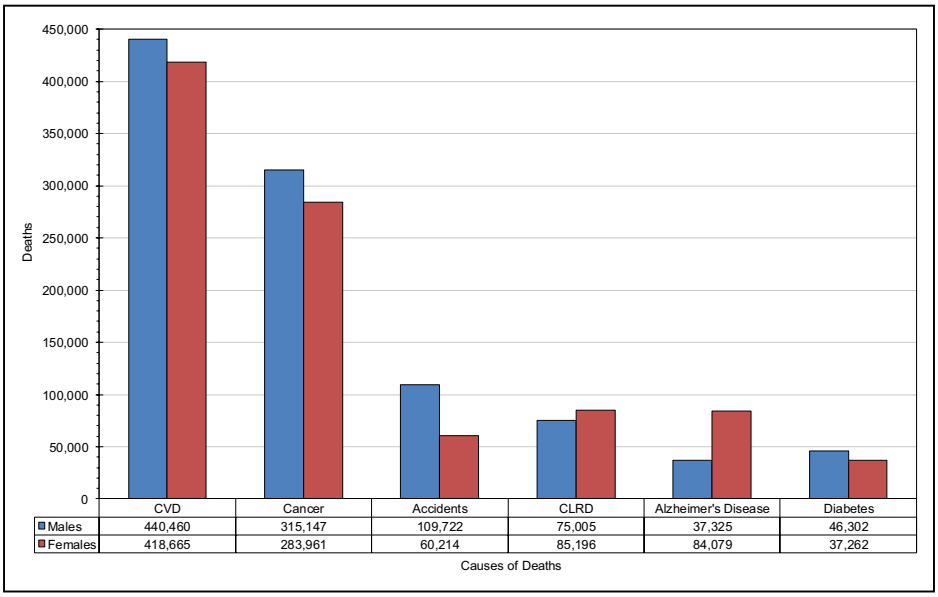


Chart 13-4. Percentage breakdown of deaths attributable to cardiovascular disease (CVD), United States, 2017.
Total may not add to 100 because of rounding. Coronary heart disease includes *International Classification of Diseases, 10th Revision* (*ICD-10*) codes I20 to I25; stroke, I60 to I69; heart failure (HF), I50; high blood pressure, I10 to I13 and I15; diseases of the arteries, I70 to I78; and other, all remaining *ICD-I0* I categories.
*Not a true underlying cause. HF appeared among the multiple causes of death on 41% of death certificates on which CVD is listed as the underlying cause.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]



	CVD	Cancer	Accidents	CLRD	Alzheimer's Disease	Diabetes
Males	440,460	315,147	109,722	75,005	37,325	46,302
Females	418,665	283,961	60,214	85,196	84,079	37,262

Chart 13-5. CVD and other major causes of death for all US males and females, 2017.
Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 and Y85–Y86); CLRD (J40–J47); diabetes mellitus (E10–E14); and Alzheimer disease (G30).
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute using National Vital Statistics System, 2017.[44]

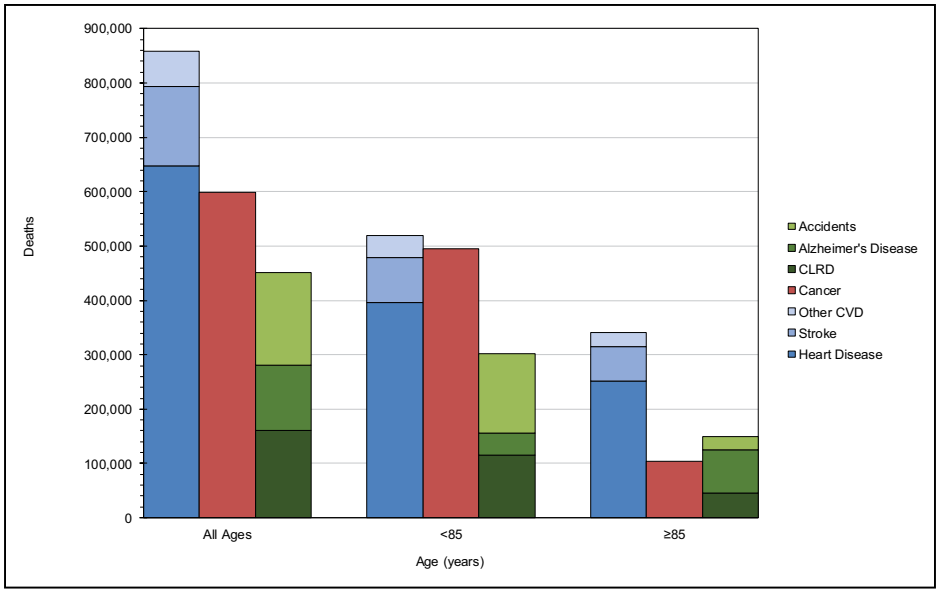


Chart 13-6. CVD and other major causes of death: all ages, <85 years of age, and ≥85 years of age, United States, 2017.
Deaths among both sexes. Deaths with age not stated are not included in the totals. Accidents includes *International Classification of Diseases, 10th Revision* codes V01 to X59, Y85, and Y86; Alzheimer disease, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and heart disease, I00 to I09, I11, I13, and I20 to I51.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

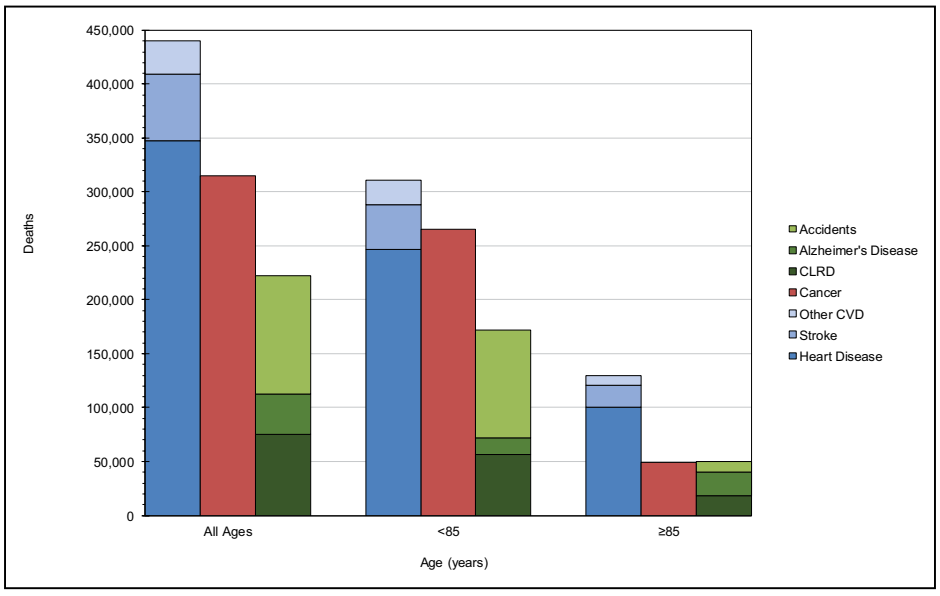


Chart 13-7. CVD and other major causes of death in US males: all ages, <85 years of age, and ≥85 years of age, 2017.
Accidents includes *International Classification of Diseases, 10th Revision* codes V01 to X59, Y85, and Y86; Alzheimer disease, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and heart disease, I00 to I09, I11, I13, and I20 to I51.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

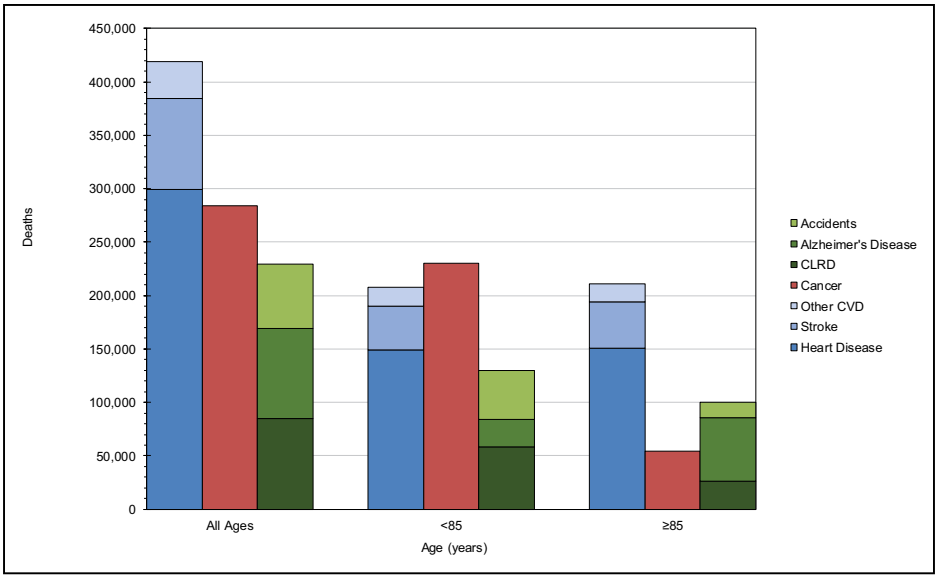


Chart 13-8. CVD and other major causes of death in US females: all ages, <85 years of age, and ≥85 years of age, 2017.
Accidents includes *International Classification of Diseases, 10th Revision* codes V01 to X59, Y85, and Y86; Alzheimer disease, G30; CLRD, J40 to J47; cancer, C00 to C97; other CVD, I10, I12, I15, and I70 to I99; stroke, I60 to I69; and heart disease, I00 to I09, I11, I13, and I20 to I51.
CLRD indicates chronic lower respiratory disease; and CVD, cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute using National Vital Statistics System, 2017.[44]

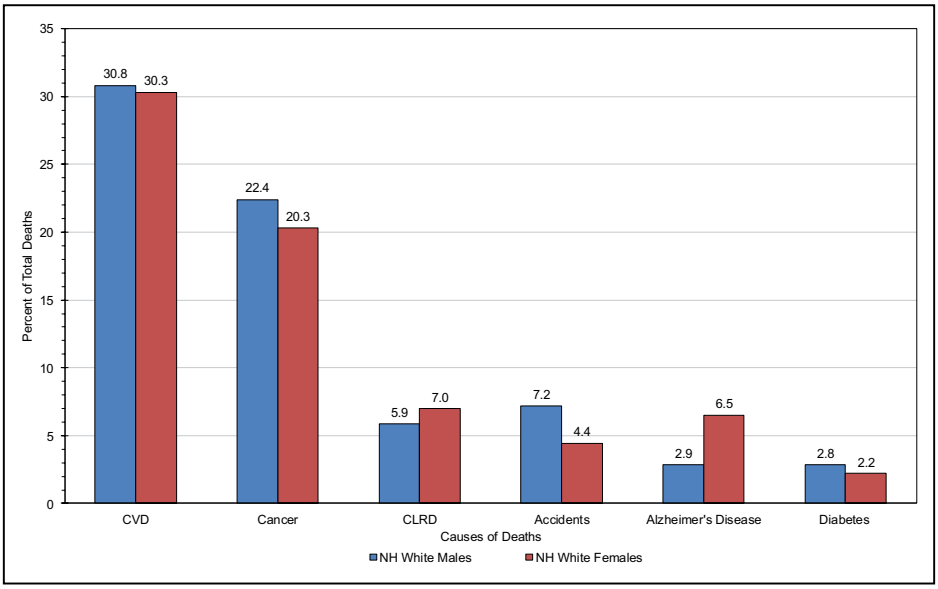


Chart 13-9. CVD and other major causes of death for NH white males and females, United States, 2017.
Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); accidents (V01–X59 andY85–Y86); Alzheimer disease (G30); and diabetes mellitus (E10–E14).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

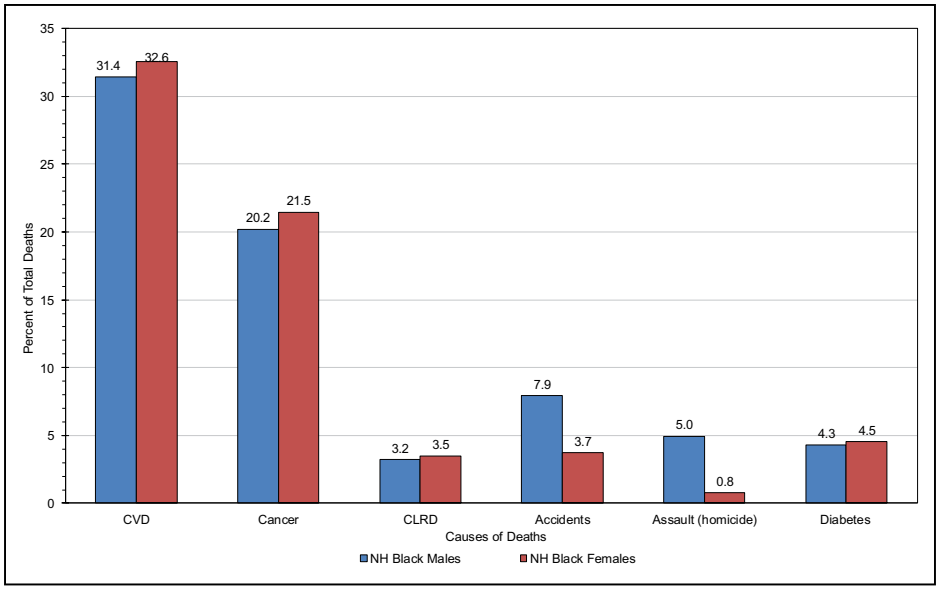


Chart 13-10. CVD and other major causes of death for NH black males and females, United States, 2017.
Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); CLRD (J40–J47); accidents (V01–X59, Y85, and Y86); assault (homicide) (U01 and U02, X85–Y09, Y87.1); and diabetes mellitus (E10–E14).
CLRD indicates chronic lower respiratory disease; CVD, cardiovascular disease; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

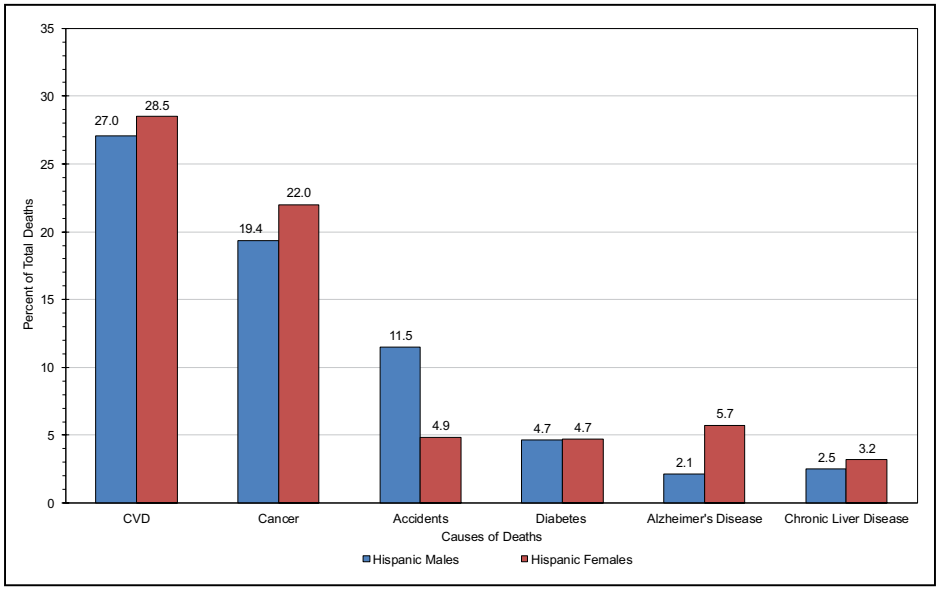


Chart 13-11. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2017.
Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included CVD (*International Classification of Diseases, 10th Revision* codes I00–I99); cancer (C00–C97); accidents (V01–X59 and Y85–Y86); diabetes mellitus (E10–E14); Alzheimer disease (G30); and chronic liver disease (K70, K73, and K74).
CVD indicates cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

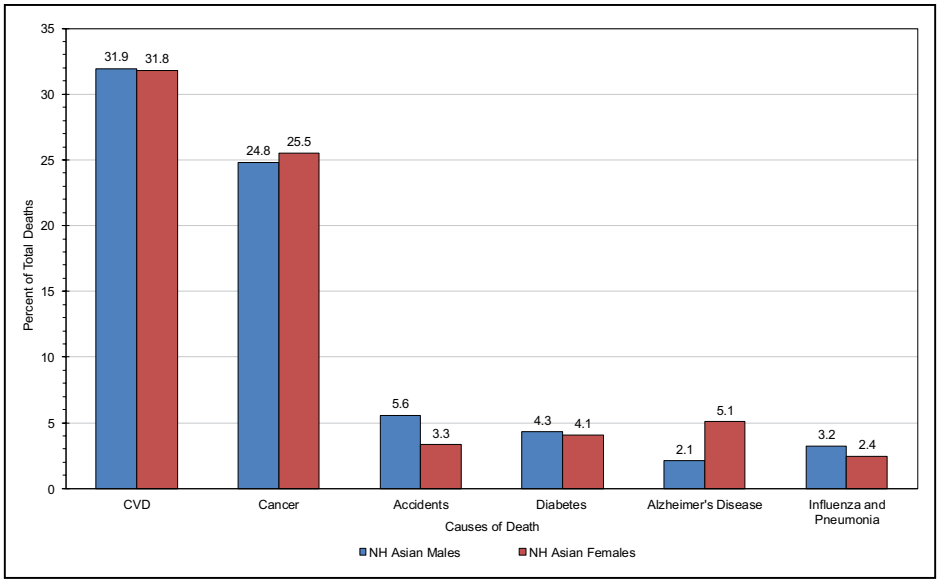


Chart 13-12. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2017.
"Asian or Pacific Islander" is a heterogeneous category that includes people at high CVD risk (eg, South Asian) and people at low CVD risk (eg, Japanese). More specific data on these groups are not available. Number of deaths shown may be lower than actual because of underreporting in this population. Diseases included: CVD (*International Classification of Diseases, 10th Revision* codes I00 –I99); cancer (C00–C97); accidents (V01–X59, Y85, and Y86); diabetes mellitus (E10–E14); Alzheimer disease (G30); and influenza and pneumonia (J09–J18).
CVD indicates cardiovascular disease; and NH, non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

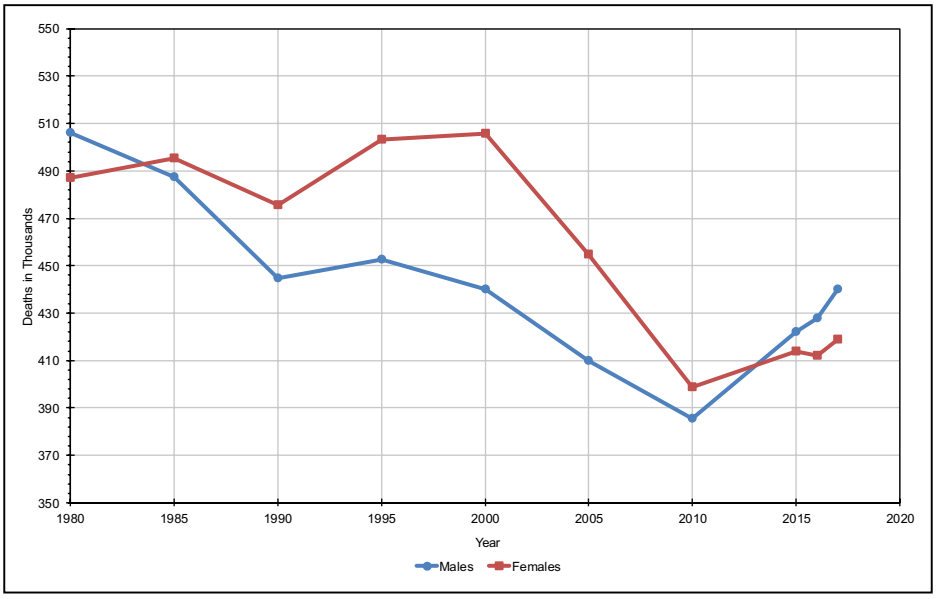


Chart 13-13. Cardiovascular disease (CVD) mortality trends for US males and females, 1980 to 2017.
CVD excludes congenital cardiovascular defects (*International Classification of Diseases, 10th Revision* [*ICD-10*] codes I00–I99). The overall comparability for CVD between the *International Classification of Diseases, 9th Revision* (1979–1998) and *ICD-10* (1999–2015) is 0.9962. No comparability ratios were applied.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.[44]

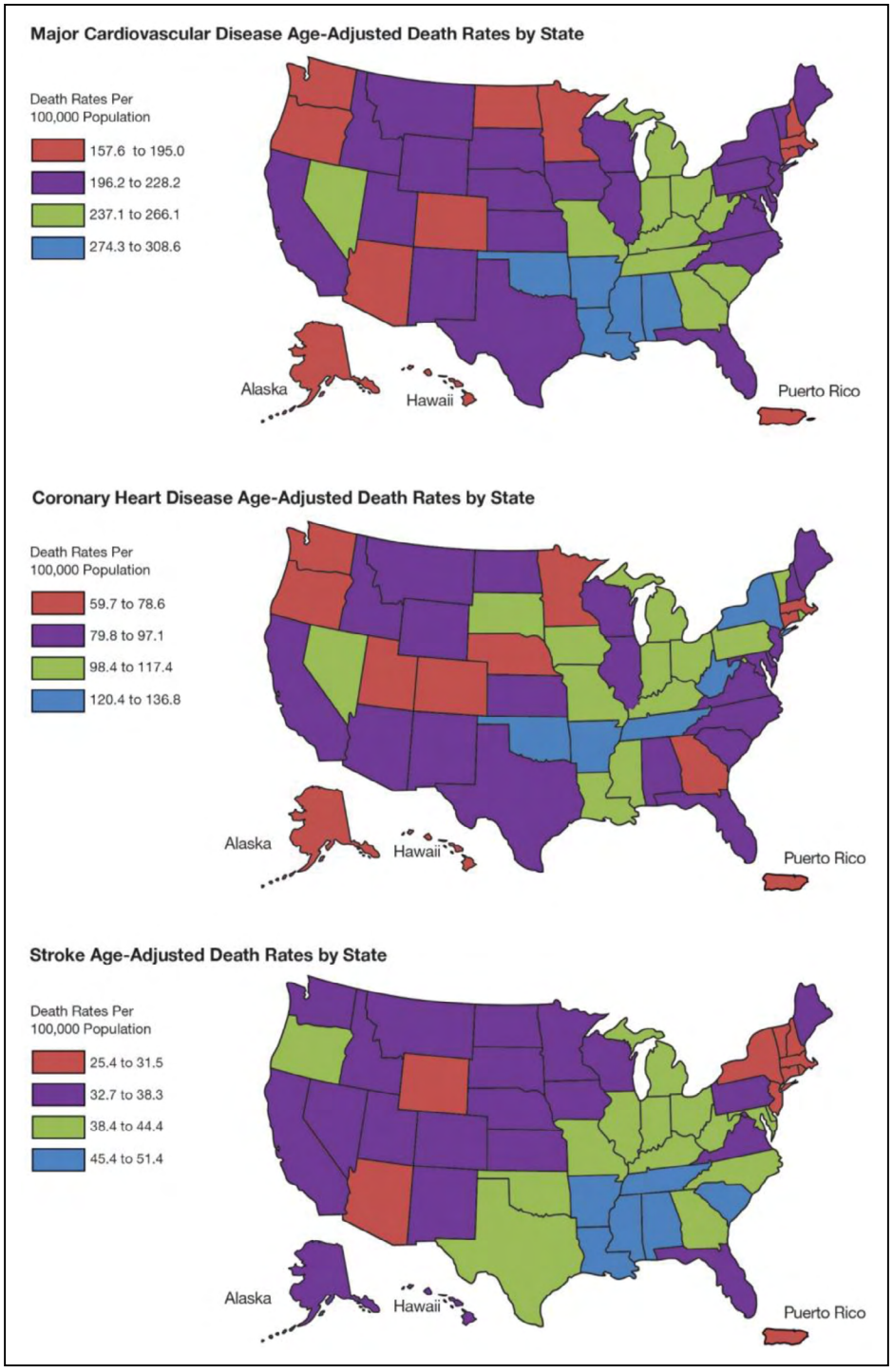


Chart 13-14. US maps corresponding to the state age-adjusted death rates per 100 000 population for cardiovascular disease, coronary heart disease, and stroke (including the District of Columbia), 2017.

Source: American Heart Association maps from unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System, 2017.[44]

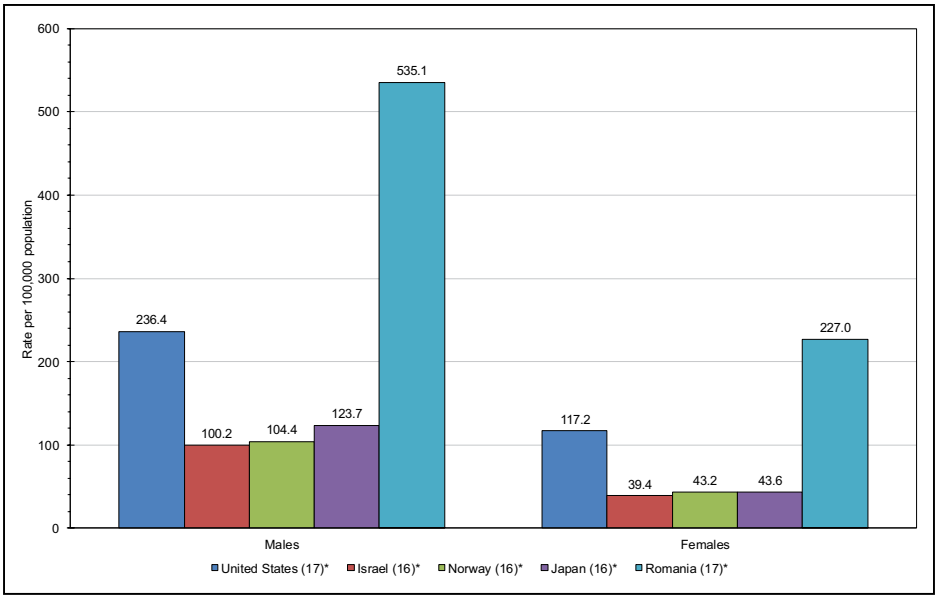


Chart 13-15. Death rates for cardiovascular disease (CVD) in selected countries for adults 35 to 74 years of age, 2015 to 2017.
Rates are adjusted to the European Standard population. *International Classification of Diseases, 10th Revision* codes are I00 to I99 for CVD.
*Number in parentheses indicates year of most recent data available (where 16 is 2016 and 17 is 2017).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[61]

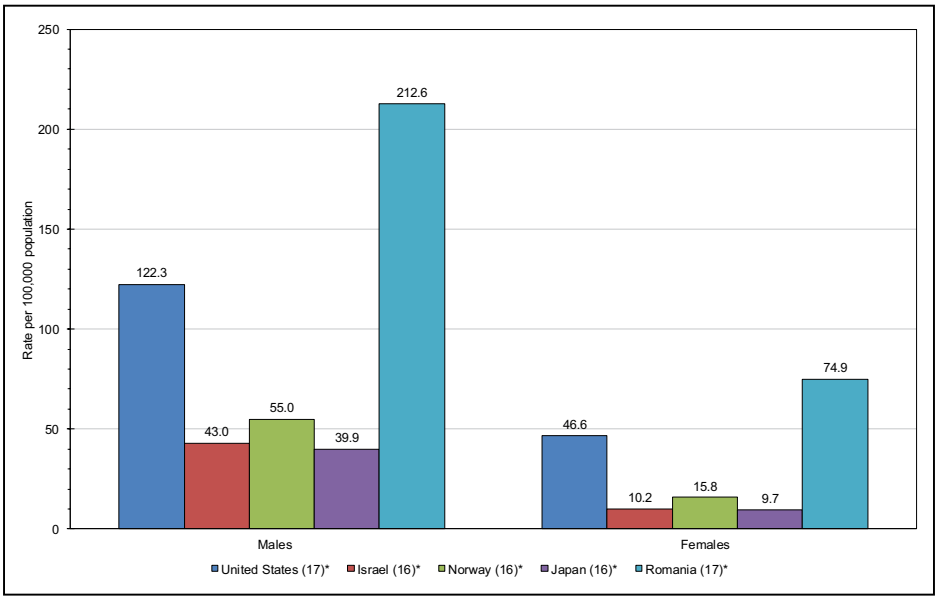


Chart 13-16. Death rates for coronary heart disease (CHD) in selected countries for adults 35 to 74 years of age, 2015 to 2017.
Rates are adjusted to the European Standard population. *International Classification of Diseases, 10th Revision* codes are I20 to I25 for CHD.
*Number in parentheses indicates year of most recent data available (where 16 is 2016 and 17 is 2017).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[61]

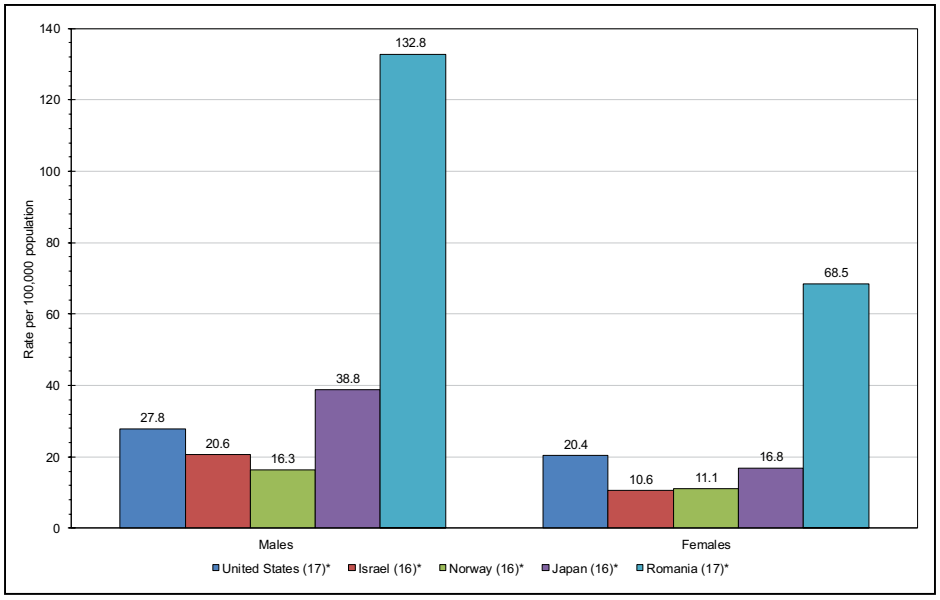


Chart 13-17. Death rates for stroke in selected countries for adults 35 to 74 years of age, 2015 to 2017.
Rates are adjusted to the European Standard population. *International Classification of Diseases, 10th Revision* codes are I60 to I69 for stroke.
*Number in parentheses indicates year of most recent data available (where 16 is 2016 and 17 is 2017).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[61]

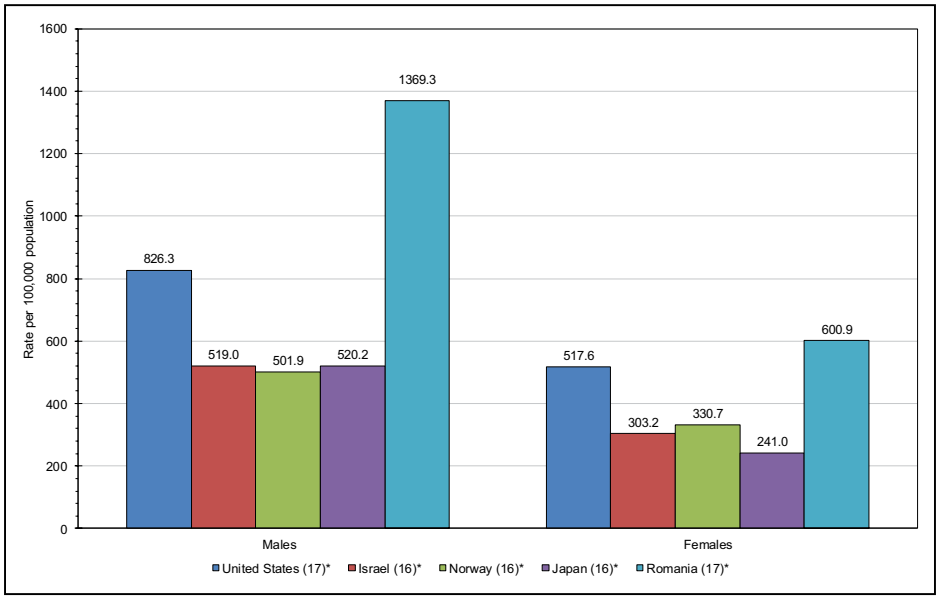


Chart 13-18. Death rates for all causes in selected countries for adults 35 to 74 years of age, 2015 to 2017.
Rates are adjusted to the European Standard population. *International Classification of Diseases, 10th Revision* codes are A00 to Y89 for all causes.
*Number in parentheses indicates year of most recent data available (where 16 is 2016 and 17 is 2017).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using World Health Organization Mortality Database.[61]

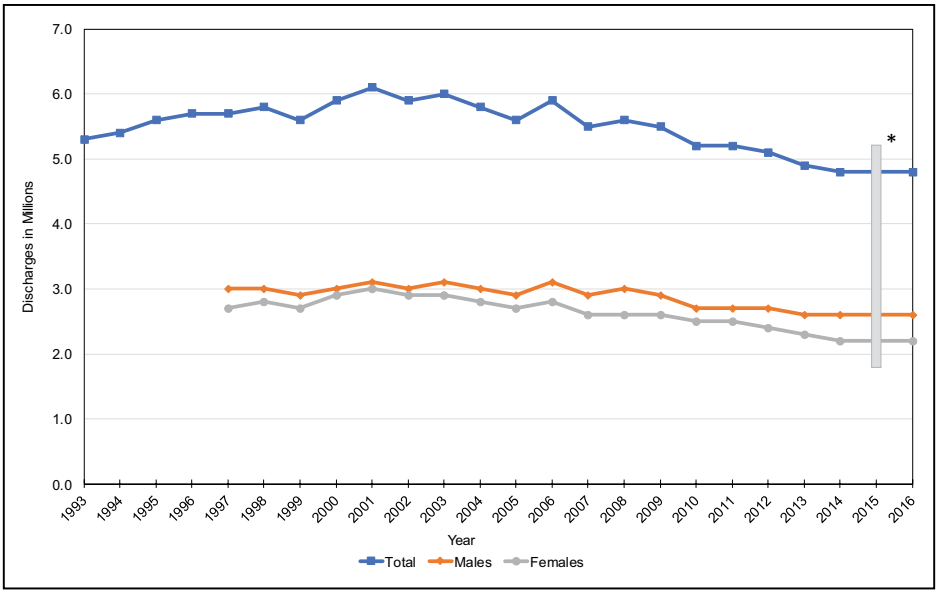


Chart 13-19. Hospital discharges for cardiovascular disease, United States, 1993 to 2016.
Hospital discharges include people discharged alive, dead, and "status unknown."
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *International Classification of Diseases, 9th Revision* to *International Classification of Diseases, 10th Revision*. This should be kept in consideration, because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[46]

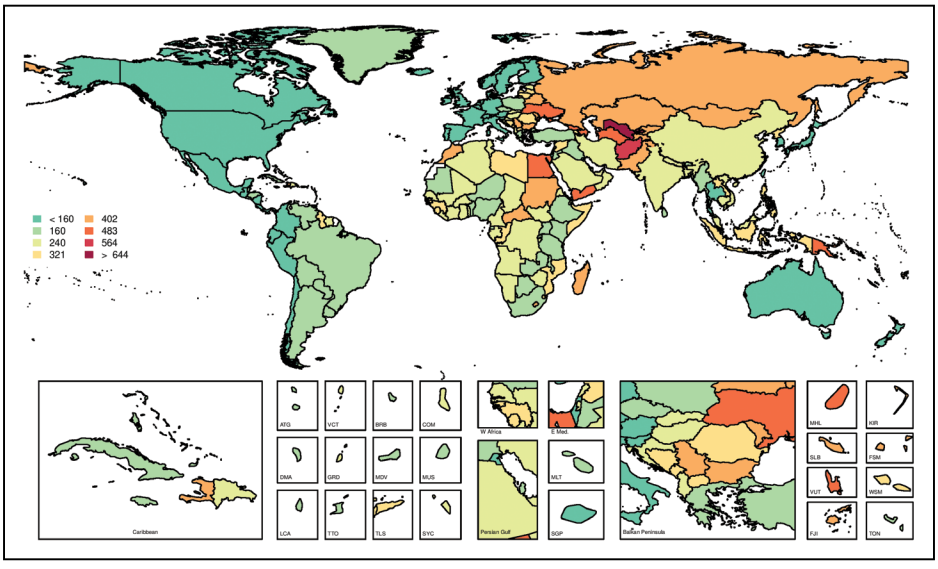


Chart 13-20. Age-standardized global mortality rates of cardiovascular disease (CVD) per 100 000, both sexes, 2017.
The highest mortality rates attributable to CVD are in Eastern Europe and Central Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[53] Printed with permission. Copyright © 2018, University of Washington.

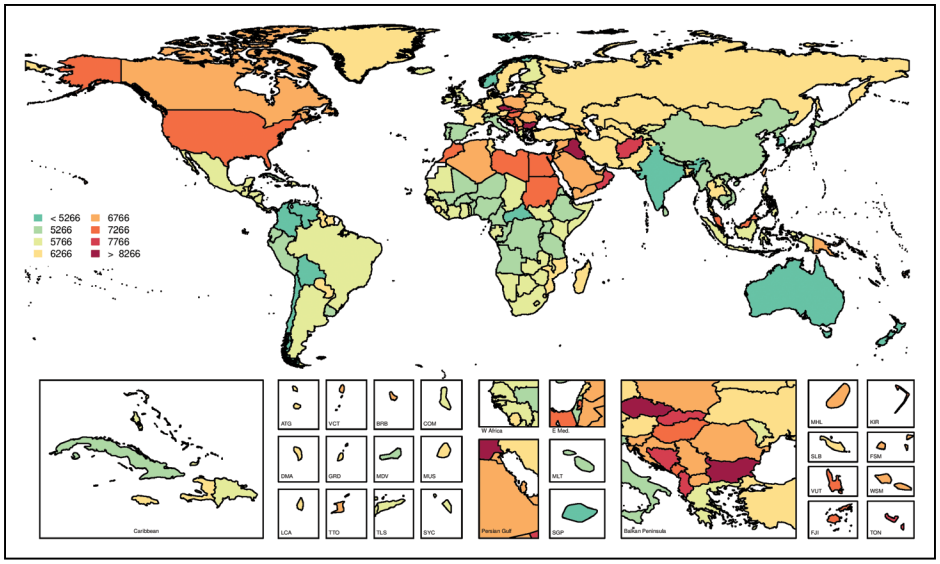


Chart 13-21. Age-standardized global prevalence rates of cardiovascular diseases (CVDs) per 100 000, both sexes, 2017.
Age-standardized CVD prevalence is high in the United States, Central Europe, North Africa, and the Middle East.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[53] Printed with permission. Copyright © 2018, University of Washington.

REFERENCES

1. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
2. Blackwell DL, Villarroel MA. Tables of Summary Health Statistics for U.S. Adults: 2017 National Health Interview Survey. Centers for Disease Control and Prevention website. 2018. http://www.cdc.gov/nchs/nhis/SHS/tables.htm. Accessed May 7, 2019.
3. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al; on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
4. Roth GA, Johnson CO, Abate KH, Abd-Allah F, Ahmed M, Alam K, Alam T, Alvis-Guzman N, Ansari H, Arnlov J, et al; Global Burden of Cardiovascular Diseases Collaboration. The burden of cardiovascular diseases among US states, 1990–2016. *JAMA Cardiol.* 2018;3:375–389. doi: 10.1001/jamacardio.2018.0385
5. Fryar CD, Chen TC, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999–2010. *NCHS Data Brief.* 2012;(103):1–8.
6. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors [published correction appears in *PLoS Med*. 2011;8]. *PLoS Med.* 2009;6:e1000058. doi: 10.1371/journal.pmed.1000058
7. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ.* 2017;357:j2099. doi: 10.1136/bmj.j2099
8. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham Heart Study. *Stroke.* 2009;40:1044–1049. doi: 10.1161/STROKEAHA.108.542993
9. Losina E, Hyle EP, Borre ED, Linas BP, Sax PE, Weinstein MC, Rusu C, Ciaranello AL, Walensky RP, Freedberg KA. Projecting 10-year, 20-year, and lifetime risks of cardiovascular disease in persons living with human immunodeficiency virus in the United States. *Clin Infect Dis.* 2017;65:1266–1271. doi: 10.1093/cid/cix547
10. Miller RG, Mahajan HD, Costacou T, Sekikawa A, Anderson SJ, Orchard TJ. A contemporary estimate of total mortality and cardiovascular disease risk in young adults with type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care.* 2016;39:2296–2303. doi: 10.2337/dc16-1162
11. Ramsay SE, Morris RW, Whincup PH, Subramanian SV, Papacosta AO, Lennon LT, Wannamethee SG. The influence of neighbourhood-level socioeconomic deprivation on cardiovascular disease mortality in older age: longitudinal multilevel analyses from a cohort of older British men. *J Epidemiol Community Health.* 2015;69:1224–1231. doi: 10.1136/jech-2015-205542
12. Xiao Q, Berrigan D, Powell-Wiley TM, Matthews CE. Ten-year change in neighborhood socioeconomic deprivation and rates of total, cardiovascular disease, and cancer mortality in older US adults. *Am J Epidemiol.* 2018;187:2642–2650. doi: 10.1093/aje/kwy181
13. Erqou S, Clougherty JE, Olafiranye O, Magnani JW, Aiyer A, Tripathy S, Kinnee E, Kip KE, Reis SE. Particulate matter air pollution and racial differences in cardiovascular disease risk. *Arterioscler Thromb Vasc Biol.* 2018;38:935–942. doi: 10.1161/ATVBAHA.117.310305
14. Olives C, Myerson R, Mokdad AH, Murray CJ, Lim SS. Prevalence, awareness, treatment, and control of hypertension in United States counties, 2001-2009. *PLoS One.* 2013;8:e60308. doi: 10.1371/journal.pone.0060308
15. Gebreab SY, Davis SK, Symanzik J, Mensah GA, Gibbons GH, Diez-Roux AV. Geographic variations in cardiovascular health in the United States: contributions of state- and individual-level factors. *J Am Heart Assoc.* 2015;4:e001673. doi: 10.1161/JAHA.114.001673
16. Schoenborn CA, Adams PF, Peregoy JA. Health behaviors of adults: United States, 2008–2010. *Vital Health Stat 10.* 2013:1–184.
17. Pearson-Stuttard J, Bandosz P, Rehm CD, Penalvo J, Whitsel L, Gaziano T, Conrad Z, Wilde P, Micha R, Lloyd-Williams F, et al. Reducing US cardiovascular disease burden and disparities through national and targeted dietary policies: a modelling study. *PLoS Med.* 2017;14:e1002311. doi: 10.1371/journal.pmed.1002311
18. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: comparison of African American with white

subjects: Atherosclerosis Risk in Communities Study. *Arch Intern Med.* 2007;167:573–579. doi: 10.1001/archinte.167.6.573
19. Eamranond PP, Legedza AT, Diez-Roux AV, Kandula NR, Palmas W, Siscovick DS, Mukamal KJ. Association between language and risk factor levels among Hispanic adults with hypertension, hypercholesterolemia, or diabetes. *Am Heart J.* 2009;157:53–59. doi: 10.1016/j.ahj.2008.08.015
20. Daviglus ML, Talavera GA, Avilés-Santa ML, Allison M, Cai J, Criqui MH, Gellman M, Giachello AL, Gouskova N, Kaplan RC, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *JAMA.* 2012;308:1775–1784. doi: 10.1001/jama.2012.14517
21. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis.* 2015;241:211–218. doi: 10.1016/j.atherosclerosis.2015.01.027
22. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, Wilson PW, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA.* 2004;291:2204–2211. doi: 10.1001/jama.291.18.2204
23. Murabito JM, Pencina MJ, Nam BH, D'Agostino RB Sr, Wang TJ, Lloyd-Jones D, Wilson PW, O'Donnell CJ. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *JAMA.* 2005;294:3117–3123. doi: 10.1001/jama.294.24.3117
24. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, Blaha MJ, Miedema MD, Sibley CT, Carr JJ, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *J Am Coll Cardiol.* 2016;67:139–147. doi: 10.1016/j.jacc.2015.10.058
25. Valerio L, Peters RJ, Zwinderman AH, Pinto-Sietsma SJ. Association of family history with cardiovascular disease in hypertensive individuals in a multiethnic population. *J Am Heart Assoc.* 2016;5:e004260. doi: 10.1161/JAHA.116.004260
26. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med.* 2006;355:138–147. doi: 10.1056/NEJMoa052948
27. Kulshreshtha A, Vaccarino V, Goyal A, McClellan W, Nahab F, Howard VJ, Judd SE. Family history of stroke and cardiovascular health in a national cohort. *J Stroke Cerebrovasc Dis.* 2015;24:447–454. doi: 10.1016/j.jstrokecerebrovasdis.2014.09.017
28. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA.* 2004;291:2851–2855. doi: 10.1001/jama.291.23.2851
29. Olsson C, Granath F, Ståhle E. Family history, comorbidity and risk of thoracic aortic disease: a population-based case-control study. *Heart.* 2013;99:1030–1033. doi: 10.1136/heartjnl-2013-303654
30. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med.* 2004;140:434–440. doi: 10.7326/0003-4819-140-6-200403160-00010
31. Ganesh SK, Arnett DK, Assimes TL, Assimes TL, Basson CT, Chakravarti A, Ellinor PT, Engler MB, Goldmuntz E, Herrington DM, et al; on behalf of the American Heart Association Council on Functional Genomics and Translational Biology; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Basic Cardiovascular Sciences; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular and Stroke Nursing; American Heart Association Stroke Council. Genetics and genomics for the prevention and treatment of cardiovascular disease: update: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2014;129:e398]. *Circulation.* 2013;128:2813–2851. doi: 10.1161/01.cir.0000437913.98912.1d
32. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults: United States, 2005. *MMWR Morb Mortal Wkly Rep.* 2009;58:421–426.
33. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA.* 2012;307:1273–1283. doi: 10.1001/jama.2012.339
34. Guasch-Ferré M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol.* 2017;70:2519–2532. doi: 10.1016/j.jacc.2017.09.035
35. Mensah GA, Brown DW, Croft JB, Greenlund KJ. Major coronary risk factors and death from coronary heart disease: baseline and follow-up mortality data from the Second National Health and Nutrition Examination Survey (NHANES II). *Am J Prev Med.* 2005;29(suppl 1):68–74. doi: 10.1016/j.amepre.2005.07.030
36. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. *N Engl J Med.* 2012;366:321–329. doi: 10.1056/NEJMoa1012848
37. Terry DF, Pencina MJ, Vasan RS, Murabito JM, Wolf PA, Hayes MK, Levy D, D'Agostino RB, Benjamin EJ. Cardiovascular risk factors predictive for survival and morbidity-free survival in the oldest-old Framingham Heart Study participants. *J Am Geriatr Soc.* 2005;53:1944–1950. doi: 10.1111/j.1532-5415.2005.00465.x
38. Gooding HC, Ning H, Gillman MW, Shay C, Allen N, Goff DC Jr, Lloyd-Jones D, Chiuve S. Application of a lifestyle-based tool to estimate premature cardiovascular disease events in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA Intern Med.* 2017;177:1354–1360. doi: 10.1001/jamainternmed.2017.2922
39. Wu H, Flint AJ, Qi Q, van Dam RM, Sampson LA, Rimm EB, Holmes MD, Willett WC, Hu FB, Sun Q. Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. *JAMA Intern Med.* 2015;175:373–384. doi: 10.1001/jamainternmed.2014.6283
40. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA; on behalf of the American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on High Blood Pressure Research, and Council on Nutrition, Physical Activity and Metabolism. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. *Circulation.* 2013;127:1254–1263. doi: 10.1161/CIR.0b013e318287cf2f
41. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019
42. National Center for Health Statistics. *Health, United States, 2017: With Special Feature on Mortality.* Hyattsville, MD: National Center for Health Statistics; 2018. https://www.cdc.gov/nchs/data/hus/hus17.pdf. Accessed April 1, 2019.
43. Ritchey MD, Wall HK, Owens PL, Wright JS. Vital signs: state-level variation in nonfatal and fatal cardiovascular events targeted for prevention by Million Hearts 2022. *MMWR Morb Mortal Wkly Rep.* 2018;67:974–982. doi: 10.15585/mmwr.mm6735a3
44. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
45. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA.* 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
46. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
47. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data Accessed April 1, 2019.
48. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data Accessed April 1, 2019.
49. Disability and Health: Healthcare Cost Data. Centers for Disease Control and Prevention website. https://www.cdc.gov/ncbddd/disabilityandhealth/data-highlights.html. Accessed May 23, 2017
50. Courtney-Long EA, Carroll DD, Zhang QC, Stevens AC, Griffin-Blake S, Armour BS, Campbell VA. Prevalence of disability and disability type among adults: United States, 2013. *MMWR Morb Mortal Wkly Rep.* 2015;64:777–783.
51. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical

conditions, United States, 1996–2015. Agency for Healthcare Research and Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed June 17, 2019.
52. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001.
53. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
54. Global Status Report on Noncommunicable Diseases 2014. Geneva, Switzerland: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf. Accessed August 19, 2019.
55. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, et al. The Global Economic Burden of Non-communicable Diseases. Geneva, Switzerland: World Economic Forum; 2011.
56. Cardiovascular diseases (CVDs). Fact sheet No. 317. World Health Organization (WHO) website. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed April 10, 2015.
57. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, Murray CJ. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation.* 2015;132:1667–1678. doi: 10.1161/CIRCULATIONAHA.114.008720
58. Smith SC Jr, Collins A, Ferrari R, Holmes DR Jr, Logstrup S, McGhie DV, Ralston J, Sacco RL, Stam H, Taubert K, et al. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). *Circulation.* 2012;126:2769–2775. doi: 10.1161/CIR.0b013e318267e99f
59. Kontis V, Mathers CD, Rehm J, Stevens GA, Shield KD, Bonita R, Riley LM, Poznyak V, Beaglehole R, Ezzati M. Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study. *Lancet.* 2014;384:427–437. doi: 10.1016/S0140-6736(14)60616-4
60. Chow CK, Islam S, Bautista L, Rumboldt Z, Yusufali A, Xie C, Anand SS, Engert JC, Rangarajan S, Yusuf S. Parental history and myocardial infarction risk across the world: the INTERHEART Study. *J Am Coll Cardiol.* 2011;57:619–627. doi: 10.1016/j.jacc.2010.07.054
61. WHO Mortality Database [database online]. World Health Organization website. https://www.who.int/healthinfo/statistics/mortality_rawdata/en/. Accessed July 10, 2019.

14. STROKE (CEREBROVASCULAR DISEASE)

ICD-9 430 to 438; ICD-10 I60 to I69. See Table 14-1 and Charts 14-1 through 14-17

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Stroke Prevalence (See Table 14-1 and Chart 14-1)

- Stroke prevalence estimates may differ slightly between studies because each study selects and recruits a sample of participants to represent the target study population (eg, state, region, or country).

Abbreviations Used in Chapter 14

ABCD2	Age, Blood Pressure, Clinical Features, Duration, Diabetes
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
AHI	apnea-hypopnea index
ARIC	Atherosclerosis Risk in Communities
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
BASIC	Brain Attack Surveillance in Corpus Christi
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAD	coronary artery disease
CAS	carotid artery stenting
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CEA	carotid endarterectomy
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CLRD	chronic lower respiratory disease
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
CRP	C-reactive protein
CSC	comprehensive stroke center
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DM	diabetes mellitus
DVT	deep vein thrombosis
ECG	electrocardiogram

(*Continued*)

Abbreviations Used in Chapter 14 Continued

ED	emergency department
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EPIC	European Prospective Investigation Into Cancer and Nutrition
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial
FHS	Framingham Heart Study
FINRISK	Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases
FUTURE	Follow-up of TIA and Stroke Patients and Unelucidated Risk Factor Evaluation
GBD	Global Burden of Disease
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
GFR	glomerular filtration rate
GWAS	genome wide association study
GWTG	Get With The Guidelines
HBP	high blood pressure
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICH	intracerebral hemorrhage
IHD	ischemic heart disease
IL	interleukin
IMT	intima-media thickness
IQR	interquartile range
IRR	incidence rate ratio
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MCP-1/ CCL2	monocyte chemoattractant protein-1
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MIDAS	Myocardial Infarction Data Acquisition System
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	magnetic resonance imaging
MUFA	monounsaturated fatty acid
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey

(*Continued*)

Abbreviations Used in Chapter 14 Continued

NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
NIS	National (Nationwide) Inpatient Sample
NOMAS	Northern Manhattan Study
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
OR	odds ratio
OSA	obstructive sleep apnea
PA	physical activity
PAR	population attributable risk
PE	pulmonary embolism
PHS	Physicians' Health Study
PREVAIL	Prevention of VTE After Acute Ischemic Stroke With LMWH Enoxaparin
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PROFESS	Prevention Regimen for Effectively Avoiding Second Stroke
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
REVASCAT	Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset
RR	relative risk
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SHS	Strong Heart Study
SNP	single-nucleotide polymorphism
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
STOP	Stroke Prevention Trial in Sickle Cell Anemia
SVT	supraventricular tachycardia
SWIFT PRIME	Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment
TC	total cholesterol
TIA	transient ischemic attack
tPA	tissue-type plasminogen activator
UI	uncertainty interval
VTE	venous thromboembolism
WHI	Women's Health Initiative

- An estimated 7.0 million Americans ≥20 years of age self-report having had a stroke (extrapolated to 2016 by use of NHANES 2013–2016 data). Overall stroke prevalence during this period was an estimated 2.5% (Table 14-1).
- Prevalence of stroke in the United States increases with advancing age in both males and females (Chart 14-1).
- According to data from the 2017 BRFSS[1] (unpublished NHLBI tabulation):
  - Stroke prevalence in adults is 3.0% (median) in the United States, with the lowest prevalence in Wisconsin (1.9%) and the highest prevalence in Arkansas (4.5%).
- The prevalence of stroke-related symptoms was found to be relatively high in a general population free of a prior diagnosis of stroke or TIA, which suggests that stroke may be underdiagnosed, that other conditions mimic stroke, or both. On the basis of data from 18462 participants enrolled in a national cohort study, 17.8% of the population >45 years of age reported at least 1 symptom.[2] Stroke symptoms were more likely among blacks than whites, among those with lower income and lower educational attainment, and among those with fair to poor perceived health status. Symptoms also were more likely in participants with higher Framingham stroke risk scores (REGARDS, NINDS).
- Projections show that by 2030, an additional 3.4 million US adults ≥18 years of age, representing 3.9% of the adult population, will have had a stroke, a 20.5% increase in prevalence from 2012.[3] The highest increase (29%) is projected to be in white Hispanic males.

Stroke Incidence (See Table 14-1 and Chart 14-2)

- Each year, ≈795000 people experience a new or recurrent stroke (Table 14-1). Approximately 610000 of these are first attacks, and 185000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS and NINDS data for 1999 provided July 9, 2008; unpublished estimates compiled by NHLBI).
- Of all strokes, 87% are ischemic, 10% are ICH, and 3% are SAH (GCNKSS, NINDS, 1999; unpublished NHLBI tabulation).
- On average, every 40 seconds, someone in the United States has a stroke (AHA computation based on the latest available data).

Temporal Trends

- In the NIS, from 1995 to the period 2011 to 2012, rates of hospitalization for acute ischemic stroke almost doubled for males 18 to 34 and 35 to 44 years of age.[4] Hospitalization rates for ICH and SAH remained stable, however, with the exception of declines among males and NH black patients 45 to 54 years of age with SAH (see Stroke in Young Adults and in the Midlife).
- In the multicenter ARIC study of black and white adults, stroke incidence rates decreased from 1987 to 2011. The decreases varied across age groups but were similar across sex and race.[5]
- Data from the BASIC Project for the time period 2000 through 2010 demonstrated that ischemic

stroke rates declined significantly in people ≥60 years of age but remained largely unchanged over time in those 45 to 59 years of age.
  - Rates of stroke decline did not differ significantly for NH whites and Mexican Americans overall in any age group; however, ethnic disparities in stroke rates persist between Mexican Americans and NH whites in the 45- to 59-year-old and 60- to 74-year-old age groups.[6]
  - Data from the BASIC Project showed that the age-, sex-, and ethnicity-adjusted incidence of ICH decreased from 2000 to 2010, from an annual incidence rate of 5.21 per 10 000 (95% CI, 4.36–6.24) to 4.30 per 10 000 (95% CI, 3.21–5.76).[7]
- Analysis of data from the FHS suggests that stroke incidence is declining over time in this largely white cohort in the northeastern United States. Data from 1950 to 1977, 1978 to 1989, and 1990 to 2004 showed that the age-adjusted incidence of first stroke per 1000 person-years in each of the 3 periods was 7.6, 6.2, and 5.3 in males and 6.2, 5.8, and 5.1 in females, respectively. Lifetime risk for incident stroke at 65 years of age decreased significantly in the latest data period compared with the first, from 19.5% to 14.5% in males and from 18.0% to 16.1% in females.[8] Data from the Tromsø Study found that changes in cardiovascular risk factors accounted for 57% of the decrease in ischemic stroke incidence for the time period from 1995 to 2012.[9]
- Despite encouraging data about declining stroke incidence, the aging population and accumulating risk factors contribute to an increasing lifetime risk of stroke. Per the GBD 2016 Lifetime Risk of Stroke Collaborators, the mean global lifetime risk of stroke increased from 22.8% in 1990 to 24.9% in 2016, a relative increase of 8.9% (95% UI, 6.2%–11.5%) after accounting for the competing risk of death attributable to any cause other than stroke.[10]
- In a systematic review/meta-analysis of trends in ischemic stroke subtypes between 1993 and 2015, an increasing temporal trend was noted for cardioembolism in whites (2.4% annually; P=0.008) and for large artery atherosclerosis in Asians (5.7% annually, P<0.001), with a corresponding decrease in small artery occlusion in whites (–4.7% annually, P=0.001).[11]

Race/Ethnicity

- Annual age-adjusted incidence for first-ever stroke was higher in black individuals than white individuals in data collected in 1993 to 1994, 1999, and 2005 for each of the following stroke types: ischemic stroke, ICH, and SAH (Chart 14-2).
- In the national REGARDS cohort, in 27 744 participants followed up for 4.4 years (2003–2007), the overall age- and sex-adjusted black/white IRR was 1.51, but for those 45 to 54 years of age, it was 4.02, whereas for those ≥85 years of age, it was 0.86.[12] Similar trends for decreasing black/white IRR with older age were seen in the GCNKSS.[13]
- The BASIC Project (NINDS) demonstrated an increased incidence of stroke among Mexican Americans compared with NH whites in a community in southeast Texas. The crude 3-year cumulative incidence (2000–2002) was 16.8 per 1000 in Mexican Americans and 13.6 per 1000 in NH whites. Specifically, Mexican Americans had a higher cumulative incidence of ischemic stroke than NH whites at younger ages (45–59 years of age: RR, 2.04 [95% CI, 1.55–2.69]; 60–74 years of age: RR, 1.58 [95% CI, 1.31–1.91]) but not at older ages (≥75 years of age: RR, 1.12 [95% CI, 0.94–1.32]). Mexican Americans also had a higher incidence of ICH and SAH than NH whites after adjustment for age.[14]
- The age-adjusted incidence of first ischemic stroke per 1000 was 0.88 in whites, 1.91 in blacks, and 1.49 in Hispanics according to data from NOMAS (NINDS) for 1993 to 1997. Among blacks, compared with whites, the RR of intracranial atherosclerotic stroke was 5.85 (95% CI, 1.82–18.73); extracranial atherosclerotic stroke, 3.18 (95% CI, 1.42–7.13); lacunar stroke, 3.09 (95% CI, 1.86–5.11); and cardioembolic stroke, 1.58 (95% CI, 0.99–2.52). Among Hispanics, compared with whites, the relative rate of intracranial atherosclerotic stroke was 5.00 (95% CI, 1.69–14.76); extracranial atherosclerotic stroke, 1.71 (95% CI, 0.80–3.63); lacunar stroke, 2.32 (95% CI, 1.48–3.63); and cardioembolic stroke, 1.42 (95% CI, 0.97–2.09).[15]
- Among 4507 American Indian or Alaska Native participants without a prior stroke in the SHS from 1989 to 1992, the age- and sex-adjusted incidence of stroke through 2004 was 6.79 per 100 person-years, with 86% of incident strokes being ischemic.[16]
- In REGARDS, the increased risk of ICH with age differed between blacks and whites: there was a 2.25-fold (95% CI, 1.63–3.12) increase per decade older age in whites but no age association of ICH risk in blacks (HR, 1.09 [95% CI, 0.70–1.68] per decade older age).[17]

Sex

- Each year, ≈55 000 more females than males have a stroke (GCNKSS, NINDS).[18]
- Females have a higher lifetime risk of stroke than males. In the FHS, lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for females

(95% CI, 20%–21%) and ≈1 in 6 for males (95% CI, 14%–17%).[19]

- Age-specific incidence rates are substantially lower in females than males in younger and middle-age groups, but these differences narrow so that in the oldest age groups, incidence rates in females are approximately equal to or even higher than in males.[20–25]
- In the GCNKSS, sex-specific incidence rates between 1993 to 1994 and 2010 declined significantly for males but not for females. This trend was seen for all strokes and ischemic stroke but not for hemorrhagic stroke.[26]

TIA: Prevalence, Incidence, and Prognosis

- In a nationwide survey of US adults, the estimated prevalence of self-reported physician-diagnosed TIA increased with age and was 2.3% overall, which translates to ≈5 million people. The true prevalence of TIA is likely to be greater, because many patients who experience neurological symptoms consistent with a TIA fail to report them to their healthcare provider.[27]
- A 2013 survey study of nearly 600 000 people in China led to a neurologist-confirmed TIA prevalence of 1.03 per 1000 people, with a slightly higher prevalence in females (1.15) than males (0.92).[28]
- In an Italian community-based registry (2007 to 2009), the crude TIA incidence rate was 0.52 per 1000,[29] and in a population-based registry from Dijon, France (2013–2015), the incidence was 0.61 per 1000.[30] In China, 2013 TIA incidence was 0.24 per 1000 person-years.[28]
- Incidence of TIA increases with age and varies by sex and race/ethnicity. Males, blacks, and Mexican Americans have higher rates of TIA than their female and NH white counterparts.[14,31] Conversely, in China, incidence was slightly higher in females (0.26 per 1000 person-years) than males (0.21).[28]
- TIAs confer a substantial short-term risk of stroke, hospitalization for CVD events, and death. Of 1707 TIA patients evaluated in the EDs of Kaiser Permanente Northern California from 1997 to 1998, 180 (11%) experienced a stroke within 90 days, and 91 (5%) had a stroke within 2 days. Predictors of stroke included age >60 years, DM, focal symptoms of weakness or speech impairment, and symptoms that lasted >10 minutes. These factors were used to create the ABCD2 scoring system, which allows for risk stratification after TIA.[32,33]
- Meta-analyses of cohorts of patients with TIA have shown the short-term risk of stroke after TIA to be ≈3% to 10% at 2 days and 9% to 17% at 90 days.[34,35]
- Prognosis after TIA may have improved over time. In a nationwide study from Sweden from 2012 to 2013, patients with low-risk TIA (ABCD2 score 0–3) had a 2.5% risk of stroke during an average of 1.7 years of follow up versus a high-risk TIA group (ABCD2 score 4–7) with a 5.2% risk.[36]
- Individuals who have a TIA and survive the initial high-risk period have a 10-year stroke risk of roughly 19% and a combined 10-year stroke, MI, or vascular death risk of 43% (4% per year).[37]
- In the GCNKSS, the 1-year mortality rate after a TIA was 12%.[31]
- In the community-based Oxford Vascular Study, among patients with TIA, disability levels increased from 14% (modified Rankin scale >2) before the TIA to 23% at 5 years after the TIA (P=0.002). In this same study, the 5-year risk of institutionalization after TIA was 11%.[38]
- In a meta-analysis of 47 studies,[39] it was estimated that approximately one-third of TIA patients have an acute lesion present on diffusion-weighted MRI and thus would be classified as having had a stroke under a tissue-based case definition[40,41]; however, substantial between-study heterogeneity was noted.

Recurrent Stroke: Incidence and Risk

- Among 128 789 Medicare beneficiaries from 1999 to 2013, the incidence of recurrent stroke per 1000 person-years was 108 (95% CI, 106–111) for whites and 154 (95% CI, 147–162) for blacks. Mortality after recurrence was 16% (95% CI, 15%–18%) for whites and 21% (95% CI, 21%–22%) for blacks. Compared with whites, blacks had higher risk of 1-year recurrent stroke (adjusted HR, 1.36 [95% CI, 1.29–1.44]) but lower risk of 30-day mortality after recurrence (adjusted RR, 0.82 [95% CI, 0.73–0.93]).[42]
- In a meta-analysis of publications through September 2017, MRI findings of multiple lesions (pooled RR, 1.7 [95% CI, 1.5–2.0]), multiple-stage lesions (pooled RR, 4.1 [95% CI, 3.1–5.5]), multiple-territory lesions (pooled RR, 2.9 [95% CI, 2.0–4.2]), chronic infarcts (pooled RR, 1.5 [95% CI, 1.2–1.9]), and isolated cortical lesions (pooled RR, 2.2 [95% CI, 1.5–3.2]) were associated with increased risk of ischemic stroke recurrence. A history of stroke or TIA was also associated with higher risk (pooled RR, 2.5 [95% CI, 2.1–3.1]). Risk of recurrence was lower for small- versus large-vessel stroke (pooled RR, 0.3 [95% CI, 0.1–0.7]) and for stroke resulting from an undetermined cause versus large-artery atherosclerosis (pooled RR, 0.5 [95% CI, 0.2–1.1]).[43]
- Children with arterial ischemic stroke, particularly those with arteriopathy, remain at high risk for

recurrent arterial ischemic stroke despite increased use of antithrombotic agents. The cumulative stroke recurrence rate was 6.8% (95% CI, 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year.[44] The 1-year recurrence rate was 32% (95% CI, 18%–51%) for moyamoya, 25% (95% CI, 12%–48%) for transient cerebral arteriopathy, and 19% (95% CI, 8.5%–40%) for arterial dissection.

- Among 6700 patients with first-ever ischemic stroke or ICH who survived the first 28 days in the Northern Sweden MONICA stroke registry from 1995 to 2008, the cumulative risk of recurrence was 6% at 1 year, 16% at 5 years, and 25% at 10 years.[45] The risk of stroke recurrence decreased 36% between 1995 to 1998 and 2004 to 2008. Approximately 62% of all recurrent strokes after ICH (63 of 101) were ischemic.
- Using data for 12 392 patients 18 to 45 years of age who were hospitalized with ischemic or hemorrhagic stroke and included in the 2013 National Readmissions Database, the rate of recurrent stroke per 100 000 index hospitalizations was 1814.0 at 30 days, 2611.1 at 60 days, and 2913.3 at 90 days.[46] Among patients without vascular risk factors at the index stroke (ie, hypertension, hypercholesterolemia, DM, smoking, AF/atrial flutter), rates per 100 000 hospitalizations were 1461.9 at 30 days, 2203.6 at 60 days, and 2534.9 at 90 days. DM was associated with greater risk of recurrent stroke in multivariable analyses (HR, 1.5 [95% CI, 1.22–1.84]).

Stroke Risk Factors

For prevalence and other information on any of these specific risk factors, refer to the specific risk factor chapters.

- In analyses using data from the GBD Study, 91% of the stroke risk could be attributed to modifiable risk factors, such as HBP, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction, and 74% could be attributed to behavioral risk factors, such as smoking, sedentary lifestyle, and an unhealthy diet.[47] Globally, 29% of the risk of stroke was attributable to air pollution.

High BP
(See Chapter 8 for more information.)

- The evidence-based 2017 Hypertension Clinical Practice Guidelines recommend intensive BP control for primary and secondary stroke prevention. The guideline proposes a target BP of <130/80 mm Hg.[48] The recommendations are supported by an extensive evidence document accompanying the guidelines that shows consistent results from trials and meta-analyses for the lower BP target for lower stroke risks and prevention.[49]
- In a recent meta-analysis, 9 trials showed high-strength evidence that BP control to <150/90 mm Hg reduces stroke (RR, 0.74 [95% CI, 0.65–0.84]), and 6 trials yielded low- to moderate-strength evidence that lower targets (≤140/85 mm Hg) are associated with significant decreases in stroke (RR, 0.79 [95% CI, 0.59–0.99]).[50]
- A special report identified the highly significant global implications of the hypertension treatment and control strategies implementation on stroke risk reduction around the world.[51]
  - There was agreement across meta-analyses that intensive BP lowering appears to be most beneficial for reduction in risk of stroke.[52–54]
  - Median SBP declined 16 mm Hg between 1959 and 2010 for different age groups in association with large, accelerated reductions in stroke mortality.[55] In a meta-analysis, there was an average decline of 41% (95% CI, 33%–48%) in stroke incidence with SBP reductions of 10 mm Hg or DBP reductions of 5 mm Hg.[56]
- Recent analyses determined that in both SPRINT and ACCORD participants, there was no increase in stroke risk with intensive lowering of SBP to achieve mean arterial pressure values below 60 mm Hg, which suggests that stroke risks in hypertensive patients do not increase with extremely low mean arterial pressure or pulse pressure values.[57]
- The consistent results from 3 recent additional meta-analyses[58–60] indicated that SBP <130 mm Hg may be the most clinically advantageous BP target in the prevention of stroke.
- Because many current hypertension treatment and control guidelines are risk based, risk prediction models include elevated BP and hypertension as key parameters in the assessment of cardiovascular and stroke risk in the determination of management protocols.[61]
- A recent scientific statement from the AHA identified resistant hypertension, defined as above-goal elevated BP of 130/80 mm Hg in a patient despite the concurrent use of 3 antihypertensive drug classes, as being significantly associated with greater risks of adverse cardiovascular events, including stroke.[62]
- In recent analyses of the SPS3 trial participants, survivors of lacunar stroke with high (top tertile) white matter hyperintensity burden were most likely to benefit from intensive BP control in preventing recurrent stroke.[63]

- In a recent commentary regarding the impact of lower target BPs in hypertension management guidelines, the World Hypertension League noted that the trend in lower levels was associated with lower stroke mortality rates.[64]

Diabetes Mellitus (See Chapter 9 for more information.)

- DM increases ischemic stroke incidence at all ages, but this risk is most prominent (risk ratio >5) before 65 years of age in both blacks and whites. Overall, ischemic stroke patients with DM are younger and more likely to have HBP, MI, and high cholesterol than nondiabetic patients.[65]
- The association between DM and stroke risk differs between sexes. A systematic review of 64 cohort studies representing 775 385 individuals and 12 539 strokes revealed that the pooled, fully adjusted RR of stroke associated with DM was 2.28 (95% CI, 1.93–2.69) in females and 1.83 (95% CI, 1.60–2.08) in males.[66] Compared with males with DM, females with DM had a 27% greater RR for stroke when baseline differences in other major cardiovascular risk factors were taken into account (pooled ratio of RR, 1.27 [95% CI, 1.10–1.46]; I^2=0%).
- Prediabetes, defined as impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance, may be associated with a higher future risk of stroke, but the RRs are modest. A meta-analysis of 15 prospective cohort studies including 760 925 participants revealed that when prediabetes was defined as fasting glucose of 110 to 125 mg/dL (5 studies), the adjusted RR for stroke was 1.21 (95% CI, 1.02–1.44; *P*=0.03).[67]
- DM is an independent risk factor for stroke recurrence; a meta-analysis of 18 studies involving 43 899 participants with prior stroke revealed higher stroke recurrence in patients with DM than in those without (HR, 1.45 [95% CI, 1.32–1.59]).[68]
- In the GWTG-Stroke registry, DM was associated with a higher risk of adverse outcomes over 3 years after stroke, including all-cause mortality (adjusted HR, 1.24 [95% CI, 1.23–1.25]), all-cause hospital readmission (adjusted HR, 1.22 [95% CI, 1.21–1.23]), a composite of mortality and cardiovascular readmission (adjusted HR, 1.19 [95% CI, 1.18–1.20]), and ischemic stroke/TIA readmission (adjusted HR, 1.18 [95% CI, 1.16–1.20]).[69]
- In a meta-analysis of 11 RCTs that included 56 161 patients with type 2 DM and 1835 stroke cases, those who were randomized to intensive glucose control did not have a reduction in stroke risk compared with those with conventional glucose control (RR, 0.94 [95% CI, 0.84–1.06]; *P*=0.33; I^2 *P*=0.20); however, there was a 10% reduction in all MI (RR, 0.90 [95% CI, 0.82–0.98]; *P*=0.02; I^2 *P*=0.20).[70]
- A meta-analysis of 28 RCTs involving 96 765 participants with DM revealed that a decrease in SBP by 10 mm Hg was associated with a lower risk of stroke (RR from 21 studies, 0.74 [95% CI, 0.66–0.83]). Significant interactions were observed, with lower RRs (RR, 0.71 [95% CI, 0.63–0.80]) observed among trials with mean baseline SBP ≥140 mm Hg and no significant associations among trials with baseline SBP <140 mm Hg (RR, 0.90 [95% CI, 0.69–1.17]). The associations between BP lowering and stroke risk reduction were present for both the achieved SBP of <130 mm Hg and the ≥130 mm Hg groups.[71]
- The ACCORD study showed that in patients with type 2 DM, targeting SBP to <120 mm Hg did not reduce the rate of cardiovascular events compared with subjects in whom the SBP target was <140 mm Hg, except for the end point of stroke, for which intensive therapy reduced the risk of any stroke (HR, 0.59 [95% CI, 0.39–0.89]) and nonfatal stroke (HR, 0.63 [95% CI, 0.41–0.96]).[72]
- ONTARGET revealed that in both patients with and without DM, the adjusted risk of stroke continued to decrease down to achieved SBP values of 115 mm Hg, whereas there was no benefit for other fatal or nonfatal cardiovascular outcomes below an SBP of 130 mm Hg.[73]
- In NOMAS, duration of DM was associated with ischemic stroke risk (adjusted HR per year with DM, 1.03 [95% CI, 1.02–1.04]).[74]
- The ATRIA Study demonstrated that the duration of DM is a stronger predictor of ischemic stroke than glycemic control for patients with DM and AF.[75] Duration of DM ≥3 years was associated with an increased rate of ischemic stroke (HR, 1.74 [95% CI, 1.10–2.76]) compared with a duration of <3 years.

Disorders of Heart Rhythm (See Chapter 16 for more information.)

- Nonvalvular AF is a powerful risk factor for stroke, independently increasing risk ≈5-fold throughout all ages. The percentage of strokes attributable to AF increases steeply from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age.[76,77]
- An analysis from the FHS demonstrated that the risk of stroke associated with AF declined by 73% in the 50 years from 1958 to 2007.[78] However, analysis from the Olmsted County, MN, database suggests that AF-associated stroke risk has not changed more recently (from 2000 to 2010).[79]
- Because AF is often asymptomatic[80] and frequently undetected clinically,[81] the stroke risk

attributed to AF could be substantially underestimated.[82] In a meta-analysis of 50 studies, AF was detected in ≈24% (95% CI, 17%–31%) of patients with embolic stroke of undetermined source, depending on duration and type of monitoring used.[83]

- In an RCT among patients with cryptogenic stroke, the cumulative incidence of AF detected with an implantable cardiac monitor was 30% by 3 years. Approximately 80% of the first AF episodes were asymptomatic.[84]
- Among 2580 participants ≥65 years of age with hypertension in whom a cardiac rhythm device that included an atrial lead was implanted, 35% developed subclinical tachyarrhythmias (defined as an atrial rate ≥190 beats per minute that lasted ≥6 minutes). These subclinical events were associated with a 2.5-fold increased risk of ischemic stroke or systemic embolism and a 13% PAR for stroke or systemic embolism.[85]
- An analysis of patients from the Veterans Administration showed that among patients with device-documented AF, the presence of relatively brief amounts of AF raised the short-term risk of stroke 4- to 5-fold. This risk was highest in the initial 5 to 10 days after the episode of AF and declined rapidly after longer periods.[86]
- Important risk factors for stroke in the setting of AF include older age, hypertension, HF, DM, previous stroke or TIA, vascular disease, renal dysfunction, and female sex.[87–91] Biomarkers including high levels of troponin and BNP are associated with an increased risk of stroke in AF after adjustment for traditional vascular risk factors.[92]
- In patients with AF who are being treated with anticoagulation, presence of persistent AF versus paroxysmal AF is associated with higher risk of stroke.[93,94]
- Atrial flutter was associated with a lower risk of stroke than AF.[95]
- Other cardiac arrhythmias and ECG findings associated with an increased risk of stroke include paroxysmal SVT; short, irregular SVTs without P waves; short-run atrial tachyarrhythmia (episodes of supraventricular ectopic beats <5 seconds long); PR-interval prolongation >200 ms; abnormal P-wave axis (any value outside 0° to 75° using 12-lead ECGs); elevated P-wave terminal force; and maximal P-wave area.[96]

High Blood Cholesterol and Other Lipids (See Chapter 7 for more information.)

- Overall, the association of each cholesterol subfraction with total stroke has shown inconsistent results, and the data are limited on associations with specific ischemic stroke subtypes.[97–100] For clarity, results for different types of cholesterol (TC, subfractions) are described in this section.
- In a nested case-control analysis using data from the Chinese Kadoorie Biobank prospective study of 489 762 Chinese individuals without prior stroke or HD who were not taking antithrombotic or lipid-modifying drugs (n=5475 ischemic strokes, n=4776 ICH, and n=6290 healthy controls), genetic markers predictive of LDL levels ("genetic instruments") were associated with ischemic stroke, and HDL level inversely associated with ischemic stroke.[101] Each 1.0 mmol/L increase in LDL was associated with a 14% lower risk of ICH, and this relationship held for the genetic instruments of LDL and was similar in those with and without hypertension at baseline. This analysis provides causal evidence that LDL levels are associated directly with ischemic stroke risk and inversely with hemorrhagic stroke risk.
- Another mendelian randomization study of lipid genetics also suggested an increased risk of large-artery ischemic stroke with increased LDL and a lower risk of small-vessel ischemic stroke with increased HDL.[102]
- An association between TC and ischemic stroke has otherwise been found in some prospective studies[103–105] but not others.[97,100,106] In the Women's Pooling Project, which included those <55 years of age without CVD, TC was associated with an increased risk of stroke at the highest quintile (mean cholesterol 7.6 mmol/L) in black (RR, 2.58 [95% CI, 1.05–6.32]) but not white (RR, 1.47 [95% CI, 0.57–3.76]) females.[98] An association of elevated TC with risk of stroke was noted to be present in those 40 to 49 years of age and 50 to 59 years of age but not in other age groups in the Prospective Studies Collaboration.[99] In a meta-analysis of data from 61 cohorts, TC was only weakly associated with risk of stroke, with no significant difference between males and females.[107]
- Elevated TC is inversely associated in multiple studies with hemorrhagic stroke. In a meta-analysis of 23 prospective cohort studies, 1 mmol higher TC was associated with a 15% lower risk of hemorrhagic stroke (HR, 0.85 [95% CI, 0.80–0.91]).[108]
- A meta-analysis of 23 studies performed in the Asia-Pacific region showed no significant association between low HDL-C and stroke risk,[109] although another meta-analysis without geographic restriction demonstrated a protective association of HDL-C with stroke.[100]
- Data from the Honolulu Heart Program found that in Japanese males 71 to 93 years of age, low concentrations of HDL-C were associated with a future risk of thromboembolic stroke.[110]

- A Finnish study of >58 000 individuals followed up for >20 years found an inverse association of HDL-C with the risks of total and ischemic stroke in females.[97] In the CHS, higher HDL-C was associated with a lower risk of ischemic stroke in males but not in females.[111]
- In the SHS, a possible interaction was noted between DM status and HDL-C for risk of stroke such that higher HDL-C was protective against stroke risk in patients with DM but not in those without DM.[112] In a meta-analysis, no significant association was observed between HDL-C levels and risk of hemorrhagic stroke.[108]
- Data from the Dallas Heart Study suggest that higher HDL-C efflux capacity is strongly associated with lower risk of stroke.[113]
- In an analysis by the Emerging Risk Factors Collaboration of individual records on 302 430 people without initial vascular disease from 68 long-term prospective studies, HR for ischemic stroke was 1.12 (95% CI, 1.04–1.20) for non–HDL-C[114] and 0.93 (95% CI, 0.84–1.02) for HDL-C. In the Women's Health Study, LDL-C was associated with an increased risk of stroke,[103] and LDL-C may have a stronger association for large-artery atherosclerotic subtype.[115] In a pooled analysis of CHS and ARIC, low LDLC (<158.8 mg/dL) was associated with an increased risk of ICH.[116]
- Among 13 951 patients in the Copenhagen Heart Study followed up for 33 years, increasing levels of nonfasting triglycerides were associated with increased risk of ischemic stroke in both males and females,[117] although in ARIC, PHS, and SHS, there was no association.[112,118,119] In the Rotterdam Study (N=9068), increasing quartiles of serum triglycerides were associated with a reduced risk of ICH.[120]

Smoking/Tobacco Use (See Chapter 3 for more information.)

- Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for >10 years.[121] Current smoking is associated with an increased prevalence of MRI-defined brain infarcts and small subcortical brain infarcts.[122]
- Cigarette smoking is a risk factor for ischemic stroke and SAH.[121,123]
- Smoking is perhaps the most important modifiable risk factor in preventing SAH, with the highest PAR (38%–43%) of any SAH risk factor.[124]
- In a large Danish cohort study, among people with AF, smoking was associated with a higher risk of ischemic stroke/arterial thromboembolism or death, even after adjustment for other traditional risk factors.[125]
- Although some studies have reported a dose-response relationship between smoking and risk of stroke across old and young age groups,[123,126] a recent meta-analysis of 141 cohort studies showed that low cigarette consumption (≈1 cigarette per day) carries a risk of developing stroke as large as 50% of that of high cigarette consumption (≈20 cigarettes per day).[127] This is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.[127]
- A meta-analysis that compared pooled data of almost 4 million smokers and nonsmokers found a similar risk of stroke associated with current smoking in females and males.[128]
- Discontinuation of smoking has been shown to reduce stroke risk across sex, race, and age groups.[126,128]
- Smoking may impact the effect of other stroke risk factors on stroke risk. For example, a synergistic effect on the risk of stroke appears to exist between smoking and SBP[129] and oral contraceptives.[130,131]
- Exposure to secondhand smoke, also termed *passive smoking* or *secondhand tobacco smoke*, is a risk factor for stroke.
  - Meta-analyses have estimated a pooled RR of 1.25 for exposure to spousal smoking (or nearest equivalent) and risk of stroke. A dose-response relationship between exposure to secondhand smoke and stroke risk was also reported.[132,133]
  - Data from REGARDS found that after adjustment for other stroke risk factors, the risk of overall stroke was 30% higher among nonsmokers who had secondhand smoke exposure during adulthood (95% CI, 2%–67%).[134]
  - Data from another large-scale prospective cohort study of females in Japan showed that secondhand tobacco smoke exposure at home during adulthood was associated with an increased risk of stroke mortality in those ≥80 years of age (HR, 1.24 [95% CI, 1.05–1.46]). Overall, the increased risk was most evident for SAH (HR, 1.66 [95% CI, 1.02–2.70]) in all age groups.[135]
  - A study using NHANES data found that individuals with a prior stroke have greater odds of having been exposed to secondhand smoke (OR, 1.46 [95% CI, 1.05–2.03]), and secondhand smoke exposure was associated with a 2-fold increase in mortality among stroke survivors compared with stroke survivors without the exposure (age-adjusted mortality rate: 96.4±20.8 versus 56.7±4.8 per 100 person-years; P=0.026).[136]

- The FINRISK study found a strong association between current smoking and SAH compared with nonsmokers (HR, 2.77 [95% CI, 2.22–3.46]) and reported a dose-dependent and cumulative association with SAH risk that was highest in females who were heavy smokers.[137]
- Use of smokeless tobacco is associated with an increased risk of fatal stroke.
  - In recent meta-analyses of studies from Europe, North America, and Asia, adult ever-users of smokeless tobacco had a higher risk of fatal stroke (OR, 1.39 [95% CI, 1.29–1.49]).[138,139]
  - US smokeless tobacco users had a higher risk of stroke than nonusers, but this association was not observed in Swedish smokeless tobacco users. This difference may be attributable to differences in product type and use patterns between the 2 countries.[140]
- Microvascular damage, more specifically, widening of the venules because of smoking, may mediate the effect of smoking on the risk of ischemic stroke.[141]

Physical Inactivity (See Chapter 4 for more information.)

- Over a mean follow-up of 17 years, the ARIC study found a significant trend among blacks toward reduced incidence of stroke with increasing level of PA; a similar trend was observed for whites in the study, although it was not statistically significant. Data from this study showed that although the highest levels of activity were most protective, even modest levels of PA appeared to be beneficial.[142]
- Among individuals >80 years of age in NOMAS, physical inactivity was associated with higher risk of stroke (physical inactivity versus PA: HR, 1.60 [95% CI, 1.05–2.42]).[143]
- In the CHS, a greater amount of leisure-time PA (across quintiles, P_{trend}=0.001), as well as exercise intensity (categories: high, moderate, low versus none, P_{trend}<0.001), were both associated with lower risk of stroke among individuals >65 years of age. The relation between greater PA and lower risk of stroke was even observed in individuals ≥75 years of age.[144] In the Cooper Center Longitudinal Study of participants who underwent evaluation at the Cooper Clinic in Dallas, TX, investigators found that cardiorespiratory fitness in midlife as measured by exercise treadmill testing was inversely associated with risk of stroke in older age, including in models that were adjusted for the interim development of stroke risk factors such as DM, hypertension, and AF.[145]
- Similarly, a prospective study of young Swedish males demonstrated that the lowest, compared with the highest, tertiles of fitness (HR, 1.70 [95% CI, 1.50–1.93]) and muscle strength (HR, 1.39 [95% CI, 1.27–1.53]) were associated with higher risk of stroke over 42 years of follow-up.[146]
- Several recent prospective studies found associations of PA and stroke risk in females.
  - In the Million Women Study, a prospective cohort study among females in England and Scotland, over an average follow-up of 9 years, self-report of any PA at baseline was associated with reduced risk of any stroke; however, more frequent or strenuous activity was not associated with increased protection against stroke.[147]
  - Similarly, a low level of leisure-time PA was associated with a 1.5 times higher risk of stroke and a 2.4 times higher risk of fatal stroke compared with intermediate to high levels of activity in a cohort of ≈1500 Swedish females followed up for up to 32 years.[148]
  - In the California Teachers Study of 61 256 females with PA data, meeting AHA guidelines of moderate PA was associated with a lower risk of ischemic stroke. No association was observed between meeting AHA guidelines for strenuous activity and risk of stroke.[149]
  - The EPIC-Heidelberg cohort included 25 000 males and females and identified stroke outcomes over a mean of 13 years of follow-up. Among females, participation in any level of PA was associated with a nearly 50% reduction in stroke risk compared with inactivity; no similar pattern was seen for males.[150]
- A dose-response effect was seen for total number of hours spent walking per week, and increased walking time was associated with reduced risk of incident stroke among 4000 males in the British Regional Heart Study. Those reporting ≥22 hours of walking per week had one-third the risk of incident stroke as those who walked <4 hours per week. No clear association between stroke and walking speed or distance walked was seen in this study.[151]
- Recent studies have also demonstrated a significant association between sedentary time duration and risk of CVD including stroke, independent of PA levels.[152,153] In the REGARDS study, screen time >4 h/d was associated with 37% higher risk (HR, 1.37 [95% CI, 1.10–1.71]) of stroke over a 7-year follow-up.[154]
- In a population-based study of 74 913 Japanese people 50 to 79 years of age and without histories of CVD or cancer, there was a nonlinear

dose-response relationship between daily total PA and stroke risk. Individuals with moderate levels of total PA had the lowest risk of total stroke (HR, 0.83 [95% CI, 0.75–0.93]), hemorrhagic stroke (HR, 0.79 [95% CI, 0.66–0.94]), and ischemic stroke (HR, 0.79 [95% CI, 0.69–0.90]). The associations of total PA level with hemorrhagic stroke showed a U or J shape, and that with ischemic stroke showed an L shape.[155]

Nutrition
(See Chapter 5 for more information.)

- Adherence to a Mediterranean-style diet that was higher in nuts and olive oil was associated with a reduced risk of stroke (diet with nuts: HR, 0.54 [95% CI, 0.35–0.82]; diet with olive oil: HR, 0.65 [95% CI, 0.44–0.95]; Mediterranean diets combined versus control: HR, 0.58 [95% CI, 0.42–0.82]) in an RCT conducted in Spain.[156]
- A recent review of trials and studies concluded that diet is a major modifiable risk factor for stroke globally and a major modifiable determinant of the global burden of stroke and identified the importance of specific foods and overall food quality and dietary patterns, rather than isolated single nutrients or metrics (eg, calorie counting), in contributing to the risk and burden of stroke.[157]
- A meta-analysis of >94 000 people with 34 817 stroke events demonstrated that eating ≥5 servings of fish per week versus eating <1 serving per week was associated with a 12% reduction in stroke risk; however, these results were not consistent across all cohort studies.[158]
- A recent study from China provided preliminary evidence that change in salt intake was a factor in stroke risks; individuals with a moderate-decreasing salt intake trajectory had significantly lower ischemic stroke risk (adjusted HR, 0.76 [95% CI, 0.63–0.92]) than individuals with a moderate-stable salt intake trajectory.[159]
- A Nordic diet, including fish, apples, pears, cabbages, root vegetables, rye bread, and oatmeal, was associated with a decreased risk of stroke among 55 338 males and females (HR, 0.86 [95% CI, 0.76–0.98] for high versus low diet adherence).[160]
- A meta-analysis of case-control and prospective cohort studies and an RCT investigating the association between olive oil consumption and the risk of stroke (N=38 673 participants) revealed a reduction in stroke risk (RR, 0.74 [95% CI, 0.60–0.92]).[161]
- A meta-analysis of 10 prospective cohort studies including 314 511 nonoverlapping individuals revealed that higher MUFA intake was not associated with risk of overall stroke (RR, 0.86 [95% CI, 0.74–1.00]) or risk of ischemic stroke (RR, 0.92 [95% CI, 0.79–1.08]) but was associated with a reduced risk of hemorrhagic stroke (RR, 0.68 [95% CI, 0.49–0.96]).[162]
- A meta-analysis of prospective cohort studies evaluating the impact of dairy intake on CVD noted that total dairy intake and calcium from dairy were associated with an inverse summary RR estimate for stroke (0.91 [95% CI, 0.83–0.99] and 0.69 [95% CI, 0.60–0.81], respectively).[163]
- A meta-analysis of 20 prospective cohort studies of the association between nut consumption and cardiovascular outcomes (N=467 389) revealed no association between nut consumption and stroke (2 studies; RR, 1.05 [95% CI, 0.69–1.61]) but did find an association with stroke mortality (3 studies; RR, 0.83 [95% CI, 0.69–1.00]).[164]
- A meta-analysis of 8 prospective studies (N=410 921) revealed no significant association between consumption of refined grains and risk of stroke.[165] A second meta-analysis[166] of 8 prospective studies (N=468 887) revealed that a diet that contained greater amounts of legumes was not associated with a lower risk of stroke; however, a diet with greater amounts of nuts was associated with lower risk of stroke (summary RR, 0.90 [95% CI, 0.81–0.99]). Sex significantly modified the effects of nut consumption on stroke risk, and high nut intake was associated with reduced risk of stroke in females (summary RR, 0.85 [95% CI, 0.75–0.97]) but not in males (summary RR, 0.95 [95% CI, 0.82–1.11]).[166]
- A recent meta-analysis confirmed an inverse association between potassium intake and stroke risk, with the highest category of potassium intake associated with a 13% reduced risk of stroke (RR, 0.87 [95% CI, 0.80–0.94]) in the BP-adjusted analysis.[167]
- A meta-analysis of 8 studies (N=280 174) indicated an inverse association between flavonol intake and stroke (summary RR, 0.86 [95% CI, 0.75–0.99]). An increase in flavonol intake of 20 mg/d was associated with a 14% decrease in the risk for developing stroke (summary RR, 0.86 [95% CI, 0.77–0.96]). Subgroup analyses suggested an inverse association between highest flavonol intake and stroke risk among males (summary RR, 0.74 [95% CI, 0.56–0.97]) but not females (summary RR, 0.99 [95% CI, 0.85–1.16]).[168]
- In a population of Chinese adults, folate therapy combined with enalapril was associated with a significant reduction in ischemic stroke risk (HR, 0.76 [95% CI, 0.64–0.91]). Although the US population is not as likely to be at risk of folate deficiency because of folate fortification of grains, this study demonstrates the importance of adequate folate levels for stroke prevention.[169]

- In the WHI prospective cohort study (n=81 714 females for this analysis), females who consumed ≥2 artificially sweetened beverages daily, on average, had an elevated risk of all stroke (adjusted HR 1.23 [95% CI, 1.02–1.47]) and ischemic stroke (adjusted HR, 1.31 [95% CI 1.06–1.63]) compared with those who consumed <1 artificially sweetened beverage weekly, after adjusting for demographics, CVD history, risk factors, BMI, health behaviors, and overall diet quality.[170]
- A study using data from the FHS Offspring cohort found that recent consumption and an increased cumulative intake of artificially sweetened soft drinks was associated with a higher risk of stroke, with the strongest association observed for ischemic stroke; no association was observed for sugary beverages or sugar-sweetened soft drinks.[171]

Kidney Disease (See Chapter 11 for more information.)

- A meta-analysis of 21 studies including >280 000 patients showed a 43% (RR, 1.43 [95% CI, 1.31–1.57]) increased incident stroke risk among patients with a GFR <60 mL·min^{-1}·1.73 m^{-2}.[172]
- A meta-analysis showed that a higher albuminuria level confers greater stroke risk, providing evidence that albuminuria is strongly linked to stroke risk, and suggested that people with elevated levels of urinary albumin excretion could benefit from more intensive vascular risk reduction.[173]
- A meta-analysis showed stroke risk increases linearly and additively with declining GFR (RR per 10 mL·min^{-1}·1.73 m^{-2} decrease in GFR, 1.07 [95% CI, 1.04–1.09]) and increasing albuminuria (RR per 25 mg/mmol increase in ACR, 1.10 [95% CI, 1.01–1.20]), which indicates that CKD staging might also be a useful clinical tool to identify people who might benefit most from interventions to reduce stroke risk.[174]
- A pooled analysis of 4 prospective community-based cohorts (ARIC, MESA, CHS, and PREVEND) including 29 595 participants showed that low eGFR (45 mL·min^{-1}·1.73 m^{-2}) was significantly associated with increased risk of ischemic stroke (HR, 1.30 [95% CI, 1.01–1.68]) but not hemorrhagic stroke (HR, 0.92 [95% CI, 0.47–1.81]) compared with normal GFR (95 mL·min^{-1}·1.73 m^{-2}). A high ACR of 300 mg/g was associated with both ischemic stroke (HR, 1.62 [95% CI, 1.27–2.07]) and hemorrhagic stroke (HR, 2.57 [95% CI, 1.37–4.83]) compared with 5 mg/g.[175]
- Proteinuria and albuminuria are better predictors of stroke risk than eGFR in patients with kidney disease.[176]
- Among 232 236 patients in the GWTG-Stroke registry, admission eGFR (in mL·min^{-1}·1.73 m^{-2}) was inversely associated with mortality and poor functional outcomes. After adjustment for potential confounders, lower eGFR was associated with increased mortality, with the highest mortality among those with eGFR <15 without dialysis (OR, 2.52 [95% CI, 2.07–3.07]) compared with eGFR ≥60. Lower eGFR was also associated with decreased likelihood of being discharged home.[177]
- In a Chinese stroke registry, low eGFR (<60 mL·min^{-1}·1.73 m^{-2}) compared with eGFR ≥90 mL·min^{-1}·1.73 m^{-2} was similarly associated with increased mortality among patients with and without hypertension, but there was an interaction between eGFR and hypertension for the effect on functional outcomes. In 5082 patients without hypertension, the risk of a poor functional outcome (defined as modified Rankin scale score of 3–6) was approximately twice as high for those with low eGFR (adjusted OR, 2.14 [95% CI, 1.45–3.16]). In 1378 patients with previously diagnosed hypertension, the magnitude of risk of a poor functional outcome associated with low eGFR was less (adjusted OR, 1.30 [95% CI, 1.11–1.52]; *P* for interaction=0.046).[178]

Risk Factor Issues Specific to Females

See the "Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" for more in-depth coverage of stroke risk factors unique to females.[179]

- In a meta-analysis of 11 studies of stroke incidence published between 1990 and January 2017, the pooled crude rate of pregnancy-related stroke was 30.0 per 100 000 pregnancies (95% CI, 18.8–47.9). The crude rates per 100 000 pregnancies were 18.3 (95% CI, 11.9–28.2) for antenatal/perinatal stroke and 14.7 (95% CI, 8.3–26.1) for postpartum stroke.[180]
- Among 80 191 parous females in the WHI Observational Study, those who reported breastfeeding for at least 1 month had a 23% lower risk of stroke than those who never breastfed (HR, 0.77 [95% CI, 0.70–0.83]). The strength of the association increased with increasing breastfeeding duration (1–6 months: HR, 0.81 [95% CI, 0.74–0.90]; 7–12 months: HR, 0.75 [95% CI, 0.66–0.85]; ≥13 months: HR, 0.74 [95% CI, 0.65–0.83]; *P* for trend<0.01). The strongest association was observed among NH black females (HR, 0.54 [95% CI, 0.37–0.71]).[181]
- Although the incidence of stroke is higher in males than in females, this difference is less pronounced with increasing age and is only partially explained by established risk factors such as hypertension, smoking, and IHD that are more prevalent in males.[182]

- In a systematic review and meta-analysis of 78 studies including >10 million participants, any hypertensive disorder during pregnancy, including gestational hypertension, preeclampsia, or eclampsia, was associated with a greater risk of ischemic stroke; late menopause (after 55 years of age) and gestational hypertension were associated with a greater risk of hemorrhagic stroke; and oophorectomy, hypertensive disorder during pregnancy, preterm delivery, and stillbirth were associated with a greater risk of any stroke.[183]
- In the setting of AF, females have a significantly higher risk of stroke than males.[184–188]
- In the UK Million Women Study, there was a U-shaped relationship between age at menarche and risk of incident stroke.[189] Compared with females experiencing menarche at 13 years of age, both those experiencing menarche at ≤10 years of age and those experiencing menarche at ≥17 years of age had an increased risk of stroke (RR, 1.16 [95% CI, 1.09–1.24] and RR, 1.13 [95% CI, 1.03–1.24], respectively).
- In a meta-analysis of 32 studies, females who experienced menopause before 45 years of age had an increased risk of stroke compared with females ≥45 years of age at menopause onset (OR, 1.23 [95% CI, 0.98–1.53]). This association was not observed for stroke mortality (OR, 0.99 [95% CI, 0.92–1.07]).[190]
- Overall, randomized clinical trial data indicate that the use of estrogen plus progestin, as well as estrogen alone, increases stroke risk in postmenopausal, generally healthy females and provides no protection for postmenopausal females with established CHD[191–194] and recent stroke or TIA.[195]
- In a nested case-control study of the UK's General Practice Research Database, stroke risk was not increased for users of low-dose (≤50 μg) estrogen patches (RR, 0.81 [95% CI, 0.62–1.05]) but was increased for users of high-dose (>50 μg) patches (RR, 1.89 [95% CI, 1.15–3.11]) compared with nonusers.[196]
- Migraine with aura is associated with ischemic stroke in younger females, particularly if they smoke or use oral contraceptives. The combination of all 3 factors increases the risk ≈9-fold compared with females without any of these factors.[197,198]
- Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.[199] Compared with HIV-uninfected females, females living with HIV had a 2-fold higher incidence of ischemic stroke.[200]

Sleep-Disordered Breathing and Sleep Duration (See Chapter 12 for more information.)

- Sleep-disordered breathing is associated with stroke risk. In a 2017 meta-analysis including 16 cohort studies (N=24 308 individuals), severe OSA was associated with a doubling in stroke risk (RR, 2.15 [95% CI, 1.42–3.24]). Severe OSA was independently associated with stroke risk among males, but not females, in stratified analyses. Neither mild nor moderate OSA was associated with stroke risk.[201]
- OSA may be particularly associated with stroke occurring at the time of waking up ("wake-up stroke"). In a meta-analysis of 5 studies (N=591 patients), patients with wake-up stroke had a higher AHI than those with non–wake-up stroke, and there was an increased incidence of severe OSA in those with wake-up stroke (OR, 3.18 [95% CI, 1.27–7.93]).[202]
- OSA is also common after stroke.[194,203,204] In a 2017 meta-analysis that included 43 studies, the prevalence of OSA (AHI >10) after stroke and TIA ranged from 24% to 92%, with a pooled estimate of 59%.[205] The proportion of patients with cerebrovascular disease with severe OSA (AHI >30) ranged from 8% to 64%.
- In the BASIC Project, Mexican Americans had a higher prevalence of poststroke sleep-disordered breathing, defined as an AHI ≥10, than NH whites after adjustment for confounders (prevalence ratio, 1.21 [95% CI, 1.01–1.46]).[203]
- Also in the BASIC Project, acute infarction involving the brainstem (versus no brainstem involvement) was associated with increased odds of sleep-disordered breathing, defined as an AHI ≥10, with OR 3.76 (95% CI, 1.44–9.81) after adjustment for demographics, risk factors, and stroke severity.[206] In this same study, ischemic stroke subtype was not found to be associated with the presence or severity of sleep-disordered breathing.[207]
- OSA is associated with higher poststroke mortality[208–210] and worse functional outcome.[211]
- Sleep duration is also associated with stroke risk. In a meta-analysis of 14 prospective cohort studies, long sleep, mostly defined as self-reported sleep of ≥8 to 9 hours per night, was associated with incident stroke, with an HR of 1.46 (95% CI, 1.26–1.69) after adjustment for demographics, vascular risk factors, and comorbidities.[212] In another meta-analysis, short sleep, defined as sleep ≤5 to 6 hours per night, was also associated, although to a lesser magnitude, with incident stroke (HR, 1.15 [95% CI, 1.07–1.24]) after adjustment for similar factors.[213]
- In a 2017 meta-analysis that included 20 reports related to stroke outcomes, there was an approximate U-shaped association between sleep duration and stroke risk, with the lowest risk at a sleep duration of ≈6 to 7 hours daily. Both short and long sleep duration were associated with increased

stroke risk. For every hour of sleep reduction below 7 hours, after adjustment for other risk factors, the pooled RR was 1.05 (95% CI, 1.01–1.09), and for each 1-hour increment of sleep above 7 hours, the RR was 1.18 (95% CI, 1.14–1.21).[214]

- In a meta-analysis of 10 studies, a J-shaped relationship was reported between sleep duration and stroke risk, with the lowest risk among those with a sleep duration of 6 to 7 h/d.[215]

Psychosocial Factors

- A meta-analysis of 28 prospective cohort studies comprising 317 540 participants with a follow-up period that ranged from 2 to 29 years found that depression was associated with an increased risk of total stroke (pooled HR, 1.45 [95% CI, 1.29–1.63]), fatal stroke (pooled HR, 1.55 [95% CI, 1.25–1.93]), and ischemic stroke (pooled HR, 1.25 [95% CI, 1.11–1.40]).[216]
- The relationship between changes in depressive symptoms and risk of first stroke was examined among 4319 participants in the CHS. Compared with participants who had persistently low depressive symptoms, those who had persistently high depressive symptoms for 2 consecutive annual assessments had an increased risk of stroke (adjusted HR, 1.65 [95% CI, 1.06–2.56]). New onset of symptoms was nonsignificantly associated with stroke risk (adjusted HR, 1.44 [95% CI, 0.97–2.14]). There was no increased stroke risk for participants whose depressive symptoms improved (HR, 1.02 [95% CI, 0.66–1.58]).[217]
- In a meta-analysis that included 46 studies (30 on psychological factors, 13 on vocational factors, 10 on interpersonal factors, and 2 on behavioral factors), the risk of stroke increased by 39% with psychological factors (HR, 1.39 [95% CI, 1.27–1.51]), 35% with vocational factors (HR, 1.35 [95% CI, 1.20–1.51]), and 16% with interpersonal factors (HR, 1.16 [95% CI, 1.03–1.31]); there was no significant relationship with behavior factors (HR, 0.94 [95% CI, 0.20–4.31]).[218]
- Among 13 930 patients with ischemic stroke and 28 026 control subjects in the NINDS Stroke Genetics Network, each 1-SD increase in the Psychiatric Genomics Consortium polygenic risk score for major depressive disorder was associated with a 3% increase in the odds of ischemic stroke (OR, 1.03 [95% CI, 1.00–1.05]) for those of European ancestry and an 8% increase (OR, 1.08 [95% CI, 1.04–1.13]) for those of African ancestry.[219] The risk score was associated with increased odds of small-artery occlusion in both ancestry samples (European: OR, 1.08 [95% CI, 1.03–1.13]; African: OR, 1.09 [95% CI, 1.01–1.19]), cardioembolic stroke in those of European ancestry (OR, 1.04 [95% CI, 1.00–1.08]), and large-artery atherosclerosis in those of African ancestry (OR, 1.12 [95% CI, 1.01–1.25]).
- Among 479 054 participants in the UK Biobank study who were followed up for a mean of 7.1 years, social isolation (HR, 1.39 [95% CI, 1.25–1.54]) and loneliness (HR, 1.36 [95% CI, 1.20–1.55]) were associated with higher risk of incident stroke in analyses adjusted for demographic characteristics. However, after adjustment for biological factors, health behaviors, depressive symptoms, socioeconomic factors, and chronic diseases, these relationships were no longer statistically significant. In fully adjusted analyses, social isolation, but not loneliness, was associated with increased risk of mortality after stroke (HR, 1.32 [95% CI, 1.08–1.61]).[220]

Social Determinants

- Adverse work conditions, including job loss and unemployment, have been linked to stroke risk. In a cohort of 21 902 Japanese males and 19 826 females followed up for 19 years, job loss (change in job status within the first 5 years of data collection) was associated with a >50% increase in incident stroke and a >2-fold increase in stroke mortality over follow-up.[221] Long work hours have also been linked to stroke. Meta-analytic findings from 24 cohort studies from the United States, Europe, and Australia revealed a dose-response relationship between working longer than 40 hours per week and incident stroke.[222]
- In ARIC, having smaller social networks (ie, contact with fewer family members, friends, and neighbors) was linked to a 44% higher risk of incident stroke over the 18.6-year follow-up, even after controlling for demographics and other relevant risk factors.[223]
- Findings from MESA have documented linkages between other psychosocial factors (including depressive symptoms, chronic stress, and hostility) and incident stroke, with participants in the highest- versus lowest-scoring categories having a 1.5- to >2-fold increased risk of stroke over a median follow-up of 8.5 years.[224]

Family History and Genetics

- Ischemic stroke is a heritable disease; family history of stroke is associated with increased risk of ischemic stroke, stroke subtypes, and carotid atherosclerosis.[225]
- In the Family Heart Study, the adjusted ORs of stroke for a positive paternal and maternal history of stroke were 2.0 and 1.4, respectively,

with similar patterns seen in blacks and European Americans.[226]

- Heritability of stroke appears to play a larger role in strokes that occur in younger people.[227]
- Genetic factors appear to be more important in large-artery and small-vessel stroke than in cryptogenic or cardioembolic stroke.[227]
- Genetic studies have identified genetic variants associated with risk of ischemic stroke, with distinct genetic associations[228] for different stroke subtypes.
  - For example, variants in the paired-like homeodomain transcription factor 2 gene (*PITX2*) discovered through an unbiased genome-wide approach for AF have been shown to be associated with cardioembolic stroke.[229]
  - Variants in the *HDAC9* gene have been associated with large-artery stroke, as have variants in the chromosome 9p21 locus originally identified through a genome-wide approach for CAD.[230,231]
- The largest multiethnic GWAS of stroke conducted to date reports 32 genetic loci, including 22 not previously reported.[232] These novel loci point to a major role of cardiac mechanisms beyond established sources of cardioembolism. Approximately half of the stroke genetic loci share genetic associations with other vascular traits, most notably BP. The identified loci were also enriched for targets of antithrombotic drugs, including alteplase and cilostazol.
- Some genetic loci were subtype specific. For example, *EDNRA* and *LINC01492* were exclusively associated with large-artery stroke. But shared genetic influences between stroke subtypes were also evident. For example, *SH2B3* showed shared influence on large-artery and small-vessel stroke and *ABO* on large-artery and cardioembolic stroke; *PMF1-SEMA4A* has been associated with both nonlobar ICH and ischemic stroke.
- A GWAS focused on small-vessel stroke from the International Stroke Consortium identified a novel association with a region on chromosome 16q24.2.[233]
- Studies have also identified genetic loci unique to non-European ethnicity populations. For example, one study of blacks from MESA found that variants within the *SERGEF* gene were associated with carotid artery IMT, as well as with stroke.[234]
- Low-frequency genetic variants (ie, allele frequency <5%) may also contribute to risk of large- and small-vessel stroke. *GUCY1A3*, for example, with an allele frequency in the lead SNP of 1.5%, was associated with large-vessel stroke.[234] The gene encodes the α1-subunit of soluble guanylyl cyclase, which plays a role both in nitric oxide–induced vasodilation and platelet inhibition, and has been associated with early MI.
- The gene *GCH1*, also with an allele frequency of only 1.5%, was associated with small-vessel stroke. This gene encodes GTP cyclohydrolase 1, which plays a role in endothelial nitric oxide synthase.[235] Rare variants thus may account for some of the unexplained heritability in stroke risk.
- Monogenic forms of ischemic stroke have much higher risk associated with the underlying genetic variant but are rare.[236]
  - For example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), an autosomal dominant disease presenting with stroke, progressive cognitive impairment, and characteristic bilateral involvement of the anterior temporal white matter and external capsule, is caused by mutations in the *NOTCH3* gene on chromosome 19q12.[237]
  - Other monogenic causes of stroke include Fabry disease, sickle cell disease, homocystinuria, Marfan syndrome, vascular Ehlers-Danlos syndrome (type IV), pseudoxanthoma elasticum, retinal vasculopathy with cerebral leukodystrophy and systemic manifestations, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS).[228]
- ICH also appears to have a genetic component, with heritability estimates of 34% to 74% depending on the subtype.[238] A GWAS of ICH suggests that 15% of this heritability is attributable to genetic variants in the apolipoprotein E gene (*APOE*), and 29% is attributable to non-*APOE* genetic variants.[238]
- Genetic variants that predispose to hypertension also have been associated with ICH risk.[227] The other genes strongly associated with ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.[239,240]
- Genetic predisposition to higher MCP-1/CCL2 concentrations was associated with high risk of any stroke, including associations with large-artery stroke, ischemic stroke, and cardioembolic stroke, but not small-vessel stroke or ICH, implicating inflammation in stroke pathogenesis.[241]
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.[242,243]

Awareness of Stroke Warning Signs and Risk Factors

- Knowledge on stroke risk factors and symptoms is limited in children; stroke knowledge is lowest for those living in communities with greater economic

need and sociodemographic distress and lower school performance.[244]

- A study of CVD awareness performed by the AHA among females in the United States who were >75 years of age (N=1205) showed that low proportions of females identified severe headache (23%), unexplained dizziness (20%), and vision loss/changes (18%) as stroke warning symptoms.[245]
- In a single-center study of 144 stroke survivors, Hispanics scored lower on a test of stroke symptoms and the appropriate response to those symptoms than NH whites (72.5% versus 79.1% of responses correct) and were less often aware of tPA as a treatment for stroke (91.5% versus 79.2%).[246]
- In the 2009 BRFSS (N=132 604), 25% of males versus 21% of females had low stroke symptom knowledge scores (correct response to 0–4 of the 7 survey questions).[247] Sudden confusion or difficulty speaking and sudden numbness or weakness of the face, arm, or leg were the most commonly correctly identified stroke symptoms, whereas sudden headache was the least; 60% of females and 58% of males incorrectly identified sudden chest pain as a stroke symptom.
- In a study of patients with AF, there was a lack of knowledge about stroke subtypes, common symptoms of stroke, and the increased risk of stroke associated with AF.[248] Only 68% of patients without a prior stroke history were able to identify the most common symptoms of stroke.

Stroke Mortality (See Table 14-1 and Charts 14-3 through 14-8)

See "Factors Influencing the Decline in Stroke Mortality: A Statement From the American Heart Association/American Stroke Association"[55] for more in-depth coverage of factors contributing to the decline in stroke mortality over the past several decades.

- In 2017 (unpublished NHLBI tabulations using CDC WONDER[249] and the NVSS[250]):
  - On average, every 3 minutes 35 seconds, someone died of a stroke.
  - Stroke accounted for ≈1 of every 19 deaths in the United States.
  - When considered separately from other CVDs, stroke ranks fifth among all causes of death, behind diseases of the heart, cancer, CLRD, and unintentional injuries/accidents.
  - The number of deaths with stroke as an underlying cause was 146 383 (Table 14-1); the age-adjusted death rate for stroke as an underlying cause of death was 37.6 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 63.3 per 100 000.
  - Approximately 63% of stroke deaths occurred outside of an acute care hospital.
  - In 2017, NH black males and females had higher age-adjusted death rates for stroke than NH white, NH Asian, NH Indian or Alaska Native, and Hispanic males and females in the United States (Chart 14-3).
  - More females than males die of stroke each year because of a larger number of elderly females than males. Females accounted for 58% of US stroke deaths in 2017.
- Conclusions about changes in stroke death rates from 2007 to 2017 are as follows[249]:
  - The age-adjusted stroke death rate decreased 13.6% (from 43.5 per 100 000 to 37.6 per 100 000), whereas the actual number of stroke deaths increased 7.7% (from 135 952 deaths to 146 383 deaths).
  - The decline in age-adjusted stroke death rates for males and females was similar (–13.0% and –14.3%, respectively).
  - Crude stroke death rates declined most among people 65 to 74 years of age (–16.4%; from 91.4 to 76.4 per 100 000), 75 to 84 years of age (–18.0%; from 320.8 to 263.1 per 100 000), and ≥85 years of age (–10.6%; from 1110.7 to 993.5 per 100 000). By comparison, crude stroke death rates declined more modestly among those 25 to 34 years of age (0%; 1.3 and 1.3 per 100 000), 35 to 44 years (–12.0%; 5.0 to 4.4 per 100 000), 45 to 54 years (–15.2%; 14.5 to 12.3 per 100 000), and 55 to 64 years (–4.4%; 31.7 to 30.3 per 100 000). Despite the improvements noted since 2007, there has been a recent flattening or increase in death rates among all age groups (Charts 14-4 and 14-5).
  - Age-adjusted stroke death rates declined by ≈11% or more among all racial/ethnic groups; however, in 2017, rates remained higher among NH blacks (52.7 per 100 000; change since 2007: –16.3%) than among NH whites (36.4 per 100 000; –12.7%), NH Asians/Pacific Islanders (30.3 per 100 000; –17.7%), NH American Indians/Alaska Natives (34.1 per 100 000; –16.4%), and Hispanics (31.8 per 100 000; –11.2%).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States, known as the "stroke belt" (Chart 14-6). This area is usually defined to include the 8 southern states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. These

geographic differences have existed since at least 1940, and despite some minor shifts, they persist.[251] Historically, the overall average stroke mortality has been ≈30% higher in the stroke belt than in the rest of the nation and ≈40% higher in the stroke "buckle" (North Carolina, South Carolina and Georgia).[55]

- The risk of dementia is also increased in the southeastern United States, the geographic area of excess stroke risk.[252,253]
- More recent analyses of the geographic disparities determined that stroke risks are highest for residents of the stroke belt who were born and resided in the Southeast for the first 2 decades of their life.[254]
- On the basis of pooled data from several large studies, the probability of death within 1 year or 5 years after a stroke was highest in individuals ≥75 years of age (Charts 14-7 and 14-8). The probability of death within 1 year of a stroke was lowest in black males 45 to 64 years of age (Chart 14-7). The probability of death within 5 years of a stroke was lowest for white males 45 to 64 years of age (Chart 14-8).
- On the basis of national death statistics for the time period 1990 to 2009, stroke mortality rates among American Indian and Alaska Native people were higher than among whites for both males and females in contract health services delivery area counties in the United States and were highest in younger age groups (35–44 years of age). Stroke mortality rates and the rate ratios for American Indians/Alaska Natives to whites varied by region, with the lowest in the Southwest and the highest in Alaska. Starting in 2001, rates among American Indian/Alaska Native people decreased in all regions.[255]
- Data from the ARIC study (1987–2011; 4 US cities) showed that the cumulative all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at 1 year, 39.8% at 5 years, and 58.4% at the end of 24 years of follow-up. Mortality rates were higher after an incident hemorrhagic stroke (67.9%) than after ischemic stroke (57.4%). Age-adjusted mortality after an incident stroke decreased over time (absolute decrease of 8.1 deaths per 100 strokes after 10 years), which was mainly attributed to the decrease in mortality among those ≤65 years of age (absolute decrease of 14.2 deaths per 100 strokes after 10 years).[5]
- Data from the BASIC Project showed there was no change in ICH case fatality or long-term mortality from 2000 to 2010 in a South Texas community. Yearly age-, sex-, and ethnicity-adjusted 30-day case fatality ranged from a low of 28.3% (95% CI, 19.9%–40.3%) in 2006 to 46.5% (95% CI, 35.5%–60.8%) in 2008.[7]
- Projections of stroke mortality from 2012 to 2030 differ based on what factors are included in the forecasting.[256] Conventional projections that only incorporate expected population growth and aging reveal that the number of stroke deaths in 2030 may increase by ≈50% compared with the number of stroke deaths in 2012. However, if previous stroke mortality trends are also incorporated into the forecasting, the number of stroke deaths among the entire population is projected to remain stable through 2030, with potential increases among the population ≥65 years of age. Moreover, the trend-based projection method reveals that the disparity in stroke deaths among NH blacks compared with NH whites could increase from an RR of 1.10 (95% CI, 1.08–1.13) in 2012 to 1.30 (95% CI, 0.45–2.44) in 2030.[256]

Complications and Recovery

- Recurrent stroke is common (Chart 14-9).
- Stroke is a leading cause of serious long-term disability in the United States (Survey of Income and Program Participation, a survey of the US Census Bureau).[257] Approximately 3% of males and 2% of females reported that they were disabled because of stroke.
- In data from the NIS (2010 to 2012), among 395 411 stroke patients, 6.2% had a palliative care encounter. There was wide variability in use of palliative care, with higher use among patients who were older, female, and white; for those with hemorrhagic stroke; and for those at larger, nonprofit hospitals.[258]
- Stroke was among the top 18 diseases contributing to years lived with disability in 2010; of these 18 causes, only the age-standardized rates for stroke increased significantly between 1990 and 2010 ($P<0.05$).[259]
- Common complications after stroke include both short-term complications, such as seizures, DVT, PE, urinary infection, aspiration pneumonia, decubitus ulcers, and constipation, as well as long-term sequelae including pain syndromes, pseudobulbar affect, depression and anxiety, cognitive impairment and dementia, epilepsy, gait instability, and falls and fractures.
- Among 1075 patients undergoing rehabilitation after stroke in a Polish cohort, at least 1 complication was reported by 77% of patients, and 20% experienced ≥3 complications.[260] Urinary tract infection (23.2%), depression (18.9%), falls (17.9%), unstable hypertension (17.6%), and

shoulder pain (14.9%) were the most common complications.

- DVT and PE are well-known complications of stroke, particularly in the acute phase. The incidence of DVT is lower now than in older studies because of the use of prophylactic treatment with subcutaneous heparin and pneumatic compression boots. In the PREVAIL trial, among 1762 ischemic stroke patients unable to walk without assistance, the incidence of symptomatic DVT was ≤1% in patients treated with either enoxaparin or unfractionated heparin.[261] PE occurred in only 1 of 666 patients (0.2%) treated with enoxaparin and 6 of 669 patients (1%) treated with unfractionated heparin.
- The risk of VTE ranged from 16% to 30% for those with severe strokes (NIHSS score ≥14) to 8% to 14% for those with mild and moderate strokes (NIHSS score <14) in PREVAIL.
- In a meta-analysis that included 7 studies, the incidence density of late-onset poststroke seizure (ie, seizure occurring at least 14 days after a stroke) was 1.12 (95% CI, 0.95–1.32) per 100 person-years.[262]
- In the PROFESS trial, among 15754 participants with ischemic stroke, 1665 patients (10.6%) reported new chronic poststroke pain, including 431 (2.7%) with central poststroke pain, 238 (1.5%) with peripheral neuropathic pain, 208 (1.3%) with pain from spasticity, and 136 (0.9%) with pain from shoulder subluxation.[263] Chronic pain was associated with greater dependence (OR, 2.16 [95% CI, 1.82–2.56]).
- Patients with stroke are at increased risk of fractures compared with those with TIA or no stroke history. In the Ontario Stroke Registry, which included 23751 stroke and 11240 patients with TIA, the risk of low-trauma fractures was 5.7% during the 2 years after stroke, compared with 4.8% in those with TIA and 4.1% in age- and sex-matched control subjects.[264] The risk among stroke survivors compared with healthy control subjects was ≈50% higher (adjusted HR for those with stroke versus control subjects, 1.47 [95% CI, 1.35–1.60]).
- Chronic insomnia occurred in 16% of stroke survivors in an Australian cohort. Insomnia was associated with depression, anxiety, disability, and failure to return to work.[265]
- In a meta-analysis of 8 studies with data available on constipation after stroke that included1385 participants, the pooled incidence of constipation was 48% (95% CI, 33%–63%).[266]
- Among 190 mild to moderately disabled survivors >6 months after stroke, 40 to 84 years of age, the prevalence of sarcopenia (loss of muscle mass) ranged between 14% and 18%, which was higher than for control subjects matched on age, sex, race, and BMI.[267]
- In CHS, among 509 participants with recovery data, prestroke walking speed and grip strength were associated with poststroke declines in both cognition and activities of daily living.[268] Inflammatory biomarkers (CRP, IL-6) were associated with poststroke cognitive decline among males, and frailty was associated with decline in activities of daily living among females.
- In data from 2011, 19% of Medicare patients were discharged to inpatient rehabilitation facilities, 25% were discharged to skilled nursing facilities, and 12% received home health care.[269]
- The 30-day readmission rate for Medicare fee-for-service beneficiaries with ischemic stroke in 2006 was 14.4%.[270]
- The 30-day hospital readmission rate after discharge from postacute rehabilitation for stroke was 12.7% among fee-for-service Medicare patients. The mean rehabilitation length of stay for stroke was 14.6 days.[271]
- After stroke, females often have greater disability than males. For example, an analysis of community-living adults (>65 years of age) found that females were half as likely to be independent in activities of daily living after stroke, even after controlling for age, race, education, and marital status.[272]
- A meta-analysis of >25 studies examining sex differences in long-term outcomes among stroke survivors found that females had worse functional recovery and greater long-term disability and handicap. However, confidence in these conclusions was limited by the quality of the studies and variability in the statistical approach to confounding.[273]
- A national study of inpatient rehabilitation after first stroke found that blacks were younger, had a higher proportion of hemorrhagic stroke, and were more disabled on admission than NH whites. Compared with NH whites, blacks and Hispanics also had a poorer functional status at discharge but were more likely to be discharged to home rather than to another institution, even after adjustment for age and stroke subtype. After adjustment for the same covariates, compared with NH whites, blacks also had less improvement in functional status per inpatient day.[274]
- Blacks were less likely to report independence in activities of daily living and instrumental activities of daily living than whites 1 year after stroke after controlling for stroke severity and comparable rehabilitation use.[275]
- Hospital characteristics also predict functional outcomes after stroke. In an analysis of the AVAIL

study, which included 2083 ischemic stroke patients enrolled from 82 US hospitals participating in GWTG-Stroke, patients treated at teaching hospitals (OR, 0.72 [95% CI, 0.54–0.96]) and certified primary stroke centers (OR, 0.69 [95% CI, 0.53–0.91]) had lower rates of 3-month death or dependence.[276]

- In a survey among 391 stroke survivors, the vast majority (87%) reported unmet needs in at least 1 of 5 domains (activities and participation, environmental factors, body functions, postacute care, and secondary prevention).[277] The greatest area of unmet need was in secondary prevention (71% of respondents). Older age, greater functional ability, and reporting that the general practitioner was the most important health professional providing care were associated with fewer unmet needs, and depression and receipt of community services after stroke were associated with more unmet needs.
- Stroke also takes its toll on caregivers. In a meta-analysis of 12 studies that included 1756 caregivers, the pooled prevalence of depressive symptoms among caregivers was 40% (95% CI, 30%–51%). Symptoms of anxiety were present in 21% (95% CI, 12%–36%).[278]

Depression

- Patients with stroke are at increased risk of depression. Approximately one-third of stroke survivors develop poststroke depression, and the frequency is highest in the first year after a stroke.[279] Suicidality is also increased after stroke.[280]
- A 2014 meta-analysis involving 61 studies (N=25 488) revealed depression in 33% (95% CI, 26%–39%) of patients at 1 year after stroke, with a decline at 1 to 5 years to 25% (95% CI, 16%–33%) and to 23% (95% CI, 14%–31%) at 5 years.[281]
- Poststroke depression is associated with higher mortality. A meta-analysis of 13 studies involving 59 598 individuals revealed a pooled OR for mortality at follow-up of 1.22 (95% CI, 1.02–1.47).[282]
- Twelve RCTs (N=1121 subjects) suggested that antidepressant medications might be effective in treating poststroke depression, with a beneficial effect of antidepressants on remission (pooled OR for meeting criteria for depression: 0.47 [95% CI, 0.22–0.98]) and response, measured as a >50% reduction in mood scores (pooled OR, 0.22 [95% CI, 0.09–0.52]).[283]
- A meta-analysis of 8 RCTs assessing the efficacy of preventive pharmacological interventions among 776 initially nondepressed stroke patients revealed that the likelihood of developing poststroke depression was reduced among subjects receiving active pharmacological treatment (OR, 0.34 [95% CI, 0.22–0.53]), especially after a 1-year treatment (OR, 0.31 [95% CI, 0.18–0.56]) and with the use of a selective serotonin reuptake inhibitor (OR, 0.37 [95% CI, 0.22–0.61]). All studies excluded those with aphasia or significant cognitive impairment, which limits their generalizability.[284]
- In the multicenter AVAIL registry, among 1444 patients, depression was associated with worsening function during the first year after stroke. Those whose depression resolved were less likely to have functional decline over time than those without depression.[285]

Functional and Cognitive Impairment and Dementia

Functional and cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up.

- Data from prospective studies provide evidence that after an initial period of recovery, function, cognition, and quality of life decline over several years after stroke, even in the absence of definite new clinical strokes.[286–288] In NOMAS, 210 of 3298 participants had an ischemic stroke during follow-up and had functional assessments using the Barthel index before and after stroke.[288] Among those with Medicaid or no insurance, in a fully adjusted model, the slope of functional decline increased after stroke compared with before stroke (P=0.04), with a decline of 0.58 Barthel index points per year before stroke (P=0.02) and 1.94 Barthel index points after stroke (P=0.001). There was no effect among those with private insurance or Medicare.
- In the REGARDS prospective cohort, 515 of 23 572 participants ≥45 years of age without baseline cognitive impairment underwent repeated cognitive testing.[289] Incident stroke was associated with a short-term decline in cognitive function, as well as accelerated and persistent cognitive decline over 6 years. Participants with stroke had faster declines in global cognition and executive function, but not in new learning and verbal memory, compared with prestroke slopes, in contrast to those without stroke. The rate of incident cognitive impairment also increased compared with the prestroke rate (OR, 1.23 per year [95% CI, 1.10–1.38]).
- Stroke also appears to accelerate natural age-related functional decline. In the CHS, 382 of 5888 participants (6.5%) had ischemic stroke during follow-up with ≥1 disability assessment afterward. The annual increase in disability before stroke (0.06 points on the Barthel index per year [95% CI, 0.002–0.12]) more than tripled after stroke (0.15 additional points per year [95% CI, 0.004–0.30]). Notably, the annual increase in disability before MI (0.04 points per year) did not change significantly

after MI (0.02 additional points per year [95% CI, –0.07 to 0.11]).[290]

- In a meta-analysis of 14 longitudinal studies with at least 2 assessments of cognitive function after stroke, there was a trend toward significant deterioration in cognition in stroke survivors in 8 studies, although cognitive stability was found in 3 studies and improvement in 3 studies.[291] Follow-up time tended to be shorter in studies without evidence of decline.
- Of 127 Swedish survivors assessed for cognition at 10 years after stroke, poststroke cognitive impairment was found in 46% using a Mini–Mental State Examination threshold of <27 and in 61% using a Montreal Cognitive Assessment threshold of <25.[292]
- In 2 prospective studies, 11% to 23% of patients with incident lacunar stroke developed vascular dementia during 3-year follow-up.[293] Vascular dementia may develop annually in 3% to 5% of patients with lacunar stroke.[294]
- Blacks are at higher risk for dementia than whites within 5 years of ischemic stroke. In an analysis of South Carolina data from 2000 to 2012 (n=68 758 individuals with a diagnosis of ischemic stroke), black race increased risk for 5 categories of dementia after incident stroke (HR, 1.37 for Alzheimer disease to HR, 1.95 for vascular dementia).[295]
- In a study of 90-day poststroke outcomes among ischemic stroke patients in the BASIC Project, Mexican Americans scored worse on neurological, functional, and cognitive outcomes than NH whites after multivariable adjustment.[296]

Stroke in Children

- On the basis of pathogenic differences, pediatric strokes are typically classified as either perinatal (occurring at ≤28 days of life and including in utero strokes) or (later) childhood. Presumed perinatal strokes are diagnosed in children with no symptoms in the newborn period who present with hemiparesis or other neurological symptoms later in infancy.
- The prevalence of perinatal strokes is 29 per 100 000 live births, or 1 per 3500 live births in the 1997 to 2003 Kaiser Permanente of Northern California population.[297]
- A history of infertility, preeclampsia, prolonged rupture of membranes, and chorioamnionitis are independent maternal risk factors for perinatal arterial ischemic stroke.[266] However, maternal health and pregnancies are normal in most cases.[298]
- Diagnostic delays are more common in ischemic than hemorrhagic stroke in children, with a median time from symptom onset to diagnostic neuroimaging of 3 hours for hemorrhagic and 24 hours for ischemic stroke in a population-based study from the south of England.[299]
- The most common cause of arterial ischemic stroke in children is a cerebral arteriopathy, found in more than half of all cases.[300,301] Childhood arteriopathies are heterogeneous and can be difficult to distinguish from a partially thrombosed artery in the setting of a cardioembolic stroke; incorporation of clinical data and serial vascular imaging is important for diagnosis.[302]
- In a retrospective population-based study in northern California, 7% of childhood ischemic strokes and 2% of childhood hemorrhagic strokes were attributable to congenital heart defects. Congenital heart defects increased a child's risk of stroke 19-fold (OR, 19 [95% CI, 4.2–83]). The majority of children with stroke related to congenital heart defects were outpatients at the time of the stroke.[303] In a single-center Australian study, infants with cyanotic congenital heart defects undergoing palliative surgery were the highest-risk group to be affected by arterial ischemic stroke during the periprocedural period; stroke occurred in 22 per 2256 cardiac surgeries (1%).[304]
- In another study of the northern Californian population, adolescents with migraine had a 3-fold increased odds of ischemic stroke compared with those without migraine (OR, 3.4 [95% CI, 1.2–9.5]); younger children with migraine had no significant difference in stroke risk.[305]
- In a post hoc analysis, head or neck trauma in the prior week was a strong risk factor for childhood arterial ischemic stroke (adjusted OR, 36 [95% CI, 5–281]), present in 10% of cases.[306]
- Exposure to minor infection in the prior month was also associated with stroke and was present in one-third of cases (adjusted OR, 3.9 [95% CI, 2.0–7.4]).[306] The effect of infection on pediatric stroke risk is short-lived, lasting for days; 80% of infections preceding childhood stroke are respiratory.[307] A prospective study of 326 children with arterial stroke revealed that serologic evidence of acute herpesvirus infection doubled the odds of childhood arterial ischemic stroke, even after adjustment for age, race, and SES (OR, 2.2 [95% CI, 1.2–4.0]; *P*=0.007).[308] Among 187 cases with acute and convalescent blood samples, 85 (45%) showed evidence of acute herpesvirus infection; herpes simplex virus 1 was found most often. Most infections were asymptomatic.
- Thrombophilias (genetic and acquired) are risk factors for childhood stroke, with summary ORs ranging from 1.6 to 8.8 in a meta-analysis.[309] In contrast, a population-based, controlled study

suggested a minimal association between perinatal stroke and thrombophilia,[310] and therefore, routine testing is not recommended in very young children.

- In a prospective Swiss registry,[311] atherosclerotic risk factors were less common in children with arterial ischemic stroke than in young adults; the most common of these factors in children was hyperlipidemia (15%). However, an analysis of the NIS suggests a low but rising prevalence of these factors among US adolescents and young adults hospitalized for ischemic stroke (1995 versus 2008).[312]
- Compared with girls, US boys have a 25% increased risk of ischemic stroke and a 34% increased risk of ICH, whereas a study in the United Kingdom found no sex difference in childhood ischemic stroke.[313] Compared with white children, black children in both the United States and United Kingdom have a >2-fold risk of stroke.[314] The increased risk among blacks is not fully explained by the presence of sickle cell disease, nor is the excess risk among boys fully explained by trauma.[314]
- The excess ischemic stroke mortality in US black children compared with white children has diminished since 1998 when the STOP trial was published, which established a method for primary stroke prevention in children with sickle cell disease.[315]
- Among young adult survivors of childhood stroke, 37% had a normal modified Rankin score, 42% had mild deficits, 8% had moderate deficits, and 15% had severe deficits.[316] Concomitant involvement of the basal ganglia, cerebral cortex, and posterior limb of the internal capsule predicts a persistent hemiparesis.[317]
- Survivors of childhood arterial ischemic stroke have, on average, low-normal cognitive performance,[318,319] with poorest performance in visual-constructive skills, short-term memory, and processing speed. Younger age at stroke and seizures, but not laterality of stroke (left versus right), predict worse cognitive outcome.[319]
- Compared with referent children with asthma, childhood stroke survivors have greater impairments in adaptive behaviors, social adjustment, and social participation, even if their intelligence quotient is normal.[320] Severity of disability after perinatal stroke correlates with maternal psychosocial outcomes such as depression and quality of life.[321]
- Despite current treatment, at least 1 of 10 children with ischemic or hemorrhagic stroke will have a recurrence within 5 years.[322,323] Among 355 children with stroke followed up prospectively as part of a multicenter study with a median follow-up of 2 years, the cumulative stroke recurrence rate was 6.8% (95% CI, 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year.[45] The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold compared with an idiopathic acute ischemic stroke (HR, 5.0 [95% CI, 1.8–14]). In a retrospective cohort, with a cerebral arteriopathy, the 5-year recurrence risk was as high as 60% among children with abnormal arteries on vascular imaging.[324] The recurrence risk after perinatal stroke, however, was negligible.[324]
- Among 59 long-term survivors of pediatric brain aneurysms, 41% developed new or recurrent aneurysms during a median follow-up of 34 years; of those, one-third developed multiple aneurysms.[325]
- More than 25% of survivors of perinatal ischemic strokes develop delayed seizures within 3 years; those with larger strokes are at higher risk.[326] The cumulative risk of delayed seizures after later childhood stroke is 13% at 5 years and 30% at 10 years.[327] Children with acute seizures (within 7 days of their stroke) have the highest risk for delayed seizures, >70% by 5 years after the stroke.[328] Among survivors of ICH in childhood, 13% developed delayed seizures and epilepsy within 2 years.[329] Elevated intracranial pressure requiring short-term intervention at the time of acute ICH is a risk factor for delayed seizures and epilepsy.
- Pediatric stroke teams and stroke centers[330] are developing worldwide. In a study of 124 children presenting to a children's hospital ED with stroke symptoms where a "stroke alert" was paged, 24% had a final diagnosis of stroke, 2% were TIAs, and 14% were other neurological emergencies, which underscores the need for prompt evaluation of children with "brain attacks."[331] Implementation of a pediatric stroke clinical pathway improved time to MRI from 17 hours to 4 hours at 1 center.[332]
- In a study of 111 pediatric stroke cases admitted to a single US children's hospital, the median 1-year direct cost of a childhood stroke (inpatient and outpatient) was ≈$50 000, with a maximum approaching $1 000 000. More severe neurological impairment after a childhood stroke correlated with higher direct costs of a stroke at 1 year and poorer quality of life in all domains.[333]
- A prospective study at 4 centers in the United States and Canada found that the median 1-year out-of-pocket cost incurred by the family of a child with a stroke was $4354 (maximum $38 666), which exceeded the median American household cash savings of $3650 at the time of the study and represented 6.8% of the family's annual income.[334]

Stroke in Young Adults and in Midlife

- Approximately 10% of all strokes occur in individuals 18 to 50 years of age.[335]

- In the NIS, hospitalizations for acute ischemic stroke increased significantly for both males and females and for certain racial/ethnic groups among younger adults, 18 to 54 years of age.[4] From 1995 to 2011 through 2012, hospitalization rates almost doubled for males 18 to 34 and 35 to 44 years of age, with a 41.5% increase among males 35 to 44 years of age from 2003 to 2004 through 2011 to 2012. Hospitalization rates for ICH and SAH remained stable, however, with the exception of declines among males and NH black patients 45 to 54 years of age with SAH.
- In the NIS, the prevalence of stroke risk factors also increased from 2003 to 2004 through 2011 to 2012 among those hospitalized for stroke.[4] These increases in prevalence were seen among both males and females 18 to 64 years of age. Absolute increases in prevalence were seen for hypertension (range of absolute increase 4%–11%), lipid disorders (12%–21%), DM (4%–7%), tobacco use (5%–16%), and obesity (4%–9%).
- The prevalence of having 3 to 5 risk factors increased from 2003 to 2004 through 2011 to 2012, as well.[4] Among males, the prevalence of ≥3 risk factors among stroke patients increased from 9% to 16% at 18 to 34 years, 19% to 35% at 35 to 44 years, 24% to 44% at 45 to 54 years, and 26% to 46% at 55 to 64 years. Among females, the prevalence of ≥3 risk factors among stroke patients increased from 6% to 13% at 18 to 34 years, 15% to 32% at 35 to 44 years, 25% to 44% at 45 to 54 years, and 27% to 48% at 55 to 65 years (*P* for trend <0.001).
- In the 2005 GCNKSS study period, the sex-adjusted incidence rate of first-ever stroke was 48 per 100 000 (95% CI, 42–53) among whites 20 to 54 years of age compared with 128 per 100 000 (95% CI, 106–149) among blacks of the same age. Both races had a significant increase in the incidence rate from 1993 to 1994.[336] Similarly, other studies suggest an increase in the incidence of stroke in young adults. According to MIDAS 29, an administrative database containing hospital records of all patients discharged from nonfederal hospitals in New Jersey with a diagnosis of CVD or an invasive cardiovascular procedure, the rate of stroke more than doubled in patients 35 to 39 years of age, from 9.5 strokes per 100 000 person-years in the period 1995 to 1999 to 23.6 strokes per 100 000 person-years from 2010 to 2014 (rate ratio, 2.47 [95% CI, 2.07–2.96]; *P*<0.0001).[337] Rates of stroke in those 40 to 44, 45 to 49, and 50 to 54 years of age also increased significantly. Stroke rates in those >55 years of age decreased during these time periods.
- Vascular risk factors are common among stroke patients 20 to 54 years of age. During 2005, in the biracial GCNKSS, hypertension prevalence was estimated at 52%, hyperlipidemia at 18%, DM at 20%, CHD at 12%, and current smoking at 46%.[336]
- Over the 13-year course of the BASIC study, mean age was estimated to decrease from 74.8 to 71.3 for NH whites, whereas for Mexican Americans, mean age was estimated to decrease from 68.9 to 66.9 years after adjustment for ethnic-specific average age of the population at risk.[338]
- In the FUTURE study, the 30-day case fatality rate among stroke patients 18 to 50 years of age was 4.5%. One-year mortality among 30-day survivors was 1.2% (95% CI, 0.0%–2.5%) for TIA, 2.4% (95% CI, 1.2%–3.7%) for ischemic stroke, and 2.9% (95% CI, 0.0%–6.8%) for ICH.[339]
- In the FUTURE study, after a mean follow-up of 13.9 years, 44.7% of young stroke patients had poor functional outcome, defined as a modified Rankin score >2. The strongest baseline predictors of poor outcome were female sex (OR, 2.7 [95% CI, 1.5–5.0]) and baseline NIHSS score (OR, 1.1 [95% CI, 1.1–1.2] per point increase).[340]

Stroke in Older Adults

- Stroke patients >85 years of age make up 17% of all stroke patients, and in this age group, stroke is more prevalent in females than in males.[341,342]
- Risk factors for stroke may be different in older adults. In the population-based multiethnic NOMAS cohort, the risk effect of physical inactivity was modified by age, and there was a significant risk only in stroke patients >80 years of age.[143] Also, the proportion of ischemic strokes attributable to AF increases with age and may reach 40% or higher in very elderly stroke patients.[343]
- Very elderly patients have a higher risk-adjusted mortality,[344] have greater disability,[344] have longer hospitalizations,[345] receive less evidence-based care,[247,248] and are less likely to be discharged to their original place of residence.[345,346]
- According to analyses from the US NIS, over the past decade, in-hospital mortality rates after stroke have declined for every age and sex group except males >84 years of age.[347]
- Over the period from 2010 to 2050, the number of incident strokes is expected to more than double, with the majority of the increase among the elderly (≥75 years of age) and minority groups.[348]
- A Danish stroke registry reported on 39 centenarians (87% females; age range, 100–107 years) hospitalized with acute stroke. Although they had more favorable risk profiles than other age groups

(lower prevalence of previous MI, stroke, and DM), their strokes were more severe and were associated with high 1-month mortality (38.5%).[349]
- Despite more severe outcomes, evidence-based treatments for stroke still benefit and should be offered to elderly stroke patients, including intravenous tPA,[350] mechanical thrombectomy,[351] and CEA.[352]

Organization of Stroke Care

- Among hospitals participating in GWTG-Stroke from 2013 to 2015, rates of defect-free care were high for both CSCs (94.6%) and primary stroke centers (94.0%). For ED admissions, CSCs had higher rates of intravenous tPA (14.3% versus 10.3%) and endovascular thrombectomy (4.1% versus 1.0%). Door-to-tPA time was shorter for CSCs (median 52 versus 61 minutes; adjusted risk ratio, 0.92 [95% CI, 0.89–0.95]), and a greater proportion of patients at CSCs had times to tPA that were ≤60 minutes (79.7% versus 65.1%; adjusted OR, 1.48 [95% CI, 1.25–1.75]). CSCs had in-hospital mortality rates that were higher for both ED admissions (4.6% versus 3.8%; adjusted OR, 1.14 [95% CI, 1.01–1.29]) and transfers (7.7% versus 6.8%; adjusted OR, 1.17 [95% CI, 1.05–1.32]).[353]
- A study of 36 981 patients admitted with a primary diagnosis of ICH or SAH in New Jersey between 1996 and 2012 found that patients admitted to a CSC were more likely to have neurosurgical or endovascular treatments and had lower 90-day mortality (OR, 0.93 [95% CI, 0.89–0.97]) than patients admitted to other hospitals.[354]
- In analyses of 1 165 960 Medicare fee-for-service beneficiaries hospitalized between 2009 and 2013 for ischemic stroke, patients treated at primary stroke centers certified between 2009 and 2013 had lower in-hospital (OR, 0.89 [95% CI, 0.84–0.94]), 30-day (HR, 0.90 [95% CI, 0.89–0.91]), and 1-year (HR, 0.90 [95% CI, 0.89–0.91]) mortality than those treated at noncertified hospitals after adjustment for demographic and clinical factors.[355] Hospitals certified between 2009 and 2013 also had lower in-hospital and 30-day mortality than centers certified before 2009.

Hospital Discharges and Ambulatory Care Visits (See Table 14-1)

- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with stroke as the principal diagnosis declined slightly, from 897 000 in 2006 to 874 000 in 2016 (Table 14-1).
- In 2016, the average length of stay for discharges with stroke as the principal diagnosis was 6.2 days (HCUP,[356] unpublished NHLBI tabulation).
- In 2016, there were 590 000 ED visits with stroke as the principal diagnosis, and in 2011, there were 209 000 outpatient visits with stroke as the first-listed diagnosis (NHAMCS,[357] unpublished NHLBI tabulation). In 2016, physician office visits for a first-listed diagnosis of stroke totaled 2 155 000 (NAMCS,[358] unpublished NHLBI tabulation).
- Age-specific acute ischemic stroke hospitalization rates from 2000 to 2010 decreased for individuals 65 to 84 years of age (–28.5%) and ≥85 years of age (–22.1%) but increased for individuals 25 to 44 years of age (43.8%) and 45 to 64 years of age (4.7%). Age-adjusted acute ischemic stroke hospitalization rates were lower in females, and females had a greater rate of decrease from 2000 to 2010 than males (–22.1% versus –17.8%, respectively).[359]
- An analysis of the 2011 to 2012 NIS for acute ischemic stroke found that after risk adjustment, all racial/ethnic minorities except Native Americans had a significantly higher likelihood of length of stay ≥4 days than whites.[360]

Operations and Procedures

- In 2014, an estimated 86 000 inpatient CEA procedures were performed in the United States. CEA is the most frequently performed surgical procedure to prevent stroke (HCUP,[356] unpublished NHLBI tabulation).
- Although rates of CEA decreased between 1997 and 2014, the use of CAS increased dramatically from 2004 to 2014 (HCUP,[356] unpublished NHLBI tabulation).
- In-hospital mortality for CEA decreased steadily from 1993 to 2014 (HCUP,[356] unpublished NHLBI tabulation).
- In a meta-analysis of cohort studies published by May 2016, the risk of procedural stroke or death after CEA was 3.44% (95% CI, 2.70%–4.23%) in symptomatic patients and 1.28% (95% CI, 0.91%–1.71%) in asymptomatic patients. After CAS, the risk of stroke or death was 4.77% (95% CI, 3.67%–5.99%) for symptomatic patients and 2.59% (95% CI, 1.77%–3.56%) for asymptomatic patients. Procedural stroke/death rates were lower in studies of CEA that completed recruitment after 2005 for both symptomatic (5.11% versus 2.68%) and asymptomatic (3.17% versus 1.50%) patients; rates for CAS did not change over time.[361]
- In a meta-analysis of 5 RCTs comparing CEA and CAS in asymptomatic patients, there was a trend

toward increased incidence of stroke or death for patients who underwent CAS versus CEA (any periprocedural stroke: RR, 1.84 [95% CI, 0.99–3.40]; periprocedural nondisabling stroke: RR, 1.95 [95% CI, 0.98–3.89]; any periprocedural stroke or death: RR, 1.72 [95% CI, 0.95–3.11]). The risk ratios were 1.24 (95% CI, 0.76–2.03) for long-term stroke and 0.92 (95% CI, 0.70–1.21) for the composite of periprocedural stroke, death, MI, or long-term ipsilateral stroke.[362]

- In a Cochrane review that analyzed data from 6092 patients in 3 trials of CEA, surgery was associated with an increased risk of ipsilateral ischemic stroke within 5 years for patients with <30% stenosis (RR, 1.27 [95% CI, 0.80–2.01]), had no benefit for those with 30% to 49% stenosis (RR, 0.93 [95% CI, 0.62–1.38]), and reduced the risk of stroke for those with 50% to 69% stenosis (RR, 0.84 [95% CI, 0.60–1.18]) and 70% to 99% stenosis without near-occlusion (RR, 0.47 [95% CI, 0.25–0.88]); there was no benefit for patients with near-occlusions (RR, 1.03 [95% CI, 0.57–1.84]).[352]
- A meta-analysis of 6526 patients from 5 trials with a mean follow-up of 5.3 years indicated no significant difference in the composite outcome of periprocedural death, stroke, MI, or nonperiprocedural ipsilateral stroke for patients who underwent CAS versus CEA. CAS was associated with increased odds of any periprocedural or nonperiprocedural ipsilateral stroke (OR, 1.50 [95% CI, 1.22–1.84]) and periprocedural minor stroke (OR, 2.43 [95% CI, 1.71–3.46]). CAS was associated with reduced odds of periprocedural MI (OR, 0.45 [95% CI, 0.27–0.75]), cranial nerve palsy (OR, 0.07 [95% CI, 0.04–0.14]), and the composite of death, stroke, MI, or cranial nerve palsy (OR, 0.75 [95% CI, 0.63–0.93]).[363]
- In the Medicare population, the in-hospital stroke rate and mortality were similar for CEA and CAS.[364]
- In the Medicare population, 30-day readmission rates and long-term risk of adverse clinical outcomes associated with CAS were similar to those for CEA after adjustment for patient- and provider-level factors.[364,365]
- Evidence on comparative costs of CEA and CAS is mixed; whereas some studies found CAS to be associated with significantly higher costs than CEA,[366] particularly among asymptomatic patients,[367] and that they might be less cost-effective in general,[368] CREST found that the overall cost of CAS was not different from that of CEA (US $15 055 versus US $14 816).[369]
- Meta-analyses of 5 trials that investigated the efficacy of modern endovascular therapies for stroke (MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND-IA, and REVASCAT) have provided strong evidence to support the use of thrombectomy initiated within 6 hours of stroke onset among patients with large-vessel occlusion, irrespective of patient age, NIHSS score above the thresholds for inclusion, or receipt of intravenous thrombolysis.[370] Retrospective analyses of patient databases have found similar results.[371]
- Within a large telestroke network, of 234 patients who met the inclusion criteria, 51% were transferred for mechanical thrombectomy by ambulance and 49% by helicopter; 27% underwent thrombectomy. The median actual transfer time was 132 minutes (IQR, 103–165 minutes). Longer transfer time was associated with lower rates of thrombectomy, and transfer at night rather than during the day was associated with significantly longer delay. Metrics and protocols for more efficient transfer, especially at night, could shorten transfer times.[372]

Cost (See Table 14-1)

- In 2014 to 2015 (average annual; MEPS,[373] unpublished NHLBI tabulation):
  - The direct and indirect cost of stroke in the United States was $45.5 billion (Table 14-1).
  - The estimated direct medical cost of stroke was $28.0 billion. This includes hospital outpatient or office-based provider visits, hospital inpatient stays, ED visits, prescribed medicines, and home health care.
  - The mean expense per patient for direct care for any type of service (including hospital inpatient stays, outpatient and office-based visits, ED visits, prescribed medicines, and home health care) in the United States was estimated at $7902.
- Between 2015 and 2035, total direct medical stroke-related costs are projected to more than double, from $36.7 billion to $94.3 billion, with much of the projected increase in costs arising from those ≥80 years of age.[374]
- The total cost of stroke in 2035 (in 2015 dollars) is projected to be $81.1 billion for NH whites, $32.2 billion for NH blacks, and $16.0 billion for Hispanics.[374]

Global Burden of Stroke (See Charts 14-10 through 14-17)

Prevalence

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate

disease burden for 359 diseases and injuries in 195 countries and territories. In 2017[375]:

- Global prevalence of stroke was 104.2 million people, whereas that of ischemic stroke was 82.4 million, that of ICH was 17.9 million, and that of SAH was 9.3 million.
- Globally, there was a 16.1% increase in the ischemic stroke prevalence rate from 2007 to 2017 and a 10.1% increase from 1990 to 2017.
- Globally, there was an 8.9% decrease in the ICH prevalence rate from 2007 to 2017 and a 15.5% decrease from 1990 to 2017.
- Globally, there was a 1.0% decrease in the SAH prevalence rate from 2007 to 2017 and a 6.5% decrease from 1990 to 2017.
- Overall, age-standardized stroke prevalence rates are highest in Eastern Europe, North Africa, the Middle East, and Central and East Asia (Chart 14-10).
- Countries in Eastern Europe and Central and East Asia have the highest prevalence rates of ischemic stroke (Chart 14-11).
- The prevalence of ICH is high in East and Central Asia (Chart 14-12).
- Age-standardized prevalence of SAH is highest in Japan (Chart 14-13).

Incidence

- In 2010, there were an estimated 11.6 million incident ischemic strokes and 5.3 million incident hemorrhagic strokes; 63% of ischemic strokes and 80% of hemorrhagic strokes occurred in low- and middle-income countries.[376]

Mortality

- In 2017[375]:
  - There were 6.2 million deaths attributable to cerebrovascular disease worldwide.
  - The absolute number of cerebrovascular disease deaths worldwide increased 41.4% between 1990 and 2017; however, the age-standardized death rate decreased 33.4%.
  - The absolute number of cerebrovascular disease deaths worldwide increased 16.6% between 2007 and 2017; however, the age-standardized death rate for the 10-year period decreased 33.4%.
  - Globally, a total of 2.7 million individuals died of ischemic stroke, 3.0 million died of ICH, and 0.4 million died of SAH.
  - Several countries in Eastern Europe, Africa, and Central Asia have the highest rates of stroke mortality (Chart 14-14).
  - Countries in Eastern Europe, North Africa, and Central Asia have among the highest mortality rates attributable to ischemic stroke (Chart 14-15).
  - ICH mortality is highest in East and Southeast Asia (Chart 14-16).
  - Mortality attributable to SAH is highest in Southeast Asia and Mongolia (Chart 14-17).
- In 2010, 39.4 million DALYs were lost because of ischemic stroke and 62.8 million because of hemorrhagic stroke (64% and 86%, respectively, in low- and middle-income countries).[376]
- In 2010, the mean age of individuals with stroke-related death in high-income countries was 80.4 years compared with 72.1 years in low- and middle-income countries.[377]

Brain Health

Like CVH, brain health can be defined both in terms of the absence of disease or the presence of a healthy state. Optimal brain health has been defined as "an optimal capacity to function adaptively in the environment."[378] This definition includes the capacity to perform all the diverse tasks for which the brain is responsible, including movement, perception, learning and memory, communication, problem solving, judgment, decision making, and emotion. Stroke and cerebrovascular disease more broadly are increasingly recognized to be important precursors to cognitive decline and dementia, indicating an absence of brain health. Conversely, measures of systemic and cerebral vascular health have been associated with healthy aging and retained cognitive function.

- In a 2010 survey of 1007 Americans, 31% of respondents reported being most afraid of developing Alzheimer disease. Alzheimer disease ranked second in feared diseases, after cancer, but ahead of HD, stroke, and DM.[379]
- In the Framingham Study, the overall lifetime risk of stroke or dementia was greater than 1 in 3,[380] depending on age cohort and sex. The lifetime risk of any type of dementia, for a 65-year-old woman, was 21.7%; the lifetime risk of any type of dementia, for a 65-year-old man, was 14.3%. The lifetime risk of Alzheimer disease was 17.2% for a 65-year-old woman and 9.1% for a 65-year-old man.
- In an analysis of administrative claims data of Medicare fee-for-service beneficiaries enrolled during 2011 to 2013 (and >68 years of age; n=21.6 million), the overall prevalence of a claim for a service or treatment for any dementia subtype was 14.4%.[381] The most common subtype was Alzheimer disease (43.5%), followed by vascular dementia (14.5%), Lewy body dementia (5.4%), frontotemporal dementia (1.0%), and alcohol-induced dementia (0.7%). The prevalence of other types of diagnosed dementia was 0.2%.

- In an analysis of the first 141 autopsies from the Rush Memory and Aging Project longitudinal cohort,[382] a mixture of brain pathologies in patients with dementia was common. Among 50 individuals with dementia, 19 (38.0%) had Alzheimer disease and infarcts, 15 (30.0%) had pure Alzheimer disease, 6 (12%) had vascular dementia, and 6 (12%) had Alzheimer disease with Lewy body disease. More than 50% had multiple diagnoses. Even among those without diagnosed dementia (n=91), pathological abnormalities were common: 22 (22.4%) had pure Alzheimer disease, and 16 (17.6%) had infarcts. Only 20 individuals (14.2%) had no acute or chronic brain abnormalities. After accounting for age, those with multiple diagnoses were almost 3 times (OR, 2.8 [95% CI, 1.2–6.7]) more likely to exhibit dementia as those with 1 pathological diagnosis.
- As the US population ages, the number of individuals with Alzheimer disease will increase dramatically from 2010 to 2050.[383] According to a modeling study, based on estimates in a population of 10 800 participants from the Chicago Health and Aging Project in the United States, in 2010, there were 4.7 million individuals ≥65 years of age with Alzheimer disease (95% CI, 4.0–5.5 million): 0.7 million 65 to 74 years of age, 2.3 million 75 to 84 years of age, and 1.8 million ≥85 years of age. By 2050, the number of people with Alzheimer disease is projected to be 13.8 million, with 7.0 million ≥85 years of age.
- Vascular disease risk factors, and particularly risk factors present in midlife, are associated with cognitive impairment, with risk of dementia overall, and with risk of Alzheimer disease.
- The AHA's ideal CVH metrics are associated with reduced cognitive decline. Among 1033 participants in NOMAS (mean age at initial cognitive assessment 72±8 years; 39% male; 65% Hispanic, 19% black, and 16% white), 3% had 0 ideal factors, 15% had 1 factor, 33% had 2 factors, 30% had 3 factors, 14% had 4 factors, 4% had 5 factors, 1% had 6 factors, and 0% had 7 factors.[384] Having more ideal CVH factors was associated with less decline in neuropsychological tests of processing speed. The association was driven by nonsmoking and better glucose levels. Among those with better cognitive performance at initial assessment, ideal CVH was also associated with less decline in executive function and episodic memory testing.
- Among 15 744 participants 44 to 66 years of age at baseline enrolled in the ARIC study, modifiable risk factors present at midlife for late-life dementia included smoking (HR, 1.41 [95% CI, 1.23–1.61]), DM (HR, 1.77 [95% CI, 1.53–2.04]), prehypertension (HR, 1.31 [95% CI, 1.14–1.51]), and hypertension (HR, 1.39 [95% CI, 1.22–1.59]).[385] Nonmodifiable and sociodemographic risk factors for dementia included older age (HR, 8.06 [95% CI, 6.69–9.72] for participants 60–66 years of age), black race (HR, 1.36 [95% CI, 1.21–1.54]), *APOE* ε4 genotype (HR, 1.98 [95% CI, 1.78–2.21]), and lower educational attainment (HR, 1.61 [95% CI, 1.28–2.03] for less than a high school education).
- Hypertension in midlife but not early adulthood is associated with late-life dementia risk among females. In an analysis of 5646 long-term members of the Kaiser Permanente Northern California integrated healthcare delivery system, among whom 532 individuals (9.4%) were diagnosed with dementia, mid-adulthood hypertension was associated with an increased risk of dementia among females (HR, 1.65 [95% CI, 1.25–2.18]) but not males.[386] Hypertension in early adulthood was not associated with dementia.
- In another analysis among members of the Kaiser Permanente Northern California healthcare delivery system who had lived in California for at least 23 years (n=7423), those who were born in a "high stroke mortality state," defined as a state in the top quintile of stroke mortality rates (ie, Alabama, Alaska, Arkansas, Louisiana, Mississippi, Oklahoma, Tennessee, South Carolina, and West Virginia) were at increased risk of dementia in late life after adjustment for age, sex, and race (HR, 1.28 [95% CI, 1.13–1.46]).[252] These results suggest that early-life behavioral and other patterning may influence late-life development of dementia.
- Imaging markers and other biomarkers of Alzheimer disease are present in individuals destined to develop dementia ≥20 years before the onset of clinical symptoms.[387] Evidence of beta-amyloid precedes development of tau-related neurodegeneration and hippocampal volume loss.[388]
- Midlife vascular risk factors are associated with amyloid deposition in the brain,[389] indicating Alzheimer pathology, as well as undifferentiated or vascular dementia. Among 322 nondemented participants in an ARIC positron emission tomography–amyloid imaging substudy (mean age 52 years; 58% female; 43% black), elevated midlife BMI was associated with a 2-fold increase in amyloid deposition (OR, 2.06 [95% CI, 1.16–3.65]). After adjustment for potential confounders, compared with no midlife vascular risk factors, those with 1 (OR 1.88 [95% CI, 0.95–3.72]) and 2 (OR 2.88 [95% CI, 1.46–5.69]) vascular risk factors had increased amyloid deposition. Late-life vascular risk factors were not significantly associated with late-life brain amyloid deposition.

- Brain infarcts without overt clinical manifestations (silent or asymptomatic infarcts) are present in a high proportion of unselected generally healthy individuals in population-based studies using MRI, ranging from 8% of those at a mean of 64 years of age in an Austrian population[390] to 28% of those at a mean age of 75 years in the CHS study.[391,392]
- Asymptomatic infarcts are associated with progression to dementia and cognitive decline.[391] Among 1015 participants 60 to 90 years of age in the Rotterdam Scan Study,[393] the presence of silent brain infarcts on baseline brain MRI doubled the risk of dementia (HR, 2.26 [95% CI, 1.09–4.70]). Silent brain infarcts on the baseline MRI were also associated with worse performance on neuropsychological tests and a steeper decline in global cognitive function.
- In CHS, 1919 participants had 2 MRI scans separated by 5 years, and worsening of white matter disease on a semiquantitative scale was evident in 538 participants (28%).[394] Those with increased interval development of white matter burden had greater decline on modified Mini-Mental State examination and the Digit Symbol Substitution test after controlling for potential confounding factors, including occurrence of interval TIA or stroke.
- A diagnosis of HF is associated with cognitive decline. Among 4864 males and females in CHS initially free of HF and stroke, 496 participants who developed incident HF had greater adjusted declines over 5 years in the Modified Mini-Mental State Examination than those without HF (10.2 points [95% CI, 8.6–11.8] versus 5.8 points [95% CI, 5.3–6.2]).[395] The effect did not vary significantly by reduced versus preserved EF.
- In a systematic review of racial disparities in dementia prevalence and incidence in the United States that included 114 studies, the prevalence of dementia for those ≥65 years of age ranged in black cohorts from 7.2% to 20.9%. Dementia prevalence was 6.3% in Japanese Americans, 12.9% in Caribbean Hispanic Americans, and 12.2% in Guamanian Chamorro. The annual incidence of dementia for blacks ≥65 years of age (mean 2.6%) and Caribbean Hispanic populations (mean 3.6%) was significantly higher than for Mexican American, Japanese American, and non-Latino white populations (0.8%–2.7%; $P<0.001$).[396]
- Data from a nationally representative population-based longitudinal survey of US adults, the Health and Retirement Study, provides evidence that the prevalence of dementia among those ≥65 years of age declined significantly in the United States from 11.6% in 2000 to 8.8% in 2012 ($P<0.001$).[397]

Table 14-1. Stroke in the United States

Population Group	Prevalence, 2013–2016: Age ≥20 y	New and Recurrent Attacks, 1999, All Ages	Mortality, 2017: All Ages*	Hospital Discharges, 2016: All Ages	Cost, 2014–2015
Both sexes	7 000 000 (2.5%)	795 000	146 383	874 000	$45.5 Billion
Males	3 200 000 (2.5%)	370 000 (46.5%)†	61 645 (42.1%)†	438 000	…
Females	3 800 000 (2.6%)	425 000 (53.5%)†	84 738 (57.9%)†	436 000	…
NH white males	2.4%	325 000‡	45 078	…	…
NH white females	2.5%	365 000‡	64 960	…	…
NH black males	3.1%	45 000‡	8566	…	…
NH black females	3.8%	60 000‡	10 522	…	…
Hispanic males	2.0%	…	5073	…	…
Hispanic females	2.2%	…	5702	…	…
NH Asian males	1.1%	…	2442§	…	…
NH Asian females	1.6%	…	2988§	…	…
NH American Indian or Alaska Native	…	…	737	…	…

Ellipses (…) indicate data not available; and NH, non-Hispanic.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total stroke incidence or mortality that applies to males vs females.

‡Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

§Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

Sources: Prevalence: Unpublished National Heart Lung and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey, 2013 to 2016.[398] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population. Incidence: Greater Cincinnati/Northern Kentucky Stroke Study and National Institutes of Neurological Disorders and Stroke data for 1999 provided on July 9, 2008. US estimates compiled by NHLBI. See also Kissela et al.[399] Data include children. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System.[250] These data represent underlying cause of death only. Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016.[356] Data include those inpatients discharged alive, dead, or status unknown. Cost: Unpublished NHLBI tabulation using Medical Expenditure Panel Survey.[373] Data include estimated direct and indirect costs for 2014 to 2015 (average annual).

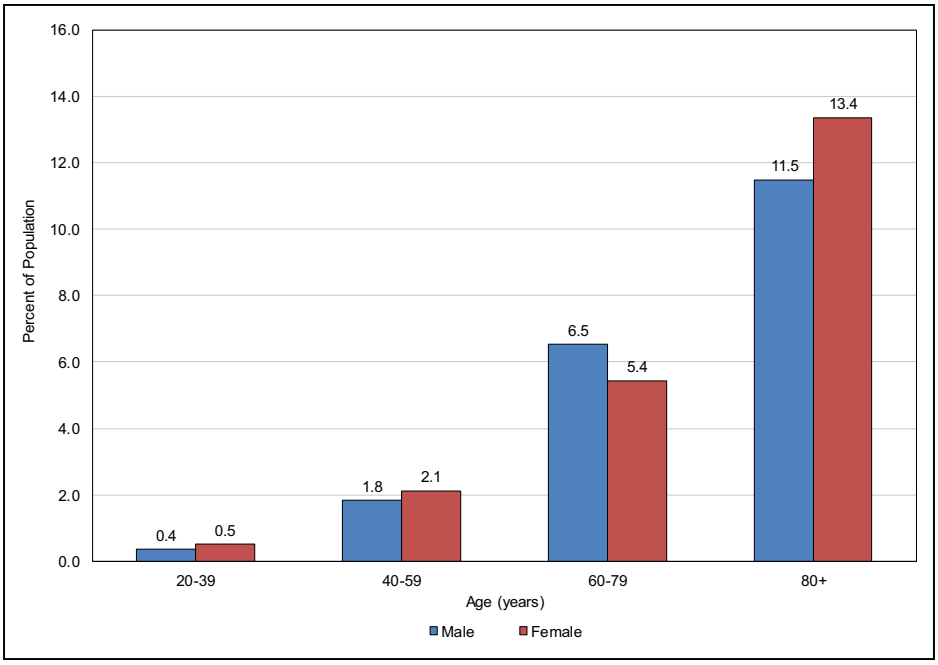

Chart 14-1. Prevalence of stroke by age and sex, United States (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[398]

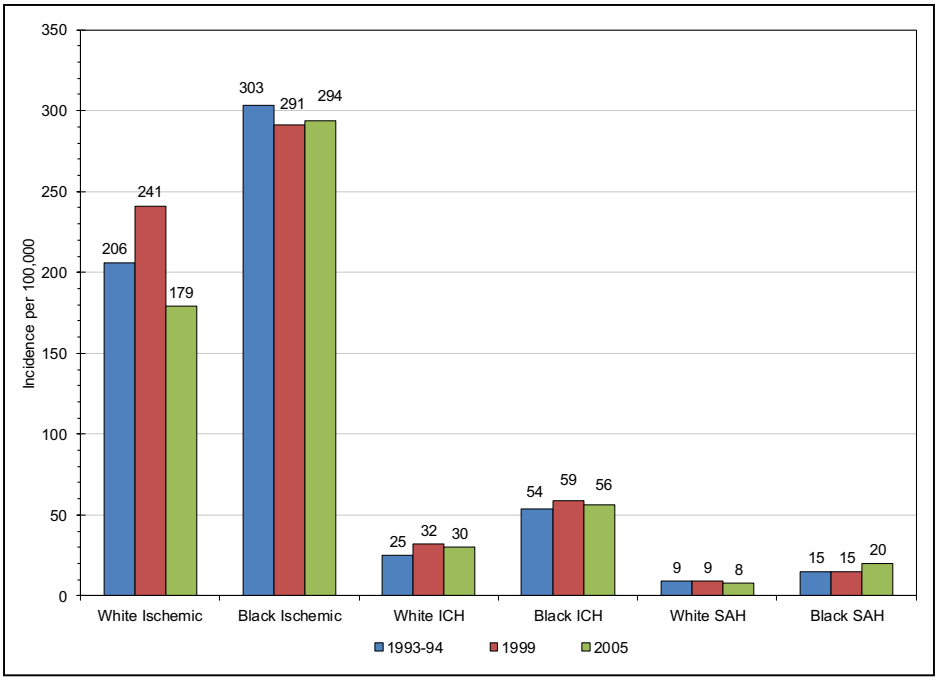

Chart 14-2. Annual age-adjusted incidence of first-ever stroke by race, United States, 1993 to 1994, 1999, and 2005.
Hospital plus out-of-hospital ascertainment. ICH indicates intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.
Source: Data derived from Kleindorfer et al.[18]

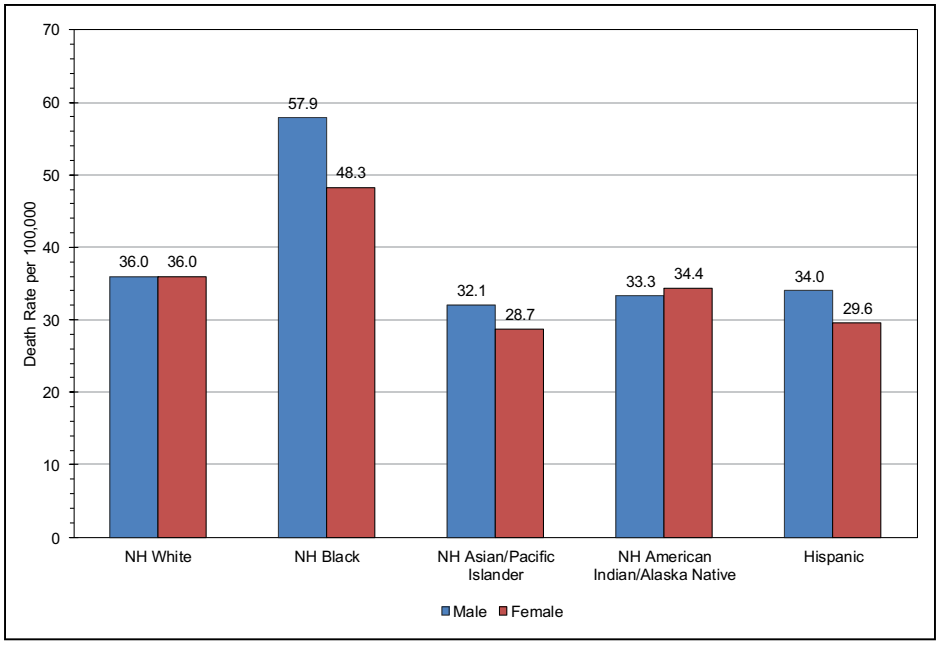

Chart 14-3. Age-adjusted death rates for stroke by sex and race/ethnicity, United States, 2017.
Death rates for the American Indian or Alaska Native and Asian or Pacific Islander populations are known to be underestimated. Stroke includes *International Classification of Diseases, 10th Revision* codes I60 through I69 (cerebrovascular disease). Mortality for NH Asians includes Pacific Islanders. NH indicates non-Hispanic.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.[249]

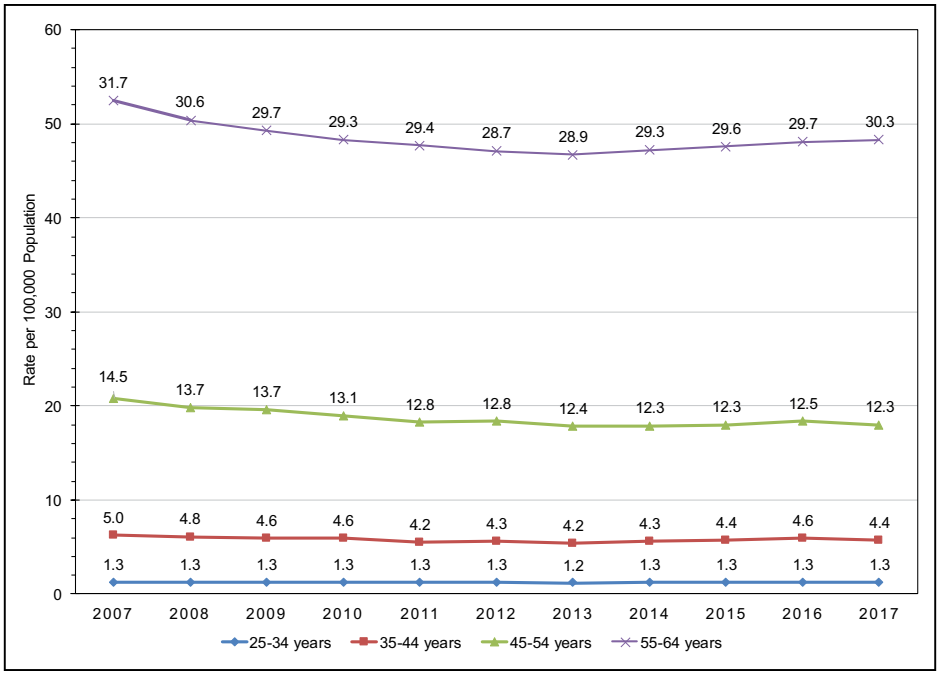

Chart 14-4. Crude stroke mortality rates among young US adults (25–64 years of age), 2007 to 2017.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.[249]

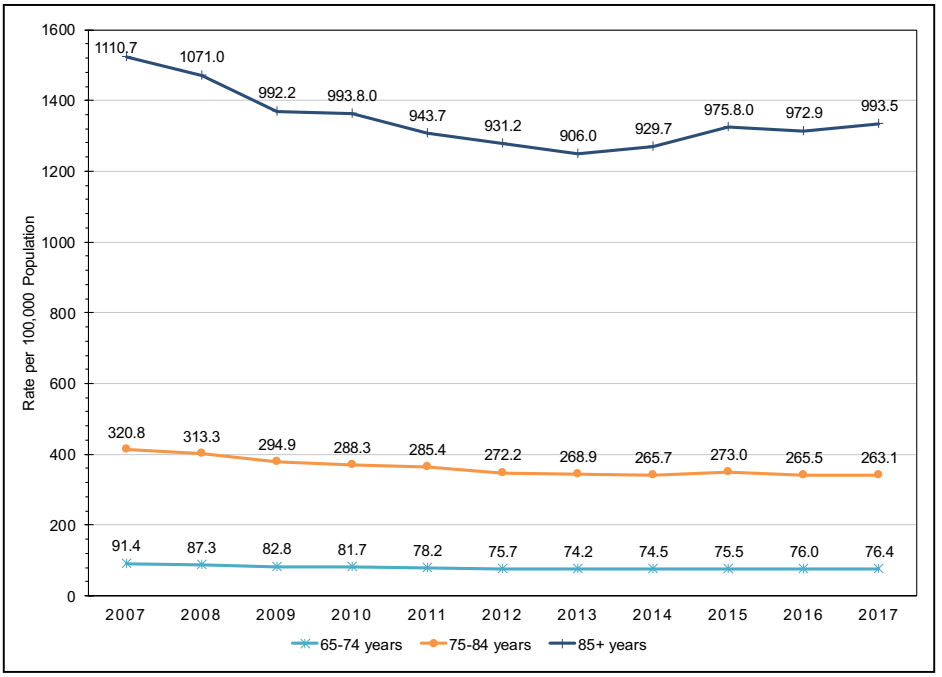

Chart 14-5. Crude stroke mortality rates among older US adults (≥65 years of age), 2007 to 2017.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.[249]

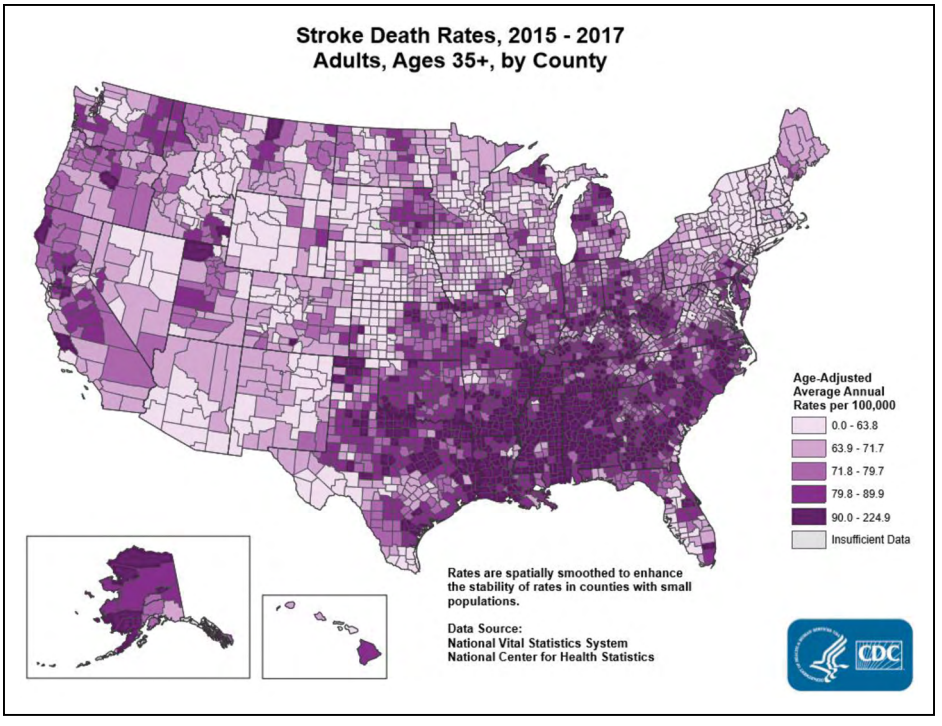

Chart 14-6. Stroke death rates, 2015 through 2017, among adults ≥35 years of age, by US county.
Rates are spatially smoothed to enhance the stability of rates in counties with small populations. *International Classification of Diseases, 10th Revision* codes for stroke: I60 through I69.
Source: National Vital Statistics System.[400]

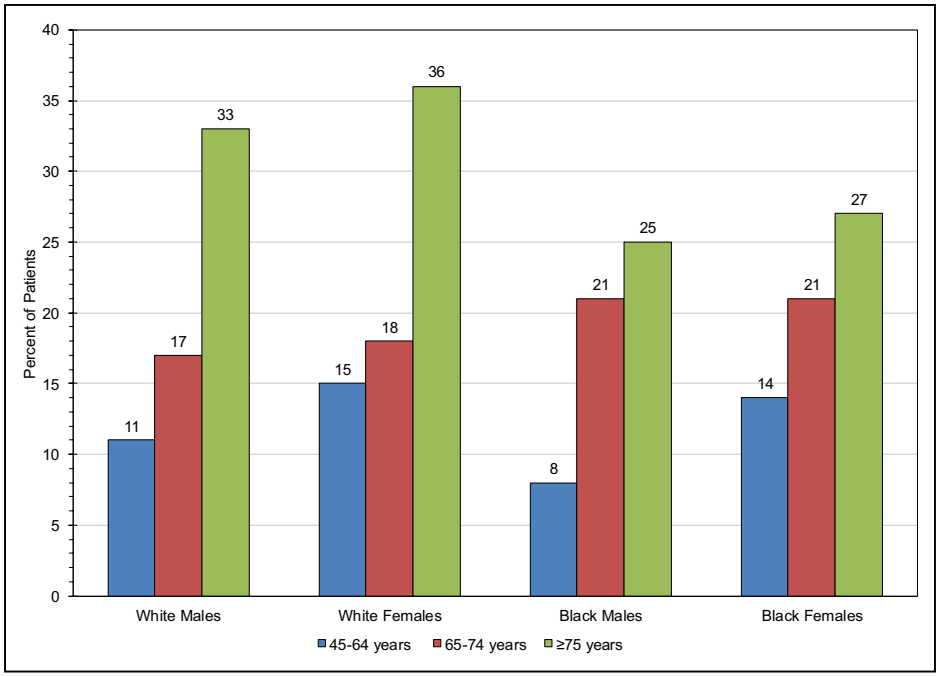

Chart 14-7. Probability of death within 1 year after first stroke, United States, 1995 to 2011.*
*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

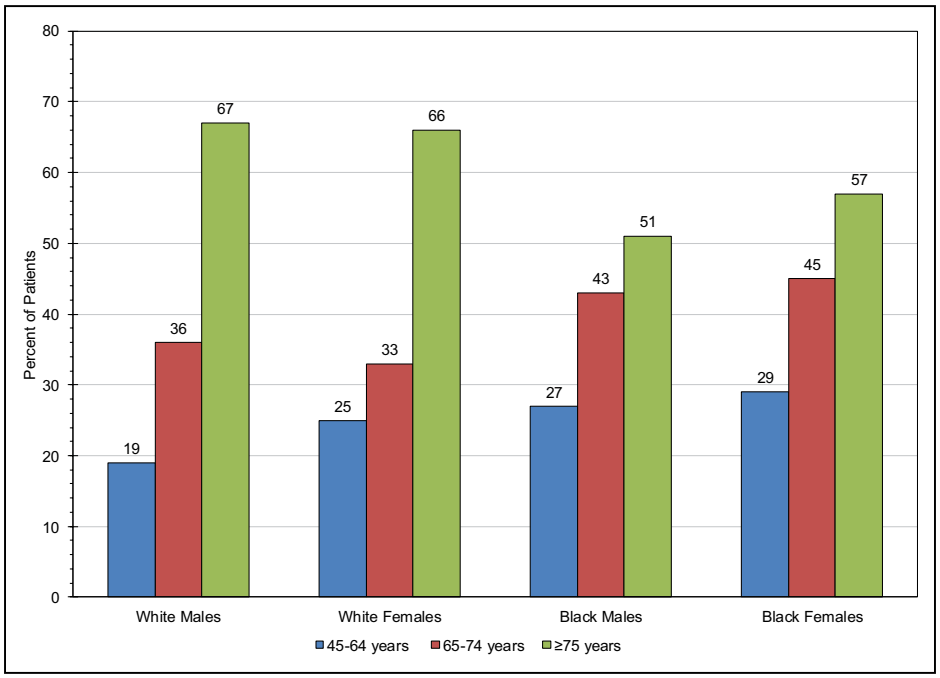

Chart 14-8. Probability of death within 5 years after first stroke, United States, 1995 to 2011.*
*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

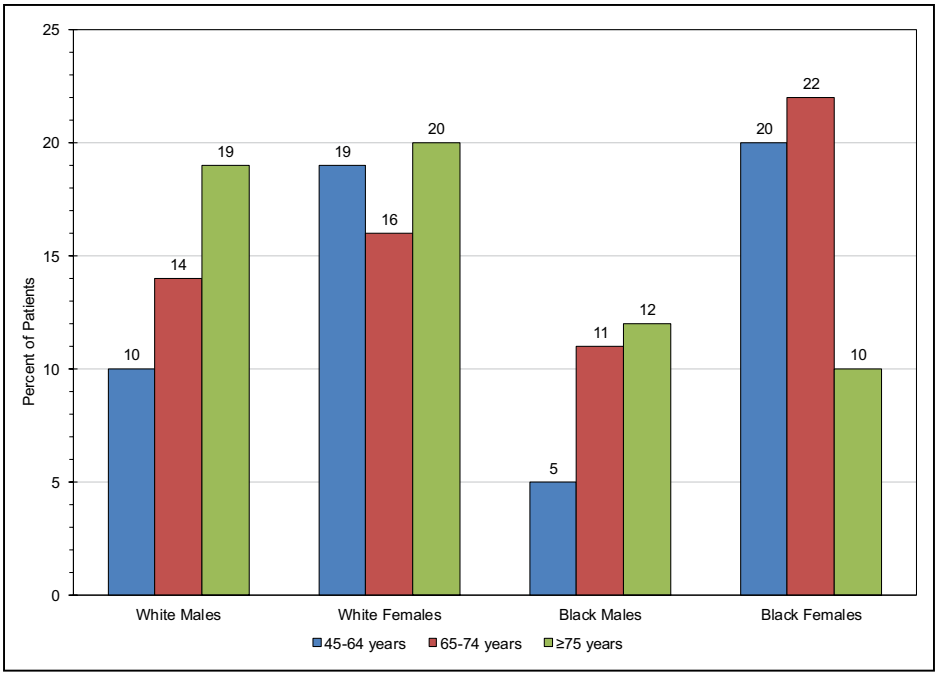

Chart 14-9. Probability of recurrent stroke in 5 years after first stroke, United States, 1995 to 2011.*
*Data years 1986 to 2011 for those who were 45 to 64 years of age because of the small number of events.
Source: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, Coronary Artery Risk Development in Young Adults, and Jackson Heart Study of the NHLBI.

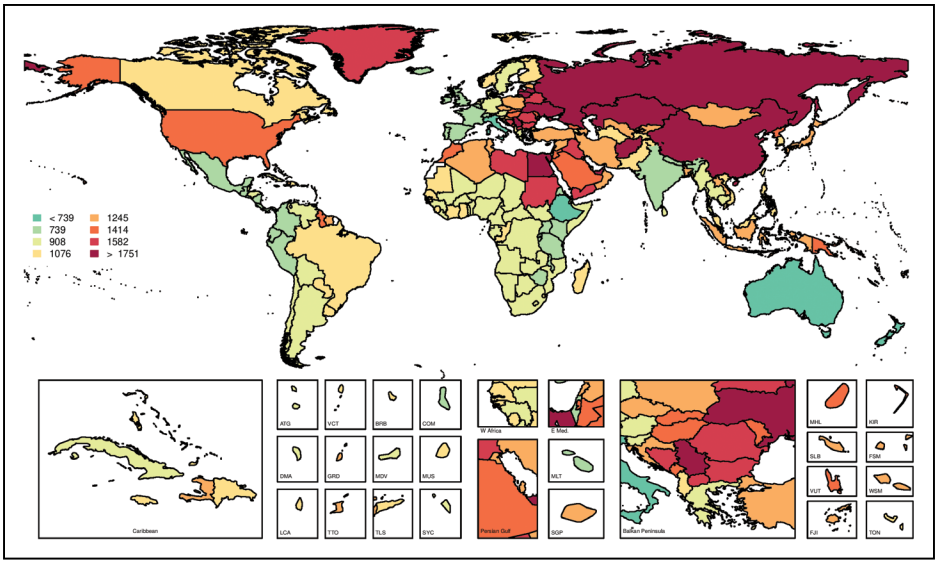

Chart 14-10. Age-standardized global prevalence rates of total stroke (all subtypes) per 100 000, both sexes, 2017.
Age-standardized stroke prevalence rates are highest in Eastern Europe, North Africa, the Middle East, and Central and East Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission. Copyright © 2018, University of Washington.

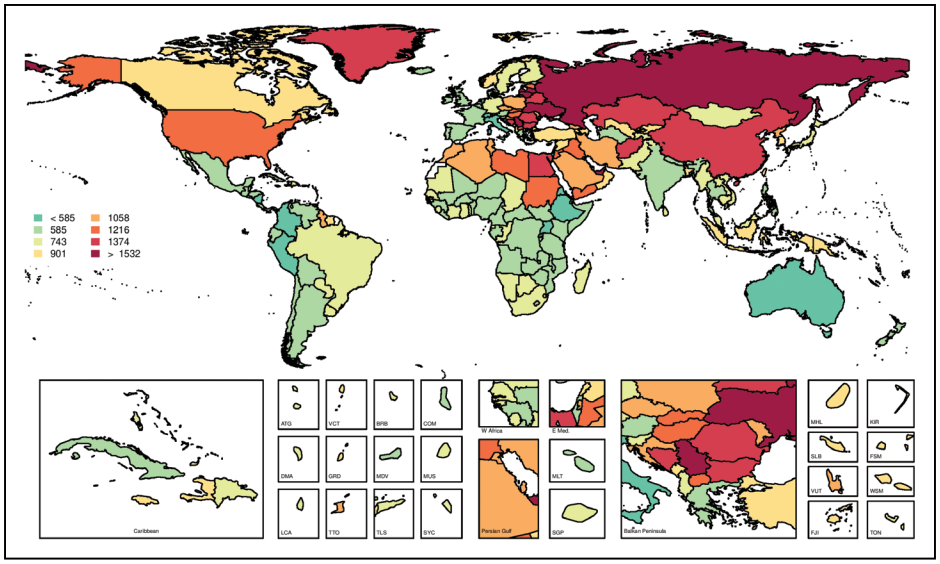

Chart 14-11. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2017.
Countries in Eastern Europe and Central and East Asia have the highest prevalence rates of ischemic stroke.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

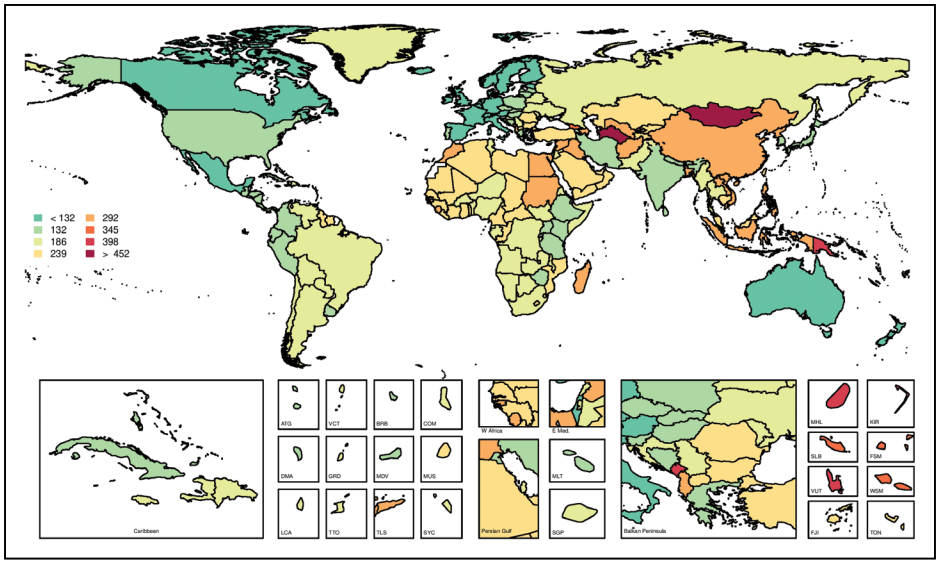

Chart 14-12. Age-standardized global prevalence rates of intracerebral hemorrhage (ICH) per 100 000, both sexes, 2017.
ICH prevalence rates are highest in East and Central Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

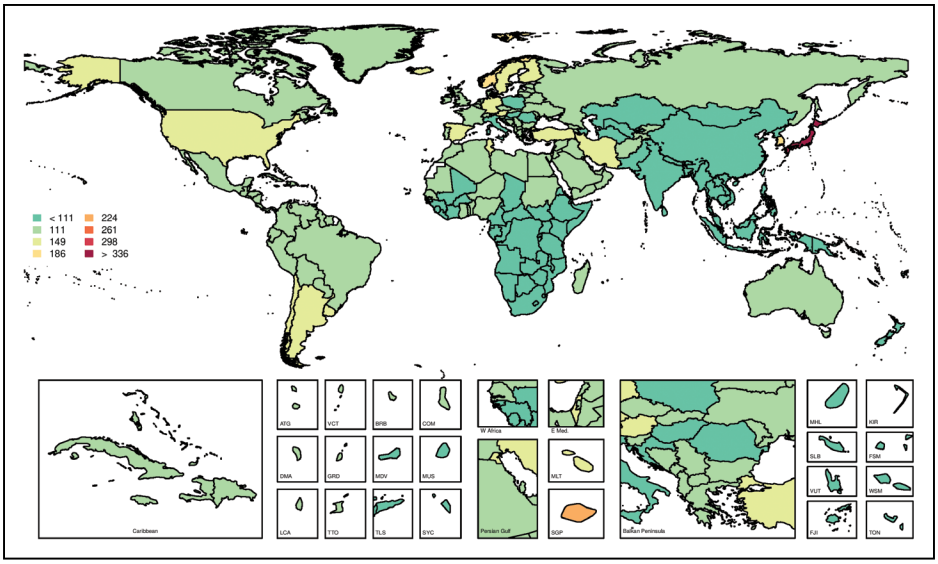

Chart 14-13. Age-standardized global prevalence rates of subarachnoid hemorrhage (SAH) per 100 000, both sexes, 2017.
Age-standardized prevalence of SAH is highest in Japan.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

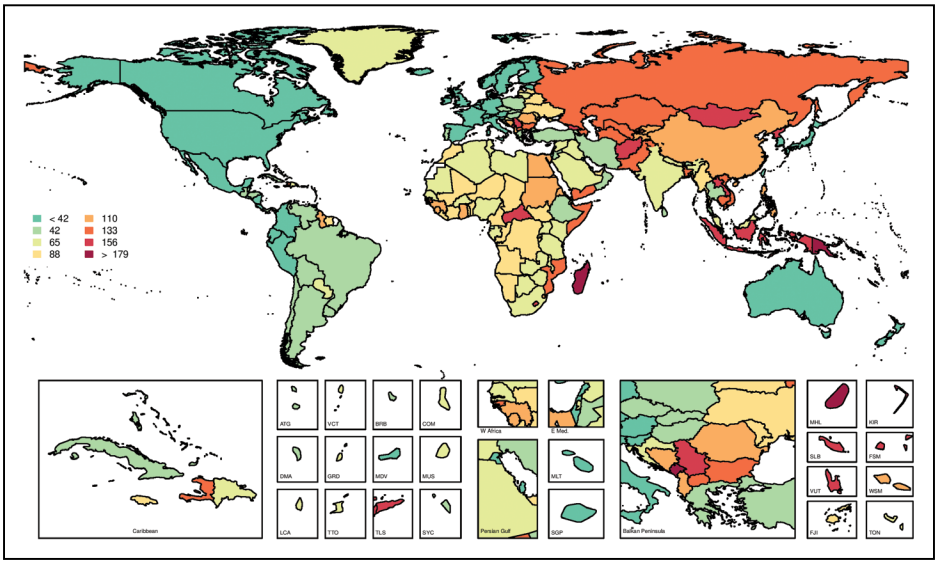

Chart 14-14. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2017.
Mortality of stroke is lowest in high income countries. Several countries in Eastern Europe, Africa, and Central Asia have the highest rates of stroke mortality.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

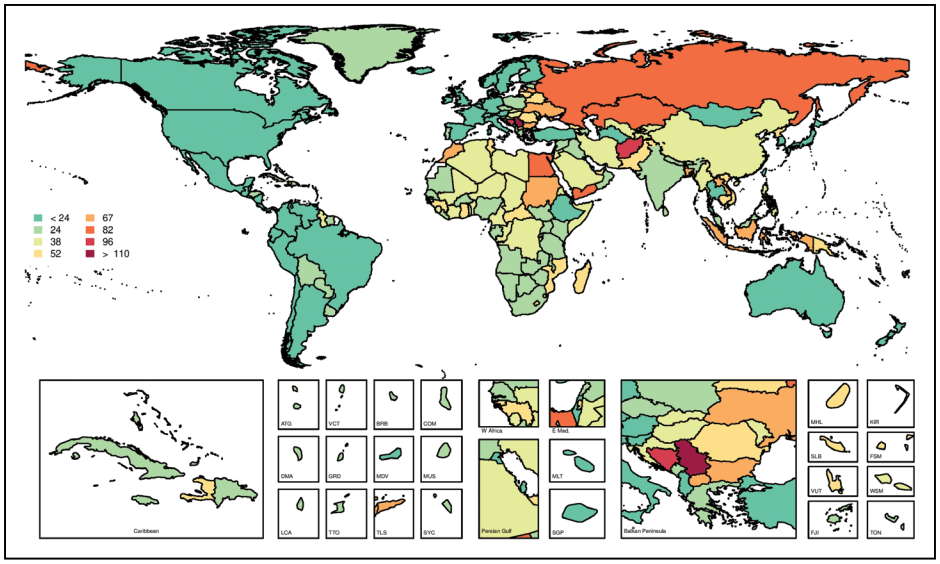

Chart 14-15. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2017.
Countries in Eastern Europe, North Africa, and Central Asia have the highest mortality rates of ischemic stroke.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

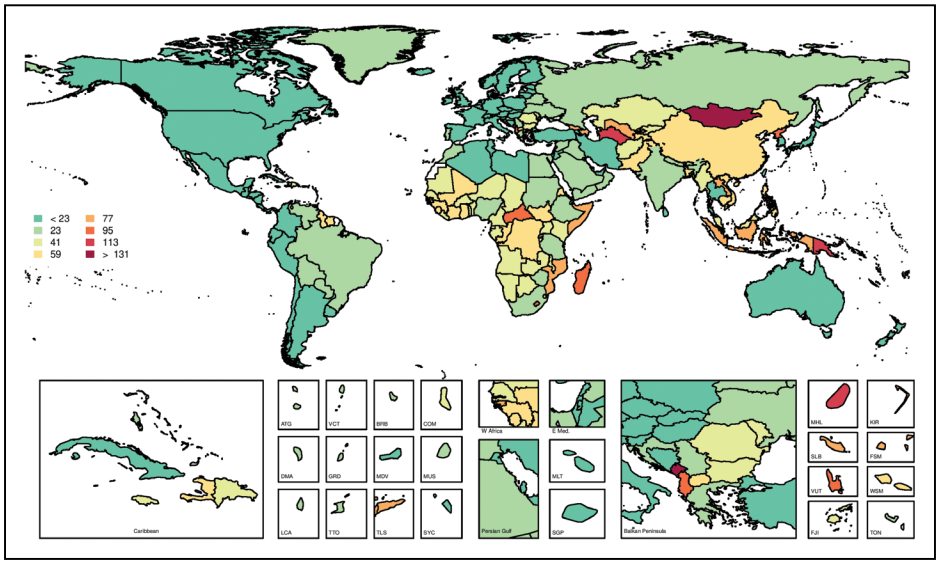

Chart 14-16. Age-standardized global mortality rates of intracerebral hemorrhage (ICH) per 100 000, both sexes, 2017.
ICH mortality rates are highest in East and Southeast Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

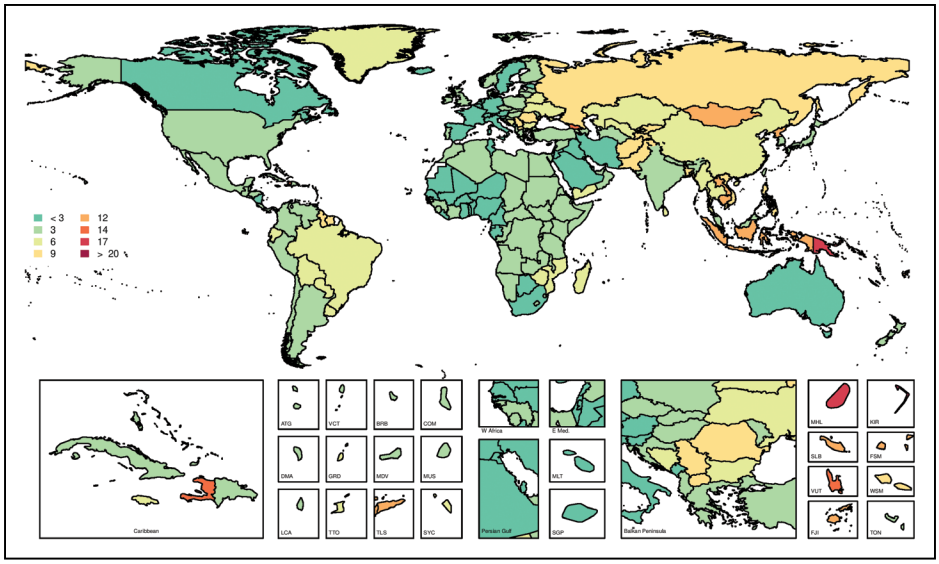

Chart 14-17. Age-standardized global mortality rates of subarachnoid hemorrhage (SAH) per 100 000, both sexes, 2017.
Mortality attributable to SAH is highest in Southeast Asia and Mongolia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[375] Printed with permission.

REFERENCES

1. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Behavioral Risk Factor Surveillance System (BRFSS). BRFSS prevalence & trends data [online] (2017). Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed April 1, 2019.
2. Howard VJ, McClure LA, Meschia JF, Pulley L, Orr SC, Friday GH. High prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Arch Intern Med.* 2006;166:1952–1958. doi: 10.1001/archinte.166.18.1952
3. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, Lackland DT, Lichtman JH, Mohl S, Sacco RL, et al; on behalf of the American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association [published correction appears in *Stroke*. 2015;46:e179]. *Stroke.* 2013;44:2361–2375. doi: 10.1161/STR.0b013e31829734f2
4. George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. *JAMA Neurol.* 2017;74:695–703. doi: 10.1001/jamaneurol.2017.0020
5. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, Coresh J. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA.* 2014;312:259–268. doi: 10.1001/jama.2014.7692
6. Morgenstern LB, Smith MA, Sánchez BN, Brown DL, Zahuranec DB, Garcia N, Kerber KA, Skolarus LE, Meurer WJ, Burke JF, et al. Persistent ischemic stroke disparities despite declining incidence in Mexican Americans. *Ann Neurol.* 2013;74:778–785. doi: 10.1002/ana.23972
7. Zahuranec DB, Lisabeth LD, Sánchez BN, Smith MA, Brown DL, Garcia NM, Skolarus LE, Meurer WJ, Burke JF, Adelman EE, et al. Intracerebral hemorrhage mortality is not changing despite declining incidence. *Neurology.* 2014;82:2180–2186. doi: 10.1212/WNL.0000000000000519
8. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, Wolf PA. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA.* 2006;296:2939–2946. doi: 10.1001/jama.296.24.2939
9. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Løchen ML, Njølstad I, Mathiesen EB. Declining incidence of ischemic stroke: what is the impact of changing risk factors? The Tromsø Study 1995 to 2012. *Stroke.* 2017;48:544–550. doi: 10.1161/STROKEAHA.116.014377
10. GBD 2016 Lifetime Risk of Stroke Collaborators. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N Engl J Med.* 2018;379:2429–2437. doi: 10.1056/NEJMoa1804492
11. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, Carolei A, Sacco S. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. *Stroke.* 2018;49:814–819. doi: 10.1161/STROKEAHA.117.020031
12. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, Cushman M, Moy CS, Soliman EZ, Kissela BM, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol.* 2011;69:619–627. doi: 10.1002/ana.22385
13. Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, et al. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. *Stroke.* 2006;37:2473–2478. doi: 10.1161/01.STR.0000242766.65550.92
14. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, Longwell PJ, McFarling DA, Akuwumi O, Al-Wabil A, et al. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol.* 2004;160:376–383. doi: 10.1093/aje/kwh225
15. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, Sacco RL. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation.* 2005;111:1327–1331. doi: 10.1161/01.CIR.0000157736.19739.D0
16. Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, et al. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation.* 2008;118:1577–1584. doi: 10.1161/CIRCULATIONAHA.108.772285
17. Howard G, Cushman M, Howard VJ, Kissela BM, Kleindorfer DO, Moy CS, Switzer J, Woo D. Risk factors for intracerebral hemorrhage: the REasons for geographic and racial differences in stroke (REGARDS) study [published correction appears in *Stroke*. 2013;44:e63]. *Stroke.* 2013;44:1282–1287. doi: 10.1161/STROKEAHA.111.000529
18. Kleindorfer DO, Khoury J, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Khatri P, Adeoye O, Ferioli S, Broderick JP, et al. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. *Stroke.* 2010;41:1326–1331. doi: 10.1161/STROKEAHA.109.575043
19. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke.* 2006;37:345–350. doi: 10.1161/01.STR.0000199613.38911.b2

20. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* 2008;7:915–926. doi: 10.1016/S1474-4422(08)70193-5
21. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population: the Rotterdam Study. *J Neurol Neurosurg Psychiatry.* 2003;74:317–321. doi: 10.1136/jnnp.74.3.317
22. Lewsey JD, Gillies M, Jhund PS, Chalmers JW, Redpath A, Briggs A, Walters M, Langhorne P, Capewell S, McMurray JJ, et al. Sex differences in incidence, mortality, and survival in individuals with stroke in Scotland, 1986 to 2005. *Stroke.* 2009;40:1038–1043. doi: 10.1161/STROKEAHA.108.542787
23. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, et al; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet.* 2005;366:1773–1783. doi: 10.1016/S0140-6736(05)67702-1
24. Sealy-Jefferson S, Wing JJ, Sánchez BN, Brown DL, Meurer WJ, Smith MA, Morgenstern LB, Lisabeth LD. Age- and ethnic-specific sex differences in stroke risk. *Gend Med.* 2012;9:121–128. doi: 10.1016/j.genm.2012.02.002
25. Vega T, Zurriaga O, Ramos JM, Gil M, Alamo R, Lozano JE, López A, Miralles MT, Vaca P, del Mar Alvarez M; Group of Research for the RECENT Project. Stroke in Spain: epidemiologic incidence and patterns; a health sentinel network study. *J Stroke Cerebrovasc Dis.* 2009;18:11–16. doi: 10.1016/j.jstrokecerebrovasdis.2008.06.010
26. Madsen TE, Khoury J, Alwell K, Moomaw CJ, Rademacher E, Flaherty ML, Woo D, Mackey J, De Los Rios La Rosa F, Martini S, et al. Sex-specific stroke incidence over time in the Greater Cincinnati/Northern Kentucky Stroke Study. *Neurology.* 2017;89:990–996. doi: 10.1212/WNL.0000000000004325
27. Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, Weiskopf T. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology.* 2003;60:1429–1434. doi: 10.1212/01.wnl.0000063309.41867.0f
28. Jiang B, Sun H, Ru X, Sun D, Chen Z, Liu H, Li Y, Zhang M, Wang L, Wang L, et al. Prevalence, incidence, prognosis, early stroke risk, and stroke-related prognostic factors of definite or probable transient ischemic attacks in China, 2013. *Front Neurol.* 2017;8:309. doi: 10.3389/fneur.2017.00309
29. Cancelli I, Janes F, Gigli GL, Perelli A, Zanchettin B, Canal G, D'Anna L, Russo V, Barbone F, Valente M. Incidence of transient ischemic attack and early stroke risk: validation of the ABCD2 score in an Italian population-based study. *Stroke.* 2011;42:2751–2757. doi: 10.1161/STROKEAHA.110.612705
30. Béjot Y, Brenière C, Graber M, Garnier L, Durier J, Blanc-Labarre C, Delpont B, Giroud M. Contemporary epidemiology of transient ischemic attack in Dijon, France (2013-2015). *Neuroepidemiology.* 2017;49:135–141. doi: 10.1159/000484638
31. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, Schneider A, Alwell K, Jauch E, Miller R, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke.* 2005;36:720–723. doi: 10.1161/01.STR.0000158917.59233.b7
32. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA.* 2000;284:2901–2906. doi: 10.1001/jama.284.22.2901
33. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet.* 2007;369:283–292. doi: 10.1016/S0140-6736(07)60150-0
34. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med.* 2007;167:2417–2422. doi: 10.1001/archinte.167.22.2417
35. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol.* 2007;6:1063–1072. doi: 10.1016/S1474-4422(07)70274-0
36. Åsberg S, Farahmand B, Hasvold P, Johansson S, Appelros P. Non-cardioembolic TIA and ischemic stroke: implications of severity. *Acta Neurol Scand.* 2018;138:369–376. doi: 10.1111/ane.12974
37. Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. *J Neurol Neurosurg Psychiatry.* 2003;74:577–580. doi: 10.1136/jnnp.74.5.577
38. Luengo-Fernandez R, Paul NL, Gray AM, Pendlebury ST, Bull LM, Welch SJ, Cuthbertson FC, Rothwell PM; Oxford Vascular Study. Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford Vascular Study. *Stroke.* 2013;44:2854–2861. doi: 10.1161/STROKEAHA.113.001584
39. Brazzelli M, Chappell FM, Miranda H, Shuler K, Dennis M, Sandercock PA, Muir K, Wardlaw JM. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol.* 2014;75:67–76. doi: 10.1002/ana.24026
40. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke.* 2009;40:2276–2293. doi: 10.1161/STROKEAHA.108.192218
41. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease and Council on Nutrition, Physical Activity, and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2019;50:e239]. *Stroke*. 2013;44:2064–2089. doi: 10.1161/STR.0b013e318296aeca
42. Albright KC, Huang L, Blackburn J, Howard G, Mullen M, Bittner V, Muntner P, Howard V. Racial differences in recurrent ischemic stroke risk and recurrent stroke case fatality. *Neurology.* 2018;91:e1741–e1750. doi: 10.1212/WNL.0000000000006467
43. Kauw F, Takx RAP, de Jong HWAM, Velthuis BK, Kappelle LJ, Dankbaar JW. Clinical and imaging predictors of recurrent ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis.* 2018;45:279–287. doi: 10.1159/000490422
44. Fullerton HJ, Wintermark M, Hills NK, Dowling MM, Tan M, Rafay MF, Elkind MS, Barkovich AJ, deVeber GA; VIPS Investigators. Risk of recurrent arterial ischemic stroke in childhood: a prospective international study. *Stroke.* 2016;47:53–59. doi: 10.1161/STROKEAHA.115.011173
45. Pennlert J, Eriksson M, Carlberg B, Wiklund PG. Long-term risk and predictors of recurrent stroke beyond the acute phase. *Stroke.* 2014;45:1839–1841. doi: 10.1161/STROKEAHA.114.005060
46. Jin P, Matos Diaz I, Stein L, Thaler A, Tuhrim S, Dhamoon MS. Intermediate risk of cardiac events and recurrent stroke after stroke admission in young adults. *Int J Stroke.* 2018;13:576–584. doi: 10.1177/1747493017733929
47. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, et al; Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 2016;15:913–924. doi: 10.1016/S1474-4422(16)30073-4
48. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published corrections appear in *Hypertension*. 2018;71:e136-e139 and *Hypertension*. 2018;72:e33]. *Hypertension.* 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
49. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, Miller EPR 3rd, Polonsky T, Thompson-Paul AM, Vupputuri S. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Hypertension*. 2018;71:e145]. *Hypertension.* 2018;71:e116–e135. doi: 10.1161/HYP.0000000000000067
50. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, Motu'apuaka M, Kondo K, Kansagara D. Benefits and harms of intensive blood pressure treatment in adults aged 60 years or older: a systematic review and meta-analysis [published corrections appear in *Ann Intern Med*. 2018;168:159 and *Ann Intern Med*. 2018;168:529-530]. *Ann Intern Med.* 2017;166:419–429. doi: 10.7326/M16-1754

51. Lackland DT, Carey RM, Conforto AB, Rosendorff C, Whelton PK, Gorelick PB. Implications of recent clinical trials and hypertension guidelines on stroke and future cerebrovascular research. *Stroke.* 2018;49:772–779. doi: 10.1161/STROKEAHA.117.019379
52. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8
53. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7: effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels: updated overview and meta-analyses of randomized trials. *J Hypertens.* 2016;34:613–622. doi: 10.1097/HJH.0000000000000881
54. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, Woodward M, MacMahon S, Turnbull F, Hillis GS, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet.* 2016;387:435–443. doi: 10.1016/S0140-6736(15)00805-3
55. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke.* 2014;45:315–353. doi: 10.1161/01.str.0000437068.30550.cf
56. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009;338:b1665. doi: 10.1136/bmj.b1665
57. O'Conor EC, Wang J, Gibney KD, Yu X, Young GR, Jones T, Alexandrov AW, Johnson KC, Cushman WC, Tsao JW. Lowering systolic blood pressure does not increase stroke risk: an analysis of the SPRINT and ACCORD trial data. *Ann Clin Transl Neurol.* 2019;6:144–153. doi: 10.1002/acn3.693
58. Verdecchia P, Angeli F, Gentile G, Reboldi G. More versus less intensive blood pressure-lowering strategy: cumulative evidence and trial sequential analysis. *Hypertension.* 2016;68:642–653. doi: 10.1161/HYPERTENSIONAHA.116.07608
59. Bangalore S, Toklu B, Gianos E, Schwartzbard A, Weintraub H, Ogedegbe G, Messerli FH. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. *Am J Med.* 2017;130:707–719.e8. doi: 10.1016/j.amjmed.2017.01.004
60. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol.* 2017;2:775–781. doi: 10.1001/jamacardio.2017.1421
61. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S74–S75]. *Circulation.* 2014;129(suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
62. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, et al; on behalf of the American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension.* 2018;72:e53–e90. doi: 10.1161/HYP.0000000000000084
63. Ikeme JC, Pergola PE, Scherzer R, Shlipak MG, Catanese L, McClure LA, Benavente OR, Peralta CA. Cerebral white matter hyperintensities, kidney function decline, and recurrent stroke after intensive blood pressure lowering: results from the Secondary Prevention of Small Subcortical Strokes (SPS 3) Trial. *J Am Heart Assoc.* 2019;8:e010091. doi: 10.1161/JAHA.118.010091
64. Lackland DT, Beilin LJ, Campbell NRC, Jaffe MG, Orias M, Ram CV, Weber MA, Zhang XH; on behalf of the World Hypertension League. Global implications of blood pressure thresholds and targets: guideline conversations from the World Hypertension League. *Hypertension.* 2018;71:985–987. doi: 10.1161/HYPERTENSIONAHA.118.11280
65. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, Broderick JP, et al. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke.* 2013;44:1500–1504. doi: 10.1161/STROKEAHA.113.001318
66. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet.* 2014;383:1973–1980. doi: 10.1016/S0140-6736(14)60040-4
67. Lee M, Saver JL, Hong KS, Song S, Chang KH, Ovbiagele B. Effect of pre-diabetes on future risk of stroke: meta-analysis. *BMJ.* 2012;344:e3564. doi: 10.1136/bmj.e3564
68. Shou J, Zhou L, Zhu S, Zhang X. Diabetes is an independent risk factor for stroke recurrence in stroke patients: a meta-analysis. *J Stroke Cerebrovasc Dis.* 2015;24:1961–1968. doi: 10.1016/j.jstrokecerebrovasdis.2015.04.004
69. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, Xian Y, Schwamm LH, Smith EE, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. *Eur Heart J.* 2018;39:2376–2386. doi: 10.1093/eurheartj/ehy036
70. Fang HJ, Zhou YH, Tian YJ, Du HY, Sun YX, Zhong LY. Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: a meta-analysis of data from 58,160 patients in 13 randomized controlled trials. *Int J Cardiol.* 2016;218:50–58. doi: 10.1016/j.ijcard.2016.04.163
71. Xie XX, Liu P, Wan FY, Lin SG, Zhong WL, Yuan ZK, Zou JJ, Liu LB. Blood pressure lowering and stroke events in type 2 diabetes: a network meta-analysis of randomized controlled trials. *Int J Cardiol.* 2016;208:141–146. doi: 10.1016/j.ijcard.2016.01.197
72. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575–1585. doi: 10.1056/NEJMoa1001286
73. Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, Fagard R, Verdecchia P, Weber M, Böhm M, et al; ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol.* 2012;59:74–83. doi: 10.1016/j.jacc.2011.09.040
74. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, Sacco RL, Elkind MS. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke.* 2012;43:1212–1217. doi: 10.1161/STROKEAHA.111.641381
75. Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, Singer DE. Effect of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA Study. *J Am Coll Cardiol.* 2016;67:239–247. doi: 10.1016/j.jacc.2015.10.080
76. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA.* 2003;290:1049–1056. doi: 10.1001/jama.290.8.1049
77. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983–988. doi: 10.1161/01.str.22.8.983
78. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet.* 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8
79. Chamberlain AM, Brown RD Jr, Alonso A, Gersh BJ, Killian JM, Weston SA, Roger VL. No decline in the risk of stroke following incident atrial fibrillation since 2000 in the community: a concerning trend. *J Am Heart Assoc.* 2016;5:e00348. doi: 10.1161/JAHA.116.003408
80. Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm.* 2005;2:125–131. doi: 10.1016/j.hrthm.2004.10.042
81. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, Jarouse J, Brillman J, Murali S, Gupta R. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology.* 2008;71:1696–1701. doi: 10.1212/01.wnl.0000325059.86313.31
82. Elijovich L, Josephson SA, Fung GL, Smith WS. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. *J Stroke Cerebrovasc Dis.* 2009;18:185–189. doi: 10.1016/j.jstrokecerebrovasdis.2008.09.005
83. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14:377–387. doi: 10.1016/S1474-4422(15)70027-X

84. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA, Rymer M, Ziegler PD, Liu S, Passman RS. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. *Circ Arrhythm Electrophysiol.* 2016;9:e003333. doi: 10.1161/CIRCEP.115.003333
85. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, et al; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke [published correction appears in *N Engl J Med*. 2016;374:998]. *N Engl J Med.* 2012;366:120–129. doi: 10.1056/NEJMoa1105575
86. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, Keung EK, Singer DE. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. *Circ Arrhythm Electrophysiol.* 2015;8:1040–1047. doi: 10.1161/CIRCEP.114.003057
87. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2015;313:603–615. doi: 10.1001/jama.2014.18574
88. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285:2864–2870. doi: 10.1001/jama.285.22.2864
89. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest.* 2010;137:263–272. doi: 10.1378/chest.09-1584
90. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ.* 2011;342:d124. doi: 10.1136/bmj.d124
91. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G, et al; for the ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation.* 2013;127:224–232. doi: 10.1161/CIRCULATIONAHA.112.107128
92. Oldgren J, Hijazi Z, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Granger CB, Hylek EM, Lopes RD, et al; on behalf of the RE-LY and ARISTOTLE Investigators. Performance and validation of a novel biomarker-based stroke risk score for atrial fibrillation. *Circulation.* 2016;134:1697–1707. doi: 10.1161/CIRCULATIONAHA.116.022802
93. Link MS, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, et al. Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). *Circ Arrhythm Electrophysiol*. 2017;10:e004267. doi: 10.1161/CIRCEP.116.004267
94. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, et al; ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J.* 2015;36:288–296. doi: 10.1093/eurheartj/ehu359
95. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
96. Kamel H, Elkind MS, Bhave PD, Navi BB, Okin PM, Iadecola C, Devereux RB, Fink ME. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke.* 2013;44:1550–1554. doi: 10.1161/STROKEAHA.113.001118
97. Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G. Total and high-density lipoprotein cholesterol and stroke risk. *Stroke.* 2012;43:1768–1774. doi: 10.1161/STROKEAHA.111.646778
98. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. *Stroke*. 2002;33:1863–1868. doi: 10.1161/01.str.0000020093.67593.0b
99. Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths [published correction appears in *Lancet*. 2008;372:292]. *Lancet*. 2007;370:1829–1839. doi: 10.1016/S0140-6736(07)61778-4
100. Amarenco P, Labreuche J, Touboul PJ. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. *Atherosclerosis.* 2008;196:489–496. doi: 10.1016/j.atherosclerosis.2007.07.033
101. Sun L, Clarke R, Bennett D, Guo Y, Walters RG, Hill M, Parish S, Millwood IY, Bian Z, Chen Y, et al; China Kadoorie Biobank Collaborative Group; International Steering Committee; International Co-ordinating Centre, Oxford; National Co-ordinating Centre, Beijing; Regional Co-ordinating Centres. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. *Nat Med.* 2019;25:569–574. doi: 10.1038/s41591-019-0366-x
102. Hindy G, Engström G, Larsson SC, Traylor M, Markus HS, Melander O, Orho-Melander M; on behalf of the Stroke Genetics Network (SiGN). Role of blood lipids in the development of ischemic stroke and its subtypes: a mendelian randomization Study. *Stroke.* 2018;49:820–827. doi: 10.1161/STROKEAHA.117.019653
103. Kurth T, Everett BM, Buring JE, Kase CS, Ridker PM, Gaziano JM. Lipid levels and the risk of ischemic stroke in women. *Neurology.* 2007;68:556–562. doi: 10.1212/01.wnl.0000254472.41810.0d
104. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet*. 1998;352:1801–1807. doi: 10.1016/S0140-6736(98)03454-0
105. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. *Neurology.* 2004;63:1868–1875. doi: 10.1212/01.wnl.0000144282.42222.da
106. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet*. 1995;346:1647–1653.
107. Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: a systematic review and meta-analysis. *Atherosclerosis.* 2016;248:123–131. doi: 10.1016/j.atherosclerosis.2016.03.016
108. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke.* 2013;44:1833–1839. doi: 10.1161/STROKEAHA.113.001326
109. Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, Shaw J, Ueshima H, Zimmet P, Jee SH, et al; for the Asia Pacific Cohort Studies Collaboration and the Obesity in Asia Collaboration. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. *Circulation.* 2011;124:2056–2064. doi: 10.1161/CIRCULATIONAHA.111.028373
110. Curb JD, Abbott RD, Rodriguez BL, Masaki KH, Chen R, Popper JS, Petrovitch H, Ross GW, Schatz IJ, Belleau GC, et al. High density lipoprotein cholesterol and the risk of stroke in elderly men: the Honolulu Heart Program. *Am J Epidemiol.* 2004;160:150–157. doi: 10.1093/aje/kwh177
111. Psaty BM, Anderson M, Kronmal RA, Tracy RP, Orchard T, Fried LP, Lumley T, Robbins J, Burke G, Newman AB, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc.* 2004;52:1639–1647. doi: 10.1111/j.1532-5415.2004.52455.x
112. Lee JS, Chang PY, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: the Strong Heart Study. *Diabetes Care.* 2017;40:529–537. doi: 10.2337/dc16-1958
113. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med.* 2014;371:2383–2393. doi: 10.1056/NEJMoa1409065
114. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, et al; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA.* 2009;302:1993–2000. doi: 10.1001/jama.2009.1619
115. Imamura T, Doi Y, Arima H, Yonemoto K, Hata J, Kubo M, Tanizaki Y, Ibayashi S, Iida M, Kiyohara Y. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. *Stroke.* 2009;40:382–388. doi: 10.1161/STROKEAHA.108.529537

116. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke*. 2007;38:2718–2725. doi: 10.1161/STROKEAHA.107.487090
117. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152. doi: 10.1001/jama.2008.621
118. Bowman TS, Sesso HD, Ma J, Kurth T, Kase CS, Stampfer MJ, Gaziano JM. Cholesterol and the risk of ischemic stroke. *Stroke*. 2003;34:2930–2934. doi: 10.1161/01.STR.0000102171.91292.DC
119. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, Sharrett AR. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2003;34:623–631. doi: 10.1161/01.STR.0000057812.51734.FF
120. Wieberdink RG, Poels MM, Vernooij MW, Koudstaal PJ, Hofman A, van der Lugt A, Breteler MM, Ikram MA. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 2011;31:2982–2989. doi: 10.1161/ATVBAHA.111.234948
121. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther*. 2010;8:917–932. doi: 10.1586/erc.10.56
122. Chauhan G, Adams HHH, Satizabal CL, Bis JC, Teumer A, Sargurupremraj M, Hofer E, Trompet S, Hilal S, Smith AV, et al; Stroke Genetics Network (SiGN), the International Stroke Genetics Consortium (ISGC), METASTROKE, Alzheimer's Disease Genetics Consortium (ADGC) and the Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting. *Neurology*. 2019;92:e486–e503. doi: 10.1212/WNL.0000000000006851
123. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2011;42:e26]. *Stroke*. 2011;42:517–584. doi: 10.1161/STR.0b013e3181fcb238
124. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, Jauch E, Moomaw CJ, Shukla R, Gebel J, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke*. 2002;33:1321–1326. doi: 10.1161/01.str.0000014773.57733.3e
125. Albertsen IE, Rasmussen LH, Lane DA, Overvad TF, Skjøth F, Overvad K, Lip GY, Larsen TB. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation: insights from the Danish Diet, Cancer, and Health study. *Chest*. 2014;145:559–566. doi: 10.1378/chest.13-1740
126. Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008;39:2439–2443. doi: 10.1161/STROKEAHA.107.510073
127. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports [published corrections appear in *BMJ*. 2018;361:k1611 and *BMJ*. 2018;363:k5035]. *BMJ*. 2018;360:j5855. doi: 10.1136/bmj.j5855
128. Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke*. 2013;44:2821–2828. doi: 10.1161/STROKEAHA.113.002342
129. Nakamura K, Barzi F, Lam TH, Huxley R, Feigin VL, Ueshima H, Woo J, Gu D, Ohkubo T, Lawes CM, et al; for the Asia Pacific Cohort Studies Collaboration. Cigarette smoking, systolic blood pressure, and cardiovascular diseases in the Asia-Pacific region. *Stroke*. 2008;39:1694–1702. doi: 10.1161/STROKEAHA.107.496752
130. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:498–505.
131. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*. 1996;348:505–510.
132. Lee PN, Forey BA. Environmental tobacco smoke exposure and risk of stroke in nonsmokers: a review with meta-analysis. *J Stroke Cerebrovasc Dis*. 2006;15:190–201. doi: 10.1016/j.jstrokecerebrovasdis.2006.05.002
133. Oono IP, Mackay DF, Pell JP. Meta-analysis of the association between secondhand smoke exposure and stroke. *J Public Health (Oxf)*. 2011;33:496–502. doi: 10.1093/pubmed/fdr025
134. Malek AM, Cushman M, Lackland DT, Howard G, McClure LA. Secondhand smoke exposure and stroke: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Prev Med*. 2015;49:e89–e97. doi: 10.1016/j.amepre.2015.04.014
135. Nishino Y, Tsuji I, Tanaka H, Nakayama T, Nakatsuka H, Ito H, Suzuki T, Katanoda K, Sobue T, Tominaga S; Three-Prefecture Cohort Study Group. Stroke mortality associated with environmental tobacco smoke among never-smoking Japanese women: a prospective cohort study. *Prev Med*. 2014;67:41–45. doi: 10.1016/j.ypmed.2014.06.029
136. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Association of secondhand smoke with stroke outcomes. *Stroke*. 2016;47:2828–2835. doi: 10.1161/STROKEAHA.116.014099
137. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. *Stroke*. 2016;47:1975–1981. doi: 10.1161/STROKEAHA.116.012957
138. Vidyasagaran AL, Siddiqi K, Kanaan M. Use of smokeless tobacco and risk of cardiovascular disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:1970–1981. doi: 10.1177/2047487316654026
139. Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ*. 2009;339:b3060. doi: 10.1136/bmj.b3060
140. Rostron BL, Chang JT, Anic GM, Tanwar M, Chang CM, Corey CG. Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis. *Open Heart*. 2018;5:e000846. doi: 10.1136/openhrt-2018-000846
141. Mutlu U, Swanson SA, Klaver CCW, Hofman A, Koudstaal PJ, Ikram MA, Ikram MK. The mediating role of the venules between smoking and ischemic stroke. *Eur J Epidemiol*. 2018;33:1219–1228. doi: 10.1007/s10654-018-0436-2
142. Bell EJ, Lutsey PL, Windham BG, Folsom AR. Physical activity and cardiovascular disease in African Americans in Atherosclerosis Risk in Communities. *Med Sci Sports Exerc*. 2013;45:901–907. doi: 10.1249/MSS.0b013e31827d87ec
143. Willey JZ, Moon YP, Sacco RL, Greenlee H, Diaz KM, Wright CB, Elkind MS, Cheung YK. Physical inactivity is a strong risk factor for stroke in the oldest old: findings from a multi-ethnic population (the Northern Manhattan Study). *Int J Stroke*. 2017;12:197–200. doi: 10.1177/1747493016676614
144. Soares-Miranda L, Siscovick DS, Psaty BM, Longstreth WT Jr, Mozaffarian D. Physical activity and risk of coronary heart disease and stroke in older adults: the Cardiovascular Health Study. *Circulation*. 2016;133:147–155. doi: 10.1161/CIRCULATIONAHA.115.018323
145. Pandey A, Patel MR, Willis B, Gao A, Leonard D, Das SR, Defina L, Berry JD. Association between midlife cardiorespiratory fitness and risk of stroke: the Cooper Center Longitudinal Study [published correction appears in *Stroke*. 2016;47:e203]. *Stroke*. 2016;47:1720–1726. doi: 10.1161/STROKEAHA.115.011532
146. Åberg ND, Kuhn HG, Nyberg J, Waern M, Friberg P, Svensson J, Torén K, Rosengren A, Åberg MA, Nilsson M. Influence of cardiovascular fitness and muscle strength in early adulthood on long-term risk of stroke in Swedish men. *Stroke*. 2015;46:1769–1776. doi: 10.1161/STROKEAHA.115.009008
147. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ; on behalf of the Million Women Study Collaborators. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation*. 2015;131:721–729. doi: 10.1161/CIRCULATIONAHA.114.010296
148. Blomstrand A, Blomstrand C, Ariai N, Bengtsson C, Björkelund C. Stroke incidence and association with risk factors in women: a 32-year follow-up of the Prospective Population Study of Women in Gothenburg. *BMJ Open*. 2014;4:e005173. doi: 10.1136/bmjopen-2014-005173
149. Willey JZ, Voutsinas J, Sherzai A, Ma H, Bernstein L, Elkind MSV, Cheung YK, Wang SS. Trajectories in leisure-time physical activity and risk of stroke in women in the California Teachers Study. *Stroke*. 2017;48:2346–2352. doi: 10.1161/STROKEAHA.117.017465
150. Tikk K, Sookthai D, Monni S, Gross ML, Lichy C, Kloss M, Kaaks R. Primary preventive potential for stroke by avoidance of major lifestyle risk factors: the European Prospective Investigation into Cancer and

Nutrition-Heidelberg cohort. *Stroke.* 2014;45:2041–2046. doi: 10.1161/STROKEAHA.114.005025
151. Jefferis BJ, Whincup PH, Papacosta O, Wannamethee SG. Protective effect of time spent walking on risk of stroke in older men. *Stroke.* 2014;45:194–199. doi: 10.1161/STROKEAHA.113.002246
152. Chomistek AK, Manson JE, Stefanick ML, Lu B, Sands-Lincoln M, Going SB, Garcia L, Allison MA, Sims ST, LaMonte MJ, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. *J Am Coll Cardiol.* 2013;61:2346–2354. doi: 10.1016/j.jacc.2013.03.031
153. Pandey A, Salahuddin U, Garg S, Ayers C, Kulinski J, Anand V, Mayo H, Kumbhani DJ, de Lemos J, Berry JD. Continuous dose-response association between sedentary time and risk for cardiovascular disease: a meta-analysis. *JAMA Cardiol.* 2016;1:575–583. doi: 10.1001/jamacardio.2016.1567
154. McDonnell MN, Hillier SL, Judd SE, Yuan Y, Hooker SP, Howard VJ. Association between television viewing time and risk of incident stroke in a general population: results from the REGARDS study. *Prev Med.* 2016;87:1–5. doi: 10.1016/j.ypmed.2016.02.013
155. Kubota Y, Iso H, Yamagishi K, Sawada N, Tsugane S; on behalf of the JPHC Study Group. Daily total physical activity and incident stroke: the Japan Public Health Center-Based Prospective Study. *Stroke.* 2017;48:1730–1736. doi: 10.1161/STROKEAHA.117.017560
156. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med.* 2018;378:e34. doi: 10.1056/NEJMoa1800389
157. Hankey GJ. The role of nutrition in the risk and burden of stroke: an update of the evidence. *Stroke.* 2017;48:3168–3174. doi: 10.1161/STROKEAHA.117.016993
158. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, Ward H, Johnson L, Crowe F, Hu FB, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *BMJ.* 2012;345:e6698. doi: 10.1136/bmj.e6698
159. Li Y, Huang Z, Jin C, Xing A, Liu Y, Huangfu C, Lichtenstein AH, Tucker KL, Wu S, Gao X. Longitudinal change of perceived salt intake and stroke risk in a Chinese population. *Stroke.* 2018;49:1332–1339. doi: 10.1161/STROKEAHA.117.020277
160. Hansen CP, Overvad K, Kyrø C, Olsen A, Tjønneland A, Johnsen SP, Jakobsen MU, Dahm CC. Adherence to a healthy Nordic diet and risk of stroke: a Danish cohort study. *Stroke.* 2017;48:259–264. doi: 10.1161/STROKEAHA.116.015019
161. Martínez-González MA, Dominguez LJ, Delgado-Rodríguez M. Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. *Br J Nutr.* 2014;112:248–259. doi: 10.1017/S0007114514000713
162. Cheng P, Wang J, Shao W. Monounsaturated fatty acid intake and stroke risk: a meta-analysis of prospective cohort studies. *J Stroke Cerebrovasc Dis.* 2016;25:1326–1334. doi: 10.1016/j.jstrokecerebrovasdis.2016.02.017
163. Alexander DD, Bylsma LC, Vargas AJ, Cohen SS, Doucette A, Mohamed M, Irvin SR, Miller PE, Watson H, Fryzek JP. Dairy consumption and CVD: a systematic review and meta-analysis [published correction appears in *Br J Nutr*. 2016;115:2268]. *Br J Nutr.* 2016;115:737–750. doi: 10.1017/S0007114515005000
164. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br J Nutr.* 2016;115:212–225. doi: 10.1017/S0007114515004316
165. Wu D, Guan Y, Lv S, Wang H, Li J. No evidence of increased risk of stroke with consumption of refined grains: a meta-analysis of prospective cohort studies. *J Stroke Cerebrovasc Dis.* 2015;24:2738–2746. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.004
166. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA,et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003497. doi: 10.1161/CIRCOUTCOMES.116.003497
167. Vinceti M, Filippini T, Crippa A, de Sesmaisons A, Wise LA, Orsini N. Meta-analysis of potassium intake and the risk of stroke. *J Am Heart Assoc.* 2016;5:e004210. doi: 10.1161/JAHA.116.004210
168. Wang ZM, Zhao D, Nie ZL, Zhao H, Zhou B, Gao W, Wang LS, Yang ZJ. Flavonol intake and stroke risk: a meta-analysis of cohort studies. *Nutrition.* 2014;30:518–523. doi: 10.1016/j.nut.2013.10.009
169. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, Tang G, Wang B, Chen D, He M, et al; CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA.* 2015;313:1325–1335. doi: 10.1001/jama.2015.2274
170. Mossavar-Rahmani Y, Kamensky V, Manson JE, Silver B, Rapp SR, Haring B, Beresford SAA, Snetselaar L, Wassertheil-Smoller S. Artificially sweetened beverages and stroke, coronary heart disease, and all-cause mortality in the Women's Health Initiative [published correction appears in *Stroke*. 2019;50:e176]. *Stroke.* 2019;50:555–562. doi: 10.1161/STROKEAHA.118.023100
171. Pase MP, Himali JJ, Beiser AS, Aparicio HJ, Satizabal CL, Vasan RS, Seshadri S, Jacques PF. Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: a prospective cohort study. *Stroke.* 2017;48:1139–1146. doi: 10.1161/STROKEAHA.116.016027
172. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ.* 2010;341:c4249. doi: 10.1136/bmj.c4249
173. Lee M, Saver JL, Chang KH, Ovbiagele B. Level of albuminuria and risk of stroke: systematic review and meta-analysis. *Cerebrovasc Dis.* 2010;30:464–469. doi: 10.1159/000317069
174. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant.* 2015;30:1162–1169. doi: 10.1093/ndt/gfv009
175. Mahmoodi BK, Yatsuya H, Matsushita K, Sang Y, Gottesman RF, Astor BC, Woodward M, Longstreth WT Jr, Psaty BM, Shlipak MG, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke.* 2014;45:1925–1931. doi: 10.1161/STROKEAHA.114.004900
176. Sandsmark DK, Messé SR, Zhang X, Roy J, Nessel L, Lee Hamm L, He J, Horwitz EJ, Jaar BG, Kallem RR, et al; on behalf of the CRIC Study Investigators. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic Renal Insufficiency Cohort Study. *Stroke.* 2015;46:2075–2080. doi: 10.1161/STROKEAHA.115.009861
177. El Husseini N, Fonarow GC, Smith EE, Ju C, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Renal dysfunction is associated with poststroke discharge disposition and in-hospital mortality: findings from Get With The Guidelines–Stroke. *Stroke.* 2017;48:327–334. doi: 10.1161/STROKEAHA.116.014601
178. Wang X, Wang Y, Patel UD, Barnhart HX, Li Z, Li H, Wang C, Zhao X, Liu L, Wang Y, et al. Comparison of associations of reduced estimated glomerular filtration rate with stroke outcomes between hypertension and no hypertension. *Stroke.* 2017;48:1691–1694. doi: 10.1161/STROKEAHA.117.016864
179. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Piña IL, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published corrections appear in *Stroke*. 2014;45;e214 and *Stroke*. 2014;45:e95]. *Stroke.* 2014;45:1545–1588. doi: 10.1161/01.str.0000442009.06663.48
180. Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, McClure JA, Lindsay MP. The incidence of pregnancy-related stroke: a systematic review and meta-analysis. *Int J Stroke.* 2017;12:687–697. doi: 10.1177/1747493017723271
181. Jacobson LT, Hade EM, Collins TC, Margolis KL, Waring ME, Van Horn LV, Silver B, Sattari M, Bird CE, Kimminau K, et al. Breastfeeding history and risk of stroke among parous postmenopausal women in the Women's Health Initiative. *J Am Heart Assoc.* 2018;7:e008739. doi: 10.1161/JAHA.118.008739
182. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke.* 2009;40:1082–1090. doi: 10.1161/STROKEAHA.108.540781
183. Poorthuis MH, Algra AM, Algra A, Kappelle LJ, Klijn CJ. Female- and male-specific risk factors for stroke: a systematic review and meta-analysis. *JAMA Neurol.* 2017;74:75–81. doi: 10.1001/jamaneurol.2016.3482
184. Friberg J, Scharling H, Gadsbøll N, Truelsen T, Jensen GB; Copenhagen City Heart Study. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (the Copenhagen City Heart Study). *Am J Cardiol.* 2004;94:889–894. doi: 10.1016/j.amjcard.2004.06.023

185. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation.* 2005;112:1687–1691. doi: 10.1161/CIRCULATIONAHA.105.553438
186. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Lévy S, Cobbe S, Kremastinos DT, Breithardt G, Cokkinos DV, Crijns HJ. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol.* 2007;49:572–577. doi: 10.1016/j.jacc.2006.10.047
187. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost.* 2009;101:938–942.
188. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA.* 2012;307:1952–1958. doi: 10.1001/jama.2012.3490
189. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, Green J, Cairns BJ; on behalf of the Million Women Study Collaborators. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation.* 2015;131:237–244. doi: 10.1161/CIRCULATIONAHA.114.010070
190. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol.* 2016;1:767–776. doi: 10.1001/jamacardio.2016.2415
191. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, Kotchen T, Curb JD, Black H, Rossouw JE, et al; WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA.* 2003;289:2673–2684. doi: 10.1001/jama.289.20.2673
192. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321–333. doi: 10.1001/jama.288.3.321
193. Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard BV, Kooperberg C, Rossouw JE, Trevisan M, Aragaki A, Baird AE, Bray PF, et al; for the WHI Investigators. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation.* 2006;113:2425–2434. doi: 10.1161/CIRCULATIONAHA.105.594077
194. Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, Barrett-Connor E, Hulley SB. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation.* 2001;103:638–642. doi: 10.1161/01.cir.103.5.638
195. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med.* 2001;345:1243–1249. doi: 10.1056/NEJMoa010534
196. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ.* 2010;340:c2519. doi: 10.1136/bmj.c2519
197. MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the Stroke Prevention in Young Women Study. *Stroke.* 2007;38:2438–2445. doi: 10.1161/STROKEAHA.107.488395
198. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ.* 2009;339:b3914. doi: 10.1136/bmj.b3914
199. Chow FC, Wilson MR, Wu K, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort. *AIDS.* 2018;32:1125–1135. doi: 10.1097/QAD.0000000000001799
200. Chow FC, Regan S, Zanni MV, Looby SE, Bushnell CD, Meigs JB, Grinspoon SK, Feske SK, Triant VA. Elevated ischemic stroke risk among women living with HIV infection. *AIDS.* 2018;32:59–67. doi: 10.1097/QAD.0000000000001650
201. Xie C, Zhu R, Tian Y, Wang K. Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. *BMJ Open.* 2017;7:e013983. doi: 10.1136/bmjopen-2016-013983
202. Xiao Z, Xie M, You Y, Wu H, Zhou G, Li M. Wake-up stroke and sleep-disordered breathing: a meta-analysis of current studies. *J Neurol.* 2018;265:1288–1294. doi: 10.1007/s00415-018-8810-2
203. Lisabeth LD, Sánchez BN, Chervin RD, Morgenstern LB, Zahuranec DB, Tower SD, Brown DL. High prevalence of poststroke sleep-disordered breathing in Mexican Americans. *Sleep Med.* 2017;33:97–102. doi: 10.1016/j.sleep.2016.01.010
204. Broadley SA, Jørgensen L, Cheek A, Salonikis S, Taylor J, Thompson PD, Antic R. Early investigation and treatment of obstructive sleep apnoea after acute stroke. *J Clin Neurosci.* 2007;14:328–333. doi: 10.1016/j.jocn.2006.01.017
205. Wu Z, Chen F, Yu F, Wang Y, Guo Z. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath.* 2018;22:729–742. doi: 10.1007/s11325-017-1604-4
206. Nicholson JS, McDermott MJ, Huang Q, Zhang H, Tyc VL. Full and home smoking ban adoption after a randomized controlled trial targeting secondhand smoke exposure reduction. *Nicotine Tob Res.* 2015;17:612–616. doi: 10.1093/ntr/ntu201
207. Brown DL, Mowla A, McDermott M, Morgenstern LB, Hegeman G 3rd, Smith MA, Garcia NM, Chervin RD, Lisabeth LD. Ischemic stroke subtype and presence of sleep-disordered breathing: the BASIC sleep apnea study. *J Stroke Cerebrovasc Dis.* 2015;24:388–393. doi: 10.1016/j.jstrokecerebrovasdis.2014.09.007
208. Martínez-García MA, Soler-Cataluña JJ, Ejarque-Martínez L, Soriano Y, Román-Sánchez P, Illa FB, Canal JM, Durán-Cantolla J. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. *Am J Respir Crit Care Med.* 2009;180:36–41. doi: 10.1164/rccm.200808-1341OC
209. Parra O, Arboix A, Montserrat JM, Quintó L, Bechich S, García-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J.* 2004;24:267–272. doi: 10.1183/09031936.04.00061503
210. Sahlin C, Sandberg O, Gustafson Y, Bucht G, Carlberg B, Stenlund H, Franklin KA. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. *Arch Intern Med.* 2008;168:297–301. doi: 10.1001/archinternmed.2007.70
211. Turkington PM, Bamford J, Wanklyn P, Elliott MW. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. *Stroke.* 2002;33:2037–2042. doi: 10.1161/01.str.0000023576.94311.27
212. Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. *Sleep Med Rev.* 2018;39:25–36. doi: 10.1016/j.smrv.2017.06.011
213. Leng Y, Cappuccio FP, Wainwright NW, Surtees PG, Luben R, Brayne C, Khaw KT. Sleep duration and risk of fatal and nonfatal stroke: a prospective study and meta-analysis. *Neurology.* 2015;84:1072–1079. doi: 10.1212/WNL.0000000000001371
214. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* 2017;6:e005947. doi: 10.1161/JAHA.117.005947
215. Li W, Wang D, Cao S, Yin X, Gong Y, Gan Y, Zhou Y, Lu Z. Sleep duration and risk of stroke events and stroke mortality: a systematic review and meta-analysis of prospective cohort studies. *Int J Cardiol.* 2016;223:870–876. doi: 10.1016/j.ijcard.2016.08.302
216. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review [published correction appears in *JAMA*. 2011;306:2565]. *JAMA.* 2011;306:1241–1249. doi: 10.1001/jama.2011.1282
217. Gilsanz P, Kubzansky LD, Tchetgen Tchetgen EJ, Wang Q, Kawachi I, Patton KK, Fitzpatrick AL, Kop WJ, Longstreth WT Jr, Glymour MM. Changes in depressive symptoms and subsequent risk of stroke in the Cardiovascular Health Study. *Stroke.* 2017;48:43–48. doi: 10.1161/STROKEAHA.116.013554
218. Lightbody CE, Clegg A, Patel K, Lucas JC, Storey H, Hackett ML, Watkins DCL. Systematic review and meta-analysis of psychosocial risk factors for stroke. *Semin Neurol.* 2017;37:294–306. doi: 10.1055/s-0037-1603758
219. Wassertheil-Smoller S, Qi Q, Dave T, Mitchell BD, Jackson RD, Liu S, Park K, Salinas J, Dunn EC, Leira EC, et al. Polygenic risk for depression increases risk of ischemic stroke: from the Stroke Genetics Network Study [published correction appears in *Stroke*. 2019;50:e24-e25]. *Stroke.* 2018;49:543–548. doi: 10.1161/STROKEAHA.117.018857
220. Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, Kivimäki M, Elovainio M. Social isolation and loneliness as risk factors for myocardial

infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women [published correction appears in *Heart*. 2019;105:e8]. *Heart.* 2018;104:1536–1542. doi: 10.1136/heartjnl-2017-312663
221. Eshak ES, Honjo K, Iso H, Ikeda A, Inoue M, Sawada N, Tsugane S. Changes in the employment status and risk of stroke and stroke types. *Stroke.* 2017;48:1176–1182. doi: 10.1161/STROKEAHA.117.016967
222. Kivimäki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, et al; IPD-Work Consortium. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. *Lancet.* 2015;386:1739–1746. doi: 10.1016/S0140-6736(15)60295-1
223. Nagayoshi M, Everson-Rose SA, Iso H, Mosley TH Jr, Rose KM, Lutsey PL. Social network, social support, and risk of incident stroke: Atherosclerosis Risk in Communities study. *Stroke.* 2014;45:2868–2873. doi: 10.1161/STROKEAHA.114.005815
224. Everson-Rose SA, Roetker NS, Lutsey PL, Kershaw KN, Longstreth WT Jr, Sacco RL, Diez Roux AV, Alonso A. Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the Multi-Ethnic Study of Atherosclerosis. *Stroke.* 2014;45:2318–2323. doi: 10.1161/STROKEAHA.114.004815
225. Fox CS, Polak JF, Chazaro I, Cupples A, Wolf PA, D'Agostino RA, O'Donnell CJ. Genetic and environmental contributions to atherosclerosis phenotypes in men and women: heritability of carotid intima-media thickness in the Framingham Heart Study. *Stroke.* 2003;34:397–401. doi: 10.1161/01.str.0000048214.56981.6f
226. Liao D, Myers R, Hunt S, Shahar E, Paton C, Burke G, Province M, Heiss G. Familial history of stroke and stroke risk: the Family Heart Study. *Stroke.* 1997;28:1908–1912. doi: 10.1161/01.str.28.10.1908
227. Schulz UG, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. *Stroke.* 2004;35:819–824. doi: 10.1161/01.STR.0000121646.23955.0f
228. Markus HS, Bevan S. Mechanisms and treatment of ischaemic stroke–insights from genetic associations. *Nat Rev Neurol.* 2014;10:723–730. doi: 10.1038/nrneurol.2014.196
229. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, Kostulas K, Kuhlenbäumer G, Bevan S, Jonsdottir T, et al. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol.* 2008;64:402–409. doi: 10.1002/ana.21480
230. Anderson CD, Biffi A, Rost NS, Cortellini L, Furie KL, Rosand J. Chromosome 9p21 in ischemic stroke: population structure and meta-analysis. *Stroke.* 2010;41:1123–1131. doi: 10.1161/STROKEAHA.110.580589
231. Dichgans M, Malik R, König IR, Rosand J, Clarke R, Gretarsdottir S, Thorleifsson G, Mitchell BD, Assimes TL, Levi C, et al; METASTROKE Consortium; CARDIoGRAM Consortium; C4D Consortium; International Stroke Genetics Consortium. Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. *Stroke.* 2014;45:24–36. doi: 10.1161/STROKEAHA.113.002707
232. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, et al; AFGen Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; INVENT Consortium; STARNET; BioBank Japan Cooperative Hospital Group; COMPASS Consortium; EPIC-CVD Consortium; EPIC-InterAct Consortium; International Stroke Genetics Consortium (ISGC); METASTROKE Consortium; Neurology Working Group of the CHARGE Consortium; NINDS Stroke Genetics Network (SiGN); UK Young Lacunar DNA Study; MEGASTROKE Consortium. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes [published correction appears in *Nat Genet*. 2019;51:1192-1193]. *Nat Genet.* 2018;50:524–537. doi: 10.1038/s41588-018-0058-3
233. Traylor M, Malik R, Nalls MA, Cotlarciuc I, Radmanesh F, Thorleifsson G, Hanscombe KB, Langefeld C, Saleheen D, Rost NS, et al; METASTROKE, UK Young Lacunar DNA Study, NINDS Stroke Genetics Network, Neurology Working Group of the CHARGE Consortium; International Stroke Genetics Consortium. Genetic variation at 16q24.2 is associated with small vessel stroke. *Ann Neurol.* 2017;81:383–394. doi: 10.1002/ana.24840
234. Malik R, Traylor M, Pulit SL, Bevan S, Hopewell JC, Holliday EG, Zhao W, Abrantes P, Amouyel P, Attia JR, et al; ISGC Analysis Group; METASTROKE collaboration; Wellcome Trust Case Control Consortium 2 (WTCCC2); NINDS Stroke Genetics Network (SiGN). Low-frequency and common genetic variation in ischemic stroke: the METASTROKE collaboration [published correction appears in *Neurology*. 2016;87:1306]. *Neurology.* 2016;86:1217–1226. doi: 10.1212/WNL.0000000000002528
235. Erdmann J, Stark K, Esslinger UB, Rumpf PM, Koesling D, de Wit C, Kaiser FJ, Braunholz D, Medack A, Fischer M, et al; CARDIoGRAM. Dysfunctional nitric oxide signalling increases risk of myocardial infarction. *Nature.* 2013;504:432–436. doi: 10.1038/nature12722
236. Dichgans M. Genetics of ischaemic stroke. *Lancet Neurol.* 2007;6:149–161. doi: 10.1016/S1474-4422(07)70028-5
237. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cécillion M, Marechal E, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature.* 1996;383:707–710. doi: 10.1038/383707a0
238. Devan WJ, Falcone GJ, Anderson CD, Jagiella JM, Schmidt H, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Cuadrado-Godia E, Soriano C, et al; on behalf of the International Stroke Genetics Consortium. Heritability estimates identify a substantial genetic contribution to risk and outcome of intracerebral hemorrhage. *Stroke.* 2013;44:1578–1583. doi: 10.1161/STROKEAHA.111.000089
239. Carpenter AM, Singh IP, Gandhi CD, Prestigiacomo CJ. Genetic risk factors for spontaneous intracerebral haemorrhage. *Nat Rev Neurol.* 2016;12:40–49. doi: 10.1038/nrneurol.2015.226
240. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TW, et al; International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet.* 2014;94:511–521. doi: 10.1016/j.ajhg.2014.02.012
241. Georgakis MK, Gill D, Rannikmäe K, Traylor M, Anderson CD, Lee JM, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, et al. Genetically determined levels of circulating cytokines and risk of stroke. *Circulation.* 2019;139:256–268. doi: 10.1161/CIRCULATIONAHA.118.035905
242. Gill D, Georgakis MK, Laffan M, Sabater-Lleal M, Malik R, Tzoulaki I, Veltkamp R, Dehghan A. Genetically determined FXI (factor XI) levels and risk of stroke. *Stroke.* 2018;49:2761–2763. doi: 10.1161/STROKEAHA.118.022792
243. de Vries PS, Sabater-Lleal M, Huffman JE, Marten J, Song C, Pankratz N, Bartz TM, de Haan HG, Delgado GE, Eicher JD, et al; INVENT Consortium; MEGASTROKE Consortium of the International Stroke Genetics Consortium. A genome-wide association study identifies new loci for factor VII and implicates factor VII in ischemic stroke etiology. *Blood.* 2019;133:967–977. doi: 10.1182/blood-2018-05-849240
244. Simmons C, Noble JM, Leighton-Herrmann E, Hecht MF, Williams O. Community-level measures of stroke knowledge among children: findings from Hip Hop Stroke. *J Stroke Cerebrovasc Dis.* 2017;26:139–142. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.045
245. Mochari-Greenberger H, Towfighi A, Mosca L. National women's knowledge of stroke warning signs, overall and by race/ethnic group. *Stroke.* 2014;45:1180–1182. doi: 10.1161/STROKEAHA.113.004242
246. Martinez M, Prabhakar N, Drake K, Coull B, Chong J, Ritter L, Kidwell C. Identification of barriers to stroke awareness and risk factor management unique to Hispanics. *Int J Environ Res Public Health.* 2015;13:ijerph13010023. doi: 10.3390/ijerph13010023
247. Madsen TE, Baird KA, Silver B, Gjelsvik A. Analysis of gender differences in knowledge of stroke warning signs. *J Stroke Cerebrovasc Dis.* 2015;24:1540–1547. doi: 10.1016/j.jstrokecerebrovasdis.2015.03.017
248. Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 survey of atrial fibrillation and stroke: gaps in knowledge and perspective, opportunities for improvement. *J Stroke Cerebrovasc Dis.* 2015;24:1691–1700. doi: 10.1016/j.jstrokecerebrovasdis.2015.06.026
249. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple causes of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019
250. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
251. Howard G, Evans GW, Pearce K, Howard VJ, Bell RA, Mayer EJ, Burke GL. Is the stroke belt disappearing? An analysis of racial, temporal, and age effects. *Stroke.* 1995;26:1153–1158. doi: 10.1161/01.str.26.7.1153

252. Gilsanz P, Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Association between birth in a high stroke mortality state, race, and risk of dementia. *JAMA Neurol.* 2017;74:1056–1062. doi: 10.1001/jamaneurol.2017.1553
253. Lackland DT. Impact of birth place and geographic location on risk disparities in cerebrovascular disease: implications for future research. *JAMA Neurol.* 2017;74:1043–1045. doi: 10.1001/jamaneurol.2017.1560
254. Howard VJ, McClure LA, Glymour MM, Cunningham SA, Kleindorfer DO, Crowe M, Wadley VG, Peace F, Howard G, Lackland DT. Effect of duration and age at exposure to the Stroke Belt on incident stroke in adulthood. *Neurology.* 2013;80:1655–1661. doi: 10.1212/WNL.0b013e3182904d59
255. Schieb LJ, Ayala C, Valderrama AL, Veazie MA. Trends and disparities in stroke mortality by region for American Indians and Alaska Natives. *Am J Public Health.* 2014;suppl 3:S368–S376. doi: 10.2105/AJPH.2013.301698
256. Pearson-Stuttard J, Guzman-Castillo M, Penalvo JL, Rehm CD, Afshin A, Danaei G, Kypridemos C, Gaziano T, Mozaffarian D, Capewell S, et al. Modeling future cardiovascular disease mortality in the United States: national trends and racial and ethnic disparities. *Circulation.* 2016;133:967–978. doi: 10.1161/CIRCULATIONAHA.115.019904
257. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults: United States, 2005. *MMWR Morb Mortal Wkly Rep.* 2009;58:421–426.
258. Singh T, Peters SR, Tirschwell DL, Creutzfeldt CJ. Palliative care for hospitalized patients with stroke: results from the 2010 to 2012 National Inpatient Sample. *Stroke.* 2017;48:2534–2540. doi: 10.1161/STROKEAHA.117.016893
259. Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, Dellavalle R, Danaei G, Ezzati M, Fahimi A, et al; U.S. Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310:591–608. doi: 10.1001/jama.2013.13805
260. Janus-Laszuk B, Mirowska-Guzel D, Sarzynska-Dlugosz I, Czlonkowska A. Effect of medical complications on the after-stroke rehabilitation outcome. *NeuroRehabilitation.* 2017;40:223–232. doi: 10.3233/NRE-161407
261. Sherman DG, Albers GW, Bladin C, Fieschi C, Gabbai AA, Kase CS, O'Riordan W, Pineo GF; PREVAIL Investigators. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet.* 2007;369:1347–1355. doi: 10.1016/S0140-6736(07)60633-3
262. Chan L, Hu CJ, Fan YC, Li FY, Hu HH, Hong CT, Bai CH. Incidence of poststroke seizures: a meta-analysis. *J Clin Neurosci.* 2018;47:347–351. doi: 10.1016/j.jocn.2017.10.088
263. O'Donnell MJ, Diener HC, Sacco RL, Panju AA, Vinisko R, Yusuf S; on behalf of the PRoFESS Investigators. Chronic pain syndromes after ischemic stroke: PRoFESS trial. *Stroke.* 2013;44:1238–1243. doi: 10.1161/STROKEAHA.111.671008
264. Kapral MK, Fang J, Alibhai SM, Cram P, Cheung AM, Casaubon LK, Prager M, Stamplecoski M, Rashkovan B, Austin PC. Risk of fractures after stroke: results from the Ontario Stroke Registry. *Neurology.* 2017;88:57–64. doi: 10.1212/WNL.0000000000003457
265. Glozier N, Moullaali TJ, Sivertsen B, Kim D, Mead G, Jan S, Li Q, Hackett ML. The course and impact of poststroke insomnia in stroke survivors aged 18 to 65 years: results from the Psychosocial Outcomes In StrokE (POISE) Study. *Cerebrovasc Dis Extra.* 2017;7:9–20. doi: 10.1159/000455751
266. Li J, Yuan M, Liu Y, Zhao Y, Wang J, Guo W. Incidence of constipation in stroke patients: a systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96:e7225. doi: 10.1097/MD.0000000000007225
267. Ryan AS, Ivey FM, Serra MC, Hartstein J, Hafer-Macko CE. Sarcopenia and physical function in middle-aged and older stroke survivors. *Arch Phys Med Rehabil.* 2017;98:495–499. doi: 10.1016/j.apmr.2016.07.015
268. Winovich DT, Longstreth WT Jr, Arnold AM, Varadhan R, Zeki Al Hazzouri A, Cushman M, Newman AB, Odden MC. Factors associated with ischemic stroke survival and recovery in older adults. *Stroke.* 2017;48:1818–1826. doi: 10.1161/STROKEAHA.117.016726
269. Medicare Payment Advisory Commission (MedPAC). Report to the Congress: Medicare payment policy. Washington, DC: MedPAC; March 2013. http://medpac.gov/docs/default-source/reports/mar13_entirereport.pdf. Accessed March 29. 2019.
270. Lichtman JH, Leifheit-Limson EC, Jones SB, Wang Y, Goldstein LB. Preventable readmissions within 30 days of ischemic stroke among Medicare beneficiaries. *Stroke.* 2013;44:3429–3435. doi: 10.1161/STROKEAHA.113.003165
271. Ottenbacher KJ, Karmarkar A, Graham JE, Kuo YF, Deutsch A, Reistetter TA, Al Snih S, Granger CV. Thirty-day hospital readmission following discharge from postacute rehabilitation in fee-for-service Medicare patients. *JAMA.* 2014;311:604–614. doi: 10.1001/jama.2014.8
272. Whitson HE, Landerman LR, Newman AB, Fried LP, Pieper CF, Cohen HJ. Chronic medical conditions and the sex-based disparity in disability: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci.* 2010;65:1325–1331. doi: 10.1093/gerona/glq139
273. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. *Stroke.* 2012;43:1982–1987. doi: 10.1161/STROKEAHA.111.632547
274. Ottenbacher KJ, Campbell J, Kuo YF, Deutsch A, Ostir GV, Granger CV. Racial and ethnic differences in postacute rehabilitation outcomes after stroke in the United States. *Stroke.* 2008;39:1514–1519. doi: 10.1161/STROKEAHA.107.501254
275. Ellis C, Boan AD, Turan TN, Ozark S, Bachman D, Lackland DT. Racial differences in poststroke rehabilitation utilization and functional outcomes. *Arch Phys Med Rehabil.* 2015;96:84–90. doi: 10.1016/j.apmr.2014.08.018
276. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, Fonarow GC, Peterson ED. Hospital variation in functional recovery after stroke. *Circ Cardiovasc Qual Outcomes.* 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.115.002391
277. Olaiya MT, Cadilhac DA, Kim J, Nelson MR, Srikanth VK, Andrew NE, Bladin CF, Gerraty RP, Fitzgerald SM, Phan T, et al; STANDFIRM (Shared Team Approach Between Nurses and Doctors for Improved Risk Factor Management) Investigators. Long-term unmet needs and associated factors in stroke or TIA survivors: an observational study. *Neurology.* 2017;89:68–75. doi: 10.1212/WNL.0000000000004063
278. Loh AZ, Tan JS, Zhang MW, Ho RC. The global prevalence of anxiety and depressive symptoms among caregivers of stroke survivors. *J Am Med Dir Assoc.* 2017;18:111–116. doi: 10.1016/j.jamda.2016.08.014
279. Towfighi A, Ovbiagele B, El Husseini N, Hackett ML, Jorge RE, Kissela BM, Mitchell PH, Skolarus LE, Whooley MA, Williams LS; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Poststroke depression: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2017;48:e30–e43. doi: 10.1161/STR.0000000000000113
280. Harnod T, Lin CL, Kao CH. Risk of suicide attempt in poststroke patients: a population-based cohort study. *J Am Heart Assoc.* 2018;7:e007830. doi: 10.1161/JAHA.117.007830
281. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke.* 2014;9:1017–1025. doi: 10.1111/ijs.12357
282. Bartoli F, Lillia N, Lax A, Crocamo C, Mantero V, Carrà G, Agostoni E, Clerici M. Depression after stroke and risk of mortality: a systematic review and meta-analysis. *Stroke Res Treat.* 2013;2013:862978. doi: 10.1155/2013/862978
283. Hackett ML, Anderson CS, House A, Xia J. Interventions fortreating depression after stroke. *Cochrane Database Syst Rev.* 2008:Cd003437. doi: 10.1002/14651858.CD003437.pub3
284. Salter KL, Foley NC, Zhu L, Jutai JW, Teasell RW. Prevention of poststroke depression: does prophylactic pharmacotherapy work? *J Stroke Cerebrovasc Dis.* 2013;22:1243–1251. doi: 10.1016/j.jstrokecerebrovasdis.2012.03.013
285. El Husseini N, Goldstein LB, Peterson ED, Zhao X, Olson DM, Williams JW Jr, Bushnell C, Laskowitz DT. Depression status is associated with functional decline over 1-year following acute stroke. *J Stroke Cerebrovasc Dis.* 2017;26:1393–1399. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.026
286. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, Elkind MS. Long-term functional recovery after first ischemic stroke: the Northern Manhattan Study. *Stroke.* 2009;40:2805–2811. doi: 10.1161/STROKEAHA.109.549576
287. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, Elkind MS. Quality of life declines after first ischemic stroke: the Northern Manhattan Study. *Neurology.* 2010;75:328–334. doi: 10.1212/WNL.0b013e3181ea9f03
288. Dhamoon MS, Moon YP, Paik MC, Sacco RL, Elkind MS. Trajectory of functional decline before and after ischemic stroke: the Northern Manhattan Study. *Stroke.* 2012;43:2180–2184. doi: 10.1161/STROKEAHA.112.658922
289. Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Wadley VG. Trajectory of cognitive decline after incident stroke. *JAMA.* 2015;314:41–51. doi: 10.1001/jama.2015.6968
290. Dhamoon MS, Longstreth WT Jr, Bartz TM, Kaplan RC, Elkind MSV. Disability trajectories before and after stroke and myocardial infarction: the Cardiovascular Health Study. *JAMA Neurol.* 2017;74:1439–1445. doi: 10.1001/jamaneurol.2017.2802

291. Tang EY, Amiesimaka O, Harrison SL, Green E, Price C, Robinson L, Siervo M, Stephan BC. Longitudinal effect of stroke on cognition: a systematic review. *J Am Heart Assoc*. 2018;7:e006443. doi: 10.1161/JAHA.117.006443
292. Delavaran H, Jönsson AC, Lövkvist H, Iwarsson S, Elmståhl S, Norrving B, Lindgren A. Cognitive function in stroke survivors: a 10-year follow-up study. *Acta Neurol Scand*. 2017;136:187–194. doi: 10.1111/ane.12709
293. Samuelsson M, Lindell D, Norrving B. Presumed pathogenetic mechanisms of re-current stroke after lacunar infarction. *Cerebrovasc Dis* 1996;6:128–136. doi: 10.1159/000108012
294. Miyao S, Takano A, Teramoto J, Takahashi A. Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke*. 1992;23:1434–1438. doi: 10.1161/01.str.23.10.1434
295. Clark DG, Boan AD, Sims-Robinson C, Adams RJ, Amella EJ, Benitez A, Lackland DT, Ovbiagele B. Differential impact of index stroke on dementia risk in African-Americans compared to whites. *J Stroke Cerebrovasc Dis*. 2018;27:2725–2730. doi: 10.1016/j.jstrokecerebrovasdis.2018.05.048
296. Lisabeth LD, Sánchez BN, Baek J, Skolarus LE, Smith MA, Garcia N, Brown DL, Morgenstern LB. Neurological, functional, and cognitive stroke outcomes in Mexican Americans. *Stroke*. 2014;45:1096–1101. doi: 10.1161/STROKEAHA.113.003912
297. Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. *Stroke*. 2009;40:3415–3421. doi: 10.1161/STROKEAHA.109.564633
298. Kirton A, Armstrong-Wells J, Chang T, Deveber G, Rivkin MJ, Hernandez M, Carpenter J, Yager JY, Lynch JK, Ferriero DM; International Pediatric Stroke Study Investigators. Symptomatic neonatal arterial ischemic stroke: the International Pediatric Stroke Study. *Pediatrics*. 2011;128:e1402–e1410. doi: 10.1542/peds.2011-1148
299. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, et al. Diagnostic delays in paediatric stroke. *J Neurol Neurosurg Psychiatry*. 2015;86:917–921. doi: 10.1136/jnnp-2014-309188
300. Medley TL, Miteff C, Andrews I, Ware T, Cheung M, Monagle P, Mandelstam S, Wray A, Pridmore C, Troedson C, et al. Australian Clinical Consensus Guideline: the diagnosis and acute management of childhood stroke. *Int J Stroke*. 2019;14:94–106. doi: 10.1177/1747493018799958
301. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. *Ann Neurol*. 2003;53:167–173. doi: 10.1002/ana.10423
302. Wintermark M, Hills NK, deVeber GA, Barkovich AJ, Elkind MS, Sear K, Zhu G, Leiva-Salinas C, Hou Q, Dowling MM, et al; on behalf of the VIPS Investigators. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the Vascular Effects of Infection in Pediatric Stroke Study. *Stroke*. 2014;45:3597–3605. doi: 10.1161/STROKEAHA.114.007404
303. Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. *Stroke*. 2015;46:336–340. doi: 10.1161/STROKEAHA.114.007218
304. Asakai H, Cardamone M, Hutchinson D, Stojanovski B, Galati JC, Cheung MM, Mackay MT. Arterial ischemic stroke in children with cardiac disease. *Neurology*. 2015;85:2053–2059. doi: 10.1212/WNL.0000000000002036
305. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, Pressman A. Is migraine a risk factor for pediatric stroke? *Cephalalgia*. 2015;35:1252–1260. doi: 10.1177/0333102415576222
306. Hills NK, Johnston SC, Sidney S, Zielinski BA, Fullerton HJ. Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke. *Ann Neurol*. 2012;72:850–858. doi: 10.1002/ana.23688
307. Hills NK, Sidney S, Fullerton HJ. Timing and number of minor infections as risk factors for childhood arterial ischemic stroke. *Neurology*. 2014;83:890–897. doi: 10.1212/WNL.0000000000000752
308. Elkind MS, Hills NK, Glaser CA, Lo WD, Amlie-Lefond C, Dlamini N, Kneen R, Hod EA, Wintermark M, deVeber GA, et al; on behalf of the VIPS Investigators. Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS Study. *Circulation*. 2016;133:732–741. doi: 10.1161/CIRCULATIONAHA.115.018595
309. Kenet G, Lütkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, Chabrier S, Chan A, deVeber G, Fiedler B, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010;121:1838–1847. doi: 10.1161/CIRCULATIONAHA.109.913673
310. Curtis C, Mineyko A, Massicotte P, Leaker M, Jiang XY, Floer A, Kirton A. Thrombophilia risk is not increased in children after perinatal stroke [published correction appears in *Blood*. 2017;130:382]. *Blood*. 2017;129:2793–2800. doi: 10.1182/blood-2016-11-750893
311. Bigi S, Fischer U, Wehrli E, Mattle HP, Boltshauser E, Bürki S, Jeannet PY, Fluss J, Weber P, Nedeltchev K, et al. Acute ischemic stroke in children versus young adults. *Ann Neurol*. 2011;70:245–254. doi: 10.1002/ana.22427
312. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol*. 2011;70:713–721. doi: 10.1002/ana.22539
313. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *Lancet Neurol*. 2014;13:35–43. doi: 10.1016/S1474-4422(13)70290-4
314. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61:189–194. doi: 10.1212/01.wnl.0000078894.79866.95
315. Lehman LL, Fullerton HJ. Changing ethnic disparity in ischemic stroke mortality in US children after the STOP trial. *JAMA Pediatr*. 2013;167:754–758. doi: 10.1001/jamapediatrics.2013.89
316. Elbers J, deVeber G, Pontigon AM, Moharir M. Long-term outcomes of pediatric ischemic stroke in adulthood. *J Child Neurol*. 2014;29:782–788. doi: 10.1177/0883073813484358
317. Boardman JP, Ganesan V, Rutherford MA, Saunders DE, Mercuri E, Cowan F. Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics*. 2005;115:321–326. doi: 10.1542/peds.2004-0427
318. Hajek CA, Yeates KO, Anderson V, Mackay M, Greenham M, Gomes A, Lo W. Cognitive outcomes following arterial ischemic stroke in infants and children. *J Child Neurol*. 2014;29:887–894. doi: 10.1177/0883073813491828
319. Studer M, Boltshauser E, Capone Mori A, Datta A, Fluss J, Mercati D, Hackenberg A, Keller E, Maier O, Marcoz JP, et al. Factors affecting cognitive outcome in early pediatric stroke. *Neurology*. 2014;82:784–792. doi: 10.1212/WNL.0000000000000162
320. Lo W, Gordon A, Hajek C, Gomes A, Greenham M, Perkins E, Zumberge N, Anderson V, Yeates KO, Mackay MT. Social competence following neonatal and childhood stroke. *Int J Stroke*. 2014;9:1037–1044. doi: 10.1111/ijs.12222
321. Bemister TB, Brooks BL, Dyck RH, Kirton A. Parent and family impact of raising a child with perinatal stroke. *BMC Pediatr*. 2014;14:182. doi: 10.1186/1471-2431-14-182
322. Danchaivijitr N, Cox TC, Saunders DE, Ganesan V. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. *Ann Neurol*. 2006;59:620–626. doi: 10.1002/ana.20800
323. Tuppin P, Samson S, Woimant F, Chabrier S. Management and 2-year follow-up of children aged 29 days to 17 years hospitalized for a first stroke in France (2009-2010). *Arch Pediatr*. 2014;21:1305–1315. doi: 10.1016/j.arcped.2014.08.023
324. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics*. 2007;119:495–501. doi: 10.1542/peds.2006-2791
325. Koroknay-Pál P, Niemelä M, Lehto H, Kivisaari R, Numminen J, Laakso A, Hernesniemi J. De novo and recurrent aneurysms in pediatric patients with cerebral aneurysms. *Stroke*. 2013;44:1436–1439. doi: 10.1161/STROKEAHA.111.676601
326. Wusthoff CJ, Kessler SK, Vossough A, Ichord R, Zelonis S, Halperin A, Gordon D, Vargas G, Licht DJ, Smith SE. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. *Pediatrics*. 2011;127:e1550–e1557. doi: 10.1542/peds.2010-1577
327. Fox CK, Glass HC, Sidney S, Lowenstein DH, Fullerton HJ. Acute seizures predict epilepsy after childhood stroke. *Ann Neurol*. 2013;74:249–256. doi: 10.1002/ana.23916
328. Hsu CJ, Weng WC, Peng SS, Lee WT. Early-onset seizures are correlated with late-onset seizures in children with arterial ischemic stroke. *Stroke*. 2014;45:1161–1163. doi: 10.1161/STROKEAHA.113.004015
329. Beslow LA, Abend NS, Gindville MC, Bastian RA, Licht DJ, Smith SE, Hillis AE, Ichord RN, Jordan LC. Pediatric intracerebral hemorrhage: acute symptomatic seizures and epilepsy. *JAMA Neurol*. 2013;70:448–454. doi: 10.1001/jamaneurol.2013.1033
330. Bernard TJ, Rivkin MJ, Scholz K, deVeber G, Kirton A, Gill JC, Chan AK, Hovinga CA, Ichord RN, Grotta JC, et al; on behalf of the Thrombolysis in Pediatric Stroke Study. Emergence of the primary pediatric stroke

center: impact of the Thrombolysis in Pediatric Stroke trial. *Stroke.* 2014;45:2018–2023. doi: 10.1161/STROKEAHA.114.004919
331. Ladner TR, Mahdi J, Gindville MC, Gordon A, Harris ZL, Crossman K, Pruthi S, Abramo TJ, Jordan LC. Pediatric acute stroke protocol activation in a children's hospital emergency department. *Stroke.* 2015;46:2328–2331. doi: 10.1161/STROKEAHA.115.009961
332. DeLaroche AM, Sivaswamy L, Farooqi A, Kannikeswaran N. Pediatric stroke clinical pathway improves the time to diagnosis in an emergency department. *Pediatr Neurol.* 2016;65:39–44. doi: 10.1016/j.pediatrneurol.2016.09.005
333. Hamilton W, Huang H, Seiber E, Lo W. Cost and outcome in pediatric ischemic stroke. *J Child Neurol.* 2015;30:1483–1488. doi: 10.1177/0883073815570673
334. Plumb P, Seiber E, Dowling MM, Lee J, Bernard TJ, deVeber G, Ichord RN, Bastian R, Lo WD. Out-of-pocket costs for childhood stroke: the impact of chronic illness on parents' pocketbooks. *Pediatr Neurol.* 2015;52:73–76.e2. doi: 10.1016/j.pediatrneurol.2014.09.010
335. Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, Schroth G, Remonda L, Sturzenegger M, Fischer U, et al. Ischaemic stroke in young adults: predictors of outcome and recurrence. *J Neurol Neurosurg Psychiatry.* 2005;76:191–195. doi: 10.1136/jnnp.2004.040543
336. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology.* 2012;79:1781–1787. doi: 10.1212/WNL.0b013e318270401d
337. Swerdel JN, Rhoads GG, Cheng JQ, Cosgrove NM, Moreyra AE, Kostis JB, Kostis WJ; for the Myocardial Infarction Data Acquisition System (MIDAS 29) Study Group. Ischemic stroke rate increases in young adults: evidence for a generational effect? *J Am Heart Assoc.* 2016;5:e004245. doi: 10.1161/JAHA.116.004245
338. Li C, Baek J, Sanchez BN, Morgenstern LB, Lisabeth LD. Temporal trends in age at ischemic stroke onset by ethnicity. *Ann Epidemiol.* 2018;28:686–690.e2. doi: 10.1016/j.annepidem.2018.07.010
339. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Long-term mortality after stroke among adults aged 18 to 50 years. *JAMA.* 2013;309:1136–1144. doi: 10.1001/jama.2013.842
340. Synhaeve NE, Arntz RM, van Alebeek ME, van Pamelen J, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, de Kort PL, van Dijk EJ, de Leeuw FE. Women have a poorer very long-term functional outcome after stroke among adults aged 18-50 years: the FUTURE study. *J Neurol.* 2016;263:1099–1105. doi: 10.1007/s00415-016-8042-2
341. Russo T, Felzani G, Marini C. Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. *J Aging Res.* 2011;2011:108785. doi: 10.4061/2011/108785
342. Dehlendorff C, Andersen KK, Olsen TS. Sex disparities in stroke: women have more severe strokes but better survival than men. *J Am Heart Assoc.* 2015;4:e001967. doi: 10.1161/JAHA.115.001967
343. Ay H, Arsava EM, Andsberg G, Benner T, Brown RD Jr, Chapman SN, Cole JW, Delavaran H, Dichgans M, Engström G, et al. Pathogenic ischemic stroke phenotypes in the NINDS-Stroke Genetics Network [published correction appears in *Stroke.* 2015;46:e17]. *Stroke.* 2014;45:3589–3596. doi: 10.1161/STROKEAHA.114.007362
344. Forti P, Maioli F, Procaccianti G, Nativio V, Lega MV, Coveri M, Zoli M, Sacquegna T. Independent predictors of ischemic stroke in the elderly: prospective data from a stroke unit [published correction appears in *Neurology.* 2013;81:1882]. *Neurology.* 2013;80:29–38. doi: 10.1212/WNL.0b013e31827b1a41
345. Saposnik G, Black S; Stroke Outcome Research Canada (SORCan) Working Group. Stroke in the very elderly: hospital care, case fatality and disposition. *Cerebrovasc Dis.* 2009;27:537–543. doi: 10.1159/000214216
346. Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS; Copenhagen Stroke Study. Short- and long-term prognosis for very old stroke patients: the Copenhagen Stroke Study. *Age Ageing.* 2004;33:149–154. doi: 10.1093/ageing/afh052
347. Ovbiagele B, Markovic D, Towfighi A. Recent age- and gender-specific trends in mortality during stroke hospitalization in the United States. *Int J Stroke.* 2011;6:379–387. doi: 10.1111/j.1747-4949.2011.00590.x
348. Howard G, Goff DC. Population shifts and the future of stroke: forecasts of the future burden of stroke. *Ann N Y Acad Sci.* 2012;1268:14–20. doi: 10.1111/j.1749-6632.2012.06665.x
349. Olsen TS, Andersen KK. Stroke in centenarians. *Geriatr Gerontol Int.* 2014;14:84–88. doi: 10.1111/ggi.12058
350. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5
351. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
352. Orrapin S, Rerkasem K. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database Syst Rev.* 2017;6:CD001081. doi: 10.1002/14651858.CD001081.pub3
353. Man S, Zhao X, Uchino K, Hussain MS, Smith EE, Bhatt DL, Xian Y, Schwamm LH, Shah S, Khan Y, et al. Comparison of acute ischemic stroke care and outcomes between comprehensive stroke centers and primary stroke centers in the United States. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004512. doi: 10.1161/CIRCOUTCOMES.117.004512
354. McKinney JS, Cheng JQ, Rybinnik I, Kostis JB; Myocardial Infarction Data Acquisition System (MIDAS 22) Study Group. Comprehensive stroke centers may be associated with improved survival in hemorrhagic stroke. *J Am Heart Assoc.* 2015;4:e001448. doi: 10.1161/JAHA.114.001448
355. Man S, Schold JD, Uchino K. Impact of stroke center certification on mortality after ischemic stroke: the Medicare cohort from 2009 to 2013. *Stroke.* 2017;48:2527–2533. doi: 10.1161/STROKEAHA.116.016473
356. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
357. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
358. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
359. Ramirez L, Kim-Tenser MA, Sanossian N, Cen S, Wen G, He S, Mack WJ, Towfighi A. Trends in acute ischemic stroke hospitalizations in the United States. *J Am Heart Assoc.* 2016;5:e003233. doi: 10.1161/JAHA.116.003233
360. Kumar N, Khera R, Pandey A, Garg N. Racial differences in outcomes after acute ischemic stroke hospitalization in the United States. *J Stroke Cerebrovasc Dis.* 2016;25:1970–1977. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.049
361. Lokuge K, de Waard DD, Halliday A, Gray A, Bulbulia R, Mihaylova B. Meta-analysis of the procedural risks of carotid endarterectomy and carotid artery stenting over time. *Br J Surg.* 2018;105:26–36. doi: 10.1002/bjs.10717
362. Moresoli P, Habib B, Reynier P, Secrest MH, Eisenberg MJ, Filion KB. Carotid stenting versus endarterectomy for asymptomatic carotid artery stenosis: a systematic review and meta-analysis. *Stroke.* 2017;48:2150–2157. doi: 10.1161/STROKEAHA.117.016824
363. Sardar P, Chatterjee S, Aronow HD, Kundu A, Ramchand P, Mukherjee D, Nairooz R, Gray WA, White CJ, Jaff MR, et al. Carotid artery stenting versus endarterectomy for stroke prevention: a meta-analysis of clinical trials. *J Am Coll Cardiol.* 2017;69:2266–2275. doi: 10.1016/j.jacc.2017.02.053
364. Jalbert JJ, Nguyen LL, Gerhard-Herman MD, Kumamaru H, Chen CY, Williams LA, Liu J, Rothman AT, Jaff MR, Seeger JD, et al. Comparative effectiveness of carotid artery stenting versus carotid endarterectomy among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes.* 2016;9:275–285. doi: 10.1161/CIRCOUTCOMES.115.002336
365. Al-Damluji MS, Dharmarajan K, Zhang W, Geary LL, Stilp E, Dardik A, Mena-Hurtado C, Curtis JP. Readmissions after carotid artery revascularization in the Medicare population. *J Am Coll Cardiol.* 2015;65:1398–1408. doi: 10.1016/j.jacc.2015.01.048
366. Obeid T, Alshaikh H, Nejim B, Arhuidese I, Locham S, Malas M. Fixed and variable cost of carotid endarterectomy and stenting in the United States: a comparative study. *J Vasc Surg.* 2017;65:1398–1406.e1. doi: 10.1016/j.jvs.2016.11.062
367. McDonald RJ, Kallmes DF, Cloft HJ. Comparison of hospitalization costs and Medicare payments for carotid endarterectomy and carotid stenting in asymptomatic patients. *AJNR Am J Neuroradiol.* 2012;33:420–425. doi: 10.3174/ajnr.A2791

368. Sternbergh WC 3rd, Crenshaw GD, Bazan HA, Smith TA. Carotid endarterectomy is more cost-effective than carotid artery stenting. *J Vasc Surg.* 2012;55:1623–1628. doi: 10.1016/j.jvs.2011.12.045
369. Vilain KR, Magnuson EA, Li H, Clark WM, Begg RJ, Sam AD 2nd, Sternbergh WC 3rd, Weaver FA, Gray WA, Voeks JH, et al; on behalf of the CREST Investigators. Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke.* 2012;43:2408–2416. doi: 10.1161/STROKEAHA.112.661355
370. Mokin M, Rojas H, Levy EI. Randomized trials of endovascular therapy for stroke–impact on stroke care. *Nat Rev Neurol.* 2016;12:86–94. doi: 10.1038/nrneurol.2015.240
371. Rebello LC, Haussen DC, Grossberg JA, Belagaje S, Lima A, Anderson A, Frankel MR, Nogueira RG. Early endovascular treatment in intravenous tissue plasminogen activator-ineligible patients. *Stroke.* 2016;47:1131–1134. doi: 10.1161/STROKEAHA.115.012586
372. Regenhardt RW, Mecca AP, Flavin SA, Boulouis G, Lauer A, Zachrison KS, Boomhower J, Patel AB, Hirsch JA, Schwamm LH, et al. Delays in the air or ground transfer of patients for endovascular thrombectomy. *Stroke.* 2018;49:1419–1425. doi: 10.1161/STROKEAHA.118.020618
373. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States, 1996–2015. Agency for Healthcare Research and Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed June 17, 2019.
374. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001.
375. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
376. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson LM, Truelsen T, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health*. 2013;1:e259–e281. doi: 10.1016/S2214-109X(13)70089-5
377. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010 [published correction appears in *Lancet*. 2013;381:628]. *Lancet.* 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0
378. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, et al; on behalf of the American Heart Association/American Stroke Association. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. *Stroke.* 2017;48:e284–e303. doi: 10.1161/STR.0000000000000148
379. MetLife Foundation. What america thinks: MetLife Foundation Alzheimer's survey. MetLife website. https://www.metlife.com/content/dam/microsites/about/corporate-profile/alzheimers-2011.pdf. Accessed May 27, 2019.
380. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol.* 2007;6:1106–1114. doi: 10.1016/S1474-4422(07)70291-0
381. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement.* 2017;13:28–37. doi: 10.1016/j.jalz.2016.04.002
382. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007;69:2197–2204. doi: 10.1212/01.wnl.0000271090.28148.24
383. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology.* 2013;80:1778–1783. doi: 10.1212/WNL.0b013e31828726f5
384. Gardener H, Wright CB, Dong C, Cheung K, DeRosa J, Nannery M, Stern Y, Elkind MS, Sacco RL. Ideal cardiovascular health and cognitive aging in the Northern Manhattan Study. *J Am Heart Assoc.* 2016;5:e002731. doi: 10.1161/JAHA.115.002731
385. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurol.* 2017;74:1246–1254. doi: 10.1001/jamaneurol.2017.1658
386. Gilsanz P, Mayeda ER, Glymour MM, Quesenberry CP, Mungas DM, DeCarli C, Dean A, Whitmer RA. Female sex, early-onset hypertension, and risk of dementia. *Neurology.* 2017;89:1886–1893. doi: 10.1212/WNL.0000000000004602
387. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron.* 2013;80:1347–1358. doi: 10.1016/j.neuron.2013.12.003
388. Jack CR Jr, Vemuri P, Wiste HJ, Weigand SD, Aisen PS, Trojanowski JQ, Shaw LM, Bernstein MA, Petersen RC, Weiner MW, et al; Alzheimer's Disease Neuroimaging Initiative. Evidence for ordering of Alzheimer disease biomarkers. *Arch Neurol.* 2011;68:1526–1535. doi: 10.1001/archneurol.2011.183
389. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA.* 2017;317:1443–1450. doi: 10.1001/jama.2017.3090
390. Schmidt R, Schmidt H, Pichler M, Enzinger C, Petrovic K, Niederkorn K, Horner S, Ropele S, Watzinger N, Schumacher M, et al. C-reactive protein, carotid atherosclerosis, and cerebral small-vessel disease: results of the Austrian Stroke Prevention Study. *Stroke.* 2006;37:2910–2916. doi: 10.1161/01.STR.0000248768.40043.f9
391. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol.* 2007;6:611–619. doi: 10.1016/S1474-4422(07)70170-9
392. Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, Anton-Culver H, O'Leary DH; on behalf of the CHS Collaborative Research Group. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults: the Cardiovascular Health Study. *Stroke.* 1997;28:1158–1164. doi: 10.1161/01.str.28.6.1158
393. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med.* 2003;348:1215–1222. doi: 10.1056/NEJMoa022066
394. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* 2005;36:56–61. doi: 10.1161/01.STR.0000149625.99732.69
395. Hammond CA, Blades NJ, Chaudhry SI, Dodson JA, Longstreth WT Jr, Heckbert SR, Psaty BM, Arnold AM, Dublin S, Sitlani CM, et al. Long-term cognitive decline after newly diagnosed heart failure: longitudinal analysis in the CHS (Cardiovascular Health Study). *Circ Heart Fail.* 2018;11:e004476. doi: 10.1161/CIRCHEARTFAILURE.117.004476
396. Mehta KM, Yeo GW. Systematic review of dementia prevalence and incidence in United States race/ethnic populations. *Alzheimers Dement.* 2017;13:72–83. doi: 10.1016/j.jalz.2016.06.2360
397. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, Weir DR. A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Intern Med.* 2017;177:51–58. doi: 10.1001/jamainternmed.2016.6807
398. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
399. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP. Epidemiology of ischemic stroke in patients with diabetes: the Greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care.* 2005;28:355-359. doi: 10.2337/diacare.28.2.355
400. National Center for Health Statistics, National Vital Statistics System. Stroke Death Rates, 2015–2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/dhdsp/maps/pdfs/stroke_all.pdf. Accessed November 19, 2019.

15. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

ICD-9 745 to 747; ICD-10 Q20 to Q28. See Tables 15-1 through 15-3 and Charts 15-1 through 15-7

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CCDs arise from abnormal or incomplete formation of the heart and blood vessels. CCDs range in severity from minor abnormalities not requiring treatment to complex malformations, including absent, hypoplastic, or atretic portions of the heart, valves, or vessels that could require multiple surgeries and interventions, including cardiac transplantation. Thus, there is significant variability in their presentation and requirements for care that can have a significant impact on morbidity, mortality, and healthcare costs both in children and adults.[1] Some types of CCDs are associated with diminished quality of life,[2] on par with what is seen in other chronic pediatric health conditions,[3] as well as deficits in cognitive functioning[4] and neurodevelopmental outcomes.[5] Health outcomes generally continue to improve for CCDs, including survival, which has led to a population shift into adulthood. There is a growing population of adults with both congenital heart defects and the more usual adult medical diagnoses,[6] which adds to the management complexity of this group of patients[7,8] and emphasizes the importance of specialty care by adult congenital HD specialists.[9]

Abbreviations Used in Chapter 15

ACS	acute coronary syndrome
AHA	American Heart Association
AMI	acute myocardial infarction
ASD	atrial septal defect
AV	atrioventricular
CABG	coronary artery bypass graft
CCD	congenital cardiovascular defect
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CI	confidence interval
DM	diabetes mellitus
GBD	Global Burden of Disease
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HLHS	hypoplastic left heart syndrome
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IHD	ischemic heart disease
IQR	interquartile range
IRR	incidence rate ratio
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PAH	pulmonary arterial hypertension
RR	relative risk
RV	right ventricle
STS	Society of Thoracic Surgeons
TGA	transposition of the great arteries
TOF	tetralogy of Fallot
UI	uncertainty interval
VSD	ventricular septal defect

Overall Lifespan Prevalence (See Tables 15-1 through 15-3)

The 32nd Bethesda Conference estimated that the total number of adults living with CCDs in the United States in 2000 was 800 000.[1] In 2010, the estimated prevalence of CCDs in all age groups was 2.4 million (Table 15-1). The annual birth prevalence of CCDs ranged from 2.4 to 13.7 per 1000 live births (Table 15-2). In the United States, 1 in 150 adults is expected to have some form of congenital heart defect, including minor lesions such as bicuspid aortic valve and severe CCD such as HLHS.[7] The estimated prevalence of CCDs ranges from 2.5% for hypoplastic right heart syndrome to 20.1% for VSD in children and from 1.8% for TGA to 20.1% for VSD in adults (Table 15-3). In population data from Canada, the measured prevalence of CCDs in the general population was 13.11 per 1000 children and 6.12 per 1000 adults in the year 2010.[10] The expected growth rates of the congenital heart defects population vary from 1% to 5% per year depending on age and the distribution of lesions.[11]

Estimates of the distribution of lesions in the CCD population using available data vary based on proposed assumptions. If all those born with CCDs between 1940 and 2002 were treated, there would be ≈750 000 survivors with simple lesions, 400 000 with moderate lesions, and 180 000 with complex lesions; in addition, there would be 3.0 million people alive with bicuspid aortic valves.[11] Without treatment, the number of survivors in each group would be 400 000, 220 000, and 30 000, respectively. The actual numbers surviving were projected to be between these 2 sets of estimates as of more than a decade ago.[11] The most common types of defects in children are VSD, 620 000 people; ASD, 235 000 people; valvar pulmonary stenosis, 185 000 people; and patent ductus arteriosus,

173 000 people.[11] The most common lesions seen in adults are ASD and TOF.[12]

Birth Prevalence

The incidence of disorders present before birth, such as CCDs, is generally described as the *birth prevalence*. The birth prevalence of CCDs is reported as 6.9 per 1000 live births in North America, 8.2 per 1000 live births in Europe, and 9.3 per 1000 live births in Asia.[13] The overall birth prevalence of CCDs at the Bhabha Atomic Research Centre Hospital in Mumbai, India, from 2006 through 2011 was 13.28 per 1000 live births.[14]

Variations in birth prevalence rates may be related to the age at detection; major defects can be identified in the prenatal or neonatal period, but minor defects might not be detected until later in childhood or, in fact, adulthood, which makes it challenging to estimate birth prevalence and population prevalence. To distinguish more serious defects, some studies report the number of new cases of sufficient severity to result in death or an invasive procedure within the first year of life (in addition to the overall birth prevalence). Birth prevalence rates are likely to increase over time because of improved technological advancements in diagnosis and screening, particularly fetal cardiac ultrasound,[15] pulse oximetry,[16] and echocardiography during infancy.

Overall Birth Prevalence (See Table 15-2)

- According to population-based data from the Metropolitan Atlanta Congenital Defects Program (Atlanta, GA), a CCD occurred in 1 of every 111 to 125 births (live, still, or >20 weeks' gestation) from 1995 to 1997 and from 1998 to 2005. Some defects showed variations by sex and racial distribution.[17]
- According to population-based data from Alberta, Canada, there was a total birth prevalence of 12.42 per 1000 total births (live, still, or >20 weeks' gestation).[18]
- An estimated minimum of 40 000 infants are expected to be affected by CCDs each year in the United States. Of these, ≈25%, or 2.4 per 1000 live births, require invasive treatment in the first year of life (Table 15-2).

Birth Prevalence of Specific Defects

- The National Birth Defects Prevention Network showed the average birth prevalence of 21 selected major birth defects for 13 states in the United States from 2004 to 2006. These data indicated that there are >6100 estimated annual cases of 5 CCDs: truncus arteriosus (0.07 per 1000 births), TGA (0.3 per 1000 births), TOF (0.4 per 1000 births), AV septal defect (0.47 per 1000 births), and HLHS (0.23 per 1000 births).[19,20]
- Metropolitan Atlanta Congenital Defects Program data for specific defects at birth showed the following: VSD, 4.2 per 1000 births; ASD, 1.3 per 1000 births; valvar pulmonic stenosis, 0.6 per 1000 births; TOF, 0.5 per 1000 births; aortic coarctation, 0.4 per 1000 births; AV septal defect, 0.4 per 1000 births; and TGA (0.2 per 1000 births).[17]
- Bicuspid aortic valve occurs in 13.7 of every 1000 people; these defects might not require treatment in infancy or childhood but could require care later in adulthood.[21]

Risk Factors

- Numerous intrinsic and extrinsic nongenetic risk factors, as well as genetic factors, are thought to contribute to CCDs.[22,23]
- Intrinsic risk factors for CCDs can include various genetic syndromes. Twins are at higher risk for CCDs[24]; one report from Kaiser Permanente data showed monochorionic twins were at particular risk (RR, 11.6 [95% CI, 9.2–14.5]).[25] Known risks generally focus on maternal exposures, but a study of paternal occupational exposure documented a higher incidence of CCDs with paternal exposure to phthalates.[26]
- Other paternal exposures that increase risk for CCDs include paternal anesthesia, which has been implicated in TOF (3.6%); sympathomimetic medication and coarctation of the aorta (5.8%); pesticides and VSDs (5.5%); and solvents and HLHS (4.6%).[27]
- Known maternal risks include smoking[28,29] during the first trimester of pregnancy, which has also been associated with a ≥30% increased risk of the following lesions in the fetus: ASD, pulmonary valvar stenosis, truncus arteriosus, TGA,[30] and septal defects (particularly for heavy smokers [≥25 cigarettes daily]).[31] Maternal smoking might account for 1.4% of all congenital heart defects.
- Exposure to secondhand smoke has also been implicated as a risk factor.[32]
- Air pollutants can also increase the risk of CCDs. In a retrospective review of singleton infants born in Florida from 2000 to 2009, maternal exposure during pregnancy to the air pollutant benzene was associated with an increased risk in the fetus of critical and noncritical CCDs (1.33 [95% CI, 1.07–1.65]).[33]
- Maternal binge drinking[34] is also associated with an increased risk of CCDs, and the combination of binge drinking and smoking can be particularly deleterious: Mothers who smoke and report any binge drinking in the 3 months before pregnancy

are at an increased risk of giving birth to a child with a CCD (adjusted OR, 12.65).[34]

- Maternal obesity is associated with CCDs. A meta-analysis of 14 studies of females without gestational DM showed infants born to mothers who were moderately and severely obese, respectively, had 1.1 and 1.4 times greater risk of CCDs than infants born to normal-weight mothers.[35–37] The risk of TOF was 1.9 times higher among infants born to mothers with severe obesity than among infants born to normal-weight mothers.[36]
- Maternal DM, including gestational DM, has also been associated with CCDs, both isolated (CCD[s] as the only major congenital anomaly) and multiple (CCD[s] plus ≥1 noncardiac major congenital anomalies).[38,39] Pregestational DM has been associated with CCDs, specifically TOF.[40]
- Preeclampsia is considered a risk factor for CCDs, although not critical defects.[41]
- Folate deficiency is a well-documented risk for congenital malformations, including CCDs, and folic acid supplementation is routinely recommended during pregnancy.[22] An observational study of folic acid supplementation in Hungarian females showed a decrease in the incidence of CCDs, including VSD (OR, 0.57 [95% CI, 0.45–0.73]), TOF (OR, 0.53 [95% CI, 0.17–0.94]), dextro-TGA (OR, 0.47 [95% CI, 0.26–0.86]), and ASD secundum (OR, 0.63 [95% CI, 0.40–0.98]).[41] A US population–based case-control study showed an inverse relationship between folic acid use and the risk of TGA (Baltimore-Washington Infant Study, 1981–1989).[42]
- An observational study from Quebec, Canada, of 1.3 million births from 1990 to 2005 found a 6% per year reduction in severe congenital heart defects using a time-trend analysis before and after public health measures were instituted that mandated folic acid fortification of grain and flour products in Canada.[43]
- Maternal infections, including rubella and chlamydia, have been associated with congenital heart defects.[44,45]
- High altitude has also been described as a risk factor for CCDs. Tibetan children living at 4200 to 4900 m had a higher prevalence of congenital heart defects (12.09 per 1000) than those living at lower altitudes of 3500 to 4100 m (4.32 per 1000); patent ductus arteriosus and ASD contributed to the increased prevalence.[46]

Screening

Pulse oximetry screening for CCDs was incorporated as part of the US recommended uniform screening panel for newborns in 2011 and has been endorsed by the AHA and the American Academy of Pediatrics.[47] At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening for identification of previously unidentified (by fetal cardiac ultrasound) newborn CCDs,[48] and several studies have demonstrated the benefit of such screening.[49–51]

- Several key factors contribute to effective screening, including probe placement (postductal), oximetry cutoff (<95%), timing (>24 hours of life), and altitude (<2643 ft [806 m]).
- If fully implemented, screening would predict identification of 1189 additional infants with critical congenital heart defects and yield 1975 false-positive results.[52]
- A simulation model estimates that screening the entire United States for critical CCDs with pulse oximetry would uncover 875 infants (95% UI, 705–1060) who truly have nonsyndromic CCDs versus 880 (95% UI, 700–1080) false-negative screenings (no CCDs).[53]
- It has been estimated that 29.5% (95% CI, 28.1%–31.0%) of nonsyndromic children with critical CCDs are diagnosed after 3 days and thus might benefit from pulse oximetry screening.[54]
- A meta-analysis of 13 studies that included 229 421 newborns found pulse oximetry had a sensitivity of 76.5% (95% CI, 67.7%–83.5%) for detection of critical CCDs and a specificity of 99.9% (95% CI, 99.7%–99.9%), with a false-positive rate of 0.14% (95% CI, 0.06%–0.33%).[55]
- A recent observational study demonstrated that statewide implementation of mandatory policies for newborn screening for critical CCDs was associated with a significant decrease (33.4% [95% CI, 10.6%–50.3%]) in infant cardiac deaths between 2007 and 2013 compared with states without such policies.[56]
- The cost of identifying a newborn with a critical CCD has been estimated at $20 862 per newborn detected and $40 385 per life-year gained (2011 US dollars).[53]
- Reports outside of the United States have shown similar performance of pulse oximetry screening in identifying critical CCDs,[57] with a sensitivity and specificity of pulse oximetry screening for critical congenital heart defects of 100% and 99.7%, respectively.

Social Determinants

Recently, several studies have demonstrated there can be variations in CCD outcomes based on factors such as ethnicity, race, and socioeconomics.[58–62]

- In a review of 15 533 infants with CCD born between 2004 and2013, survival among infants with univentricular CCDs was improved for those

whose fathers were >35 years of age (71.6% [95% CI, 63.8%–80.3%]) compared with those who were younger (59.7% [95% CI, 54.6%–65.2%]), and factors associated with survival in biventricular CCDs included maternal education, race or ethnicity, and marital status.[58]
- All infants undergoing cardiac intervention in England and Wales from 2005 to 2010 were identified through a national registry, and CCD incidence was shown to be higher in Asian and black ethnic groups than in the Caucasian reference population (IRR 1.5 for Asians [95% CI, 1.4–1.7] and 1.4 for blacks [95% CI, 1.3–1.6]).[59]

Genetics and Family History

- CCDs can have a heritable component. There is a greater concordance of CCDs in monozygotic than dizygotic twins.[63] Among parents with ASD or VSD, 2.6% and 3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.[64] However, the majority of CCDs occur in families with no other history of CCDs, which supports the possibility of de novo genetic events.
- Large chromosomal abnormalities are associated with some CCDs. For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.[54] The specific genes responsible for CCDs that are disrupted by these abnormalities are difficult to identify. There are studies that suggest that *DSCAM* and *COL6A* contribute to Down syndrome–associated CCDs.[65]
- Copy number variants also contribute to CCDs and have been shown to be overrepresented in larger cohorts of patients with specific forms of CCDs.[66] The most common copy number variant is del22q11, which encompasses the T-box transcription factor (*TBX1*) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.[67]
- Single point mutations are also a cause of CCDs and include mutations in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, and *MEF2*),[67,68] ZIC3, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related NOTCH signaling genes.[69]
- Advances in whole-exome sequencing have suggested that 10% of sporadic severe cases of CCDs are caused by de novo mutations,[70] particularly in chromatin-regulating genes.
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.[67]
- Complications related to CCD may also have a genetic component; a recent whole-exome sequence study identified *SOX17* as a novel candidate gene for PAH in patients with CCD patients.[71]
- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,[67] but it should be offered to patients with multiple congenital abnormalities or congenital syndromes (including CCD lesions associated with a high prevalence of 22q11 deletion or DiGeorge syndrome), and it can be considered in patients with a family history, in those with developmental delay, and in patients with left-sided obstructive lesions.[1]
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.[72,73] Use of whole-exome genetic testing has been shown to improve rates of detection.[74]
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.[75]

Mortality (See Tables 15-1 and 15-4 and Charts 15-1 through 15-5)

Overall mortality attributable to CCDs:
- In 2017:
  - Mortality related to CCDs was 2906 deaths (Table 15-1), an 18.1% decrease from 2007 (unpublished NHLBI tabulation using NVSS[76]).
  - CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99); 22.5% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS[76]).
  - The age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.9, a 25.0% decrease from 2007 (unpublished NHLBI tabulation using CDC WONDER[77]).
- According to a review of Norwegian national mortality data in live-born children with CCDs from 1994 to 2009, the all-cause mortality rate was 17.4% for children with severe congenital heart defects and 3.0% for children with milder forms of CCDs, with declining mortality rates over the analysis period related to declining operative mortality and more frequent pregnancy terminations.[78]
- Death rates attributed to CCDs decrease as gestational age advances toward 40 weeks.[79] In-hospital mortality of infants with major CCDs is independently associated with late-preterm birth (OR, 2.70

[95% CI, 1.69–4.33]) compared with delivery at later gestational ages.[80,81]

- Similarly, postoperative mortality of infants with CCDs born near term (37 weeks) is 1.34 (95% CI, 1.05–1.71; *P*=0.02) higher than for those born full term, with higher complication rates and longer lengths of stay.[82] The presence of CCDs substantially increases mortality of very low-birth-weight infants; in a study of very low-birth-weight infants, the mortality rate with serious congenital heart defects was 44% compared with 12.7% in very low-birth-weight infants without serious CCDs.[83]
- Analysis of the STS Congenital Heart Surgery Database, a voluntary registry with self-reported data for a 3-year cycle (2013–2016) from 116 centers performing CCD surgery (112 based in 40 US states, 3 in Canada, and 1 in Turkey),[84] showed that of 122 193 total patients who underwent an operation with analyzable data, the aggregate hospital discharge mortality rate was 3.0% (95% CI, 2.9%–3.1%).[85] The mortality rate was 8.6% (95% CI, 8.2%–9.1%) for neonates, 2.8% (95% CI, 2.6%–3.0%) for infants, 1.0% (95% CI, 0.9%–1.1%) for children (>1 year to 18 years of age), and 1.5% (95% CI, 1.3%–1.8%) for adults (>18 years of age).[85]
- Another recent analysis of mortality after CCD surgery, culled from the Pediatric Cardiac Care Consortium's US-based multicenter data registry, demonstrated that although standardized mortality ratios continue to decrease, there remains increased mortality in CCD patients compared with the general population. The data included 35 998 patients with median follow-up of 18 years and an overall standardized mortality ratio of 8.3% (95% CI, 8.0%–8.7%).[86]
- The Japan Congenital Cardiovascular Surgery Database reported similar surgical outcomes for congenital HD from 28 810 patients operated on between 2008 and 2012, with 2.3% and 3.5% mortality at 30 and 90 days, respectively.[87]
- In Mexico, there were 70 741 deaths attributed to CCD during the years 2000 to 2015, with the standardized mortality rates increased from 3.3 to 4 per 100 000 individuals, and an increase in mortality rates in the age group <1 year of age from 114.4 to 146.4 per 100 000 live births.[88]
- In population-based data from Canada, 8123 deaths occurred among 71 686 patients with CCDs followed up for nearly 1 million patient-years.[7]
- Among 12 644 adults with CCDs followed up at a single Canadian center from 1980 to 2009, 308 patients in the study cohorts (19%) died.[89]
- Trends in age-adjusted death rates attributable to CCD mortality showed a decline from 1999 to 2017 (Chart 15-1); this varied by race/ethnicity and sex (Charts 15-2 and 15-3).
- From 1999 to 2017, there was a decline in the age-adjusted death rates attributable to CCDs in black, white, and Hispanic people (Chart 15-2), in both males and females (Chart 15-3), and in age groups 1 to 4 years, 5 to 14 years, 15 to 24 years, and ≥25 years (Chart 15-4) in the United States.
- CCD-related mortality varies substantially by age, with 1- to 4-year-old children demonstrating higher mortality rates than any age group other than infants from 1999 to 2017 (Chart 15-4).
- The US 2017 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.01 for NH white males, 1.28 for NH black males, 0.91 for Hispanic males, 0.77 for NH white females, 1.03 for NH black females, and 0.73 for Hispanic females (Chart 15-5). Infant (<1 year of age) mortality rates were 27.4 for NH white infants, 38.6 for NH black infants, and 30.0 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER[77]).
- Mortality after congenital heart surgery also differs between races/ethnicities, even after adjustment for access to care. One study found that a higher risk of in-hospital mortality was associated with nonwhite race (OR, 1.36 [95% CI, 1.19–1.54]) and Medicaid insurance (OR, 1.26 [95% CI, 1.09–1.46]).[90] One center's experience suggested race was independently associated with neonatal surgical outcomes only in patients with less complex CCDs.[91] Another center found that a home monitoring program can reduce mortality even in this vulnerable population.[92]
- Data from the HCUP's Kids' Inpatient Database from 2000, 2003, and 2006 show male children had more CCD surgeries in infancy, more high-risk surgeries, and more procedures to correct multiple cardiac defects. Female infants with high-risk CCDs had a 39% higher adjusted mortality than males.[92,93] According to CDC multiple-cause death data from 1999 to 2006, sex differences in mortality over time varied with age. Between the ages of 18 and 34 years, mortality over time decreased significantly in females but not in males.[94]
- In studies that examined trends since 1979, age-adjusted death rates declined 22% for critical CCDs[95] and 39% for all CCDs,[96] and deaths tended to occur at progressively older ages. Population-based data from Canada showed overall mortality decreased by 31% and the median age of death increased from 2 to 23 years between 1987 and 2005.[7]
- Further analysis of the Kids' Inpatient Database from 2000 to 2009 showed a decrease in HLHS stage 3 mortality by 14% and a decrease in stage 1 mortality by 6%.[97] Surgical interventions are the primary treatment for reducing mortality. A Pediatric

Heart Network study of 15 North American centers revealed that even in lesions associated with the highest mortality, such as HLHS, aggressive palliation can lead to an increase in the 12-month survival rate, from 64% to 74%.[98]

- Surgical interventions are common in adults with CCDs. Mortality rates for 12 CCD procedures were examined with data from 1988 to 2003 reported in the NIS. A total of 30 250 operations were identified, which yielded a national estimate of 152 277±7875 operations. Of these, 27% were performed in patients ≥18 years of age. The overall in-hospital mortality rate for adult patients with CCDs was 4.71% (95% CI, 4.19%–5.23%), with a significant reduction in mortality observed when surgery was performed on such adult patients by pediatric versus nonpediatric heart surgeons (1.87% versus 4.84%; $P<0.0001$).[99] For adults with CCDs, specialist care is a key determinant of mortality and morbidity. In a single-center report of 4461 adult patients with CCDs with 48 828 patient-years of follow-up, missed appointments and delay in care were predictors of mortality.[100]

Hospitalizations (See Table 15-1)

- In 2016, the total number of hospital discharges for CCDs for all ages was 45 000 (Table 15-1).
- Hospitalization of infants with CCDs is common; one-third of patients with congenital heart defects require hospitalization during infancy,[101,102] often in an ICU.

Cost

- Using HCUP 2013 NIS data, one study noted that hospitalization costs for individuals of all ages with CCDs exceeded $6.1 billion in 2013, which represents 27% of all birth defect–associated hospital costs.[103]
- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2012 Kids' Inpatient Database[104]:
  - Pediatric hospitalizations with CCDs (4.4% of total pediatric hospitalizations) accounted for $6.6 billion in hospitalization spending (23% of total pediatric hospitalization costs).
  - 26.7% of all CCD costs were attributed to critical CCDs, with the highest costs attributable to HLHS, coarctation of the aorta, and TOF.
  - Median (IQR) hospital cost was $51 302 ($32 088–$100 058) in children who underwent cardiac surgery, $21 920 ($13 068–$51 609) in children who underwent cardiac catheterization, $4134 ($1771–$10 253) in children who underwent noncardiac surgery, and $23 062 ($5529–$71 887) in children admitted for medical treatments.
  - The mean cost of CCDs was higher in infancy ($36 601) than in older ages and in those with critical congenital heart defects ($52 899).
- Other studies confirm the high cost of HLHS. An analysis of 1941 neonates with HLHS showed a median cost of $99 070 for stage 1 palliation (Norwood or Sano procedure), $35 674 for stage 2 palliation (Glenn procedure), $36 928 for stage 3 palliation (Fontan procedure), and $289 292 for transplantation.[105]
- Other CCD lesions, often which are either less complex or preserve a biventricular circulation, are less costly. In 2124 patients undergoing congenital heart operations between 2001 and 2007, total costs for the other surgeries were $12 761 (ASD repair), $18 834 (VSD repair), $28 223 (TOF repair), and $55 430 (arterial switch operation).[106]
- A Canadian study published in 2017 demonstrated increasing hospitalization costs for children and adults with CCDs, particularly those with complex lesions, which appeared to be independent from inflation or length of stay.[107]
- A recent US study evaluating cost and length of stay in neonates with HLHS revealed significant regional differences in cost, length of stay, and mortality.[108]

Global Burden of CCDs (See Charts 15-6 and 15-7)

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[109] In 2017:
  - Prevalence of congenital heart anomalies was an estimated 12.0 million people.
  - There were 300 000 deaths attributed to congenital heart anomalies worldwide.
  - Age-standardized mortality rates of congenital heart anomalies are lowest in high-income countries and several African nations (Chart 15-6).
  - The age-standardized prevalence of congenital heart anomalies is highest in Central Europe (Chart 15-7).

Kawasaki Disease *ICD-9* 446.1; *ICD-10* M30.3.

KD is an acute inflammatory illness characterized by fever, rash, nonexudative limbal-sparing conjunctivitis, extremity changes, red lips and strawberry tongue, and

a swollen lymph node. In areas where bacille Calmette-Guerin vaccination is common, the site can reactivate in KD.[110] The most feared consequence of this vasculitis is coronary artery aneurysms, which can result in coronary ischemic events and other cardiovascular outcomes in the acute period or years later.[111] The cause of KD is unknown, but it could be an immune response to an acute infectious illness based in part on genetic susceptibilities.[112,113] This is supported by the occurrence of epidemics and variation in incidence by age, geography, and season, but also by race/ethnicity, sex, and family history.[113,114] The Nationwide Longitudinal Survey in Japan has shown that breastfeeding is protective against developing KD.[115]

Prevalence

- KD is the most common cause of acquired HD in children in the United States and other developed countries.[114]

Incidence

- The incidence was 20.8 per 100 000 US children <5 years of age in 2006.[116] This is the most recent national estimate available and is limited by reliance on weighted hospitalization data from 38 states.
- Boys have a 1.5-fold higher incidence of KD than girls.[116]
- Although KD can occur into adolescence (and rarely beyond), 76.8% of US children with KD are <5 years of age.[116]
- Race-specific incidence rates indicate that KD is most common among Americans of Asian and Pacific Island descent (30.3 per 100 000 children <5 years of age), occurs with intermediate frequency in NH blacks (17.5 per 100 000 children <5 years of age) and Hispanics (15.7 per 100 000 children <5 years of age), and is least common in whites (12.0 per 100 000 children <5 years of age).[116]
- There is also geographic variation in KD incidence within the United States. States with higher Asian American populations have higher rates of KD; for example, rates are 2.5-fold higher in Hawaii (50.4 per 100 000 children <5 years of age) than in the continental United States.[117] Within Hawaii, the race-specific rates of KD per 100 000 children <5 years of age in 1996 to 2006 were 210.5 for Japanese, 86.9 for Native Hawaiian, 83.2 for Chinese, 64.5 for Filipino, and 13.7 for white children.[117]
- There are seasonal variations in KD; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.[116,117]
- KD can recur. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,[118] and incidence of first recurrence among children with a history of KD has been reported as 6.5 per 1000 person-years in Japan (2007–2010) and 2.6 per 1000 person-years in Canada (2004–2014).[119,120]

Secular Trends

- Although the incidence of KD is rising worldwide, there has been no clear secular trend in the United States, but recent data are lacking. US hospitalizations for KD were 17.5 and 20.8 per 100 000 children <5 years of age in 1997 and 2006, respectively, but the test for linear trend was not significant.[116]

Genetics/Family History

- Approximately 1% of KD cases have a positive family history of KD. Among siblings of KD patients, the RR of KD is ≈10-fold compared with the general population (2.1% rate within 1 year of index case onset). Among identical twins, concordance is ≈13 percent.[114]
- A variety of genetic variants have been associated with KD susceptibility or development of coronary artery lesions in KD; however, thus far these have not explained differences in incidence between ancestry groups (eg, Japanese versus European).[112,121]

Treatment and Control

- Treatment of acute KD rests on diminishing the inflammatory response with IVIG, which clearly reduces the incidence of coronary artery aneurysms (from 25% to ≈4% for aneurysms defined by absolute dimensions).[114] Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.
  - On the basis of a Cochrane review, addition of prednisolone to the standard IVIG regimen could further reduce the incidence of coronary artery abnormalities (RR, 0.29 [95% CI, 0.18–0.46]), but the applicability of these data to non-Asian and less severe KD cases is not certain.[122]
  - On the basis of limited data, other anti-inflammatory treatments have also been used, and several clinical trials are under way.[123]
  - Resistance to IVIG, defined as recurrent or persistent fever ≥36 hours after completion of IVIG infusion, occurs in 10% to 20% of KD patients. Predictive models for IVIG resistance have been developed in Asian populations but have not been useful in North American patients. Treatment of IVIG resistance is currently not standardized.[114]
- Management of established coronary artery aneurysms in the short and long term is centered on

thromboprophylaxis. Successful coronary intervention for late coronary stenosis or thrombosis has been accomplished percutaneously and surgically (eg, CABG).[124,125]

Complications of KD

- In the acute phase (up to ≈6 weeks from fever onset), several important cardiovascular complications can occur.
  - KD shock syndrome, with variable contributions from myocardial dysfunction and decreased peripheral resistance, occurs in 5% to 7% of KD cases and is associated with higher risk of coronary arterial dilation, resistance to IVIG treatment, and rarely, long-term myocardial dysfunction or death.[114,126]
  - It is estimated that even with current therapy (high-dose IVIG within the first 10 days of illness), 20% of children develop transient coronary artery dilation (*Z* score >2), 5% develop coronary artery aneurysms (*Z* score ≥2.5), and 1% develop giant aneurysms (*Z* score ≥10 or >8 mm).[114] Estimates are complicated by variability in ascertainment method (administrative codes or research measurement), size criteria, timing (because the majority of dilated segments and approximately half of aneurysms reduce to normal dimensions over time), and therapeutic regimens in the underlying studies. In the most recent US data from 2 centers in 2004 to 2008, maximal coronary artery dimensions reached *Z* scores ≥2.5 in 30% of KD cases up to 12 weeks from fever onset, including medium (*Z* score ≥5 to <10) and giant aneurysms in ≈6% and ≈3% of KD cases, respectively.[127] Risk factors for coronary artery abnormalities include younger age, male sex, late treatment, and failure to respond to initial IVIG with defervescence.[127–130]
  - Peak KD-associated mortality occurs during the acute phase but is rare, estimated at 0% to 0.17% in older US data and 0.03% in recent data from Japan.[131–133] Mortality is related to thrombosis or rupture of rapidly expanding aneurysms, or less commonly, shock or macrophage activation syndrome with multiorgan failure.[114,133,134]
- Long term, IHD and death are related to coronary artery stenosis or thrombosis.
  - Prognosis is predicted largely by coronary artery size 1 month from illness onset. In a Taiwanese study of 1073 KD cases from 1980 to 2012, coronary artery aneurysms were present in 18.3% beyond 1 month, including 11.6% with small, 4.1% with medium, and 2.5% with giant aneurysms. Among those with persistent aneurysms beyond 1 month, IHD death occurred in 2%, nonfatal AMI occurred in another 2%, and myocardial ischemia occurred in another 3%, for a total 7% ischemic event rate during 1 to 46 years of follow-up. Nearly all events occurred in those with giant aneurysms, for whom the ischemia event–free survival rates were 0.63 and 0.36 at 10 and 20 years, respectively, after KD onset.[135] Findings were similar in a Japanese study of 76 patients with giant aneurysms diagnosed since 1972 and followed up through 2011 and in a Canadian study of 1356 KD patients diagnosed in 1990 to 2007 and followed up for up to 15 years.[124,136]
  - —A recent Japanese multicenter cohort study of 1006 individuals identified risk factors for 10-year incidence of coronary events (thrombosis, stenosis, obstruction, acute ischemic events, or coronary intervention).[137] Significant risk factors included giant-sized aneurysm (HR, 8.9 [95% CI, 5.1–15.4]), male sex (HR, 2.8 [95% CI, 1.7–4.8]), and resistance to IVIG therapy (HR, 2.2 [95% CI, 1.4–3.6]).
  - Among 261 adults <40 years of age with ACS who underwent coronary angiography for suspected myocardial ischemia in San Diego, CA, from 2005 to 2009, 5% had aneurysms consistent with late sequelae of KD.[138]
- In 2017, US mortality attributable to KD was 5 patients for underlying mortality and 10 patients for all-cause mortality (unpublished NHLBI tabulation using CDC WONDER[77]).

Healthcare Utilization

- In 2016, there were 6000 all-listed diagnoses hospital discharges for KD, with 4000 males and 2000 females (HCUP,[139] unpublished NHLBI tabulation).

Global Burden of KD

- The annual incidence of KD is highest in Japan, at 308.0 per 100 000 children <5 years of age in 2014, followed by South Korea at 194.7 per 100 000 children <5 years of age in 2014 and Taiwan at 55.9 per 100 000 in children <5 years of age for the period 2000 to 2014.[133,140,141] National incidence data are lacking for China, but the most recent estimates for Shanghai are 55.5 per 100 000 children <5 years of age in 2012.[142]
- In Japan, the cumulative incidence of KD at 10 years of age has been calculated with national survey data as >1%, at 1.5 per 100 boys and 1.2 per 100 girls for 2007 to 2010.[143] Using different methodology with complete capture of cases through the national health insurance program,

Taiwan recorded a cumulative incidence of 2.8% by 5 years of age in 2014.[141]

- The incidence of KD is lower in Canada, at 19.6 per 100 000 children <5 years of age for the period 2004 to 2014, and in European countries, such as Italy with 14.7 per 100 000 children <5 years of age in 2008 to 2013, Spain with 8 per 100 000 children <5 years of age in 2004 to 2014, Germany with 7.2 per 100 000 children <5 years of age in 2011 to 2012, and the United Kingdom and Ireland with 4.6 per 100 000 children <5 years of age in 2014 to 2015.[120,144–148]
- The incidence of KD is rising worldwide, with potential contributions from improved recognition, diagnosis of incomplete KD more often, and true increasing incidence.[133,141,145,148]

Table 15-1. CCDs in the United States

Population Group	Estimated Prevalence, 2010, All Ages	Mortality, 2017, All Ages*	Hospital Discharges, 2016, All Ages
Both sexes	2.4 million	2906	45 000
Males	…	1583 (54.5%)†	25 000
Females	…	1323 (45.5%)†	20 000
NH white males	…	923	…
NH white females	…	779	…
NH black males	…	273	…
NH black females	…	225	…
Hispanic males	…	301	…
Hispanic females	…	239	…
NH Asian or Pacific Islander males	…	62	…
NH Asian or Pacific Islander females	…	59	…
NH American Indian or Alaska Native	…	31	…

CCD indicates congenital cardiovascular defect; ellipses (…), data not available; and NH, non-Hispanic.

*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

Sources: Prevalence: Gilboa et al.[149] Mortality: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.[76] These data represent underlying cause of death only. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016.[139] Data include those inpatients discharged alive, dead, or status unknown.

Table 15-2. Annual Birth Prevalence of CCDs in the United States, 1930 to 2010

Type of Presentation	Rate per 1000 Live Births	Estimated Number (Variable With Yearly Birth Rate)
Fetal loss	Unknown	Unknown
Invasive procedure during the first year	2.4	9200
Detected during first year*	8	36 000
Bicuspid aortic valve	13.7	54 800

CCD indicates congenital cardiovascular defect.

*Includes stillbirths and pregnancy termination at <20 weeks' gestation; includes some defects that resolve spontaneously or do not require treatment.

Source: Data derived from van der Linde et al[13] and Parker et al.[19]

Table 15-3. Estimated US Prevalence of CCDs and Percent Distribution by Type, 2002* (in Thousands)

Type	Prevalence, N			Percent of Total		
	Total	Children	Adults	Total	Children	Adults
Total	994	463	526	100	100	100
VSD†	199	93	106	20.1	20.1	20.1
ASD	187	78	109	18.8	16.8	20.6
Patent ductus arteriosus	144	58	86	14.2	12.4	16.3
Valvular pulmonic stenosis	134	58	76	13.5	12.6	14.4
Coarctation of aorta	76	31	44	7.6	6.8	8.4
Valvular aortic stenosis	54	25	28	5.4	5.5	5.2
TOF	61	32	28	6.1	7	5.4
AV septal defect	31	18	13	3.1	3.9	2.5
TGA	26	17	9	2.6	3.6	1.8
Hypoplastic right heart syndrome	22	12	10	2.2	2.5	1.9
Double-outlet RV	9	9	0	0.9	1.9	0.1
Single ventricle	8	6	2	0.8	1.4	0.3
Anomalous pulmonary venous connection	9	5	3	0.9	1.2	0.6
Truncus arteriosus	9	6	2	0.7	1.3	0.5
HLHS	3	3	0	0.3	0.7	0
Other	22	12	10	2.1	2.6	1.9

ASD indicates atrial septal defect; AV, atrioventricular; CCD, congenital cardiovascular defect; HLHS, hypoplastic left heart syndrome; RV, right ventricle; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

*Excludes an estimated 3 million bicuspid aortic valve prevalence (2 million in adults and 1 million in children).

†Small VSD, 117 000 (65 000 adults and 52 000 children); large VSD, 82 000 (41 000 adults and 41 000 children).

Source: Data derived from Hoffman et al.[11]

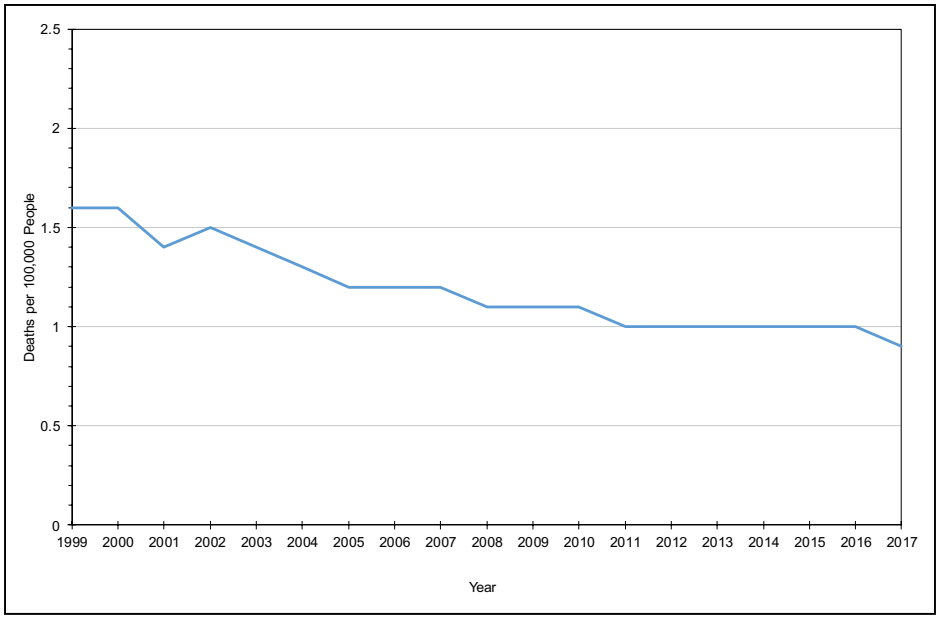

Chart 15-1. Trends in age-adjusted death rates attributable to congenital cardiovascular defects, United States, 1999 to 2017.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.[77]

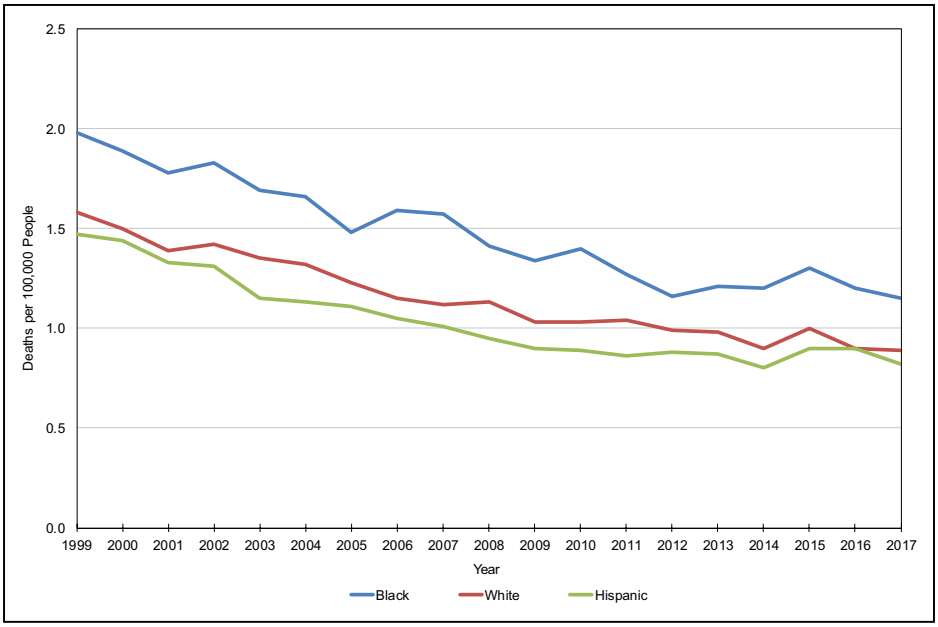

Chart 15-2. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by race/ethnicity, United States, 1999 to 2017.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.[77]

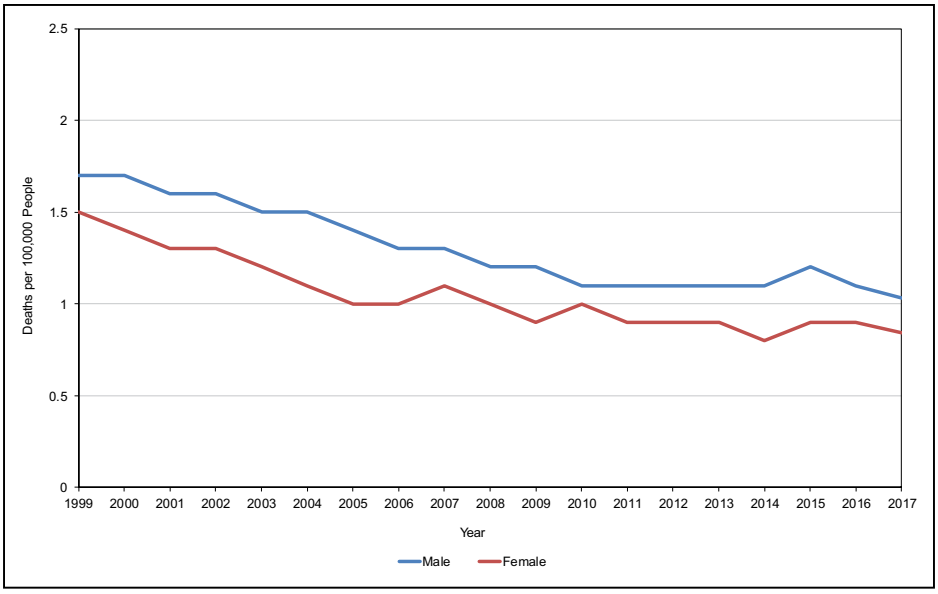

Chart 15-3. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by sex, United States, 1999 to 2017.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.[77]

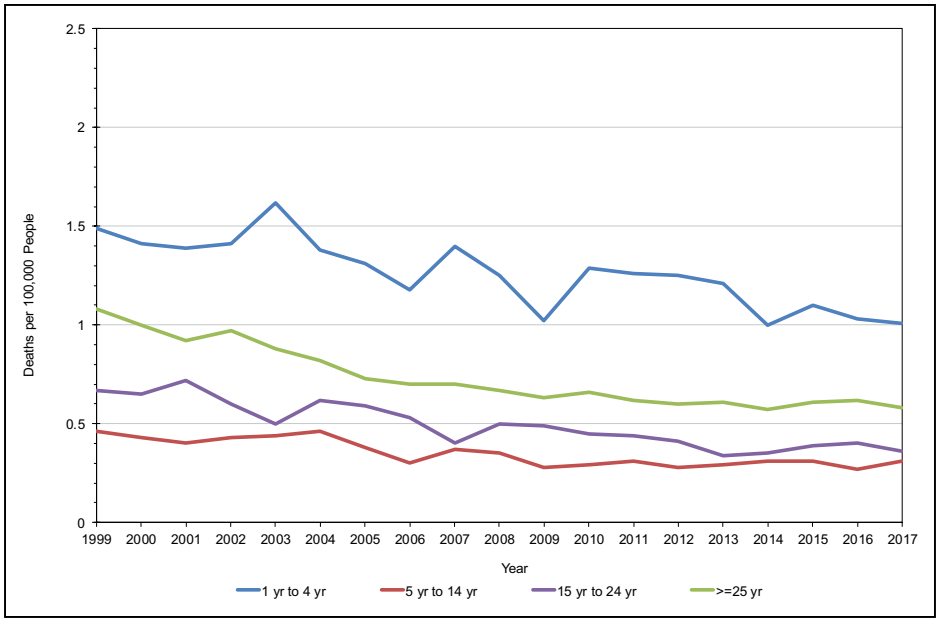

Chart 15-4. Trends in age-specific death rates attributable to congenital cardiovascular defects by age at death, United States, 1999 to 2017.
Yr indicates year.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.[77]

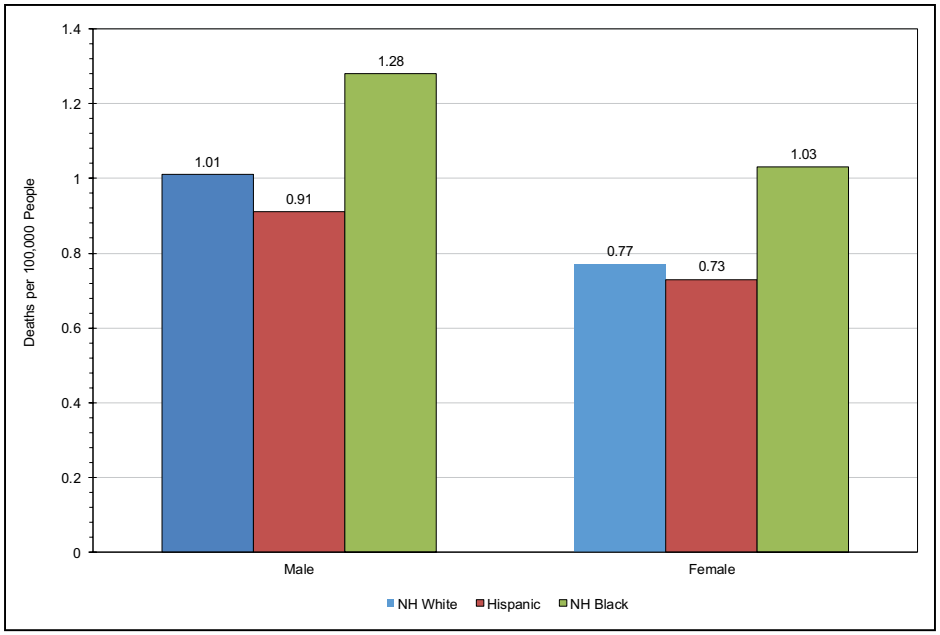

Chart 15-5. Age-adjusted death rates attributable to congenital cardiovascular defects, by sex and race/ethnicity, United States, 2017.
NH indicates non-Hispanic.
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.[77]

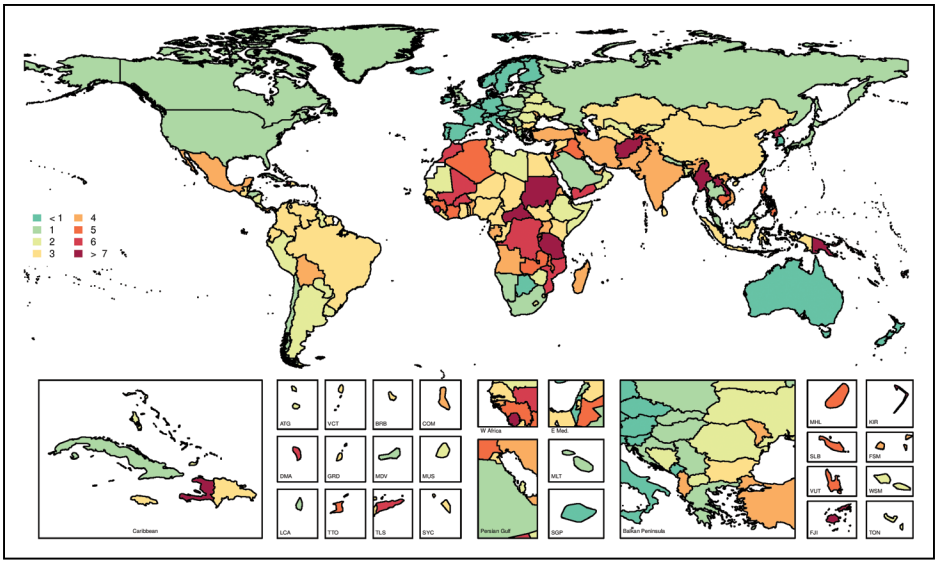

Chart 15-6. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2017.
Age-standardized mortality rates of congenital heart anomalies are lowest in high-income countries and several African nations.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[109] Printed with permission.

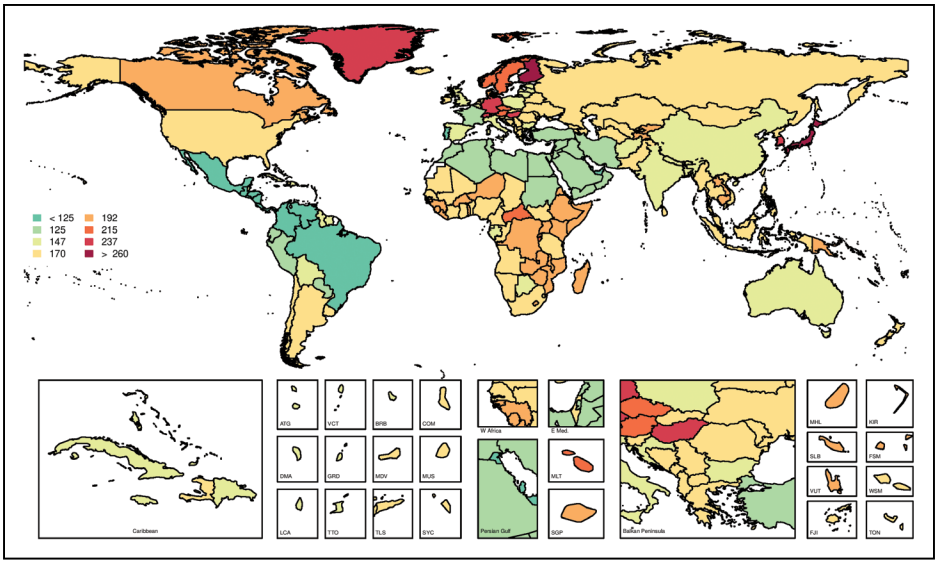

Chart 15-7. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2017.
The age-standardized prevalence of congenital heart anomalies is highest in Central Europe.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[109] Printed with permission.

REFERENCES

1. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation.* 2008;118:e714–e833. doi: 10.1161/CIRCULATIONAHA.108.190690
2. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. *Cardiol Young.* 2013;23:473–485. doi: 10.1017/S1047951112002351
3. Mellion K, Uzark K, Cassedy A, Drotar D, Wernovsky G, Newburger JW, Mahony L, Mussatto K, Cohen M, Limbers C, et al; Pediatric Cardiac Quality of Life Inventory Testing Study Consortium. Health-related quality of life outcomes in children and adolescents with congenital heart disease. *J Pediatr.* 2014;164:781–788.e1. doi: 10.1016/j.jpeds.2013.11.066
4. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. *J Pediatr Psychol.* 2007;32:527–541. doi: 10.1093/jpepsy/jsl047
5. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, et al; on behalf of the American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation.* 2012;126:1143–1172. doi: 10.1161/CIR.0b013e318265ee8a
6. Roche SL, Silversides CK. Hypertension, obesity, and coronary artery disease in the survivors of congenital heart disease. *Can J Cardiol.* 2013;29:841–848. doi: 10.1016/j.cjca.2013.03.021
7. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol.* 2010;56:1149–1157. doi: 10.1016/j.jacc.2010.03.085
8. Sable C, Foster E, Uzark K, Bjornsen K, Canobbio MM, Connolly HM, Graham TP, Gurvitz MZ, Kovacs A, Meadows AK, et al; on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Best practices in managing transition to adulthood for adolescents with congenital heart disease: the transition process and medical and psychosocial issues: a scientific statement from the American Heart Association. *Circulation.* 2011;123:1454–1485. doi: 10.1161/CIR.0b013e3182107c56
9. Gurvitz M, Valente AM, Broberg C, Cook S, Stout K, Kay J, Ting J, Kuehl K, Earing M, Webb G, et al; Alliance for Adult Research in Congenital Cardiology (AARCC) and Adult Congenital Heart Association. Prevalence and predictors of gaps in care among adult congenital heart disease patients: HEART-ACHD (the Health, Education, and Access Research Trial). *J Am Coll Cardiol.* 2013;61:2180–2184. doi: 10.1016/j.jacc.2013.02.048
10. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation.* 2014;130:749–756. doi: 10.1161/CIRCULATIONAHA.113.008396
11. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J.* 2004;147:425–439. doi: 10.1016/j.ahj.2003.05.003
12. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol.* 2001;37:1170–1175. doi: 10.1016/s0735-1097(01)01272-4
13. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241–2247. doi: 10.1016/j.jacc.2011.08.025
14. Sawant SP, Amin AS, Bhat M. Prevalence, pattern and outcome of congenital heart disease in Bhabha Atomic Research Centre Hospital, Mumbai. *Indian J Pediatr.* 2013;80:286–291. doi: 10.1007/s12098-012-0910-x
15. Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics.* 2001;107:E32. doi: 10.1542/peds.107.3.e32
16. Koppel RI, Druschel CM, Carter T, Goldberg BE, Mehta PN, Talwar R, Bierman FZ. Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. *Pediatrics.* 2003;111:451–455. doi: 10.1542/peds.111.3.451
17. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. *J Pediatr.* 2008;153:807–813. doi: 10.1016/j.jpeds.2008.05.059
18. Bedard T, Lowry RB, Sibbald B, Harder JR, Trevenen C, Horobec V, Dyck JD. Congenital heart defect case ascertainment by the Alberta Congenital Anomalies Surveillance System. *Birth Defects Res A Clin Mol Teratol.* 2012;94:449–458. doi: 10.1002/bdra.23007
19. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, et al; National Birth Defects Prevention Network. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol.* 2010;88:1008–1016. doi: 10.1002/bdra.20735
20. Mai CT, Riehle-Colarusso T, O'Halloran A, Cragan JD, Olney RS, Lin A, Feldkamp M, Botto LD, Rickard R, Anderka M, et al; National Birth Defects Prevention Network. Selected birth defects data from population-based birth defects surveillance programs in the United States, 2005–2009: featuring critical congenital heart defects targeted for pulse oximetry screening. *Birth Defects Res A Clin Mol Teratol.* 2012;94:970–983.
21. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol.* 2002;39:1890–1900. doi: 10.1016/s0735-1097(02)01886-7
22. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL; on behalf of the American Heart Association Council on Cardiovascular Disease in the Young. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young. *Circulation.* 2007;115:2995–3014. doi: 10.1161/CIRCULATIONAHA.106.183216
23. Patel SS, Burns TL. Nongenetic risk factors and congenital heart defects. *Pediatr Cardiol.* 2013;34:1535–1555. doi: 10.1007/s00246-013-0775-4
24. Herskind AM, Almind Pedersen D, Christensen K. Increased prevalence of congenital heart defects in monozygotic and dizygotic twins. *Circulation.* 2013;128:1182–1188. doi: 10.1161/CIRCULATIONAHA.113.002453
25. Pettit KE, Merchant M, Machin GA, Tacy TA, Norton ME. Congenital heart defects in a large, unselected cohort of monochorionic twins. *J Perinatol.* 2013;33:457–461. doi: 10.1038/jp.2012.145
26. Snijder CA, Vlot IJ, Burdorf A, Obermann-Borst SA, Helbing WA, Wildhagen MF, Steegers EA, Steegers-Theunissen RP. Congenital heart defects and parental occupational exposure to chemicals. *Hum Reprod.* 2012;27:1510–1517. doi: 10.1093/humrep/des043
27. Wilson PD, Loffredo CA, Correa-Villaseñor A, Ferencz C. Attributable fraction for cardiac malformations. *Am J Epidemiol.* 1998;148:414–423. doi: 10.1093/oxfordjournals.aje.a009666
28. Lee LJ, Lupo PJ. Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systematic review and metaanalysis. *Pediatr Cardiol.* 2013;34:398–407. doi: 10.1007/s00246-012-0470-x
29. Sullivan PM, Dervan LA, Reiger S, Buddhe S, Schwartz SM. Risk of congenital heart defects in the offspring of smoking mothers: a population-based study. *J Pediatr.* 2015;166:978–984.e2. doi: 10.1016/j.jpeds.2014.11.042
30. Alverson CJ, Strickland MJ, Gilboa SM, Correa A. Maternal smoking and congenital heart defects in the Baltimore-Washington Infant Study. *Pediatrics.* 2011;127:e647–e653. doi: 10.1542/peds.2010-1399
31. Malik S, Cleves MA, Honein MA, Romitti PA, Botto LD, Yang S, Hobbs CA; National Birth Defects Prevention Study. Maternal smoking and congenital heart defects. *Pediatrics.* 2008;121:e810–e816. doi: 10.1542/peds.2007-1519
32. Patel SS, Burns TL, Botto LD, Riehle-Colarusso TJ, Lin AE, Shaw GM, Romitti PA; National Birth Defects Prevention Study. Analysis of selected maternal exposures and non-syndromic atrioventricular septal defects in the National Birth Defects Prevention Study, 1997-2005. *Am J Med Genet A.* 2012;158A:2447–2455. doi: 10.1002/ajmg.a.35555
33. Tanner JP, Salemi JL, Stuart AL, Yu H, Jordan MM, DuClos C, Cavicchia P, Correia JA, Watkins SM, Kirby RS. Associations between exposure to ambient benzene and PM(2.5) during pregnancy and the risk of selected birth defects in offspring. *Environ Res.* 2015;142:345–353. doi: 10.1016/j.envres.2015.07.006
34. Mateja WA, Nelson DB, Kroelinger CD, Ruzek S, Segal J. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. *J Womens Health (Larchmt).* 2012;21:26–34. doi: 10.1089/jwh.2010.2582
35. Baardman ME, Kerstjens-Frederikse WS, Corpeleijn E, de Walle HE, Hofstra RM, Berger RM, Bakker MK. Combined adverse effects of maternal smoking and high body mass index on heart development in offspring: evidence for interaction? *Heart.* 2012;98:474–479. doi: 10.1136/heartjnl-2011-300822

36. Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. *Am J Obstet Gynecol.* 2014;211:91–117. doi: 10.1016/j.ajog.2014.03.028
37. Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A; National Birth Defects Prevention Study. Prepregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med.* 2007;161:745–750. doi: 10.1001/archpedi.161.8.745
38. Øyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, Quertermous T, Wohlfahrt J, Melbye M. Prepregnancy diabetes and offspring risk of congenital heart disease: a nationwide cohort study. *Circulation.* 2016;133:2243–2253. doi: 10.1161/CIRCULATIONAHA.115.017465
39. Simeone RM, Devine OJ, Marcinkevage JA, Gilboa SM, Razzaghi H, Bardenheier BH, Sharma AJ, Honein MA. Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. *Am J Prev Med.* 2015;48:195–204. doi: 10.1016/j.amepre.2014.09.002
40. Priest JR, Yang W, Reaven G, Knowles JW, Shaw GM. Maternal midpregnancy glucose levels and risk of congenital heart disease in offspring. *JAMA Pediatr.* 2015;169:1112–1116. doi: 10.1001/jamapediatrics.2015.2831
41. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. *JAMA.* 2015;314:1588–1598. doi: 10.1001/jama.2015.12505
42. Scanlon KS, Ferencz C, Loffredo CA, Wilson PD, Correa-Villaseñor A, Khoury MJ, Willett WC; Baltimore-Washington Infant Study Group. Preconceptional folate intake and malformations of the cardiac outflow tract. *Epidemiology.* 1998;9:95–98.
43. Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada. *BMJ.* 2009;338:b1673. doi: 10.1136/bmj.b1673
44. Dong DY, Binongo JN, Kancherla V. Maternal chlamydia infection during pregnancy and risk of cyanotic congenital heart defects in the offspring. *Matern Child Health J.* 2016;20:66–76. doi: 10.1007/s10995-015-1804-0
45. Oster ME, Riehle-Colarusso T, Correa A. An update on cardiovascular malformations in congenital rubella syndrome. *Birth Defects Res A Clin Mol Teratol.* 2010;88:1–8. doi: 10.1002/bdra.20621
46. Zheng JY, Tian HT, Zhu ZM, Li B, Han L, Jiang SL, Chen Y, Li DT, He JC, Zhao Z, et al. Prevalence of symptomatic congenital heart disease in Tibetan school children. *Am J Cardiol.* 2013;112:1468–1470. doi: 10.1016/j.amjcard.2013.07.028
47. Mahle WT, Martin GR, Beekman RH 3rd, Morrow WR; Section on Cardiology and Cardiac Surgery Executive Committee. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. *Pediatrics.* 2012;129:190–192. doi: 10.1542/peds.2011-3211
48. Glidewell J, Olney RS, Hinton C, Pawelski J, Sontag M, Wood T, Kucik JE, Daskalov R, Hudson J; Centers for Disease Control and Prevention (CDC). State legislation, regulations, and hospital guidelines for newborn screening for critical congenital heart defects: United States, 2011-2014. *MMWR Morb Mortal Wkly Rep.* 2015;64:625–630.
49. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganäs L, Eriksson M, Segerdahl N, Agren A, Ekman-Joelsson BM, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ.* 2009;338:a3037. doi: 10.1136/bmj.a3037
50. Meberg A, Brügmann-Pieper S, Due R Jr, Eskedal L, Fagerli I, Farstad T, Frøisland DH, Sannes CH, Johansen OJ, Keljalic J, et al. First day of life pulse oximetry screening to detect congenital heart defects [published correction appears in *J Pediatr*. 2009;154:629]. *J Pediatr.* 2008;152:761–765. doi: 10.1016/j.jpeds.2007.12.043
51. Riede FT, Wörner C, Dähnert I, Möckel A, Kostelka M, Schneider P. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine: results from a prospective multicenter study. *Eur J Pediatr.* 2010;169:975–981. doi: 10.1007/s00431-010-1160-4
52. Peterson C, Grosse SD, Oster ME, Olney RS, Cassell CH. Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. *Pediatrics.* 2013;132:e595–e603. doi: 10.1542/peds.2013-0332
53. Ailes EC, Gilboa SM, Honein MA, Oster ME. Estimated number of infants detected and missed by critical congenital heart defect screening. *Pediatrics.* 2015;135:1000–1008. doi: 10.1542/peds.2014-3662
54. Hartman RJ, Rasmussen SA, Botto LD, Riehle-Colarusso T, Martin CL, Cragan JD, Shin M, Correa A. The contribution of chromosomal abnormalities to congenital heart defects: a population-based study. *Pediatr Cardiol.* 2011;32:1147–1157. doi: 10.1007/s00246-011-0034-5
55. Peterson C, Ailes E, Riehle-Colarusso T, Oster ME, Olney RS, Cassell CH, Fixler DE, Carmichael SL, Shaw GM, Gilboa SM. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. *JAMA Pediatr.* 2014;168:361–370. doi: 10.1001/jamapediatrics.2013.4779
56. Abouk R, Grosse SD, Ailes EC, Oster ME. Association of US state implementation of newborn screening policies for critical congenital heart disease with early infant cardiac deaths [published correction appears in *JAMA*. 2018;320:1288]. *JAMA.* 2017;318:2111–2118. doi: 10.1001/jama.2017.17627
57. Jawin V, Ang HL, Omar A, Thong MK. Beyond critical congenital heart disease: newborn screening using pulse oximetry for neonatal sepsis and respiratory diseases in a middle-income country. *PLoS One.* 2015;10:e0137580. doi: 10.1371/journal.pone.0137580
58. Pace ND, Oster ME, Forestieri NE, Enright D, Knight J, Meyer RE. Sociodemographic factors and survival of infants with congenital heart defects. *Pediatrics*. 2018;142:e20180302. doi: 10.1542/peds.2018-0302
59. Knowles RL, Ridout D, Crowe S, Bull C, Wray J, Tregay J, Franklin RC, Barron DJ, Cunningham D, Parslow RC, et al. Ethnic and socioeconomic variation in incidence of congenital heart defects. *Arch Dis Child.* 2017;102:496–502. doi: 10.1136/archdischild-2016-311143
60. Knowles RL, Ridout D, Crowe S, Bull C, Wray J, Tregay J, Franklin RCG, Barron DJ, Parslow RC, Brown K. Ethnic-specific mortality of infants undergoing congenital heart surgery in England and Wales. *Arch Dis Child.* 2019;104:844–850. doi: 10.1136/archdischild-2018-315505
61. Wong P, Denburg A, Dave M, Levin L, Morinis JO, Suleman S, Wong J, Ford-Jones E, Moore AM. Early life environment and social determinants of cardiac health in children with congenital heart disease. *Paediatr Child Health.* 2018;23:92–95. doi: 10.1093/pch/pxx146
62. van Hagen IM, Baart S, Fong Soe Khioe R, Sliwa-Hahnle K, Taha N, Lelonek M, Tavazzi L, Maggioni AP, Johnson MR, Maniadakis N, et al; ROPAC Investigators. Influence of socioeconomic factors on pregnancy outcome in women with structural heart disease. *Heart.* 2018;104:745–752. doi: 10.1136/heartjnl-2017-311910
63. Wang X, Li P, Chen S, Xi L, Guo Y, Guo A, Sun K. Influence of genes and the environment in familial congenital heart defects. *Mol Med Rep.* 2014;9:695–700. doi: 10.3892/mmr.2013.1847
64. Nora JJ, Dodd PF, McNamara DG, Hattwick MA, Leachman RD, Cooley DA. Risk to offspring of parents with congenital heart defects. *JAMA.* 1969;209:2052–2053.
65. Korbel JO, Tirosh-Wagner T, Urban AE, Chen XN, Kasowski M, Dai L, Grubert F, Erdman C, Gao MC, Lange K, et al. The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. *Proc Natl Acad Sci U S A.* 2009;106:12031–12036. doi: 10.1073/pnas.0813248106
66. Soemedi R, Wilson IJ, Bentham J, Darlay R, Töpf A, Zelenika D, Cosgrove C, Setchfield K, Thornborough C, Granados-Riveron J, et al. Contribution of global rare copy-number variants to the risk of sporadic congenital heart disease. *Am J Hum Genet.* 2012;91:489–501. doi: 10.1016/j.ajhg.2012.08.003
67. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. *Circ Res.* 2017;120:923–940. doi: 10.1161/CIRCRESAHA.116.309140
68. Xie H, Zhang E, Hong N, Fu Q, Li F, Chen S, Yu Y, Sun K. Identification of TBX2 and TBX3 variants in patients with conotruncal heart defects by target sequencing. *Hum Genomics.* 2018;12:44. doi: 10.1186/s40246-018-0176-0
69. Preuss C, Capredon M, Wünnemann F, Chetaille P, Prince A, Godard B, Leclerc S, Sobreira N, Ling H, Awadalla P, et al; MIBAVA Leducq Consortium. Family based whole exome sequencing reveals the multifaceted role of Notch signaling in congenital heart disease. *PLoS Genet.* 2016;12:e1006335. doi: 10.1371/journal.pgen.1006335
70. Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, Romano-Adesman A, Bjornson RD, Breitbart RE, Brown KK, et al. De novo mutations in histone-modifying genes in congenital heart disease. *Nature.* 2013;498:220–223. doi: 10.1038/nature12141
71. Zhu N, Welch CL, Wang J, Allen PM, Gonzaga-Jauregui C, Ma L, King AK, Krishnan U, Rosenzweig EB, Ivy DD, et al. Rare variants in SOX17 are associated with pulmonary arterial hypertension with congenital heart disease. *Genome Med.* 2018;10:56. doi: 10.1186/s13073-018-0566-x
72. Blue GM, Kirk EP, Giannoulatou E, Dunwoodie SL, Ho JW, Hilton DC, White SM, Sholler GF, Harvey RP, Winlaw DS. Targeted next-generation sequencing identifies pathogenic variants in familial congenital heart disease. *J Am Coll Cardiol.* 2014;64:2498–2506. doi: 10.1016/j.jacc.2014.09.048
73. Jia Y, Louw JJ, Breckpot J, Callewaert B, Barrea C, Sznajer Y, Gewillig M, Souche E, Dehaspe L, Vermeesch JR, et al. The diagnostic value of next generation sequencing in familial nonsyndromic congenital heart defects. *Am J Med Genet A.* 2015;167A:1822–1829. doi: 10.1002/ajmg.a.37108
74. Szot JO, Cuny H, Blue GM, Humphreys DT, Ip E, Harrison K, Sholler GF, Giannoulatou E, Leo P, Duncan EL, et al. A screening approach

to identify clinically actionable variants causing congenital heart disease in exome data. *Circ Genom Precis Med.* 2018;11:e001978. doi: 10.1161/CIRCGEN.117.001978
75. Hoang TT, Goldmuntz E, Roberts AE, Chung WK, Kline JK, Deanfield JE, Giardini A, Aleman A, Gelb BD, Mac Neal M, et al. The Congenital Heart Disease Genetic Network Study: cohort description. *PLoS One.* 2018;13:e0191319. doi: 10.1371/journal.pone.0191319
76. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death microdata files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
77. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
78. Jortveit J, Øyen N, Leirgul E, Fomina T, Tell GS, Vollset SE, Eskedal L, Døhlen G, Birkeland S, Holmstrøm H. Trends in mortality of congenital heart defects. *Congenit Heart Dis.* 2016;11:160–168. doi: 10.1111/chd.12307
79. Cnota JF, Gupta R, Michelfelder EC, Ittenbach RF. Congenital heart disease infant death rates decrease as gestational age advances from 34 to 40 weeks. *J Pediatr.* 2011;159:761–765. doi: 10.1016/j.jpeds.2011.04.020
80. Swenson AW, Dechert RE, Schumacher RE, Attar MA. The effect of late preterm birth on mortality of infants with major congenital heart defects. *J Perinatol.* 2012;32:51–54. doi: 10.1038/jp.2011.50
81. Best KE, Tennant PWG, Rankin J. Survival, by birth weight and gestational age, in individuals with congenital heart disease: a population-based study. *J Am Heart Assoc*. 2017;6:e005213. doi: 10.1161/JAHA.116.005213
82. Costello JM, Pasquali SK, Jacobs JP, He X, Hill KD, Cooper DS, Backer CL, Jacobs ML. Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *Circulation.* 2014;129:2511–2517. doi: 10.1161/CIRCULATIONAHA.113.005864
83. Archer JM, Yeager SB, Kenny MJ, Soll RF, Horbar JD. Distribution of and mortality from serious congenital heart disease in very low birth weight infants. *Pediatrics.* 2011;127:293–299. doi: 10.1542/peds.2010-0418
84. Shahian DM, Jacobs JP, Edwards FH, Brennan JM, Dokholyan RS, Prager RL, Wright CD, Peterson ED, McDonald DE, Grover FL. The Society of Thoracic Surgeons national database. *Heart*. 2013;99:1494–1501.
85. The Society of Thoracic Surgeons. The Society of Thoracic Surgeons (STS) National Database: Congenital Heart Surgery Database participants, Spring 2017 Harvest [database online]. https://www.sts.org/sites/default/files/documents/CHSD_ExecutiveSummary_Neonates_Spring2017.pdf. Accessed May 4, 2019.
86. Jacobs ML, Jacobs JP, Hill KD, Hornik C, O'Brien SM, Pasquali SK, Vener D, Kumar SR, Habib RH, Shahian DM, et al. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2017 update on research. *Ann Thorac Surg.* 2017;104:731–741. doi: 10.1016/j.athoracsur.2017.07.001
87. Spector LG, Menk JS, Knight JH, McCracken C, Thomas AS, Vinocur JM, Oster ME, St Louis JD, Moller JH, Kochilas L. Trends in long-term mortality after congenital heart surgery. *J Am Coll Cardiol.* 2018;71:2434–2446. doi: 10.1016/j.jacc.2018.03.491
88. Sánchez-Barriga JJ. Mortality trends from congenital malformations of the heart and the great vessels in children and adults in the seven socioeconomic regions of Mexico, 2000-2015. *Congenit Heart Dis.* 2018;13:690–699. doi: 10.1111/chd.12631
89. Hoashi T, Miyata H, Murakami A, Hirata Y, Hirose K, Matsumura G, Ichikawa H, Sawa Y, Takamoto S. The current trends of mortality following congenital heart surgery: the Japan Congenital Cardiovascular Surgery Database. *Interact Cardiovasc Thorac Surg.* 2015;21:151–156. doi: 10.1093/icvts/ivv109
90. Oster ME, Strickland MJ, Mahle WT. Racial and ethnic disparities in post-operative mortality following congenital heart surgery. *J Pediatr.* 2011;159:222–226. doi: 10.1016/j.jpeds.2011.01.060
91. Chan T, Pinto NM, Bratton SL. Racial and insurance disparities in hospital mortality for children undergoing congenital heart surgery. *Pediatr Cardiol.* 2012;33:1026–1039. doi: 10.1007/s00246-012-0221-z
92. Lasa JJ, Cohen MS, Wernovsky G, Pinto NM. Is race associated with morbidity and mortality after hospital discharge among neonates undergoing heart surgery? *Pediatr Cardiol.* 2013;34:415–423. doi: 10.1007/s00246-012-0475-5
93. Castellanos DA, Herrington C, Adler S, Haas K, Ram Kumar S, Kung GC. Home monitoring program reduces mortality in high-risk sociodemographic single-ventricle patients [published correction appears in *Pediatr Cardiol*. 2017;38:206]. *Pediatr Cardiol.* 2016;37:1575–1580. doi: 10.1007/s00246-016-1472-x
94. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation.* 2010;122:2254–2263. doi: 10.1161/CIRCULATIONAHA.110.947002
95. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics.* 2013;131:e1502–e1508. doi: 10.1542/peds.2012-3435
96. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. *Circulation.* 2001;103:2376–2381. doi: 10.1161/01.cir.103.19.2376
97. Czosek RJ, Anderson JB, Heaton PC, Cassedy A, Schnell B, Cnota JF. Staged palliation of hypoplastic left heart syndrome: trends in mortality, cost, and length of stay using a national database from 2000 through 2009. *Am J Cardiol.* 2013;111:1792–1799. doi: 10.1016/j.amjcard.2013.02.039
98. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, et al; Pediatric Heart Network Investigators. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med.* 2010;362:1980–1992. doi: 10.1056/NEJMoa0912461
99. Karamlou T, Diggs BS, Person T, Ungerleider RM, Welke KF. National practice patterns for management of adult congenital heart disease: operation by pediatric heart surgeons decreases in-hospital death. *Circulation.* 2008;118:2345–2352. doi: 10.1161/CIRCULATIONAHA.108.776963
100. Kempny A, Diller GP, Dimopoulos K, Alonso-Gonzalez R, Uebing A, Li W, Babu-Narayan S, Swan L, Wort SJ, Gatzoulis MA. Determinants of outpatient clinic attendance amongst adults with congenital heart disease and outcome. *Int J Cardiol.* 2016;203:245–250. doi: 10.1016/j.ijcard.2015.10.081
101. Marino BS, Bird GL, Wernovsky G. Diagnosis and management of the newborn with suspected congenital heart disease. *Clin Perinatol.* 2001;28:91–136.
102. Dorfman AT, Marino BS, Wernovsky G, Tabbutt S, Ravishankar C, Godinez RI, Priestley M, Dodds KM, Rychik J, Gruber PJ, et al. Critical heart disease in the neonate: presentation and outcome at a tertiary care center. *Pediatr Crit Care Med.* 2008;9:193–202. doi: 10.1097/PCC.0b013e318166eda5
103. Arth AC, Tinker SC, Simeone RM, Ailes EC, Cragan JD, Grosse SD. Inpatient hospitalization costs associated with birth defects among persons of all ages: United States, 2013. *MMWR Morb Mortal Wkly Rep.* 2017;66:41–46. doi: 10.15585/mmwr.mm6602a1
104. Faraoni D, Nasr VG, DiNardo JA. Overall hospital cost estimates in children with congenital heart disease: analysis of the 2012 Kid's Inpatient Database. *Pediatr Cardiol.* 2016;37:37–43. doi: 10.1007/s00246-015-1235-0
105. Dean PN, Hillman DG, McHugh KE, Gutgesell HP. Inpatient costs and charges for surgical treatment of hypoplastic left heart syndrome. *Pediatrics.* 2011;128:e1181–e1186. doi: 10.1542/peds.2010-3742
106. Pasquali SK, Sun JL, d'Almada P, Jaquiss RD, Lodge AJ, Miller N, Kemper AR, Lannon CM, Li JS. Center variation in hospital costs for patients undergoing congenital heart surgery. *Circ Cardiovasc Qual Outcomes.* 2011;4:306–312. doi: 10.1161/CIRCOUTCOMES.110.958959
107. Mackie AS, Tran DT, Marelli AJ, Kaul P. Cost of congenital heart disease hospitalizations in Canada: a population-based study. *Can J Cardiol.* 2017;33:792–798. doi: 10.1016/j.cjca.2017.01.024
108. Essaid L, Strassle PD, Jernigan EG, Nelson JS. Regional differences in cost and length of stay in neonates with hypoplastic left heart syndrome. *Pediatr Cardiol.* 2018;39:1229–1235. doi: 10.1007/s00246-018-1887-7
109. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
110. Park SH, Yu JJ, You J, Kim MJ, Shin EJ, Jun HO, Baek JS, Kim YH, Ko JK. Clinical significance of the Bacille Calmette-Guérin site reaction in Kawasaki disease patients aged less than 18 months. *Pediatr Infect Vaccine*. 2018;25:148–155. doi: 10.14776/piv.2018.25.e11
111. Gordon JB, Daniels LB, Kahn AM, Jimenez-Fernandez S, Vejar M, Numano F, Burns JC. The spectrum of cardiovascular lesions requiring intervention in adults after Kawasaki disease. *JACC Cardiovasc Interv.* 2016;9:687–696. doi: 10.1016/j.jcin.2015.12.011

112. Xie X, Shi X, Liu M. The roles of genetic factors in Kawasaki disease: a systematic review and meta-analysis of genetic association studies. *Pediatr Cardiol.* 2018;39:207–225. doi: 10.1007/s00246-017-1760-0
113. Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. *Int J Rheum Dis.* 2018;21:16–19. doi: 10.1111/1756-185X.13211
114. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, et al; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation*. 2019;140:e181–e184]. *Circulation.* 2017;135:e927–e999. doi: 10.1161/CIR.0000000000000484
115. Yorifuji T, Tsukahara H, Doi H. Breastfeeding and risk of Kawasaki disease: a nationwide longitudinal survey in Japan. *Pediatrics*. 2016;137:e20153919. doi: 10.1542/peds.2015-3919
116. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997–2007. *Pediatr Infect Dis J*. 2010;29:483–488. doi: 10.1097/INF.0b013e3181cf8705
117. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, Forbes S, Schonberger LB, Melish M. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J*. 2010;69:194–197.
118. Maddox RA, Holman RC, Uehara R, Callinan LS, Guest JL, Schonberger LB, Nakamura Y, Yashiro M, Belay ED. Recurrent Kawasaki disease: USA and Japan. *Pediatr Int*. 2015;57:1116–1120. doi: 10.1111/ped.12733
119. Sudo D, Nakamura Y. Nationwide surveys show that the incidence of recurrent Kawasaki disease in Japan has hardly changed over the last 30 years. *Acta Paediatr.* 2017;106:796–800. doi: 10.1111/apa.13773
120. Manlhiot C, O'Shea S, Bernknopf B, LaBelle M, Chahal N, Dillenburg RF, Lai LS, Bock D, Lew B, Masood S, et al. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. *Can J Cardiol.* 2018;34:303–309. doi: 10.1016/j.cjca.2017.12.009
121. Onouchi Y. The genetics of Kawasaki disease. *Int J Rheum Dis.* 2018;21:26–30. doi: 10.1111/1756-185X.13218
122. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev.* 2017;1:CD011188. doi: 10.1002/14651858.CD011188.pub2
123. Tremoulet AH. Adjunctive therapies in Kawasaki disease. *Int J Rheum Dis.* 2018;21:76–79. doi: 10.1111/1756-185X.13208
124. Suda K, Iemura M, Nishiono H, Teramachi Y, Koteda Y, Kishimoto S, Kudo Y, Itoh S, Ishii H, Ueno T, et al. Long-term prognosis of patients with Kawasaki disease complicated by giant coronary aneurysms: a single-institution experience. *Circulation.* 2011;123:1836–1842. doi: 10.1161/CIRCULATIONAHA.110.978213
125. Dionne A, Bakloul M, Manlhiot C, McCrindle BW, Hosking M, Houde C, Pepelassis D, Dahdah N. Coronary artery bypass grafting and percutaneous coronary intervention after Kawasaki disease: the pediatric Canadian series. *Pediatr Cardiol.* 2017;38:36–43. doi: 10.1007/s00246-016-1480-x
126. Taddio A, Rossi ED, Monasta L, Pastore S, Tommasini A, Lepore L, Bronzetti G, Marrani E, Mottolese BD, Simonini G, et al. Describing Kawasaki shock syndrome: results from a retrospective study and literature review. *Clin Rheumatol*. 2017;36:223–228. doi: 10.1007/s10067-016-3316-8
127. Ogata S, Tremoulet AH, Sato Y, Ueda K, Shimizu C, Sun X, Jain S, Silverstein L, Baker AL, Tanaka N, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. *Int J Cardiol.* 2013;168:3825–3828. doi: 10.1016/j.ijcard.2013.06.027
128. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, Tremoulet AH. High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. *J Pediatr.* 2017;185:112–116.e1. doi: 10.1016/j.jpeds.2017.03.025
129. Satoh K, Wakejima Y, Gau M, Kiguchi T, Matsuda N, Takasawa R, Takasawa K, Nishioka M, Shimohira M. Risk of coronary artery lesions in young infants with Kawasaki disease: need for a new diagnostic method. *Int J Rheum Dis.* 2018;21:746–754. doi: 10.1111/1756-185X.13223
130. Yamashita M, Ae R, Yashiro M, Aoyama Y, Sano T, Makino N, Nakamura Y. Difference in risk factors for subtypes of acute cardiac lesions resulting from Kawasaki disease. *Pediatr Cardiol.* 2017;38:375–380. doi: 10.1007/s00246-016-1525-1
131. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics*. 2003;112:495–501. doi: 10.1542/peds.112.3.495
132. Chang RK. Hospitalizations for Kawasaki disease among children in the United States, 1988-1997. *Pediatrics.* 2002;109:e87. doi: 10.1542/peds.109.6.e87
133. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, Kojo T, Aoyama Y, Kotani K, Yanagawa H. Epidemiological observations of Kawasaki disease in Japan, 2013-2014. *Pediatr Int.* 2018;60:581–587. doi: 10.1111/ped.13544
134. García-Pavón S, Yamazaki-Nakashimada MA, Báez M, Borjas-Aguilar KL, Murata C. Kawasaki disease complicated with macrophage activation syndrome: a systematic review. *J Pediatr Hematol Oncol.* 2017;39:445–451. doi: 10.1097/MPH.0000000000000872
135. Lin MT, Sun LC, Wu ET, Wang JK, Lue HC, Wu MH. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous γ-immunoglobulin therapy. *Arch Dis Child.* 2015;100:542–547. doi: 10.1136/archdischild-2014-306427
136. Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol.* 2010;31:242–249. doi: 10.1007/s00246-009-9599-7
137. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, Fuse S, Hamaoka K, Hirono K, Kato T, et al; The Z-score Project 2nd Stage Study Group. Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. *JAMA Pediatr.* 2018;172:e180030. doi: 10.1001/jamapediatrics.2018.0030
138. Daniels LB, Tjajadi MS, Walford HH, Jimenez-Fernandez S, Trofimenko V, Fick DB Jr, Phan HA, Linz PE, Nayak K, Kahn AM, et al. Prevalence of Kawasaki disease in young adults with suspected myocardial ischemia. *Circulation.* 2012;125:2447–2453. doi: 10.1161/CIRCULATIONAHA.111.082107
139. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
140. Kim GB, Park S, Eun LY, Han JW, Lee SY, Yoon KL, Yu JJ, Choi JW, Lee KY. Epidemiology and clinical features of Kawasaki disease in South Korea, 2012-2014. *Pediatr Infect Dis J.* 2017;36:482–485. doi: 10.1097/INF.0000000000001474
141. Wu MH, Lin MT, Chen HC, Kao FY, Huang SK. Postnatal risk of acquiring Kawasaki disease: a nationwide birth cohort database study. *J Pediatr.* 2017;180:80–86.e2. doi: 10.1016/j.jpeds.2016.09.052
142. Chen JJ, Ma XJ, Liu F, Yan WL, Huang MR, Huang M, Huang GY; Shanghai Kawasaki Disease Research Group. Epidemiologic features of Kawasaki disease in Shanghai from 2008 through 2012. *Pediatr Infect Dis J.* 2016;35:7–12. doi: 10.1097/INF.0000000000000914
143. Nakamura Y, Yashiro M, Yamashita M, Aoyama N, Otaki U, Ozeki Y, Sano T, Kojo T, Ae R, Aoyama Y, et al. Cumulative incidence of Kawasaki disease in Japan. *Pediatr Int.* 2018;60:19–22. doi: 10.1111/ped.13450
144. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child.* 2015;100:1084–1088. doi: 10.1136/archdischild-2014-307536
145. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr.* 2017;176:1061–1065. doi: 10.1007/s00431-017-2947-3
146. Sánchez-Manubens J, Antón J, Bou R, Iglesias E, Calzada-Hernandez J, Rodó X, Morguí JA; el Grupo de Trabajo en Enfermedad de Kawasaki en Cataluña. Kawasaki disease is more prevalent in rural areas of Catalonia (Spain) [in Spanish]. *An Pediatr (Barc).* 2017;87:226–231. doi: 10.1016/j.anpedi.2016.12.009
147. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, Arnold R, von Kries R, Neumann E, Roubinis N, Robert M, et al. Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting. *Pediatr Infect Dis J.* 2016;35:129–134. doi: 10.1097/INF.0000000000000953
148. Tulloh RMR, Mayon-White R, Harnden A, Ramanan AV, Tizard EJ, Shingadia D, Michie CA, Lynn RM, Levin M, Franklin OD, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. *Arch Dis Child*. 2018;104:640–646. doi: 10.1136/archdischild-2018-315087
149. Gilboa SM, Devine OJ, Kucik JE, Oster ME, Riehle-Colarusso T, Nembhard WN, Xu P, Correa A, Jenkins K, Marelli AJ. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. *Circulation.* 2016;134:101–109. doi: 10.1161/CIRCULATIONAHA.115.019307

16. DISORDERS OF HEART RHYTHM

See Table 16-1 and Charts 16-1 through 16-10

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Arrhythmias (Disorders of Heart Rhythm)

2017: Mortality—54 145. Any-mention mortality—558 408.

Bradyarrhythmias
ICD-9 426.0, 426.1, 427.81; *ICD-10* I44.0 to I44.3, I49.5

2017: Mortality—1327. Any-mention mortality—7018.

2016: Hospital discharges—97 000.

Mean hospital charges: $74 846; in-hospital death rate: 1.15%; mean length of stay: 3.9 days.

Abbreviations Used in Chapter 16

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
AF	atrial fibrillation
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
AV	atrioventricular
BiomarCaRE	Biomarker for Cardiovascular Risk Assessment in Europe
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHA_2DS_2-VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes mellitus, and sex (1 point each); age ≥75 y and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65–74 y, and (female) sex category
$CHADS_2$	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, age ≥75 y, diabetes mellitus (1 point each), and prior stroke/transient ischemic attack/thromboembolism (2 points)
CHARGE-AF	Cohorts for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DM	diabetes mellitus

(*Continued*)

Abbreviations Used in Chapter 16 Continued

DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulant
ECG	Electrocardiogram
ED	emergency department
EF	ejection fraction
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPIC	European Prospective Investigation Into Cancer and Nutrition
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GLORIA-AF	Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GRS	genetic risk score
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	*intensive care unit*
IQR	interquartile range
IRR	incidence rate ratio
Look AHEAD	Look: Action for Health in Diabetes
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
NVSS	National Vital Statistics System
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OSA	obstructive sleep apnea

(*Continued*)

Abbreviations Used in Chapter 16 Continued

PA	physical activity
PAD	peripheral artery disease
PAF	population attributable fraction
PAR	population attributable risk
PCI	percutaneous coronary intervention
PINNACLE	Practice Innovation and Clinical Excellence
PREDIMED	Prevención con Dieta Mediterránea
PREVEND	Prevention of Renal and Vascular End-Stage Disease
QALY	quality-adjusted life-year
RACE 3	Routine vs. Aggressive Risk Factor Driven Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RE-LY	Randomized Evaluation of Long-term Anticoagulant Therapy
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
STROKESTOP	Systematic ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm and Halland, Sweden
SVT	supraventricular tachycardia
TIA	transient ischemic attack
UI	uncertainty interval
USD	US dollars
VF	ventricular fibrillation
WHS	Women's Health Study
WPW	Wolff-Parkinson-White

AV Block

Prevalence and Incidence

- In a healthy sample of participants from the ARIC study (mean age 53 years), the prevalence of first-degree AV block was 7.8% in black males, 3.0% in black females, 2.1% in white males, and 1.3% in white females.[1] Lower prevalence estimates were noted in the relatively younger population (mean age 45 years) of the CARDIA study at its year 20 follow-up examination: 2.6% in black males, 1.9% in black females, 1.2% in white males, and 0.1% in white females.[2]
- The prevalence of PR-interval prolongation was observed to be 2.1% in Finnish middle-aged adults, but the authors noted that the PR interval normalized in follow-up in 30% of these people.[3]
- No population-based studies have reported the prevalence of second-degree AV block. On the basis of results from clinical series, Mobitz II second-degree AV block is rare in healthy individuals (≈0.003%), whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.[4]
- The prevalence of third-degree AV block in the general adult population is very low. The prevalence was 0.04% in the Icelandic Reykjavik Study[5] and 0.6% in a large sample of people with hypertension and without DM enrolled with Veterans Health Administration hospitals.[6]
- In an analysis of standard 12-lead ECGs from 264 324 Brazilian primary care patients, prevalence of complete AV block was 0.05%, ranging from 0.02% in individuals 20 to <40 years of age to 0.3% in persons ≥80 years of age.[7]
- In 122 815 recordings from 122 454 unique patients prescribed 14-day continuous single-lead electrocardiographic monitoring with the Zio patch device between 2011 and 2013, prevalence of high-grade AV block (defined as either Mobitz II or complete heart block) was 1.2% (1486 of all tracings).[8]
- An English registry study estimated the incidence of infant complete AV block as 2.1 per 100 000 live births.[9] Congenital complete heart block could be attributable to transplacental transfer of maternal anti-SSA/Ro or SSB/La antibodies.[10]

Risk Factors

- In healthy individuals from MESA without CVD or its risk factors, PR interval was longer with advancing age, in males compared with females, and in blacks compared with whites.[11]
- Although first-degree AV block and Mobitz type I second-degree AV block can occur in apparently healthy people, presence of Mobitz II second- or third-degree AV block usually indicates underlying HD, including CHD, and HF.[4]
- Reversible causes of AV block include electrolyte abnormalities, drug-induced AV block, perioperative AV block attributable to hypothermia, or inflammation near the AV conduction system after surgery in this region. Some conditions may warrant pacemaker implantation because of the potential for disease progression even if the AV block reverses transiently (eg, sarcoidosis, amyloidosis, and neuromuscular diseases).[12]
- Long sinus pauses and AV block can occur during sleep apnea. In the absence of symptoms, these abnormalities are reversible and do not require pacing.[12,13]
- Although the majority of determinants of heart rate are acquired, there are genetic components that are associated with heart rate. For example, a GWAS has identified 21 genetic loci associated with heart rate.[14]

Prevention

- Detection and correction of reversible causes of acquired AV block could be of potential importance

in preventing symptomatic bradycardia and other complications of AV block.[12]

Complications (See Chart 16-1)

- In the FHS, PR-interval prolongation (>200 ms) was associated with increased risk of AF (HR, 2.06 [95% CI, 1.36–3.12]), pacemaker implantation (HR, 2.89 [95% CI, 1.83–4.57]), and all-cause mortality (HR, 1.44 [95% CI, 1.09–1.91]).[15] Compared with people with a PR interval ≤200 ms, those with a PR interval >200 ms had an absolute increased risk per year of 1.0% for AF, 0.5% for pacemaker implantation, and 2.1% for death (Chart 16-1).
- Decisions about the need for a pacemaker are influenced by the presence or absence of symptoms directly attributable to bradycardia and the likelihood of the arrhythmia progressing to complete heart block. Permanent pacing improves survival in patients with third-degree AV block, especially if syncope has occurred.[12]
- In a large, prospective, regional French registry of 6662 STEMI patients (2006–2013), high-degree AV block was noted in 3.5% of individuals. In 64% of cases, high-degree AV block was present on admission. Although patients with high-degree AV block on admission or occurring during the first 24 hours of hospitalization had higher in-hospital mortality rates than patients without heart block, it was not an independent predictor of mortality after multivariable analysis (OR, 0.99 [95% CI, 0.60–1.66]).[16]
- Little evidence exists to suggest that pacemakers improve survival in patients with isolated first-degree AV block.[17] However, marked first-degree AV block (PR >300 ms) can lead to symptoms even in the absence of higher degrees of AV block, with uncontrolled studies suggesting that those patients benefit from pacemaker implantation.[12,18]

Sinus Node Dysfunction

Prevalence and Incidence

- There are no accurate estimates of the prevalence of sinus node dysfunction in the general population.
- According to a survey of members of the North American Society of Pacing and Electrophysiology, sick sinus syndrome accounted for 48% of implantations of first permanent pacemakers in the United States in 1997.[19,20]
- Sinus node dysfunction is commonly present with other causes of bradyarrhythmias (carotid sinus hypersensitivity in 42% of patients and advanced AV conduction abnormalities in 17%).[21,22]
- Incidence rates of sinus node dysfunction hospitalization among Medicare beneficiaries >65 years of age were 207 per 100 000 person-years in 1998. Rates increased with age and were higher in males than females and in whites than blacks.[23]
- The incidence rate of sick sinus syndrome was 0.8 per 1000 person-years of follow-up in 2 US cohorts that included whites and blacks, ARIC and CHS.[24] The incidence increased with advancing age (HR, 1.73 [95% CI, 1.47–2.05] per 5-year increment), and blacks were at 41% lower risk of sick sinus syndrome than their white counterparts (HR, 0.59 [95% CI, 0.37–0.98]). Investigators projected that in the United States, the number of new cases of sick sinus syndrome per year would rise from 78 000 in 2012 to 172 000 in 2060.[24]

Risk Factors

- The causes of sinus node dysfunction can be classified as intrinsic (secondary to pathological conditions involving the sinus node) or extrinsic (caused by depression of sinus node function by external factors such as drugs or autonomic influences).[25]
- Idiopathic degenerative disease is probably the most common cause of sinus node dysfunction.[26]
- Investigators collected data from 28 different studies on atrial pacing for sinus node dysfunction that showed a median annual incidence of second- and third-degree AV block of 0.6% (range, 0%–4.5%) and an overall prevalence of 2.1% (range, 0%–11.9%). This suggests that the degenerative process also affects the specialized conduction system, although the rate of progression is slow and does not dominate the clinical course of disease.[27]
- In the CHS and ARIC studies, factors associated with incident sick sinus syndrome included white (versus black) race, higher mean BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, N-terminal pro-BNP, cystatin C, and history of a major cardiovascular event.[24]

Complications (See Chart 16-2)

- The survival of patients with sinus node dysfunction appears to depend primarily on the severity of underlying cardiac disease, is not different from survival in the general population when treated with pacemaker, and is not significantly changed by type of pacemaker therapy.[28–30]
- In a retrospective study[31] of patients with sinus node dysfunction who had pacemaker therapy, mortality among those with ventricular pacing only was 63% compared with 40% among those with DDD pacing at 7-year follow-up.
- In 19 893 males and females >45 years of age from the ARIC and CHS cohorts, incidence of sick sinus syndrome was associated with increased mortality (HR, 1.4 [95% CI, 1.1–1.7]), CHD (HR, 1.7 [95% CI, 1.1–2.7]), HF (HR, 2.9 [95% CI, 2.2–3.8]), stroke (HR, 1.6 [95% CI, 1.0–2.5]), AF (HR, 5.8

[95% CI, 4.4–7.5]), and pacemaker implantation (HR, 53.7 [95% CI, 42.9–67.2]).[32]

- In a multicenter study from the Netherlands of people with bradycardia treated with pacemaker implantation, the actuarial 1-, 3-, 5-, and 7-year survival rates were 93%, 81%, 69%, and 61%, respectively. Individuals without CVD at baseline had similar survival rates as age- and sex-matched control subjects.[33]
- With sinus node dysfunction, the incidence of sudden death is extremely low, and pacemaker implantation does not appear to alter longevity.[12,34] SVT including AF was prevalent in 53% of patients with sinus node dysfunction.[29]
- On the basis of records from the NIS, pacemaker implantation rates per million increased from 467 in 1993 to 616 in 2009, although overall use plateaued in 2001. The patients' mean age and number of comorbidities at implantation increased over time. Total hospital charges associated with pacemaker implantation increased 45% from $53 693 in 1993 to $78 015 in 2009 (in 2011 dollars).[35]
- On the basis of NHDS data, the escalating implantation rate was attributable to increasing implantation for isolated sinus node dysfunction; implantation for sinus node dysfunction increased by 102%, whereas implantation for all other indications did not increase (Chart 16-2).[36]
- In 5831 participants of the MESA cohort, a heart rate <50 beats per minute was not associated with mortality or incident CVD among individuals not taking heart rate–modifying drugs compared with those with heart rate between 50 and 59 beats per minute.[37]

SVT (Excluding AF and Atrial Flutter) *ICD-9* 427.0; *ICD-10* I47.1.

2017: Mortality—179. Any-mention mortality—1511. 2016: Hospital discharges—40 000 (18 000 male; 22 000 female).

Prevalence and Incidence (See Chart 16-3)

- Data from the Marshfield Epidemiologic Study Area in Wisconsin suggested the incidence of documented paroxysmal SVT was 35 per 100 000 person-years, whereas the prevalence was 225 per 100 000 people. The mean age at SVT onset was 57 years, and both female sex (RR, 2.0) and age ≥65 years (versus <65 years: RR, 5.3) were significant risk factors (Chart 16-3).[38]
- A review of ED visits in US hospitals using NHAMCS data from 1993 to 2003 revealed that an estimated 550 000 visits were for SVT (0.05% of all visits [95% CI, 0.04%–0.06%]), or ≈50 000 visits per year (incidence rate of 1.8 ED visits per 10 000 person-years [95% CI, 1.4–2.3]). Of these patients, 24% (95% CI, 15%–34%) were admitted to the hospital, and 44% (95% CI, 32%–56%) were discharged without specific follow-up.[39] Rates were higher in individuals ≥65 years of age than in those <65 years of age (3.9 versus 1.5 per 10 000 person-years) and lower in males than in females (1.1 versus 2.6 per 10 000 person-years).
- The prevalence of SVT that is clinically undetected is likely much greater than the estimates from ED visits and electrophysiology procedures would suggest. Among 26 751 individual patients receiving a Zio Patch monitor for clinical indications, prevalence of SVT (defined as at least a single run of ≥8 beats) was 31%.[40]
- Of 1383 participants in the Baltimore Longitudinal Study of Aging undergoing maximal exercise testing, 6% exhibited SVT during the test; increasing age was a significant risk factor. Only 16% exhibited >10 beats of SVT, and only 4% were symptomatic. Over an average of 6 years of follow-up, people with exercise-induced SVT were more likely to develop SVT or AF.[41]
- In a study of 3554 consecutive males 17 to 21 years of age applying for a pilot's license and 3700 symptomatic arrhythmia patients, the surface ECG revealed that the prevalence of ectopic atrial tachycardia was estimated to be 0.34% in asymptomatic applicants and 0.46% in symptomatic applicants.[42]

Complications

- Rare cases of incessant SVT can lead to a tachycardia-induced cardiomyopathy,[43] and rare cases of sudden death attributed to SVT as a trigger have been described.[44]
- Among 2 350 328 pregnancies included in Taiwan's national insurance database between 2001 and 2012, 769 females experienced paroxysmal SVT during pregnancy. Compared with those females without paroxysmal SVT during pregnancy, paroxysmal SVT during pregnancy was associated with a higher risk for poor maternal outcomes (severe morbidity and cesarean delivery) and poor fetal outcomes (low birth weight, preterm labor, fetal stress, and obvious fetal abnormalities).[45]
- A California administrative database study of almost 5 million patients suggested that after the exclusion of people with diagnosed AF, SVT was associated with an adjusted doubling of the risk of stroke in follow-up (HR, 2.10 [95% CI, 1.69–2.62]). The absolute stroke rate was low, however. The cumulative stroke rate was 0.94% (95% CI, 0.76%–1.16%) over 1 year in patients with SVT

versus 0.21% (95% CI, 0.21%–0.22%; *P*<0.001, log-rank test) in those without SVT.[46]

- In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia (16.2±14.6 versus 9.9±13.1 years), were more likely to report not being taken seriously when consulting for their symptoms (17% versus 7%), and were more symptomatic after 6 months of ablation than males.[47]

Specific Types

- Among those presenting for invasive electrophysiological study and ablation, AV nodal reentrant tachycardia (a circuit that requires 2 AV nodal pathways) is the most common mechanism of SVT[48,49] and usually represents the majority of cases (56% in one series of 1754 cases).[49]
- AV reentrant tachycardia (an arrhythmia that requires the presence of an extranodal connection between the atria and ventricles or specialized conduction tissue) is the second most common type of SVT (27% in a study by Porter et al[49]), and atrial tachycardia is the third most common (17% in a series of 1754 SVT cases from Porter et al[49]).
- In a US-based national pediatric electrophysiology registry study, AV reentrant tachycardia was the most common SVT mechanism (68%), whereas the remainder of the patients had AV nodal reentrant tachycardia (32%).[50]
- AV reentrant tachycardia prevalence decreases with age, whereas AV nodal reentrant tachycardia and atrial tachycardia prevalence increase with advancing age.[49]
- The majority of patients with AV reentrant tachycardia were males (55%), whereas females constituted the majority with AV nodal reentrant tachycardia (70%) or atrial tachycardia (62%) in the study by Porter et al.[49]
- Multifocal atrial tachycardia is an arrhythmia that is commonly confused with AF and is characterized by 3 distinct P-wave morphologies, irregular R-R intervals, and a rate >100 beats per minute. It is uncommon in both children[51] and adults,[52] with a prevalence in hospitalized adults estimated at 0.05% to 0.32%.[52] The average age of onset in adults is 72 years. Adults with multifocal atrial tachycardia have a high mortality rate, with estimates around 45%, but this is generally ascribed to the underlying condition(s).[52] In a study of older ambulatory adults in Greece, the mortality in follow-up did not differ by whether or not multifocal atrial rhythms were detected on baseline ECG.[53]

WPW Syndrome

Prevalence

- A WPW electrocardiographic pattern was observed in 0.11% of males and 0.04% of females among 47 358 ECGs from adults participating in 4 large Belgian epidemiological studies.[54] In a study of 32 837 Japanese students who were required by law to receive ECGs before entering school, a WPW electrocardiographic pattern was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.[55]

Complications

- WPW syndrome, a diagnosis reserved for those with both ventricular preexcitation (evidence of an anterograde conducting AV accessory pathway on a 12-lead ECG) and tachyarrhythmias, deserves special attention because of the associated risk of sudden death. Sudden death is generally attributed to rapid heart rates in AF conducting down an accessory pathway and leading to VF.[56]
- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between WPW and control patients without WPW. In follow-up, WPW was associated with a significantly higher risk of AF (HR, 1.55 [95% CI, 1.29–1.87]); 7.0% of the WPW patients developed AF compared with 3.8% of those without WPW.[57]
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population.[58,59]
- In a single-center prospective registry study of 2169 patients who agreed to undergo an electrophysiology study for WPW syndrome from 2005 to 2010, 1168 patients (206 asymptomatic) underwent radiofrequency ablation, none of whom had malignant arrhythmias or VF in up to 8 years of follow-up. Of those who did not receive radiofrequency ablation (n=1001; 550 asymptomatic) in follow-up, 1.5% had VF, most of whom (13 of 15) were children. The authors noted that poor prognosis was related to accessory pathway electrophysiological properties rather than patient symptoms.[60]
- In a meta-analysis of 20 studies involving 1869 asymptomatic patients with a WPW electrocardiographic pattern followed up for a total of 11 722 person-years, the rate of sudden death in a random effects model that was used because of heterogeneity across studies was estimated to be 1.25 (95% CI, 0.57–2.19) per 1000 person-years. Risk factors for sudden death included male sex, inclusion in a study of children (<18 years of age), and inclusion in an Italian study.[61]
- Several studies in asymptomatic children with ventricular preexcitation detected by screening suggested a benign prognosis.[59,62] A referral-based registry study reported that electrophysiological testing can identify a group of asymptomatic

children with a risk of sudden death or VF as high as 11% over 19 months of follow-up.[63] In a pediatric hospital retrospective review of 446 children with WPW syndrome, 64% were symptomatic at presentation, and 20% had onset of symptoms during a median of 3 years of follow-up. The incidence of sudden death was 1.1 per 1000 person-years in patients without structural HD.[64]

AF and Atrial Flutter

Prevalence

- The prevalence of AF in the United States was estimated to rise from ≈5.2 million in 2010 to 12.1 million in 2030.[65]
- In the European Union, the prevalence of AF in adults >55 years of age was estimated to be 8.8 million (95% CI, 6.5–12.3 million) in 2010 and was projected to rise to 17.9 million in 2060 (95% CI, 13.6–23.7 million).[66]
- Data from a California health plan suggested that compared with whites, blacks (OR, 0.49 [95% CI, 0.47–0.52]), Asians (OR, 0.68 [95% CI, 0.64–0.72]), and Hispanics (OR, 0.58 [95% CI, 0.55–0.61]) have a significantly lower adjusted prevalence of AF.[67]
- Among Medicare patients ≥65 years of age who were diagnosed from 1993 to 2007, the prevalence of AF increased ≈5% per year, from 41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.[68]
  - In 2007 in the 5% Medicare sample, there were 105 701 older adults with AF: 3.7% were black, 93.8% were white, and 2.6% were other/unknown race.[68]
  - The prevalence rate per 1000 beneficiaries was 46.3 in blacks, 90.8 in whites, and 47.5 in other/unknown race.[68]
- In an analysis involving the entire South Korean population, prevalence of AF more than doubled, from 0.73% in 2006 to 1.53% in 2015, and was estimated to reach 5.81% in 2060.[69]

Incidence (See Table 16-1 and Chart 16-4)

- In a Medicare sample, per 1000 person-years, the age- and sex-standardized incidence of AF was 27.3 in 1993 and 28.3 in 2007, representing a 0.2% mean annual increase (P=0.02).[68]
- Investigators from MESA estimated the age- and sex-adjusted incidence rate of hospitalized AF per 1000 person-years (95% CI) as 11.2 (9.8–12.8) in NH whites, 6.1 (4.7–7.8) in Hispanics, 5.8 (4.8–7.0) in NH blacks, and 3.9 (2.5–6.1) in Chinese.[70]
- Data from California administrative databases were analyzed with regard to racial variation in incidence of AF. After adjustment for AF risk factors, compared with their white counterparts, lower incidence rates were found in blacks (HR, 0.84 [95% CI, 0.82–0.85]; P<0.001), Hispanics (HR, 0.78 [95% CI, 0.77–0.79]; P<0.001), and Asians (HR, 0.78 [95% CI, 0.77–0.79]; P<0.001; Chart 16-4).[71]
- Racial variation in AF incidence is also observed in other countries. For instance, in a study of the UK Clinical Practice Research Datalink cohort ≥45 years of age, the incidence rates per 1000 person-years standardized to the UK population were 8.1 (95% CI, 8.1–8.2) in whites versus 5.4 (95% CI, 4.6–6.3) in Asians and 4.6 (95% CI, 4.0–5.3) in black patients.[72]
- Using data from a health insurance claims database covering 5% of the United States, the incidence of AF was estimated at 1.2 million new cases in 2010 and was projected to increase to 2.6 million new cases in 2030.[65]
- In an analysis involving the entire South Korean population, incidence of AF between 2006 and 2015 has remained flat, with an overall incidence during this period of 1.77 new cases per 1000 person-years.[69]

Lifetime Risk and Cumulative Risk (See Chart 16-5)

- In studies from FHS and the BiomarCaRE Consortium, the lifetime risk for AF in individuals of European ancestry was estimated to be ≈1 in 3.
  - In the BiomarCaRE study based on 4 European community-based studies, the incidence increased after 50 years of age in males and 60 years in females, but the cumulative incidence of AF was similar, at >30%, by 90 years of age.[73]
  - In an FHS report based on participants with DNA collected after 1980, the lifetime risk of AF after 55 years of age was 37.1%, which was influenced by both clinical and genetic risk.[74] In a subsequent study from FHS, the lifetime risk of AF varied by risk factor burden. In individuals with optimal risk profile, the lifetime risk was 23.4% (95% CI, 12.8%–34.5%), whereas the risk was 33.4% (95% CI, 27.9%–38.9%) with a borderline risk profile and 38.4% (95% CI, 35.5%–41.4%) with an elevated risk profile (Chart 16-5).[75]
- In a medical insurance database study from the Yunnan Province in China, the estimated lifetime risk of AF at 55 years of age was 21.1% (95% CI, 19.3%–23.0%) for females and 16.7% (95% CI, 15.4%–18.0%) for males.[76] In a Taiwanese study, the lifetime risk of AF was estimated to be 16.9% (95% CI, 16.7%–14.2%) in males and 14.6% (95% CI, 14.4%–14.9%) in females.[77]
- Investigators from the NHLBI-sponsored ARIC study observed that the lifetime risk of AF was 36% in

white males (95% CI, 32%–38%), 30% in white females (95% CI, 26%–32%), 21% in black males (95% CI, 13%–24%), and 22% in black females (95% CI, 16%–25%).[78]

Secular Trends

- During 50 years of observation of the FHS (1958–1967 to 1998–2007), the age-adjusted prevalence and incidence of AF approximately quadrupled. However, when only AF that was ascertained on ECGs routinely collected in the FHS was considered, the prevalence but not the incidence increased, which suggests that part of the changing epidemiology was attributable to enhanced surveillance. Although the prevalence of most risk factors changed over time, the hazards associated with specific risk factors did not change. Hence, the PAR associated with BMI, hypertension treatment, and DM increased (consistent with increasing prevalence). Over time, the multivariable-adjusted hazards of stroke and mortality associated with AF declined by 74% and 25%, respectively.[79]
- Between 2000 and 2010 in Olmsted County, MN, age- and sex-adjusted incidence rates and survival did not change over time.[80] However, over a similar time frame in the United Kingdom (2001–2013), the incidence of nonvalvular AF in people ≥45 years of age increased modestly from 5.9 (95% CI, 5.8–6.1) to 6.9 (95% CI, 6.8–7.1) per 1000 patient-years, with the largest increase observed in those >80 years of age.[72]
- In data from the ARIC study, the prevalence of AF in the setting of MI increased slightly, from 11% to 15%, between 1987 and 2009; however, the increased risk of death (OR, 1.47 [95% CI, 1.07–2.01]) in the year after MI accompanied by AF did not change over time.[81]
- Between 1999 and 2013, among Medicare fee-for-service beneficiaries, rates of hospitalization for AF increased ≈1% per year. Although the median hospital length of stay, 3 days (IQR, 2.0–5.0 days), did not change, the mortality declined by 4% per year, and hospital readmissions at 30 days declined by 1% per year. During the same years, median Medicare inpatient costs per hospitalization increased substantially, from $2932 (IQR, $2232–$3870) to $4719 (IQR, $3124–$7209).[82]
- Similar trends have been observed globally. For instance, on the basis of data from a national health insurance database, in Korea between 2006 and 2015 the prevalence of AF increased 2.10-fold, and the incidence remained flat (1.8 per 1000 person-years), whereas the mortality rate (HR, 0.70 [95% CI, 0.68–0.93]) and ischemic stroke rate (HR, 0.91 [95% CI, 0.88–0.93]) after AF declined. Investigators projected that the adult prevalence of AF would reach 5.8% in 2060.[69]

Risk Factors (See Chart 16-6)

- The highest PAF for AF was hypertension, followed by BMI, smoking, cardiac disease, and DM in ARIC (Chart 16-6).

BP and Hypertension

- Hypertension accounted for ≈22%[83] of AF cases.
- In MESA, the PAF of AF attributable to hypertension appeared to be higher in US NH blacks (33.1%), Chinese (46.3%), and Hispanics (43.9%) than in NH whites (22.2%).[70]

BMI and Obesity

- In a meta-analysis of 16 studies involving >580 000 individuals, of whom ≈91 000 had obesity, AF developed in 6.3% of those who had obesity and 3.1% of those without it. Individuals with obesity had an RR of 1.51 for developing AF (95% CI, 1.35–1.68) compared with those without obesity.[84]
- Another meta-analysis of 29 studies examined various anthropometric components in relation to incident AF. A 5 kg/m^2 increment in BMI was associated with an RR of 1.28 (95% CI, 1.20–1.38) in relation to AF. The risk was nonlinear (P<0.0001), with stronger associations observed at higher BMIs, but a BMI of 22 to 24 kg/m^2 was still associated with excess risk compared with a BMI of 20 kg/m^2. Waist, waist-hip ratio, fat mass, and waist gain were also associated with increased risk of AF.[85]
- A causal relationship between higher BMI and incident AF gained further support from a genetic mendelian randomization study, which observed that a BMI GRS that included 39 SNPs was associated with a higher risk of AF.[86]

Smoking

- A meta-analysis of 29 studies from 22 publications revealed that smoking was associated with an increased risk of AF. Compared to never-smokers, the RR of current smoking was 1.32 (95% CI, 1.12–1.56), former smoking was 1.09 (95% CI, 1.00–1.18), and ever smoking was 1.21 (95% CI, 1.12–1.31). There appeared to be a dose-response relationship such that the RR per 10 cigarettes per day was 1.14 (95% CI 1.10–1.20), and the RR per 10 pack-years was 1.16 (95% CI, 1.09–1.25).[87]

DM and HbA_{1c}

- In a meta-analysis restricted to prospective studies, HbA_{1c} was associated with an increased risk of AF when analyzed as a continuous (RR, 1.11 [95% CI, 1.06–1.16]) or categorical (RR, 1.09 [95% CI, 1.00–1.18]) variable.[88]

- In a meta-analysis of observational studies (excluding a large outlier study) the RR of incident AF was 1.28 (31 cohort studies [95% CI, 1.22–1.35]) for DM and 1.20 (4 studies [95% CI, 1.03–1.39]) for prediabetes.[89]
- A machine learning meta-analysis reported similar risks of incident AF in individuals with type 1 and type 2 DM. However, compared with males with DM (RR, 1.11 [95% CI, 1.01–1.22]), females with DM appeared to have a higher risk (RR, 1.38 [95% CI, 1.19–1.60]) of incident AF.[90]

Activity and Exercise

- A multiracial longitudinal study from Detroit, MI, reported a dose-response relation between objectively assessed exercise capacity and lower risk of new-onset AF.[91] In unadjusted analyses, the incidence rates of AF over 5 years were 3.7%, 5.0%, 9.5%, and 18.8% for >11, 10 to 11, 6 to 9, and <6 METs, respectively. Every 1-higher peak MET was associated with an adjusted 7% lower risk of AF (HR, 0.93 [95% CI, 0.92–0.94]). The protective association of fitness was observed in all subgroups examined but was particularly beneficial in obese individuals.
- Whereas regular PA is associated with lower risk of AF, a meta-analysis of 9 studies supports that athletes have a higher risk of AF than the general population (OR, 2.34 [95% CI, 1.04–5.28]). However, the investigators reported substantial heterogeneity in the data, with the highest risks observed among males and individuals <60 years of age.[92]

Miscellaneous Risk Factors

- Other consistently reported risk factors for AF include clinical and subclinical hyperthyroidism,[93] CKD,[94,95] and moderate[96] or heavy alcohol consumption.[97]
- In a meta-analysis of 8 studies, the sleep apnea-hypopnea syndrome was associated with an increased risk of AF after adjustment for confounders (RR, 1.40 [95% CI, 1.12–1.74]; $P<0.001$).[98] A meta-analysis of 3 studies of sleep quality also reported an association between insomnia and increased odds of AF (OR, 1.30 [95% CI, 1.26–1.35]) of AF.[99]
- Air pollution:
  - Investigators from the Danish Diet, Cancer, and Health cohort reported that individuals with higher exposure to NO_2, a traffic-related air pollutant, had higher risk of AF (adjusted IRR, 1.08 [95% CI, 1.01–1.14] per 10 μg/m^3 higher 10-year time-weighted mean exposure to NO_2).[100]
  - Using the Korean National Health Insurance Service investigators similarly reported that per 10 μg/m^3 increments, both fine particles ($PM_{2.5}$, or those ≤2.5 μm in diameter; HR, 1.179 [95% CI, 1.176–1.183]) and coarse dust particles (PM_{10} , or those 2.5–10 μm in diameter; HR, 1.034 [95% CI, 1.033–1.036]) were associated with incident AF.[101]
- There is increasing research on the relation between social determinants of health and AF risk. In a study from REGARDS, involuntary unemployment was associated with increased risk of prevalent (OR, 1.60 [95% CI, 1.24–2.07]) and incident (OR, 1.54 [95% CI, 1.04–2.37]) AF.[102]
- AF frequently occurs secondary to other comorbidities.
  - In the FHS, 31% of AF was diagnosed in the context of a secondary, reversible condition. The most common triggers of AF were cardiothoracic surgery (30%), infection (23%), and AMI (18%). Paroxysmal AF in the context of a secondary precipitant frequently recurred over follow-up.[103]
  - Sepsis is associated with an increased risk of AF. In a Medicare sample, 25.5% of patients with sepsis had AF; 18.3% of AF was preexisting, and 7.2% was newly diagnosed.[104] AF occurring in the context of sepsis is associated with an increased risk of stroke and death.[105]
  - A meta-analysis reported that new-onset AF has been observed in 10.9% of patients undergoing noncardiac general surgery.[106]
  - AF also occurs after CABG, with a risk-adjusted incidence of 33.1%, which has not varied over time.[107]
- Prevalence of AF is particularly elevated in adults with congenital HD.[108]

Risk Prediction of AF

- Life's Simple 7:
  - In the biracial REGARDS study, better CVH, as classified by Life's Simple 7, predicted decreased risk of AF similarly between sexes and in blacks and whites. Individuals with optimal CVH (score 10–14 points) had an adjusted 32% lower risk of AF (OR, 0.68 [95% CI, 0.47–0.99]).[109]
  - The ARIC study, which includes white and black participants, also observed that patients with average (HR, 0.59 [95% CI, 0.51–0.67]) and optimal (HR, 0.38 [95% CI, 0.32–0.44]) CVH had a lower risk of incident AF. For every 1-point higher Life's Simple 7 score, the risk of AF was 12% lower (HR, 0.88 [95% CI, 0.86–0.89]).[110]
- ARIC,[111] the FHS,[112] and the WHS[113] have developed risk prediction models to predict new-onset

AF. Predictors of increased risk of new-onset AF include advancing age, European ancestry, body size (greater height and BMI), electrocardiographic features (LVH, left atrial enlargement), DM, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD).

- More recently, the ARIC, CHS, and FHS investigators developed and validated a risk prediction model for AF in blacks and whites, which was replicated in 2 European cohorts.[114] The CHARGE-AF model has been validated in US multiethnic cohorts including Hispanics,[115] in MESA,[116] in a UK cohort (EPIC Norfolk),[117] and in a post-CABG cohort.[118]

Borderline Risk Factors

- Data from the ARIC study indicated that having at least 1 elevated risk factor explained 50% and having at least 1 borderline risk factor explained 6.5% of incident AF cases. The estimated overall incidence rate per 1000 person-years at a mean of 54.2 years of age was 2.19 for those with optimal risk, 3.68 for those with borderline risk, and 6.59 for those with elevated risk factors.[83]

Subclinical Atrial Tachyarrhythmias, Unrecognized AF, Screening for AF

Device-Detected AF

- Cardiac implantable electronic devices (eg, pacemakers and defibrillators) have increased clinician awareness of the frequency of subclinical AF and atrial high-rate episodes in people without a documented history of AF.
- In a meta-analysis of 28 studies including patients with pacemakers or defibrillators followed up for a mean of 22 months, new-onset device-detected atrial tachyarrhythmias were observed in 23% of patients. In 9 studies, device-detected atrial tachyarrhythmias were associated with a 2.88 (95% CI, 1.79–4.64; $P<0.001$) RR of thromboembolism, which was higher with longer duration (≥5 minutes RR, 3.86 versus <1 minute RR, 1.77).[119]
- Another meta-analysis reported that high atrial rate episodes detected by cardiac implantable electronic devices were associated with higher risk of clinical AF (n=2 studies, including 2892 participants; OR, 5.7 [95% CI, 4.0–8.0]; $P< 0.001$) and a higher risk of stroke (n=7 studies, including 17 247 participants; OR, 2.4 [95% CI, 1.8–3.3]; $P< 0.001$). The annual stroke rate was 1.89 with versus 0.93/100 person-years without high atrial rate episodes.[120]
- The temporal association of AF and stroke risk was evaluated in a case-crossover analysis among 9850 patients with cardiac implantable electronic devices enrolled in the Veterans Health Administration healthcare system. The OR for an acute ischemic stroke was the highest within a 5-day period after a qualifying AF episode, which was defined as at least 5.5 hours of AF on a given day. This estimate reduced as the period after the AF occurrence extended beyond 30 days.[121]

Community Screening

- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercials claims data, investigators have estimated that in 2009, ≈0.7 million (13.1%) of the ≈5.3 million AF cases in the United States were undiagnosed. Of the undiagnosed AF cases, investigators estimated 535 400 (95% CI, 331 900–804 400; 1.3%) were in individuals ≥65 years of age, and 163 500 (95% CI, 17 700–400 000; 0.09%) were in individuals 18 to 64 years of age.[122]
- The incidence of detecting previously undiagnosed AF by screening depends on the underlying risk of AF in the population studied, the intensity and duration of screening, and the method used to detect AF.[123]
- Methods vary in their sensitivity and specificity in the detection of undiagnosed AF, increasing from palpation, to devices such as handheld single-lead ECGs, modified BP devices, and plethysmographs.[123]
- There has been increasing interest in the use of smart phone technology to aid in community screening.[124,125]
- In a community-based study in Sweden (STROKESTOP), half of the population 75 to 76 years of age were invited to a stepwise screening program for AF, and 7173 participated in the screening, of whom 218 had newly diagnosed AF (3.0% [95% CI, 2.7%–3.5%]) and an additional 666 (9.3% [95% CI, 8.6%–10.0%]) had previously diagnosed AF. Of the 218 newly diagnosed AF cases, only 37 were diagnosed by initial screening electrocardiography, whereas intermittent monitoring detected 4 times as many cases. Of those individuals with newly diagnosed AF, 93% initiated treatment with oral anticoagulant drugs.[126]
- There have been several systematic reviews regarding the effectiveness of screening to detect unknown AF.
  - Lowres et al[127] identified 30 separate studies that included outpatient clinics or community screening. In individuals without a prior diagnosis of AF, they observed that 1.0% (95% CI, 0.89%–1.04%) of those screened had AF (14 studies, N=67 772), whereas among those individuals ≥65 years of age, 1.4% (95% CI, 1.2%–1.6%; 8 studies, N=18 189) had AF.
  - Another systematic review by Moran et al[128] observed that in individuals >65 years of

age, systematic screening (OR, 1.57 [95% CI, 1.08–2.26]) and opportunistic screening (OR, 1.58 [95% CI, 1.10–2.29]) were associated with enhanced detection of AF. The number needed to screen by either method was ≈170 individuals.
  - A systematic review by the US Preventive Services Task Force of asymptomatic adults at least 65 years of age included 17 studies (135 300 individuals). Compared with no screening, systematic screening with ECG detected more new cases of AF (over 1 year, absolute increase from 0.6% [95% CI, 0.1%-0.9%] to 2.8% [95% CI, 0.9%-4.7%]). However, the systematic ECGs did not detect more cases than pulse palpation. Furthermore, none of the studies compared systematic screening versus usual care, and none examined health outcomes.[129]
- At present, the detection of AF, even in an asymptomatic stage, is the basis for risk stratification for stroke and appropriate decision making on the need for anticoagulant drugs. Ongoing trials are evaluating the risks and benefits of anticoagulation among patients at high risk for stroke but without a prior history of AF. The findings from these studies will help to determine optimal strategies for subclinical AF screening and treatment.[123] To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications.

Family History and Genetics

- Although unusual, early-onset lone AF has long been recognized to cluster in families.[12,130] In the past decade, the heritability of AF in the community has been appreciated.
- In studies from the FHS:
  - Adjusted for coexistent risk factors, having at least 1 parent with AF was associated with a 1.85-fold increased risk of AF in the adult offspring (multivariable-adjusted 95% CI, 1.12–3.06; *P*=0.02).[131]
  - A history of a first-degree relative with AF also was associated with an increased risk of AF (HR, 1.40 [95% CI, 1.13–1.74]). The risk was greater if the first-degree relative's age of onset was ≤65 years (HR, 2.01 [95% CI, 1.49–2.71]) and with each additional affected first-degree relative (HR, 1.24 [95% CI, 1.05–1.46]).[132] Similar findings were reported from Sweden.[133]
- A prospectively enrolled University of Illinois at Chicago AF Registry revealed that individuals with early-onset AF in the absence of structural HD had a 3-fold adjusted odds of having a first-degree relative with AF (adjusted OR, 3.02 [95% CI, 1.82–4.95]; *P*<.001) compared with individuals with AF without early-onset AF. Higher odds of having a proband with AF in the setting of early-onset AF were observed in individuals of African (OR, 2.69), Hispanic (OR, 9.25), and European (OR, 2.51) descent.[134]
- A Taiwanese population-based study reported that a history of a first-degree relative with AF was associated with a 1.92-fold (95% CI, 1.84–1.99) increased risk of newly diagnosed AF. They estimated that 19.9% of the increased risk was attributable to genetic (heritability) factors, with the remaining risk related to shared (3.5%) and nonshared (76.5%) environmental factors.[135]
- A study from the UK Biobank estimated that the heritability of AF was 22.1% (95% CI, 15.6%–28.5%). The heritability was similar by sex and in older (>65 years) versus younger (≤65 years) people. Most of the variation was explained by common (minor allele frequency ≥5%) genetic variation.[136]
- Racial variation in AF incidence is complex and not fully understood. One study of blacks and whites from CHS and ARIC suggested that genetic markers of European ancestry were associated with an increased risk of incident AF.[137]
- A GWAS that included >65 000 patients with AF reported 97 AF-associated loci, 67 of which were novel in combined-ancestry analyses.[138] Another recent GWAS of >1 000 000 individuals identified 111 independent genes associated with AF, many of which are near deleterious mutations that cause more serious heart defects or genes important for striated muscle function and integrity.[139]
- Whole exome/genome sequencing studies have identified rare mutations in additional genes, including *MYL4*.[140]
- Additional rare mutations identified from other studies include *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel; loss-of-function mutations in these genes have been shown to be associated with AF.[141,142] Recently, loss-of-function variants in the titin gene have been associated with early-onset AF.[143,144]
- Investigators in the FHS examined the lifetime risk of AF at 55 years of age using both clinical and genetic risk factors. They derived polygenic risk scores of 1000 variants (many were subthreshold hits) associated with AF in the UK Biobank. They divided participants into tertiles of clinical and genetic risk and reported that individuals within the lowest tertile of clinical and of polygenic risk had a lifetime risk of AF of 22.3% (95% CI, 15.4%–29.1%), whereas those in the highest

tertile of clinical and polygenic risk had a lifetime risk of 48.2% (95% CI, 41.3%–55.1%).[74]
- Some studies suggest that genetic markers of AF could improve risk prediction for AF over models that include clinical factors.[113]
- GRS could also identify patients at higher risk of cardioembolic stroke[145]; however, the utility of clinical genetic testing for AF-related genetic variants is currently unclear.
- SNPs associated with increased risk of AF are also associated with increased risk of AF recurrence after catheter ablation[146] and after CABG.[147]

Prevention: Observational Data

Primary Prevention of AF: Observational Data

- An observational prospective Swedish study revealed that individuals having bariatric surgery had a 29% lower risk (HR, 0.71 [95% CI, 0.60–0.83]; *P*<0.001) of developing AF in 19 years of median follow-up than matched referents.[148]

Secondary Prevention of AF: Observational Data

- There are increasingly more data supporting the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.
  - In individuals referred for catheter ablation, those who agreed to aggressive risk factor modification had lower symptom burden in follow-up and higher adjusted AF-free survival (HR, 4.8 [95% CI, 2.0–11.4]; *P*<0.001).[149]
  - The same Australian investigators reported that overweight and obese individuals with symptomatic AF who opted to participate in weight loss and aggressive risk factor management interventions had fewer hospitalizations, cardioversions, and ablation procedures than their counterparts who declined enrollment. The risk factor management group was associated with a predicted 10-year cost savings of $12 094 per patient.[150]
  - In adjusted analyses, overweight and obese individuals with paroxysmal or persistent AF who achieved at least 10% weight loss were 6-fold more likely to be AF free (86.2% AF free; HR, 5.9 [95% CI, 3.4–10.3]; *P*<0.001) than those with <3% weight loss (39.6% AF free). In addition, individuals losing at least 10% weight reported fewer symptoms.[151]
  - The same Australian group also reported that among consecutive overweight and obese patients with AF who agreed to participate in an exercise program, those who achieved less improvement in cardiorespiratory fitness (<2 METs gained) had lower AF-free survival (40%; HR, 3.9 [95% CI, 2.1–7.3]; *P*<0.001) than those with greater improvement in fitness (≥2 METs gained, 89% AF free).[152]
- Treatment of OSA has been noted to decrease risk of progression to permanent AF.[153] In a meta-analysis, CPAP was reported to be associated with a reduced risk of recurrent AF after ablation.[154] However, there is a lack of robust randomized data supporting the role of CPAP in the primary and secondary prevention of AF in individuals with sleep-disordered breathing.
- In a national outpatient registry of AF patients (ORBIT-AF), 94% had indications for guideline-based primary or secondary prevention in addition to oral anticoagulant drugs; however, only 47% received all guideline-indicated therapies, consistent with an underutilization of evidence-based preventive therapies for comorbid conditions in individuals with AF.[155]
- Predictors of not receiving all guideline-indicated therapies included frailty, comorbid illness, geographic region, and antiarrhythmic drug therapy. Factors most strongly associated with the 17% warfarin discontinuation rate in the first year prescribed included hospitalization because of bleeding (OR, 10.9 [95% CI, 7.9–15.0]), prior catheter ablation (OR, 1.8 [95% CI, 1.4–2.4]), noncardiovascular/nonbleeding hospitalization (OR, 1.8 [95% CI, 1.4–2.2]), cardiovascular hospitalization (OR, 1.6 [95% CI, 1.3–2.0]), and permanent AF (OR, 0.25 [95% CI, 0.17–0.36]).[156]
- A study of 2 national Canadian primary care audits similarly observed that 84.3% of individuals enrolled were eligible for at least 1 cardiovascular evidence-based therapy. The proportions receiving evidence-based therapy varied by diagnosis, at 40.8% of those with CAD, 48.9% of those with DM, 40.2% of those with HF, and 96.7% of those with hypertension.[157]

Prevention: Randomized Data

Primary Prevention of AF: Randomized Data

- Intensive glycemic control was not found to prevent incident AF in the ACCORD study.[158]
- In the Look AHEAD randomized trial of individuals with type 2 DM who were overweight to obese, an intensive lifestyle intervention associated with modest weight loss did not significantly affect the rate of incident AF (6.1 versus 6.7 cases per 1000 person-years of follow-up; multivariable HR, 0.99 [95% CI, 0.77–1.28]); however, AF was not prespecified as a primary or secondary outcome.[159]
- Meta-analyses have suggested that BP lowering might be useful in prevention of AF in trials of hypertension, after MI, in HF, and after cardioversion.[160,161] However, the studies were primarily

secondary or post hoc analyses, the intervention duration was modest, and the results were fairly heterogeneous.

- Recently, in an analysis of the EMPHASIS-HF trial, in one of many secondary outcomes, eplerenone was nominally observed to reduce the incidence of new-onset AF. However, the number of AF events was modest.[162]
- A post hoc analysis of the PREDIMED randomized primary prevention study suggested a significant reduction in incident AF with the Mediterranean diet that included extra-virgin olive oil (HR, 0.62 [95% CI, 0.45–0.85]).[163]
- Although heterogeneous in their findings, modest-sized short-term studies suggested that the use of statins might prevent AF; however, larger longer-term studies do not provide support for the concept that statins are effective in AF prevention.[164]

Secondary Prevention of AF: Randomized Data

- Randomized trials of overweight or obese patients referred to an Adelaide, Australia, arrhythmia clinic for management of symptomatic paroxysmal or persistent AF demonstrated that individuals randomized to a weight loss intervention reported lower symptom burden.[165]
- The RACE 3 study randomized individuals with early persistent AF and mild to moderate HF to conventional therapy or targeted therapy, which comprised mineralocorticoid receptor antagonists, statins, ACE inhibitors or angiotensin receptor blockers, and cardiac rehabilitation (counseling, PA, dietary counseling). At 1 year, individuals in the intervention group had higher prevalence of sinus rhythm (75%) than those in the conventional treatment group (63%; OR, 1.77 [95% CI, 1.02–3.05]; *P*=0.04).[166]

Awareness

- In REGARDS, a US national biracial study, compared with whites, blacks had approximately one-third the likelihood (OR, 0.32 [95% CI, 0.20–0.52]) of being aware that they had AF.[167] The REGARDS investigators also reported that compared with individuals aware of their diagnosis, individuals who were unaware of their AF had a 94% higher risk of mortality in follow-up.[168]
- A study from Kaiser Permanente in California examined the relation between AF diagnosis (2006–2009) and self-report questionnaire data (2010). Of the >12 000 individuals with diagnosed AF, 14.5% were unaware of their diagnosis and 20.4% had inadequate health literacy. In adjusted analyses, low health literacy was associated with a lack of awareness of their AF diagnosis (literacy prevalence ratio, 0.96 [95% CI, 0.94–0.98]).[169]

Treatment and Control

Anticoagulation Undertreatment

- Studies have demonstrated underutilization of oral anticoagulation therapy. In a meta-analysis, males and individuals with prior stroke were more likely to receive warfarin, whereas factors associated with lower use included alcohol and substance use disorder, noncompliance, warfarin contraindications, dementia, falls, both gastrointestinal and intracranial hemorrhage, renal impairment, and advancing age.[170] The underutilization of anticoagulation in AF has been demonstrated to be a global problem.[171]
- The GWTG–Stroke program conducted a retrospective analysis consisting of 1622 hospitals and 94 474 patients with acute ischemic stroke in the setting of known AF from 2012 to 2015. In that analysis, 79 008 patients (83.6%) were not receiving therapeutic anticoagulation: 13.5% had a subtherapeutic international normalized ratio, 39.9% were receiving antiplatelet treatment only, and 30.3% were not receiving any antithrombotic therapy. In adjusted analyses, versus patients receiving no antithrombotic medications, patients receiving antecedent therapeutic warfarin, non–vitamin K antagonist oral anticoagulant drugs, or antiplatelet therapy had lower odds of moderate or severe stroke (adjusted OR, 0.56 [95% CI, 0.51–0.60], 0.65 [95% CI, 0.61–0.71], and 0.88 [95% CI, 0.84–0.92], respectively) and lower in-hospital mortality.[172]
- In the NCDR PINNACLE registry of outpatients with AF:
  - Less than half of high-risk patients, defined as those with a CHA_2DS_2-VASc score ≥4, were receiving an oral anticoagulant prescription.[173]
  - Between 2008 and 2014, in individuals with a CHA_2DS_2-VASc score >1, direct anticoagulant use increased from 0% to 24.8%, and use of warfarin decreased from 52.4% to 34.8%. Although over the time period, the prevalence of oral anticoagulation treatment increased from 52.4% to 60.7%, substantive gaps remain.[174]
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulant drugs at all levels of CHA_2DS_2-VASc scores (56.7% versus 61.3%; *P*<0.001).[175]
  - The PINNACLE registry investigators also reported that receipt of warfarin versus a DOAC varied significantly by type of insurance, with military, private, and Medicare insured patients more likely to receive newer anticoagulants than individuals with Medicaid and other insurance.[176]

- The GLORIA-AF Registry reported North American anticoagulation patterns in 3320 patients with AF between 2011 and 2014, observing that factors associated with increased likelihood of receiving indicated oral anticoagulant prescription included nonparoxysmal AF (OR, 2.02), prior stroke/TIA (OR, 2.00), specialist care (OR, 1.50), more concomitant medications (OR, 1.47), commercial insurance (OR, 1.41), and HF (OR, 1.44), whereas factors inversely related were antiplatelet drugs (OR, 0.18), prior falls (OR, 0.41), and prior bleeding (OR, 0.50).[177]

Disparities in Treatment

- In the ORBIT AF II US-based registry study of outpatients with nontransient AF, black individuals were less likely than their white counterparts to receive DOACs if an anticoagulant was prescribed, after adjustment for socioeconomic and clinical factors, (adjusted OR, 0.73 [95% CI, 0.55–0.95]); there were no significant differences in DOAC use for AF between white and Hispanic groups. However, black and Hispanic patients were more likely than their white counterparts to receive inappropriate doses of DOACs.[178]
- Disparities in treatment patterns have also been observed in Sweden. In adjusted analyses, compared with individuals with AF living in middle-income neighborhoods, those living in high-SES neighborhoods were more likely to be prescribed warfarin (males: OR, 1.44 [95% CI, 1.27–1.67]; females: OR, 1.19 [95% CI, 1.05–1.36]).[179]

Role of Coordinated Care

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.[180] The investigators reported that AF integrated care approaches were associated with reduced all-cause mortality (OR, 0.51 [95% CI, 0.32–0.80]; *P*=0.003) and cardiovascular hospitalizations (OR, 0.58 [95% CI, 0.44–0.77]; *P*=0.0002).

Mortality
(See Chart 16-7)
2016 ICD-9 427.3; ICD-10 I48.

In 2017, AF was the underlying cause of death in 26 077 people and was listed on 166 793 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS[181] and CDC Wonder[182]).

- The age-adjusted mortality rate from AF was 6.6 per 100 000 people in 2017 (unpublished NHLBI tabulation using CDC WONDER[182]).
- In adjusted analyses from the FHS, AF was associated with an increased risk of death in both males (OR, 1.5 [95% CI, 1.2–1.8]) and females (OR, 1.9 [95% CI, 1.5–2.2]).[183] Furthermore, there was an interaction with sex, such that AF appeared to diminish the survival advantage typically observed in females.
- Although there was significant between-study heterogeneity (*P*<0.001), a meta-analysis confirmed that the adjusted risk of death was significantly higher in females than in males with AF (RR, 1.12 [95% CI, 1.07–1.17]).[184]
- An observational study of Olmsted County, MN, residents with first diagnosis of AF or atrial flutter between 2000 and 2010 reported a high early mortality compared with individuals of similar age and sex; the standardized mortality ratio was 19.4 (95% CI, 17.3–21.7) in the first 30 days and 4.2 (95% CI, 3.5–5.0) for days 31 to 90. Survival within the first 90 days did not change over time (adjusted HR, 0.96 [95% CI, 0.85–1.31] for 2010 versus 2000).[80]
- Although stroke is the most feared complication of AF, the RE-LY clinical trial reported that stroke accounted for only ≈7.0% of deaths in AF, with SCD (22.25%), progressive HF (15.1%), and noncardiovascular death (35.8%) accounting for the majority of deaths.[185]
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - Individuals with other cardiovascular conditions and procedures, including HCM,[186] MI,[187,188] pre-CABG,[189] post-CABG[187,188,190,191] (both short-term[190] and long-term[190,191]), post–transcatheter aortic valve implantation,[192] PAD,[193] and stroke.[194]
  - Individuals with AF have increased mortality with concomitant HF,[195,196] including HF with preserved EF,[197,198] and HF with reduced EF.[197] In a meta-analysis that examined the timing of AF in relation to HF onset with regard to mortality, the risk of death associated with incident AF was higher (RR, 2.21 [95% CI, 1.96–2.49]) than with prevalent AF (RR, 1.19 [95% CI, 1.03–1.38]; $P_{interaction}$<0.001).[199]
  - AF is also associated with an increased risk of death in other conditions, including DM,[158,200] ESRD,[201] sepsis,[105,202] critically ill patients in the ICU,[203] after primary PCI,[204] and noncardiac surgery.[205]
- In a Medicare unadjusted analysis, blacks and Hispanics had a higher risk of death than their white counterparts with AF; however, after adjustment for comorbidities, blacks (HR, 0.95 [95% CI, 0.93–0.96]; *P*<0.001) and Hispanics (HR, 0.82 [95% CI, 0.80–0.84]; *P*<0.001) had a lower risk of death than whites with AF.[206] In contrast, in the population-based ARIC study, the rate difference for all-cause mortality for individuals with versus without AF per 1000 person-years was 106.0 (95% CI, 86.0–125.9)[200] in blacks, which was

higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for whites.[207]

- In a US-based study, there was substantial variation in mortality with AF in US counties from 1980 to 2014.[208] Investigators estimated there were ≈22 700 (95% UI, 19 300–26 300) deaths attributable to AF in 2014 and 191 500 (95% UI, 168 000–215 300) years of life lost. In an examination of county-level data, the age-standardized AF mortality rates were 5.6 per 100 000 for the 10th percentile and 9.7 per 100 000 for the 90th percentile. The counties with age-standardized death rates greater than the 90th percentile were clustered in Oregon, California, Utah, Idaho, northeastern Montana, areas east of Kansas City, MO, and southwest West Virginia.[208]
- In a study using the NIS for the period 2010 to 2015, adjusted in-hospital mortality in the setting of AF was higher (4.8% vs 4.3%; *P*=0.02) among Medicaid beneficiaries than among patients with private insurance.[209]
- Investigators conducted multivariable cross-sectional analyses of the NIS between 2012 and 2014 and observed that patients admitted to rural hospitals had a 17% higher risk of death than those admitted to urban hospitals (OR, 1.17 [95% CI, 1.04–1.32]).[210]
- In a Swedish study based on 75 primary care centers, an adjusted analysis of patients diagnosed with AF revealed that males living in low SES neighborhoods were 49% (HR, 1.49 [95% CI, 1.13–1.96]) more likely to die than their counterparts living in middle-income neighborhoods. The results were similar in models that additionally adjusted for anticoagulant and statin treatment (HR, 1.39 [95% CI, 1.05–1.83]).[211] In another study from the same group, unmarried and divorced males and males with lower educational levels with AF had higher risk of mortality than their married and better-educated male counterparts.[212]

Complications

- Five years after diagnosis with AF, the cumulative incidence rate of mortality, HF, MI, stroke, and gastrointestinal bleeding was higher in older age groups (80–84, 85–89, and ≥90 years of age) than in younger age groups (67–69, 70–74, and 75–79 years of age; Table 16-1).

Extracranial Systemic Embolic Events

- In a Danish population-based registry of individuals 50 to 89 years of age discharged from the hospital, individuals with new-onset AF had an elevated risk of thromboembolic events to the aorta and renal mesenteric, pelvic, and peripheral arteries. The excess thromboembolic event rate was 3.6 in males and 6.3 in females per 1000 person-years of follow-up. Compared with referents in the Danish population, the RR of diagnosed extracranial embolism was 4.0 (95% CI, 3.5–4.6) in males and 5.7 (95% CI, 5.1–6.3) in females.[213]
- Investigators pooled data from 4 large, contemporary, randomized anticoagulation trials and observed 221 systemic emboli in 91 746 person-years of follow-up. The systemic embolic event rate was 0.24 versus a stroke rate of 1.92 per 100 person-years. Compared with individuals experiencing stroke, patients experiencing systemic emboli were more likely to be females (56% versus 47%; *P*=0.01) but had similar mean age and $CHADS_2$ score as those with stroke. Both stroke (RR, 6.79 [95% CI, 6.22–7.41]) and systemic emboli (RR, 4.33 [95% CI, 3.29–5.70]) were associated with an increased risk of death compared with patients with neither event.[214]

Stroke
(See Chart 16-7)

- A systematic review of prospective studies found wide variability in stroke risk between studies and between AF patients, ranging between 0.5% and 9.3% per year.[215]
- Before the widespread use of anticoagulant drugs, after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke. Although the RR of stroke associated with AF (≈3- to 5-fold increased risk) did not vary substantively with advancing age, the proportion of strokes attributable to AF increased significantly. In the FHS, AF accounted for ≈1.5% of strokes in individuals 50 to 59 years of age and ≈23.5% in those 80 to 89 years of age.[216]
- AF was also an independent risk factor for ischemic stroke severity, recurrence, and mortality.[194] In an observational study, at 5 years, only 39.2% (95% CI, 31.5%–46.8%) of ischemic stroke patients with AF were alive, and 21.5% (95% CI, 14.5%–31.3%) had experienced recurrent stroke.[217]
- In Medicare analyses that were adjusted for comorbidities, blacks (HR, 1.46 [95% CI, 1.38–1.55]; *P*<0.001) and Hispanics (HR, 1.11 [95% CI, 1.03–1.18]; *P*<0.001) had a higher risk of stroke than whites with AF.[206] The increased risk persisted in analyses adjusted for anticoagulant therapy status.[206] Additional analyses from the Medicare registry demonstrated that the addition of black race to the CHA_2DS_2-VASc scoring system significantly improved the prediction of stroke events among newly diagnosed AF patients ≥65 years of age.[218]
- In a University of Pennsylvania AF inception cohort without a history of remote stroke, compared with whites, blacks with AF were more likely to be younger and female and to have more

cardiovascular risk factors. In addition, in adjusted analyses, compared with whites with AF, blacks with new-onset AF were more likely to have an ischemic stroke precede (OR, 1.37 [95% CI, 1.03–1.81]) or follow (HR, 1.67 [95% CI, 1.30–2.14]) the diagnosis of AF. The rate of ischemic stroke per year after AF diagnosis was 1.5% (95% CI, 1.3%–1.8%) in whites and 2.5% (95% CI, 2.1%–2.9%) in blacks.[219]

- A meta-analysis that examined stroke risk by sex and presence of AF reported that AF conferred a multivariable-adjusted 2-fold stroke risk in females compared with males (RR, 1.99 [95% CI, 1.46–2.71]); however, the studies were noted to have significant heterogeneity.[184]

Cognition

- A meta-analysis of 21 studies indicated that AF was associated with increased risk of cognitive impairment in patients with (RR, 2.70 [95% CI, 1.82–4.00]) and without (RR 1.37 [95% CI, 1.08–1.73]) a history of stroke. The risk of dementia was similarly increased (RR, 1.38 [95% CI, 1.22–1.56]).[220]
- In individuals with AF without evidence of cognitive dysfunction or stroke from Olmsted County, MN, the cumulative rate of dementia at 1 and 5 years was 2.7% and 10.5%, respectively.[221]
- In a multicenter study of individuals with diagnosed AF (mean age 73 years) from Switzerland, among 1390 patients without a history of stroke or TIA, clinically silent infarcts were observed in 245 patients (18%) with small noncortical infarcts and 201 (15%) with large noncortical or cortical infarcts based on brain MRIs.[222] Furthermore, in adjusted analyses of all the vascular brain features, large noncortical or cortical infarcts had the strongest association with reduced Montreal Cognitive Assessment (β=–0.26 [95% CI, –0.40 to –0.13]; P<0.001), even when restricted to individuals with clinically silent infarcts.

Physical Disability and Subjective Health

- AF has been associated with physical disability, poor subjective health,[223,224] and diminished quality of life.[225] A recent systematic review suggested that among people with AF, moderate-intensity activity improved exercise capacity and quality of life.[226]

Falls

- In the REGARDS study, AF was significantly associated with an adjusted higher risk of falls (10%) than among those without AF (6.6%; OR, 1.22 [95% CI, 1.04–1.44]). The presence of a history of both AF and falls was associated with a significantly higher risk of mortality (per 1000 person-years: AF plus falls, 51.2; AF and no falls, 34.4; no AF and falls, 29.8; no AF and no falls, 15.6). Compared with those with neither AF nor falls, those with both conditions had an adjusted 2-fold increased risk of death (HR, 2.12 [95% CI, 1.64–2.74]).[227]
- A systematic review and Markov decision analytic modeling report focused on people with AF ≥65 years of age noted that warfarin treatment was associated with 12.9 QALYs per patient with typical risks of stroke and falls versus 10.2 QALYs for those treated with neither warfarin nor aspirin. Of interest, sensitivity analyses of the probability of falls or stroke did not substantively influence the results.[228]
- A Medicare study noted that patients at high risk for falls with a $CHADS_2$ score of at least 2 who had been prescribed warfarin had a 25% lower risk (HR, 0.75 [95% CI, 0.61–0.91]; P=0.004) of a composite cardiovascular outcome (out-of-hospital death or hospitalization for stroke, MI, or hemorrhage) than those who did not receive anticoagulant drugs.[229]

Heart Failure
(See Chart 16-7)

- AF and HF share many antecedent risk factors, and ≈40% of people with either AF or HF will develop the other condition.[196]
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3[196] to 5.8[230] per 100 person-years of follow-up. In Olmsted County, MN, in individuals with AF, per 100 person-years of follow-up, the incidence of HF with preserved EF was 3.3 (95% CI, 3.0–3.7), which was more common than HF with reduced EF (2.1 [95% CI, 1.9–2.4]).[230]
- Among older adults with AF in Medicare, the 5-year event rate was high, with rates of death and HF exceeding those for stroke (Chart 16-7). Higher event rates after new-onset AF were associated with older age and higher mean $CHADS_2$ score.[231]
- Investigators examined the incidence rate of HF with systolic dysfunction versus preserved LVEF (<40% versus >50%, respectively) in a Netherlands community-based cohort study (PREVEND) by AF status. Per 1000 person-years, the incidence rate of systolic HF was 12.75 versus 1.99 for those with versus those without AF, with a multivariable-adjusted HR of AF of 5.79 (95% CI, 2.40–13.98). Corresponding numbers for preserved EF were 4.90 versus 0.85 with and without AF, with a multivariable-adjusted HR of AF of 4.80 (95% CI, 1.30–17.70).[232]
- A meta-analysis of 9 studies reported that individuals with AF have a 5-fold increased risk of HF (RR, 4.62 [95% CI, 3.13–6.83]).[233]

Myocardial Infarction (See Chart 16-7)

- A meta-analysis of 16 cohort studies reported that AF was associated with a 1.54 (95% CI, 1.26–1.85) increased risk of MI in follow-up.[233]
- In the REGARDS study in individuals with AF, the age-adjusted MI incidence rate per 1000 person-years was 12.0 (95% CI, 9.6–14.9) in those with AF compared with 6.0 (95% CI, 5.6–6.6) in those without AF.[234]
- Both REGARDS[234] and the ARIC study[235] observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in both REGARDS[234] and the CHS,[236] a higher risk of MI was observed in blacks than whites. For instance, the CHS observed that individuals with AF who were black had a higher risk of MI (HR, 3.1 [95% CI, 1.7–5.6]) than whites (HR, 1.6 [95% CI, 1.2–2.1]; $P_{interaction}$=0.03).[236]
- In ARIC, AF was associated with an adjusted increased risk of NSTEMI (HR, 1.80 [95% CI, 1.39–2.31]) but not STEMI (HR, 0.49 [95% CI, 0.18–0.34]; *P* for comparison of HR=0.004).[235]

Chronic Kidney Disease

- In a Japanese community-based study, individuals with AF had approximately a doubling in increased risk of developing kidney dysfunction or proteinuria, even in those without baseline DM or hypertension. Per 1000 person-years of follow-up, the incidence of kidney dysfunction was 6.8 in those without and 18.2 in those with AF at baseline.[237]
- In a Kaiser Permanente study of people with CKD, new-onset AF was associated with an adjusted 1.67-fold increased risk of developing ESRD compared with those without AF (74 versus 64 per 1000 person-years of follow-up).[238]

SCD and VF

- In a study that examined data from 2 population-based studies, AF was associated with a doubling in the risk of SCD after accounting for baseline and time-varying confounders. In ARIC, the unadjusted incidence rate per 1000 person-years was 1.30 (95% CI, 1.14–1.47) in those without AF and 2.89 (95% CI, 2.00–4.05) in those with AF; corresponding rates in CHS were 3.82 (95% CI, 3.35–4.35) and 12.00 (95% CI, 9.45–15.25). The multivariable-adjusted HR associated with AF for sudden death was 2.47 (95% CI, 1.95–3.13).[239]
- An increased risk of VF was observed in a community-based case-control study from the Netherlands. Individuals with ECG-documented VF during OHCA were matched with non-VF community control subjects. The prevalence of AF in the 1397 VF cases was 15.4% versus 2.6% in the community referents. Individuals with AF had an overall adjusted 3-fold increased risk of VF (adjusted OR, 3.1 [95% CI, 2.1–4.5]). The association was similar across age and sex categories and was observed in analyses of individuals without comorbidities, without AMI, and not using antiarrhythmic or QT-prolonging drugs.[240]
- In a meta-analysis of 27 studies, AF was associated with a doubling in risk of sudden death (pooled RR, 2.02 [95% CI, 1.77–2.35]; *P*<0.01). When restricted to 7 studies that conducted multivariable analyses, AF remained associated with an increased risk of sudden death (pooled RR, 2.22 [95% CI, 1.59–3.09]; *P*<0.01).[241]

AF Type and Complications

- A meta-analysis of 12 studies reported that compared with paroxysmal AF, nonparoxysmal AF was associated with a multivariable-adjusted increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61]; *P*<0.001) and death (HR, 1.22 [95% CI, 1.09–1.37]; *P*<0.001).[242]
- In the Canadian Registry of AF, 755 patients with paroxysmal AF were followed up for a median of 6.35 years. At 1, 5, and 10 years, 8.6%, 24.3%, and 36.3% had progressed to persistent AF. Within 10 years, >50% of the patients had progressed to persistent AF or had died.[243]

Atrial Flutter Versus AF

- Using a 5% Medicare sample from 2008 to 2014, investigators reported the annual stroke rate to be 2.02% (95% CI, 1.99%–2.05%) in patients with AF and 1.38% (95% CI, 1.22%–1.57%) in patients with atrial flutter. After adjustment for demographics and vascular risk factors, the risk of stroke was significantly lower in patients with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).[244]
- A national Taiwanese study compared the prognosis of 175 420 patients with AF and 6239 patients with atrial flutter. Using propensity scoring, they observed that compared with atrial flutter, individuals with AF had significantly higher incidences of ischemic stroke (1.63-fold), HF hospitalization (1.70-fold), and all-cause mortality (1.08-fold).[245]

Hospitalizations and Ambulatory Care Visits

- According to HCUP data,[246] in 2016, there were 465 000 hospital discharges with AF and atrial flutter as the principal diagnosis; ≈50.4% were males (unpublished NHLBI tabulation).
  - The rate per 100 000 discharges increased with advancing age, from 15.1 in those 18 to 44 years of age, 149.2 in those 45 to 64 years, and 577.5 in those 65 to 84 years, to 1158.6 in individuals ≥85 years of age; however, 53.2% of all hospital discharges

for AF occurred in patients 65 to 84 years of age.

- In 2016, there were 7 042 000 physician office visits and 647 000 ED visits for AF (NAMCS, NHAMCS, unpublished NHLBI tabulation).[247,248]
- Using cross-sectional data (2006–2014) from the HCUP's NEDS, the NIS, and the NVSS, investigators estimated that in 2014, AF listed as a primary diagnosis accounted for ≈599 790 ED visits and 453 060 hospitalizations, with a mean length of stay of 3.5 days. Including AF listed as a comorbid condition, there were ≈4 million (3.6% of total) ED visits and 3.5 million (12.0% of total) hospitalizations.[249]
- On the basis of Medicare and MarketScan databases, annually, people with AF (37.5%) are approximately twice as likely to be hospitalized as age- and sex-matched referents (17.5%).[250]

Cost (See Chart 16-8)

- Investigators examined Medicare and Optum Touchstone databases (2004–2010) to estimate costs attributed to nonvalvular AF versus propensity-matched control subjects in 2014 US dollars[251]:
  - For patients 18 to 64 years of age, average per capita medical spending was $38 861 (95% CI, $35 781–$41 950) versus $28 506 (95% CI, $28 409–$28 603) for matched patients without AF. Corresponding numbers for patients ≥65 years of age were $25 322 for those with AF (95% CI, $25 049–$25 595) versus $21 706 (95% CI, $21 563–$21 849) for matched non-AF patients.
  - The authors estimated that the incremental cost of AF was $10 355 for commercially insured patients and $3616 for Medicare patients.
  - Estimating that the prevalence of diagnosed versus undiagnosed nonvalvular AF, respectively, was 0.83% versus 0.07% for individuals 18 to 64 years of age and 8.8% versus 1.1% for those ≥65 years of age, the investigators estimated that the incremental cost of undiagnosed AF was $3.1 billion (95% CI, $2.7–3.7 billion).
- Investigators examined Medicare and MarketScan databases (2004–2006) to estimate costs attributed to AF in 2008 US dollars (Chart 16-8)[250]:
  - Extrapolating to the US population, it was estimated that the incremental cost of AF was ≈$26 billion, of which $6 billion was attributed to AF, $9.9 billion to other cardiovascular expenses, and $10.1 billion to noncardiovascular expenses.
  - Using cross-sectional data (2006–2014) from the HCUP's NEDS, the NIS, and the NVSS, investigators estimated that in 2014, for AF listed as a primary diagnosis, the mean charge for ED visits was ≈$4000, and the mean cost of hospitalizations was ≈$8819.[249]
- A systematic review that examined costs of ischemic stroke in individuals with AF included 16 studies from 9 countries. In international dollars adjusted to 2015 values, they estimated that stroke-related healthcare costs were $8184, $12 895, and $41 420 for lower middle-, middle-, and high-income economies, respectively.[252]
- Costs of AF have been estimated for many other countries. Investigators estimated that the 3-year societal costs of AF were ≈€20 403 to €26 544 per person and €219 to 295 million for Denmark as a whole.[253]

Global Burden of AF (See Charts 16-9 and 16-10)

- The vast majority of research studies on the epidemiology of AF have been conducted in Europe and North America. Investigators from the GBD project noted that the global prevalence, incidence, mortality, and DALYs associated with AF increased from 1990 to 2010.[254]
- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[255]
  - Total number of global deaths attributable to AF/atrial flutter was ≈300 000 in 2017 (200 000 females and 100 000 males).
  - Globally, 37.6 million individuals had prevalent AF/atrial flutter in 2017 (17.8 million females and 19.8 million males).
  - Age-standardized mortality attributable to AF is highest in Northern Europe and Australasia and lowest in parts of sub-Saharan Africa and Western and Central Asia (Chart 16-9).
  - Age-standardized prevalence of AF is highest in Northern Europe, Central Europe, Australasia, and the United States (Chart 16-10).
- Investigators conducted a prospective registry of >15 000 AF patients presenting to EDs in 47 countries. They observed substantial regional variability in annual AF mortality: South America (17%) and Africa (20%) had double the mortality rate of North America, Western Europe, and Australia (10%; $P<0.001$). HF deaths (30%) exceeded deaths attributable to stroke (8%).[256]

Table 16-1. Cumulative Incidence Rate Over 5 Years After AF Diagnosis, by Age,* United States, Diagnosed 1999 to 2007

Age Group, y	Mortality	HF	MI	Stroke	Gastrointestinal Bleeding
67–69	28.8	11.0	3.3	5.0	4.4
70–74	32.3	12.1	3.6	5.7	4.9
75–79	40.1	13.3	3.9	6.9	5.9
80–84	52.1	15.1	4.3	8.1	6.4
85–89	67.0	15.8	4.4	8.9	6.6
≥90	84.3	13.7	3.6	6.9	5.4

All values are percentages. AF indicates atrial fibrillation; HF, heart failure; and MI, myocardial infarction.
*See Chart 16-7.
Source: Adapted from Piccini et al[231] by permission of the European Society of Cardiology. Copyright © 2013, The Authors.

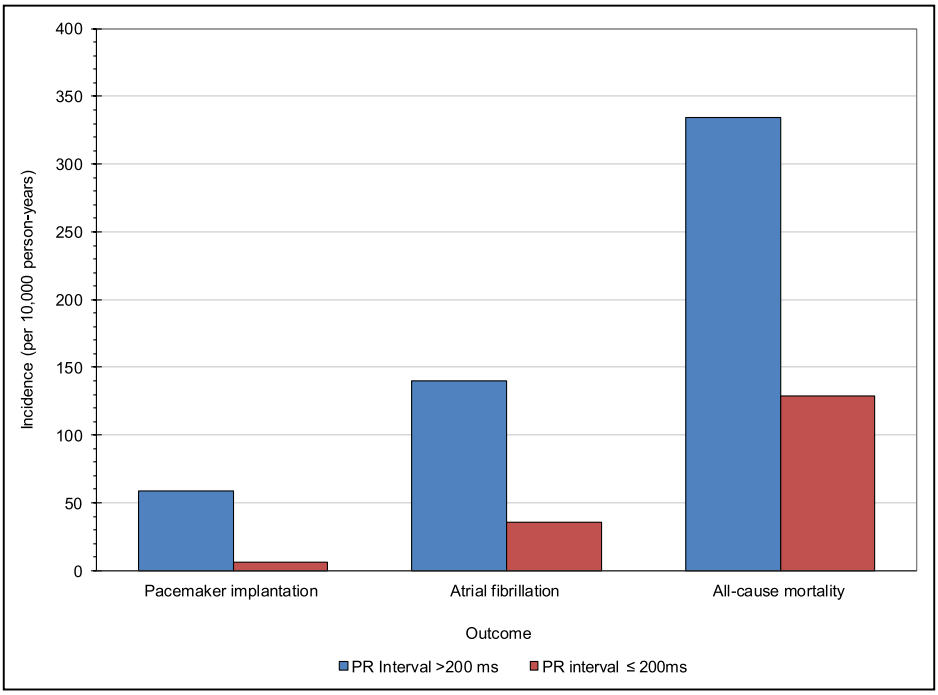

Chart 16-1. Long-term outcomes in individuals with prolonged PR interval (>200 ms; first-degree atrioventricular block) compared with individuals with normal PR interval in the FHS, 1968 to 2007.
FHS indicates Framingham Heart Study.
Source: Data derived from Cheng et al.[15]

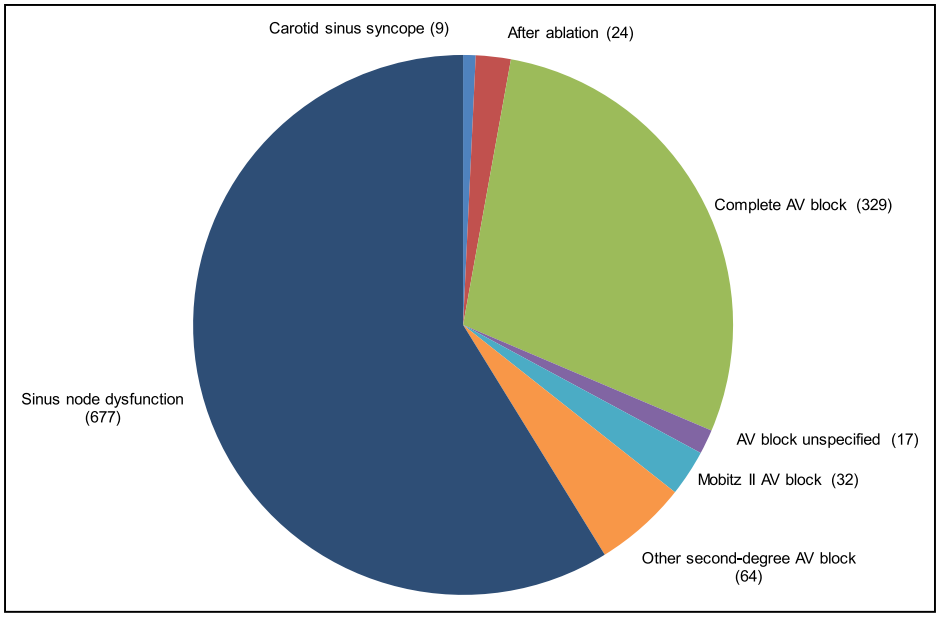

Chart 16-2. Primary indications (in thousands) for pacemaker placement between 1990 and 2002, United States (NHDS, NCHS).
AV indicates atrioventricular, NCHS, National Center for Health Statistics; NHDS, National Hospital Discharge Survey.
Source: Data derived from Birnie et al.[36]

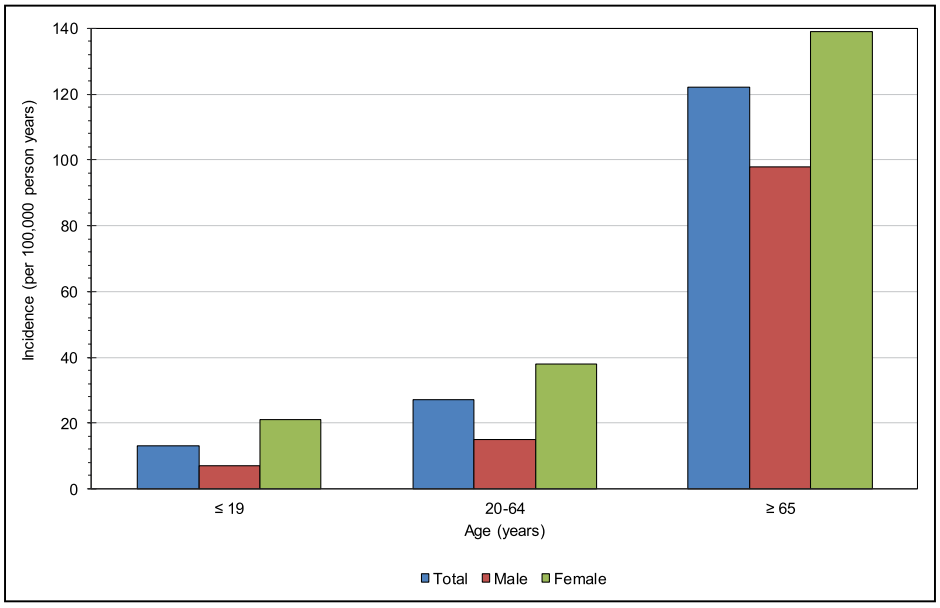

Chart 16-3. Incidence rate of paroxysmal supraventricular tachycardia per 100 000 person-years by age and sex, Marshfield Area, Wisconsin, July 1, 1991, to June 30, 1993.
Source: Data derived from Orejarena et al.[38]

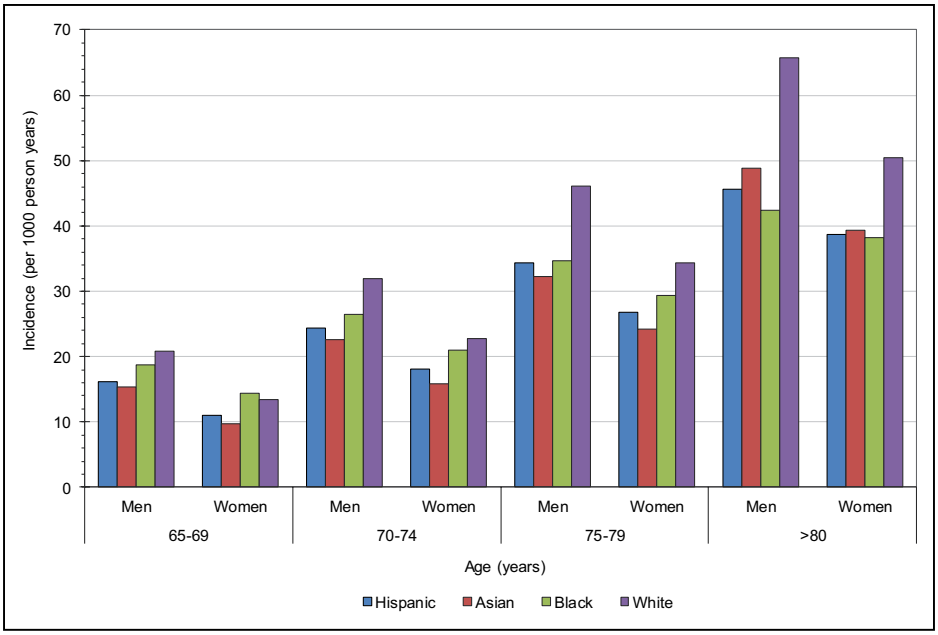

Chart 16-4. Atrial fibrillation incidence by race, 2005 to 2009.
Incidence increased with advancing age among different races and sexes in California.
Source: Data derived from Dewland et al.[71]

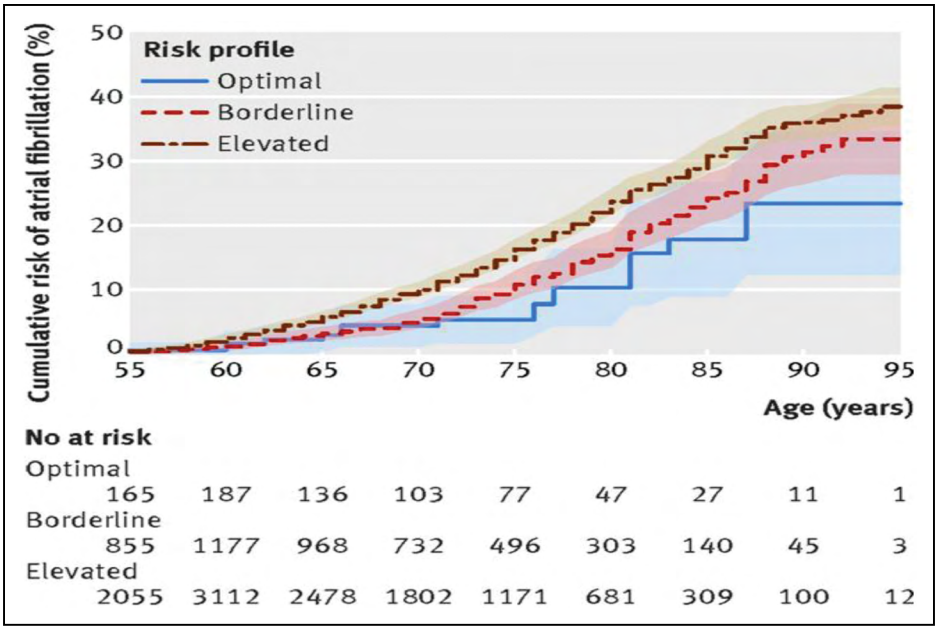

Chart 16-5. Lifetime risk (cumulative incidence at 95 years of age) for atrial fibrillation at different ages (through 94 years of age) by sex in the FHS, 1968 to 2014.
FHS indicates Framingham Heart Study.
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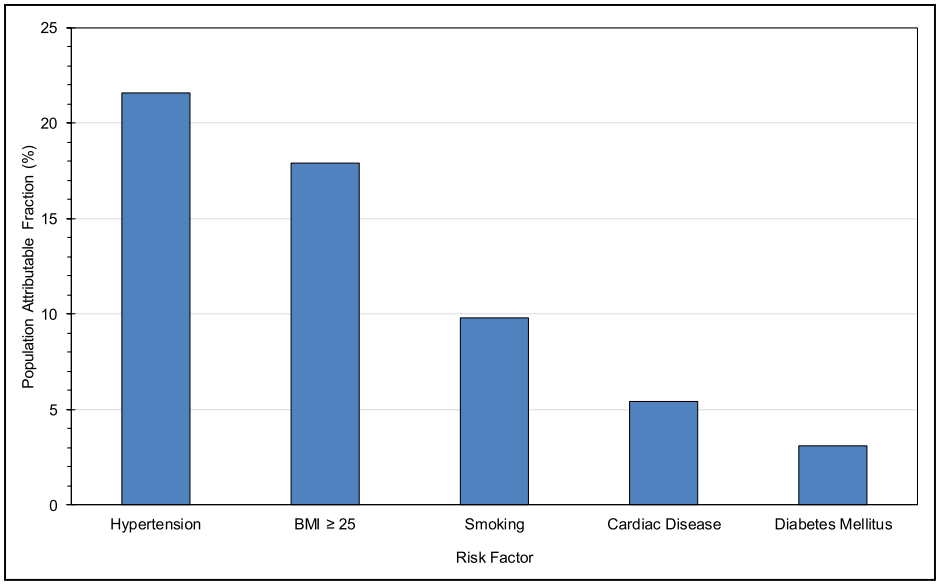

Chart 16-6. Population attributable fraction of major risk factors for atrial fibrillation in the ARIC study, 1987 to 2007.
ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index (in kg/m^2); cardiac disease, patients with history of coronary artery disease or heart failure; and smoking, current smoker.
Source: Data derived from Huxley et al.[83]

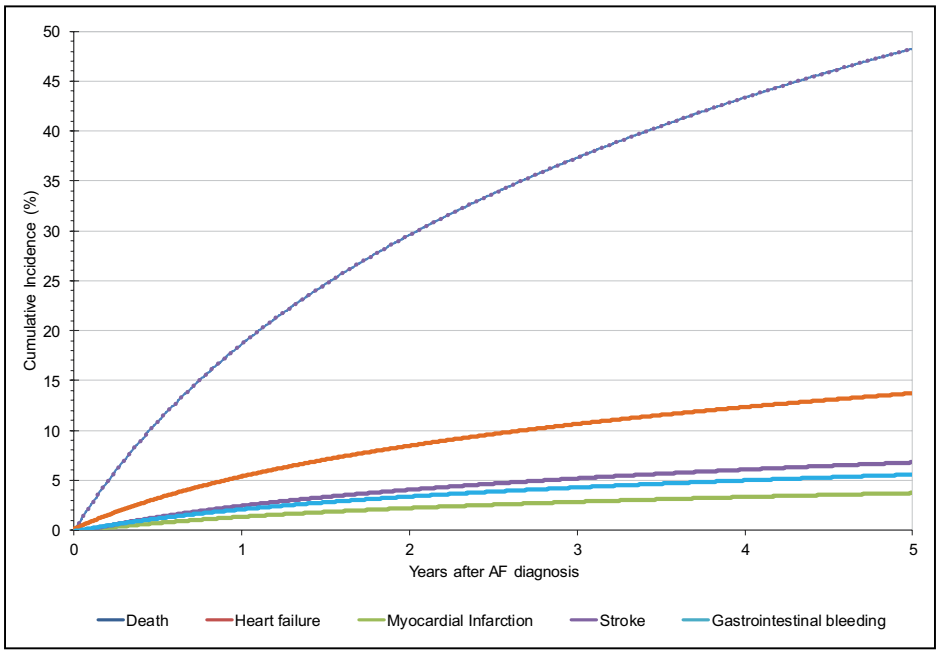

Chart 16-7. Cumulative incidence of events in the 5 years after diagnosis of incident AF in Medicare patients in the United States, diagnosed 1999 to 2007.
AF indicates atrial fibrillation.
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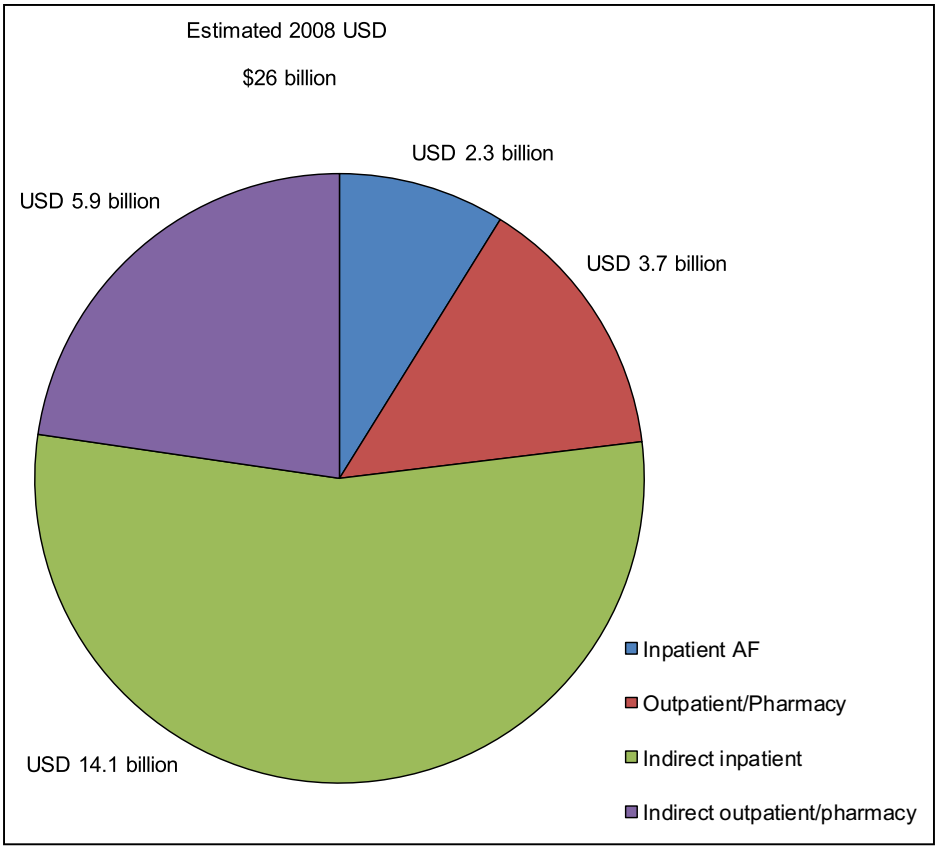

Chart 16-8. AF cost estimates in 2008 USD, in which AF is diagnosed in inpatient and outpatient encounters, United States, 2004 to 2006.
Indirect costs are incremental costs of inpatient and outpatient visits. AF indicates atrial fibrillation; and USD, US dollars.
Adapted from Kim et al.[250] Copyright © 2011, American Heart Association, Inc.

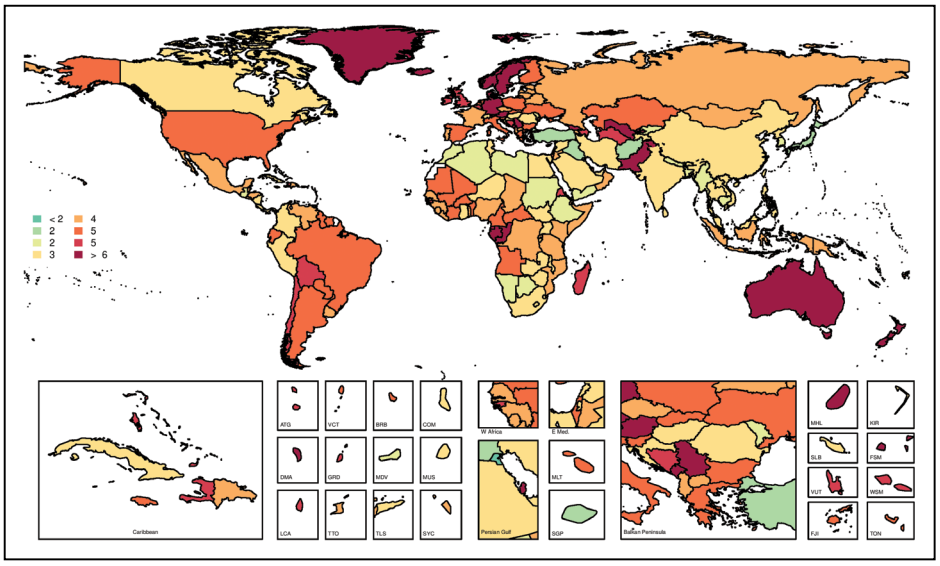

Chart 16-9. Age-standardized global mortality rates of atrial fibrillation (AF) and atrial flutter per 100 000, both sexes, 2017.
Age-standardized mortality attributable to AF is highest in Northern Europe and Australasia and lowest in parts of sub-Saharan Africa and Western and Central Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[255] Printed with permission. Copyright © 2018, University of Washington.

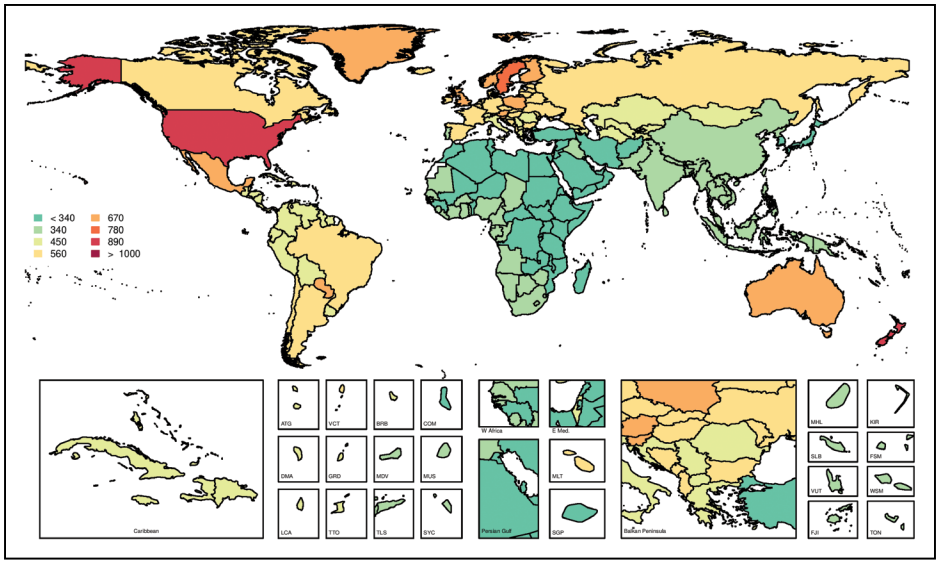

Chart 16-10. Age-standardized global prevalence rates of atrial fibrillation (AF) per 100 000, both sexes, 2017.
Age-standardized prevalence of AF is highest in Northern Europe, Central Europe, Australasia, and the United States.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[255] Printed with permission.

REFERENCES

1. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR; Atherosclerosis Risk in Communities (ARIC) Study Investigators. Electrocardiographic findings in a healthy biracial population. *Am J Cardiol.* 1998;81:453–459. doi: 10.1016/s0002-9149(97)00937-5
2. Walsh JA 3rd, Prineas R, Daviglus ML, Ning H, Liu K, Lewis CE, Sidney S, Schreiner PJ, Iribarren C, Lloyd-Jones DM. Prevalence of electrocardiographic abnormalities in a middle-aged, biracial population: Coronary Artery Risk Development in Young Adults study. *J Electrocardiol.* 2010;43:385.e1–385.e9. doi: 10.1016/j.jelectrocard.2010.02.001
3. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, Reunanen A, Huikuri HV. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J.* 2014;35:123–129. doi: 10.1093/eurheartj/eht176
4. Wolbrette D, Naccarelli G. Bradycardias: sinus nodal dysfunction and atrioventricular conduction disturbances. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:1038–1049.
5. Kojic EM, Hardarson T, Sigfusson N, Sigvaldason H. The prevalence and prognosis of third-degree atrioventricular conduction block: the Reykjavik study. *J Intern Med.* 1999;246:81–86. doi: 10.1046/j.1365-2796.1999.00521.x
6. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of third-degree atrioventricular block in patients with type II diabetes mellitus. *Chest.* 2005;128:2611–2614. doi: 10.1378/chest.128.4.2611
7. Santos JPAD, Ribeiro ALP, Andrade-Junior D, Marcolino MS. Prevalence of electrocardiographic abnormalities in primary care patients according to sex and age group: a retrospective observational study. *Sao Paulo Med J.* 2018;136:20–28. doi: 10.1590/1516-3180.2017.0222290817
8. Solomon MD, Yang J, Sung SH, Livingston ML, Sarlas G, Lenane JC, Go AS. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. *BMC Cardiovasc Disord.* 2016;16:35. doi: 10.1186/s12872-016-0210-x
9. Turner CJ, Wren C. The epidemiology of arrhythmia in infants: a population-based study. *J Paediatr Child Health.* 2013;49:278–281. doi: 10.1111/jpc.12155
10. Bordachar P, Zachary W, Ploux S, Labrousse L, Haissaguerre M, Thambo JB. Pathophysiology, clinical course, and management of congenital complete atrioventricular block. *Heart Rhythm.* 2013;10:760–766. doi: 10.1016/j.hrthm.2012.12.030
11. Soliman EZ, Alonso A, Misialek JR, Jain A, Watson KE, Lloyd-Jones DM, Lima J, Shea S, Burke GL, Heckbert SR. Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Electrocardiol.* 2013;46:702–706. doi: 10.1016/j.jelectrocard.2013.05.006
12. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, et al; on behalf of the American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2013;127:e283–e352. doi: 10.1161/CIR.0b013e318276ce9b
13. Grimm W, Koehler U, Fus E, Hoffmann J, Menz V, Funck R, Peter JH, Maisch B. Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy. *Am J Cardiol.* 2000;86:688–692, A9. doi: 10.1016/s0002-9149(00)01055-9
14. den Hoed M, Eijgelsheim M, Esko T, Brundel BJ, Peal DS, Evans DM, Nolte IM, Segrè AV, Holm H, Handsaker RE, et al; Global BPgen Consortium; CARDIoGRAM Consortium; PR GWAS Consortium; QRS GWAS Consortium; QT-IGC Consortium; CHARGE-AF Consortium. Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. *Nat Genet.* 2013;45:621–631. doi: 10.1038/ng.2610
15. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA.* 2009;301:2571–2577. doi: 10.1001/jama.2009.888
16. Auffret V, Loirat A, Leurent G, Martins RP, Filippi E, Coudert I, Hacot JP, Gilard M, Castellant P, Rialan A, et al. High-degree atrioventricular block complicating ST segment elevation myocardial infarction in the contemporary era. *Heart.* 2016;102:40–49. doi: 10.1136/heartjnl-2015-308260
17. Mymin D, Mathewson FA, Tate RB, Manfreda J. The natural history of primary first-degree atrioventricular heart block. *N Engl J Med.* 1986;315:1183–1187. doi: 10.1056/NEJM198611063151902
18. Barold SS, Ilercil A, Leonelli F, Herweg B. First-degree atrioventricular block: clinical manifestations, indications for pacing, pacemaker management & consequences during cardiac resynchronization. *J Interv Card Electrophysiol.* 2006;17:139–152. doi: 10.1007/s10840-006-9065-x

19. Bernstein AD, Parsonnet V. Survey of cardiac pacing and implanted defibrillator practice patterns in the United States in 1997. *Pacing Clin Electrophysiol.* 2001;24:842–855. doi: 10.1046/j.1460-9592.2001.00842.x
20. Rodriguez RD, Schocken DD. Update on sick sinus syndrome, a cardiac disorder of aging. *Geriatrics.* 1990;45:26–30, 33–36.
21. Brignole M, Menozzi C, Lolli G, Oddone D, Gianfranchi L, Bertulla A. Pacing for carotid sinus syndrome and sick sinus syndrome. *Pacing Clin Electrophysiol.* 1990;13(pt 2):2071–2075. doi: 10.1111/j.1540-8159.1990.tb06944.x
22. Sutton R, Kenny RA. The natural history of sick sinus syndrome. *Pacing Clin Electrophysiol.* 1986;9:1110–1114. doi: 10.1111/j.1540-8159.1986.tb06678.x
23. Baine WB, Yu W, Weis KA. Trends and outcomes in the hospitalization of older Americans for cardiac conduction disorders or arrhythmias, 1991-1998. *J Am Geriatr Soc.* 2001;49:763–770. doi: 10.1046/j.1532-5415.2001.49153.x
24. Jensen PN, Gronroos NN, Chen LY, Folsom AR, deFilippi C, Heckbert SR, Alonso A. Incidence of and risk factors for sick sinus syndrome in the general population. *J Am Coll Cardiol.* 2014;64:531–538. doi: 10.1016/j.jacc.2014.03.056
25. Issa Z, Miller J, Zipes D. *Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease*. Philadelphia, PA: Saunders Elsevier; 2008.
26. Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. *Circulation.* 2007;115:1921–1932. doi: 10.1161/CIRCULATIONAHA.106.616011
27. Rosenqvist M, Obel IW. Atrial pacing and the risk for AV block: is there a time for change in attitude? *Pacing Clin Electrophysiol.* 1989;12(pt 1):97–101. doi: 10.1111/pace.1989.12.p1.97
28. Alt E, Völker R, Wirtzfeld A, Ulm K. Survival and follow-up after pacemaker implantation: a comparison of patients with sick sinus syndrome, complete heart block, and atrial fibrillation. *Pacing Clin Electrophysiol.* 1985;8:849–855. doi: 10.1111/j.1540-8159.1985.tb05904.x
29. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ, et al; Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med.* 2002;346:1854–1862. doi: 10.1056/NEJMoa013040
30. Simon AB, Janz N. Symptomatic bradyarrhythmias in the adult: natural history following ventricular pacemaker implantation. *Pacing Clin Electrophysiol.* 1982;5:372–383. doi: 10.1111/j.1540-8159.1982.tb02245.x
31. Hesselson AB, Parsonnet V, Bernstein AD, Bonavita GJ. Deleterious effects of long-term single-chamber ventricular pacing in patients with sick sinus syndrome: the hidden benefits of dual-chamber pacing. *J Am Coll Cardiol.* 1992;19:1542–1549. doi: 10.1016/0735-1097(92)90616-u
32. Alonso A, Jensen PN, Lopez FL, Chen LY, Psaty BM, Folsom AR, Heckbert SR. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities study and Cardiovascular Health Study. *PLoS One.* 2014;9:e109662. doi: 10.1371/journal.pone.0109662
33. Udo EO, van Hemel NM, Zuithoff NP, Doevendans PA, Moons KG. Prognosis of the bradycardia pacemaker recipient assessed at first implantation: a nationwide cohort study. *Heart.* 2013;99:1573–1578. doi: 10.1136/heartjnl-2013-304445
34. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, et al; on behalf of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) [published correction appears in *Circulation*. 2009;120:e34–e35]. *Circulation.* 2008;117:e350–e408. doi: 10.1161/CIRCUALTIONAHA.108.189742
35. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol.* 2012;60:1540–1545. doi: 10.1016/j.jacc.2012.07.017
36. Birnie D, Williams K, Guo A, Mielniczuk L, Davis D, Lemery R, Green M, Gollob M, Tang A. Reasons for escalating pacemaker implants. *Am J Cardiol.* 2006;98:93–97. doi: 10.1016/j.amjcard.2006.01.069
37. Dharod A, Soliman EZ, Dawood F, Chen H, Shea S, Nazarian S, Bertoni AG; MESA Investigators. Association of asymptomatic bradycardia with incident cardiovascular disease and mortality: the Multi-Ethnic Study of Atherosclerosis (MESA). *JAMA Intern Med.* 2016;176:219–227. doi: 10.1001/jamainternmed.2015.7655
38. Orejarena LA, Vidaillet H Jr, DeStefano F, Nordstrom DL, Vierkant RA, Smith PN, Hayes JJ. Paroxysmal supraventricular tachycardia in the general population. *J Am Coll Cardiol.* 1998;31:150–157. doi: 10.1016/s0735-1097(97)00422-1
39. Murman DH, McDonald AJ, Pelletier AJ, Camargo CA Jr. U.S. emergency department visits for supraventricular tachycardia, 1993-2003. *Acad Emerg Med.* 2007;14:578–581. doi: 10.1197/j.aem.2007.01.013
40. Turakhia MP, Hoang DD, Zimetbaum P, Miller JD, Froelicher VF, Kumar UN, Xu X, Yang F, Heidenreich PA. Diagnostic utility of a novel leadless arrhythmia monitoring device. *Am J Cardiol.* 2013;112:520–524. doi: 10.1016/j.amjcard.2013.04.017
41. Maurer MS, Shefrin EA, Fleg JL. Prevalence and prognostic significance of exercise-induced supraventricular tachycardia in apparently healthy volunteers. *Am J Cardiol.* 1995;75:788–792. doi: 10.1016/s0002-9149(99)80412-3
42. Poutiainen AM, Koistinen MJ, Airaksinen KE, Hartikainen EK, Kettunen RV, Karjalainen JE, Huikuri HV. Prevalence and natural course of ectopic atrial tachycardia. *Eur Heart J.* 1999;20:694–700. doi: 10.1053/euhj.1998.1313
43. Wu EB, Chia HM, Gill JS. Reversible cardiomyopathy after radiofrequency ablation of lateral free-wall pathway-mediated incessant supraventricular tachycardia. *Pacing Clin Electrophysiol.* 2000;23:1308–1310. doi: 10.1111/j.1540-8159.2000.tb00951.x
44. Wang YS, Scheinman MM, Chien WW, Cohen TJ, Lesh MD, Griffin JC. Patients with supraventricular tachycardia presenting with aborted sudden death: incidence, mechanism and long-term follow-up. *J Am Coll Cardiol.* 1991;18:1711–1719. doi: 10.1016/0735-1097(91)90508-7
45. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Chiou MJ, Zhang W, Doherty M, Wen MS, et al. Outcomes associated with paroxysmal supraventricular tachycardia during pregnancy. *Circulation.* 2017;135:616–618. doi: 10.1161/CIRCULATIONAHA.116.025064
46. Kamel H, Elkind MS, Bhave PD, Navi BB, Okin PM, Iadecola C, Devereux RB, Fink ME. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke.* 2013;44:1550–1554. doi: 10.1161/STROKEAHA.113.001118
47. Carnlöf C, Iwarzon M, Jensen-Urstad M, Gadler F, Insulander P. Women with PSVT are often misdiagnosed, referred later than men, and have more symptoms after ablation. *Scand Cardiovasc J.* 2017;51:299–307. doi: 10.1080/14017431.2017.1385837
48. Brembilla-Perrot B, Houriez P, Beurrier D, Claudon O, Burger G, Vançon AC, Mock L. Influence of age on the electrophysiological mechanism of paroxysmal supraventricular tachycardias. *Int J Cardiol.* 2001;78:293–298. doi: 10.1016/s0167-5273(01)00392-8
49. Porter MJ, Morton JB, Denman R, Lin AC, Tierney S, Santucci PA, Cai JJ, Madsen N, Wilber DJ. Influence of age and gender on the mechanism of supraventricular tachycardia. *Heart Rhythm.* 2004;1:393–396. doi: 10.1016/j.hrthm.2004.05.007
50. Anand RG, Rosenthal GL, Van Hare GF, Snyder CS. Is the mechanism of supraventricular tachycardia in pediatrics influenced by age, gender or ethnicity? *Congenit Heart Dis.* 2009;4:464–468. doi: 10.1111/j.1747-0803.2009.00336.x
51. Bradley DJ, Fischbach PS, Law IH, Serwer GA, Dick M 2nd. The clinical course of multifocal atrial tachycardia in infants and children. *J Am Coll Cardiol.* 2001;38:401–408. doi: 10.1016/s0735-1097(01)01390-0
52. McCord J, Borzak S. Multifocal atrial tachycardia. *Chest.* 1998;113:203–209. doi: 10.1378/chest.113.1.203
53. Lazaros G, Chrysohoou C, Oikonomou E, Tsiachris D, Mazaris S, Venieri E, Zisimos K, Zaromytidou M, Kariori M, Kioufis S, et al. The natural history of multifocal atrial rhythms in elderly outpatients: insights from the "Ikaria study." *Ann Noninvasive Electrocardiol.* 2014;19:483–489. doi: 10.1111/anec.12165
54. De Bacquer D, De Backer G, Kornitzer M. Prevalences of ECG findings in large population based samples of men and women. *Heart.* 2000;84:625–633. doi: 10.1136/heart.84.6.625
55. Sano S, Komori S, Amano T, Kohno I, Ishihara T, Sawanobori T, Ijiri H, Tamura K. Prevalence of ventricular preexcitation in Japanese schoolchildren. *Heart.* 1998;79:374–378. doi: 10.1136/hrt.79.4.374
56. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, et al; on behalf of the American College of Cardiology; American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee

for Practice Guidelines. Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation.* 2003;108:1871–1909. doi: 10.1161/01.CIR.0000091380.04100.84

57. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ, Jacobs V, Mallender C, Muhlestein JB, Osborn JS, et al. Long-term natural history of adult Wolff-Parkinson-White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol.* 2015;8:1465–1471. doi: 10.1161/CIRCEP.115.003013
58. Munger TM, Packer DL, Hammill SC, Feldman BJ, Bailey KR, Ballard DJ, Holmes DR Jr, Gersh BJ. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953-1989. *Circulation.* 1993;87:866–873. doi: 10.1161/01.cir.87.3.866
59. Goudevenos JA, Katsouras CS, Graekas G, Argiri O, Giogiakas V, Sideris DA. Ventricular pre-excitation in the general population: a study on the mode of presentation and clinical course. *Heart.* 2000;83:29–34. doi: 10.1136/heart.83.1.29
60. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, Ciaccio C, Giannelli L, Ionescu B, Petretta A, et al. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. *Circulation.* 2014;130:811–819. doi: 10.1161/CIRCULATIONAHA.114.011154
61. Obeyesekere MN, Leong-Sit P, Massel D, Manlucu J, Modi S, Krahn AD, Skanes AC, Yee R, Gula LJ, Klein GJ. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. *Circulation.* 2012;125:2308–2315. doi: 10.1161/CIRCULATIONAHA.111.055350
62. Inoue K, Igarashi H, Fukushige J, Ohno T, Joh K, Hara T. Long-term prospective study on the natural history of Wolff-Parkinson-White syndrome detected during a heart screening program at school. *Acta Paediatr.* 2000;89:542–545. doi: 10.1080/080352500750027817
63. Pappone C, Manguso F, Santinelli R, Vicedomini G, Sala S, Paglino G, Mazzone P, Lang CC, Gulletta S, Augello G, et al. Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome. *N Engl J Med.* 2004;351:1197–1205. doi: 10.1056/NEJMoa040625
64. Cain N, Irving C, Webber S, Beerman L, Arora G. Natural history of Wolff-Parkinson-White syndrome diagnosed in childhood. *Am J Cardiol.* 2013;112:961–965. doi: 10.1016/j.amjcard.2013.05.035
65. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol.* 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
66. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* 2013;34:2746–2751. doi: 10.1093/eurheartj/eht280
67. Shen AY, Contreras R, Sobnosky S, Shah AI, Ichiuji AM, Jorgensen MB, Brar SS, Chen W. Racial/ethnic differences in the prevalence of atrial fibrillation among older adults–a cross-sectional study. *J Natl Med Assoc.* 2010;102:906–913. doi: 10.1016/s0027-9684(15)30709-4
68. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes.* 2012;5:85–93. doi: 10.1161/CIRCOUTCOMES.111.962688
69. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J.* 2018;202:20–26. doi: 10.1016/j.ahj.2018.04.017
70. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC Jr, Heckbert SR. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol.* 2015;25:71–76.e1. doi: 10.1016/j.annepidem.2014.11.024
71. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation.* 2013;128:2470–2477. doi: 10.1161/CIRCULATIONAHA.113.002449
72. Martinez C, Katholing A, Wallenhorst C, Granziera S, Cohen AT, Freedman SB. Increasing incidence of non-valvular atrial fibrillation in the UK from 2001 to 2013. *Heart.* 2015;101:1748–1754. doi: 10.1136/heartjnl-2015-307808
73. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, et al; BiomarCaRE Consortium. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation.* 2017;136:1588–1597. doi: 10.1161/CIRCULATIONAHA.117.028981
74. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, Trinquart L, McManus DD, Staerk L, Lin H, et al. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation.* 2018;137:1027–1038. doi: 10.1161/CIRCULATIONAHA.117.031431
75. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ.* 2018;361:k1453. doi: 10.1136/bmj.k1453
76. Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest.* 2015;147:109–119. doi: 10.1378/chest.14-0321
77. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, Chen SA. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest.* 2018;153:453–466. doi: 10.1016/j.chest.2017.10.001
78. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC Study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol.* 2018;11:e006350. doi: 10.1161/CIRCEP.118.006350
79. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet.* 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8
80. Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, Killian JM, Weston SA, Roger VL. Decade-long trends in atrial fibrillation incidence and survival: a community study. *Am J Med.* 2015;128:260–267.e1. doi: 10.1016/j.amjmed.2014.10.030
81. Bengtson LG, Chen LY, Chamberlain AM, Michos ED, Whitsel EA, Lutsey PL, Duval S, Rosamond WD, Alonso A. Temporal trends in the occurrence and outcomes of atrial fibrillation in patients with acute myocardial infarction (from the Atherosclerosis Risk in Communities Surveillance Study). *Am J Cardiol.* 2014;114:692–697. doi: 10.1016/j.amjcard.2014.05.059
82. Freeman JV, Wang Y, Akar J, Desai N, Krumholz H. National trends in atrial fibrillation hospitalization, readmission, and mortality for Medicare beneficiaries, 1999-2013. *Circulation.* 2017;135:1227–1239. doi: 10.1161/CIRCULATIONAHA.116.022388
83. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2011;123:1501–1508. doi: 10.1161/CIRCULATIONAHA.110.009035
84. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol.* 2018;29:725–732. doi: 10.1111/jce.13458
85. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol.* 2017;32:181–192. doi: 10.1007/s10654-017-0232-4
86. Chatterjee NA, Giulianini F, Geelhoed B, Lunetta KL, Misialek JR, Niemeijer MN, Rienstra M, Rose LM, Smith AV, Arking DE, et al. Genetic obesity and the risk of atrial fibrillation: causal estimates from mendelian randomization. *Circulation.* 2017;135:741–754. doi: 10.1161/CIRCULATIONAHA.116.024921
87. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of atrial fibrillation: a systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol.* 2018;25:1437–1451. doi: 10.1177/2047487318780435
88. Qi W, Zhang N, Korantzopoulos P, Letsas KP, Cheng M, Di F, Tse G, Liu T, Li G. Serum glycated hemoglobin level as a predictor of atrial fibrillation: a systematic review with meta-analysis and meta-regression. *PLoS One.* 2017;12:e0170955. doi: 10.1371/journal.pone.0170955
89. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications.* 2018;32:501–511. doi: 10.1016/j.jdiacomp.2018.02.004

90. Xiong Z, Liu T, Tse G, Gong M, Gladding PA, Smaill BH, Stiles MK, Gillis AM, Zhao J. A machine learning aided systematic review and meta-analysis of the relative risk of atrial fibrillation in patients with diabetes mellitus. *Front Physiol.* 2018;9:835. doi: 10.3389/fphys.2018.00835
91. Qureshi WT, Alirhayim Z, Blaha MJ, Juraschek SP, Keteyian SJ, Brawner CA, Al-Mallah MH. Cardiorespiratory fitness and risk of incident atrial fibrillation: results from the Henry Ford Exercise Testing (FIT) Project. *Circulation.* 2015;131:1827–1834. doi: 10.1161/CIRCULATIONAHA.114.014833
92. Li X, Cui S, Xuan D, Xuan C, Xu D. Atrial fibrillation in athletes and general population: a systematic review and meta-analysis. *Medicine (Baltimore).* 2018;97:e13405. doi: 10.1097/MD.0000000000013405
93. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, Cappola AR, Heckbert SR, Ceresini G, Gussekloo J, et al; Thyroid Studies Collaboration. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation.* 2017;136:2100–2116. doi: 10.1161/CIRCULATIONAHA.117.028753
94. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, Soliman EZ, Astor BC, Coresh J. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2011;123:2946–2953. doi: 10.1161/CIRCULATIONAHA.111.020982
95. Bansal N, Zelnick LR, Alonso A, Benjamin EJ, de Boer IH, Deo R, Katz R, Kestenbaum B, Mathew J, Robinson-Cohen C, et al. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin J Am Soc Nephrol.* 2017;12:1386–1398. doi: 10.2215/CJN.01860217
96. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol.* 2014;64:281–289. doi: 10.1016/j.jacc.2014.03.048
97. Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y, Anasako Y, Nishigaki Y, Yachi Y, Iida KT, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol.* 2011;57:427–436. doi: 10.1016/j.jacc.2010.08.641
98. Zhao E, Chen S, Du Y, Zhang Y. Association between sleep apnea hypopnea syndrome and the risk of atrial fibrillation: a meta-analysis of cohort study. *Biomed Res Int.* 2018;2018:5215868. doi: 10.1155/2018/5215868
99. Chokesuwattanaskul R, Thongprayoon C, Sharma K, Congrete S, Tanawuttiwat T, Cheungpasitporn W. Associations of sleep quality with incident atrial fibrillation: a meta-analysis. *Intern Med J.* 2018;48:964–972. doi: 10.1111/imj.13764
100. Monrad M, Sajadieh A, Christensen JS, Ketzel M, Raaschou-Nielsen O, Tjønneland A, Overvad K, Loft S, Sørensen M. Long-term exposure to traffic-related air pollution and risk of incident atrial fibrillation: a cohort study. *Environ Health Perspect.* 2017;125:422–427. doi: 10.1289/EHP392
101. Kim IS, Yang PS, Lee J, Yu HT, Kim TH, Uhm JS, Pak HN, Lee MH, Joung B. Long-term exposure of fine particulate matter air pollution and incident atrial fibrillation in the general population: a nationwide cohort study. *Int J Cardiol.* 2019;283:178–183. doi: 10.1016/j.ijcard.2018.12.048
102. Soliman EZ, Zhang ZM, Judd S, Howard VJ, Howard G. Comparison of risk of atrial fibrillation among employed versus unemployed (from the REasons for Geographic and Racial Differences in Stroke Study). *Am J Cardiol.* 2017;120:1298–1301. doi: 10.1016/j.amjcard.2017.07.001
103. Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, Rahman F, McManus DD, Tadros TM, Levy D, et al. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. *Circulation.* 2015;131:1648–1655. doi: 10.1161/CIRCULATIONAHA.114.014058
104. Walkey AJ, Greiner MA, Heckbert SR, Jensen PN, Piccini JP, Sinner MF, Curtis LH, Benjamin EJ. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J.* 2013;165:949–955.e3. doi: 10.1016/j.ahj.2013.03.020
105. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest.* 2014;146:1187–1195. doi: 10.1378/chest.14-0003
106. Chebbout R, Heywood EG, Drake TM, Wild JRL, Lee J, Wilson M, Lee MJ. A systematic review of the incidence of and risk factors for postoperative atrial fibrillation following general surgery. *Anaesthesia.* 2018;73:490–498. doi: 10.1111/anae.14118
107. Filardo G, Damiano RJ Jr, Ailawadi G, Thourani VH, Pollock BD, Sass DM, Phan TK, Nguyen H, da Graca B. Epidemiology of new-onset atrial fibrillation following coronary artery bypass graft surgery. *Heart.* 2018;104:985–992. doi: 10.1136/heartjnl-2017-312150
108. Loomba RS, Buelow MW, Aggarwal S, Arora RR, Kovach J, Ginde S. Arrhythmias in adults with congenital heart disease: what are risk factors for specific arrhythmias? *Pacing Clin Electrophysiol.* 2017;40:353–361. doi: 10.1111/pace.12983
109. Garg PK, O'Neal WT, Ogunsua A, Thacker EL, Howard G, Soliman EZ, Cushman M. Usefulness of the American Heart Association's Life Simple 7 to predict the risk of atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol.* 2018;121:199–204. doi: 10.1016/j.amjcard.2017.09.033
110. Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, Alonso A. American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: the ARIC (Atherosclerosis Risk in Communities) Study. *J Am Heart Assoc.* 2018;7:e008424. doi: 10.1161/JAHA.117.008424
111. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol.* 2011;107:85–91. doi: 10.1016/j.amjcard.2010.08.049
112. Schnabel RB, Aspelund T, Li G, Sullivan LM, Suchy-Dicey A, Harris TB, Pencina MJ, D'Agostino RB Sr, Levy D, Kannel WB, et al. Validation of an atrial fibrillation risk algorithm in whites and African Americans. *Arch Intern Med.* 2010;170:1909–1917. doi: 10.1001/archinternmed.2010.434
113. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J.* 2013;34:2243–2251. doi: 10.1093/eurheartj/eht033
114. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc.* 2013;2:e000102. doi: 10.1161/JAHA.112.000102
115. Shulman E, Kargoli F, Aagaard P, Hoch E, Di Biase L, Fisher J, Gross J, Kim S, Krumerman A, Ferrick KJ. Validation of the Framingham Heart Study and CHARGE-AF risk scores for atrial fibrillation in Hispanics, African-Americans, and non-Hispanic whites. *Am J Cardiol.* 2016;117:76–83. doi: 10.1016/j.amjcard.2015.10.009
116. Alonso A, Roetker NS, Soliman EZ, Chen LY, Greenland P, Heckbert SR. Prediction of atrial fibrillation in a racially diverse cohort: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Heart Assoc.* 2016;5:e003077. doi: 10.1161/JAHA.115.003077
117. Pfister R, Brägelmann J, Michels G, Wareham NJ, Luben R, Khaw KT. Performance of the CHARGE-AF risk model for incident atrial fibrillation in the EPIC Norfolk cohort. *Eur J Prev Cardiol.* 2015;22:932–939. doi: 10.1177/2047487314544045
118. Pollock BD, Filardo G, da Graca B, Phan TK, Ailawadi G, Thourani V, Damiano RJ Jr, Edgerton JR. Predicting new-onset post-coronary artery bypass graft atrial fibrillation with existing risk scores. *Ann Thorac Surg.* 2018;105:115–121. doi: 10.1016/j.athoracsur.2017.06.075
119. Belkin MN, Soria CE, Waldo AL, Borleffs CJW, Hayes DL, Tung R, Singh JP, Upadhyay GA. Incidence and clinical significance of new-onset device-detected atrial tachyarrhythmia: a meta-analysis. *Circ Arrhythm Electrophysiol.* 2018;11:e005393. doi: 10.1161/CIRCEP.117.005393
120. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, Khokhar KB, Thiyagarajah A, Middeldorp ME, Nalliah CJ, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J.* 2018;39:1407–1415. doi: 10.1093/eurheartj/ehx731
121. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, Keung EK, Singer DE. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. *Circ Arrhythm Electrophysiol.* 2015;8:1040–1047. doi: 10.1161/CIRCEP.114.003057
122. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, Goldman DP. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One.* 2018;13:e0195088. doi: 10.1371/journal.pone.0195088
123. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, et al; on behalf of the AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation.* 2017;135:1851–1867. doi: 10.1161/CIRCULATIONAHA.116.026693
124. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: the SEARCH-AF study. *Thromb Haemost.* 2014;111:1167–1176. doi: 10.1160/TH14-03-0231

125. McManus DD, Lee J, Maitas O, Esa N, Pidikiti R, Carlucci A, Harrington J, Mick E, Chon KH. A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm.* 2013;10:315–319. doi: 10.1016/j.hrthm.2012.12.001
126. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP Study. *Circulation.* 2015;131:2176–2184. doi: 10.1161/CIRCULATIONAHA.114.014343
127. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation: a systematic review. *Thromb Haemost.* 2013;110:213–222. doi: 10.1160/TH13-02-0165
128. Moran PS, Flattery MJ, Teljeur C, Ryan M, Smith SM. Effectiveness of systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev.* 2013;(4):CD009586. doi: 10.1002/14651858.CD009586.pub2
129. Jonas DE, Kahwati LC, Yun JDY, Middleton JC, Coker-Schwimmer M, Asher GN. Screening for atrial fibrillation with electrocardiography: evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2018;320:485–498. doi: 10.1001/jama.2018.4190
130. Wolff L. Familial auricular fibrillation. *N Engl J Med.* 1943;229:396–398. doi: 10.1056/NEJM194309022291002
131. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA.* 2004;291:2851–2855. doi: 10.1001/jama.291.23.2851
132. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, Villalon ML, Vasan RS, Pencina MJ, Levy D, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA.* 2010;304:2263–2269. doi: 10.1001/jama.2010.1690
133. Zöller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. *J Am Heart Assoc.* 2012;2:e003384. doi: 10.1161/JAHA.112.003384
134. Alzahrani Z, Ornelas-Loredo A, Darbar SD, Farooqui A, Mol D, Chalazan B, Villagrana NE, McCauley M, Lazar S, Wissner E, et al. Association between family history and early-onset atrial fibrillation across racial and ethnic groups. *JAMA Netw Open.* 2018;1:e182497. doi: 10.1001/jamanetworkopen.2018.2497
135. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Huang LH, Zhang W, Doherty M, Wen MS, et al. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a population-based family cohort study. *JAMA Cardiol.* 2017;2:863–870. doi: 10.1001/jamacardio.2017.1855
136. Weng LC, Choi SH, Klarin D, Smith JG, Loh PR, Chaffin M, Roselli C, Hulme OL, Lunetta KL, Dupuis J, et al. Heritability of atrial fibrillation. *Circ Cardiovasc Genet.* 2017;10:e001838. doi: 10.1161/CIRCGENETICS.117.001838
137. Marcus GM, Alonso A, Peralta CA, Lettre G, Vittinghoff E, Lubitz SA, Fox ER, Levitzky YS, Mehra R, Kerr KF, et al; on behalf of the Candidate-Gene Association Resource (CARe) Study. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation.* 2010;122:2009–2015. doi: 10.1161/CIRCULATIONAHA.110.958306
138. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, et al. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet.* 2018;50:1225–1233. doi: 10.1038/s41588-018-0133-9
139. Nielsen JB, Thorolfsdottir RB, Fritsche LG, Zhou W, Skov MW, Graham SE, Herron TJ, McCarthy S, Schmidt EM, Sveinbjornsson G, et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet.* 2018;50:1234–1239. doi: 10.1038/s41588-018-0171-3
140. Gudbjartsson DF, Helgason H, Gudjonsson SA, Zink F, Oddson A, Gylfason A, Besenbacher S, Magnusson G, Halldorsson BV, Hjartarson E, et al. Large-scale whole-genome sequencing of the Icelandic population. *Nat Genet.* 2015;47:435–444. doi: 10.1038/ng.3247
141. Xiong H, Yang Q, Zhang X, Wang P, Chen F, Liu Y, Wang P, Zhao Y, Li S, Huang Y, et al. Significant association of rare variant p.Gly8Ser in cardiac sodium channel beta4-subunit SCN4B with atrial fibrillation. *Ann Hum Genet.* 2019;83:239–248. doi: 10.1111/ahg.12305
142. Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M, Sattiraju S, Ballew JD, Jahangir A, Terzic A. Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet.* 2006;15:2185–2191. doi: 10.1093/hmg/ddl143
143. Ahlberg G, Refsgaard L, Lundegaard PR, Andreasen L, Ranthe MF, Linscheid N, Nielsen JB, Melbye M, Haunsø S, Sajadieh A, et al. Rare truncating variants in the sarcomeric protein titin associate with familial and early-onset atrial fibrillation. *Nat Commun.* 2018;9:4316. doi: 10.1038/s41467-018-06618-y
144. Choi SH, Weng LC, Roselli C, Lin H, Haggerty CM, Shoemaker MB, Barnard J, Arking DE, Chasman DI, Albert CM, et al; DiscovEHR Study and the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Association between titin loss-of-function variants and early-onset atrial fibrillation. *JAMA.* 2018;320:2354–2364. doi: 10.1001/jama.2018.18179
145. Lubitz SA, Parsons OE, Anderson CD, Benjamin EJ, Malik R, Weng LC, Dichgans M, Sudlow CL, Rothwell PM, Rosand J, et al; WTCCC2, International Stroke Genetics Consortium, and AFGen Consortia. Atrial fibrillation genetic risk and ischemic stroke mechanisms. *Stroke.* 2017;48:1451–1456. doi: 10.1161/STROKEAHA.116.016198
146. Rattanawong P, Chenbhanich J, Vutthikraivit W, Chongsathidkiet P. A chromosome 4q25 variant is associated with atrial fibrillation recurrence after catheter ablation: a systematic review and meta-analysis. *J Atr Fibrillation.* 2018;10:1666. doi: 10.4022/jafib.1666
147. Virani SS, Brautbar A, Lee VV, Elayda M, Sami S, Nambi V, Frazier L, Wilson JM, Willerson JT, Boerwinkle E, et al. Usefulness of single nucleotide polymorphism in chromosome 4q25 to predict in-hospital and long-term development of atrial fibrillation and survival in patients undergoing coronary artery bypass grafting. *Am J Cardiol.* 2011;107:1504–1509. doi: 10.1016/j.amjcard.2011.01.026
148. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects. *J Am Coll Cardiol.* 2016;68:2497–2504. doi: 10.1016/j.jacc.2016.09.940
149. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol.* 2014;64:2222–2231. doi: 10.1016/j.jacc.2014.09.028
150. Pathak RK, Evans M, Middeldorp ME, Mahajan R, Mehta AB, Meredith M, Twomey D, Wong CX, Hendriks JML, Abhayaratna WP, et al. Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation: the CENT Study. *JACC Clin Electrophysiol.* 2017;3:436–447. doi: 10.1016/j.jacep.2016.12.015
151. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol.* 2015;65:2159–2169. doi: 10.1016/j.jacc.2015.03.002
152. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: the CARDIO-FIT Study. *J Am Coll Cardiol.* 2015;66:985–996. doi: 10.1016/j.jacc.2015.06.488
153. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J.* 2015;169:647–654.e2. doi: 10.1016/j.ahj.2014.12.024
154. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, Soliman EZ, Al-Mallah MH. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. *Am J Cardiol.* 2015;116:1767–1773. doi: 10.1016/j.amjcard.2015.08.046
155. Hess PL, Kim S, Piccini JP, Allen LA, Ansell JE, Chang P, Freeman JV, Gersh BJ, Kowey PR, Mahaffey KW, et al. Use of evidence-based cardiac prevention therapy among outpatients with atrial fibrillation. *Am J Med.* 2013;126:625–632.e1. doi: 10.1016/j.amjmed.2013.01.037
156. O'Brien EC, Simon DN, Allen LA, Singer DE, Fonarow GC, Kowey PR, Thomas LE, Ezekowitz MD, Mahaffey KW, Chang P, et al. Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J.* 2014;168:487–494. doi: 10.1016/j.ahj.2014.07.002
157. Silberberg A, Tan MK, Yan AT, Angaran P, Dorian P, Bucci C, Gregoire JC, Bell AD, Gladstone DJ, Green MS, et al; FREEDOM AF and CONNECT AF Investigators. Use of evidence-based therapy for cardiovascular risk factors in Canadian outpatients with atrial fibrillation: from the Facilitating Review and Education to Optimize Stroke Prevention in Atrial Fibrillation (FREEDOM AF) and Co-ordinated National Network to Engage Physicians in the Care and Treatment of Patients With Atrial Fibrillation (CONNECT AF). *Am J Cardiol.* 2017;120:582–587. doi: 10.1016/j.amjcard.2017.05.027
158. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, et al. Impact of intensive glycemic

control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol.* 2014;114:1217–1222. doi: 10.1016/j.amjcard.2014.07.045
159. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, Vetter M, Mantzoros CS, Jeffery RW, Soliman EZ; Look AHEAD Research Group. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. *Am Heart J.* 2015;170:770–777.e5. doi: 10.1016/j.ahj.2015.07.026
160. Emdin CA, Callender T, Cao J, Rahimi K. Effect of antihypertensive agents on risk of atrial fibrillation: a meta-analysis of large-scale randomized trials. *Europace.* 2015;17:701–710. doi: 10.1093/europace/euv021
161. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol.* 2005;45:1832–1839. doi: 10.1016/j.jacc.2004.11.070
162. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B; EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol.* 2012;59:1598–1603. doi: 10.1016/j.jacc.2011.11.063
163. Martínez-González MÁ, Toledo E, Arós F, Fiol M, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fernández-Crehuet J, Lapetra J, et al; on behalf of the PREDIMED Investigators. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation.* 2014;130:18–26. doi: 10.1161/CIRCULATIONAHA.113.006921
164. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW; PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. *BMJ.* 2011;342:d1250. doi: 10.1136/bmj.d1250
165. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA.* 2013;310:2050–2060. doi: 10.1001/jama.2013.280521
166. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brügemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, et al; RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J.* 2018;39:2987–2996. doi: 10.1093/eurheartj/ehx739
167. Meschia JF, Merrill P, Soliman EZ, Howard VJ, Barrett KM, Zakai NA, Kleindorfer D, Safford M, Howard G. Racial disparities in awareness and treatment of atrial fibrillation: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke.* 2010;41:581–587. doi: 10.1161/STROKEAHA.109.573907
168. O'Neal WT, Efird JT, Judd SE, McClure LA, Howard VJ, Howard G, Soliman EZ. Impact of awareness and patterns of nonhospitalized atrial fibrillation on the risk of mortality: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Clin Cardiol.* 2016;39:103–110. doi: 10.1002/clc.22501
169. Reading SR, Go AS, Fang MC, Singer DE, Liu IA, Black MH, Udaltsova N, Reynolds K; Anticoagulation and Risk Factors in Atrial Fibrillation–Cardiovascular Research Network (ATRIA-CVRN) Investigators. Health literacy and awareness of atrial fibrillation. *J Am Heart Assoc.* 2017;6:e005128. doi: 10.1161/JAHA.116.005128
170. Baczek VL, Chen WT, Kluger J, Coleman CI. Predictors of warfarin use in atrial fibrillation in the United States: a systematic review and meta-analysis. *BMC Fam Pract.* 2012;13:5. doi: 10.1186/1471-2296-13-5
171. Gamra H, Murin J, Chiang CE, Naditch-Brûlé L, Brette S, Steg PG; RealiseAF Investigators. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. *Arch Cardiovasc Dis.* 2014;107:77–87. doi: 10.1016/j.acvd.2014.01.001
172. Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, Bhatt DL, Smith EE, Olson DM, Maisch L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA.* 2017;317:1057–1067. doi: 10.1001/jama.2017.1371
173. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE Registry. *JAMA Cardiol.* 2016;1:55–62. doi: 10.1001/jamacardio.2015.0374
174. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol.* 2017;69:2475–2484. doi: 10.1016/j.jacc.2017.03.540
175. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, Masoudi FA, Turchin A, Song Y, Doros G, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR) PINNACLE Registry. *J Am Heart Assoc.* 2017;6:e005801. doi: 10.1161/JAHA.117.005801
176. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J.* 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
177. McIntyre WF, Conen D, Olshansky B, Halperin JL, Hayek E, Huisman MV, Lip GYH, Lu S, Healey JS. Stroke-prevention strategies in North American patients with atrial fibrillation: the GLORIA-AF registry program. *Clin Cardiol.* 2018;41:744–751. doi: 10.1002/clc.22936
178. Essien UR, Holmes DN, Jackson LR 2nd, Fonarow GC, Mahaffey KW, Reiffel JA, Steinberg BA, Allen LA, Chan PS, Freeman JV, et al. Association of race/ethnicity with oral anticoagulant use in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II. *JAMA Cardiol.* 2018;3:1174–1182. doi: 10.1001/jamacardio.2018.3945
179. Carlsson AC, Wändell P, Gasevic D, Sundquist J, Sundquist K. Neighborhood deprivation and warfarin, aspirin and statin prescription: a cohort study of men and women treated for atrial fibrillation in Swedish primary care. *Int J Cardiol.* 2015;187:547–552. doi: 10.1016/j.ijcard.2015.04.005
180. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart.* 2017;103:1947–1953. doi: 10.1136/heartjnl-2016-310952
181. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
182. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019
183. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946–952. doi: 10.1161/01.cir.98.10.946
184. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ.* 2016;532:h7013. doi: 10.1136/bmj.h7013
185. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, et al; on behalf of the RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation.* 2013;128:2192–2201. doi: 10.1161/CIRCULATIONAHA.112.000491
186. Masri A, Kanj M, Thamilarasan M, Wazni O, Smedira NG, Lever HM, Desai MY. Outcomes in hypertrophic cardiomyopathy patients with and without atrial fibrillation: a survival meta-analysis. *Cardiovasc Diagn Ther.* 2017;7:36–44. doi: 10.21037/cdt.2016.11.23
187. Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA, Roger VL. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation.* 2011;123:2094–2100. doi: 10.1161/CIRCULATIONAHA.110.990192
188. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F, Jouven X. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation.* 2011;123:1587–1593. doi: 10.1161/CIRCULATIONAHA.110.986661
189. Saxena A, Virk SA, Bowman S, Chan L, Jeremy R, Bannon PG. Preoperative atrial fibrillation portends poor outcomes after coronary bypass graft surgery: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg.* 2018;155:1524–1533.e2. doi: 10.1016/j.jtcvs.2017.11.048

190. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg.* 2011;141:1305–1312. doi: 10.1016/j.jtcvs.2010.10.040
191. Phan K, Ha HS, Phan S, Medi C, Thomas SP, Yan TD. New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. *Eur J Cardiothorac Surg.* 2015;48:817–824. doi: 10.1093/ejcts/ezu551
192. Mojoli M, Gersh BJ, Barioli A, Masiero G, Tellaroli P, D'Amico G, Tarantini G. Impact of atrial fibrillation on outcomes of patients treated by transcatheter aortic valve implantation: a systematic review and meta-analysis. *Am Heart J.* 2017;192:64–75. doi: 10.1016/j.ahj.2017.07.005
193. Vrsalović M, Presečki AV. Atrial fibrillation and risk of cardiovascular events and mortality in patients with symptomatic peripheral artery disease: a meta-analysis of prospective studies. *Clin Cardiol.* 2017;40:1231–1235. doi: 10.1002/clc.22813
194. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation: the Framingham Study. *Stroke.* 1996;27:1760–1764. doi: 10.1161/01.str.27.10.1760
195. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail.* 2009;11:676–683. doi: 10.1093/eurjhf/hfp085
196. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation.* 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E
197. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail.* 2014;16:1317–1322. doi: 10.1002/ejhf.187
198. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study [published correction appears in *Circulation*. 2013;128:e465]. *Circulation.* 2013;128:1085–1093. doi: 10.1161/CIRCULATIONAHA.113.001475
199. Odutayo A, Wong CX, Williams R, Hunn B, Emdin CA. Prognostic importance of atrial fibrillation timing and pattern in adults with congestive heart failure: a systematic review and meta-analysis. *J Card Fail.* 2017;23:56–62. doi: 10.1016/j.cardfail.2016.08.005
200. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, Singer DE, Hylek EM, Go AS, Peterson ED, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF Registry. *J Am Coll Cardiol*. 2017;70:1325–1335. doi: 10.1016/j.jacc.2017.07.755
201. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis [published correction appears in *Nephrol Dial Transplant*. 2014;29:2152]. *Nephrol Dial Transplant.* 2012;27:3816–3822. doi: 10.1093/ndt/gfs416
202. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA.* 2011;306:2248–2254. doi: 10.1001/jama.2011.1615
203. Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, Horn B, Chongsathidkiet P, Garvia V, Putthapiban P, Sirinvaravong N, Figueredo VM. New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. *Acta Cardiol.* 2019;74:162–169. doi: 10.1080/00015385.2018.1477035
204. Garg L, Agrawal S, Agarwal M, Shah M, Garg A, Patel B, Agarwal N, Nanda S, Sharma A, Cox D. Influence of atrial fibrillation on outcomes in patients who underwent primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am J Cardiol.* 2018;121:684–689. doi: 10.1016/j.amjcard.2017.12.003
205. van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38 047 patients. *Circulation.* 2011;124:289–296. doi: 10.1161/CIRCULATIONAHA.110.011130
206. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *Am J Cardiol.* 2015;116:230–235. doi: 10.1016/j.amjcard.2015.04.012
207. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, Alonso A. Racial differences in atrial fibrillation-related cardiovascular disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Cardiol.* 2016;1:433–441. doi: 10.1001/jamacardio.2016.1025
208. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA.* 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
209. Doshi R, Al-Khafaji JF, Dave M, Taha M, Patel K, Goyal H, Gullapalli N. Comparison of baseline characteristics and in-hospital outcomes in Medicaid versus private insurance hospitalizations for atrial fibrillation. *Am J Cardiol.* 2019;123:776–781. doi: 10.1016/j.amjcard.2018.11.045
210. O'Neal WT, Sandesara PB, Kelli HM, Venkatesh S, Soliman EZ. Urban-rural differences in mortality for atrial fibrillation hospitalizations in the United States. *Heart Rhythm.* 2018;15:175–179. doi: 10.1016/j.hrthm.2017.10.019
211. Wändell P, Carlsson AC, Gasevic D, Sundquist J, Sundquist K. Neighbourhood socio-economic status and all-cause mortality in adults with atrial fibrillation: a cohort study of patients treated in primary care in Sweden. *Int J Cardiol.* 2016;202:776–781. doi: 10.1016/j.ijcard.2015.09.027
212. Wändell P, Carlsson AC, Gasevic D, Holzmann MJ, Ärnlöv J, Sundquist J, Sundquist K. Socioeconomic factors and mortality in patients with atrial fibrillation: a cohort study in Swedish primary care. *Eur J Public Health.* 2018;28:1103–1109. doi: 10.1093/eurpub/cky075
213. Frost L, Engholm G, Johnsen S, Møller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Intern Med.* 2001;161:272–276. doi: 10.1001/archinte.161.2.272
214. Bekwelem W, Connolly SJ, Halperin JL, Adabag S, Duval S, Chrolavicius S, Pogue J, Ezekowitz MD, Eikelboom JW, Wallentin LG, et al. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. *Circulation.* 2015;132:796–803. doi: 10.1161/CIRCULATIONAHA.114.013243
215. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation.* 2017;135:208–219. doi: 10.1161/CIRCULATIONAHA.116.024057
216. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983–988. doi: 10.1161/01.str.22.8.983
217. Hayden DT, Hannon N, Callaly E, Ní Chróinín D, Horgan G, Kyne L, Duggan J, Dolan E, O'Rourke K, Williams D, et al. Rates and determinants of 5-year outcomes after atrial fibrillation-related stroke: a population study [published correction appears in *Stroke*. 2015;46:e262]. *Stroke.* 2015;46:3488–3493. doi: 10.1161/STROKEAHA.115.011139
218. Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. *J Am Coll Cardiol.* 2016;68:461–470. doi: 10.1016/j.jacc.2016.05.044
219. Patel PJ, Katz R, Borovskiy Y, Killian A, Levine JM, McNaughton NW, Callans D, Supple G, Dixit S, Epstein AE, et al. Race and stroke in an atrial fibrillation inception cohort: findings from the Penn Atrial Fibrillation Free study. *Heart Rhythm.* 2018;15:487–493. doi: 10.1016/j.hrthm.2017.11.025
220. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 2013;158(pt 1):338–346. doi: 10.7326/0003-4819-158-5-201303050-00007
221. Miyasaka Y, Barnes ME, Petersen RC, Cha SS, Bailey KR, Gersh BJ, Casaclang-Verzosa G, Abhayaratna WP, Seward JB, Iwasaka T, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. *Eur Heart J.* 2007;28:1962–1967. doi: 10.1093/eurheartj/ehm012
222. Conen D, Rodondi N, Müller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, et al; Swiss-AF Study Investigators. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol.* 2019;73:989–999. doi: 10.1016/j.jacc.2018.12.039
223. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation.* 2012;125:2933–2943. doi: 10.1161/CIRCULATIONAHA.111.069450
224. Rienstra M, Lyass A, Murabito JM, Magnani JW, Lubitz SA, Massaro JM, Ellinor PT, Benjamin EJ. Reciprocal relations between physical disability, subjective health, and atrial fibrillation: the Framingham Heart Study. *Am Heart J.* 2013;166:171–178. doi: 10.1016/j.ahj.2013.02.025
225. Zhang L, Gallagher R, Neubeck L. Health-related quality of life in atrial fibrillation patients over 65 years: a review. *Eur J Prev Cardiol.* 2015;22:987–1002. doi: 10.1177/2047487314538855

226. Giacomantonio NB, Bredin SS, Foulds HJ, Warburton DE. A systematic review of the health benefits of exercise rehabilitation in persons living with atrial fibrillation. *Can J Cardiol.* 2013;29:483–491. doi: 10.1016/j.cjca.2012.07.003
227. O'Neal WT, Qureshi WT, Judd SE, Bowling CB, Howard VJ, Howard G, Soliman EZ. Effect of falls on frequency of atrial fibrillation and mortality risk (from the REasons for Geographic And Racial Differences in Stroke Study). *Am J Cardiol.* 2015;116:1213–1218. doi: 10.1016/j.amjcard.2015.07.036
228. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med.* 1999;159:677–685. doi: 10.1001/archinte.159.7.677
229. Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. *Am J Med.* 2005;118:612–617. doi: 10.1016/j.amjmed.2005.02.022
230. Chamberlain AM, Gersh BJ, Alonso A, Kopecky SL, Killian JM, Weston SA, Roger VL. No decline in the risk of heart failure after incident atrial fibrillation: a community study assessing trends overall and by ejection fraction. *Heart Rhythm.* 2017;14:791–798. doi: 10.1016/j.hrthm.2017.01.031
231. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, Curtis LH, Heckbert SR. Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. *Eur Heart J.* 2014;35:250–256. doi: 10.1093/eurheartj/eht483
232. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, Van Gilst WH, Van Gelder IC, Rienstra M. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. *J Am Coll Cardiol.* 2015;66:1000–1007. doi: 10.1016/j.jacc.2015.06.1314
233. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2017;24:1555–1566. doi: 10.1177/2047487317715769
234. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, et al. Atrial fibrillation and the risk of myocardial infarction [published correction appears in *JAMA Intern Med*. 2014;174:308]. *JAMA Intern Med.* 2014;174:107–114. doi: 10.1001/jamainternmed.2013.11912
235. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 2015;131:1843–1850. doi: 10.1161/CIRCULATIONAHA.114.014145
236. O'Neal WT, Sangal K, Zhang ZM, Soliman EZ. Atrial fibrillation and incident myocardial infarction in the elderly. *Clin Cardiol.* 2014;37:750–755. doi: 10.1002/clc.22339
237. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J.* 2009;158:629–636. doi: 10.1016/j.ahj.2009.06.031
238. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation.* 2013;127:569–574. doi: 10.1161/CIRCULATIONAHA.112.123992
239. Chen LY, Sotoodehnia N, Bůžková P, Lopez FL, Yee LM, Heckbert SR, Prineas R, Soliman EZ, Adabag S, Konety S, et al. Atrial fibrillation and the risk of sudden cardiac death: the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study. *JAMA Intern Med.* 2013;173:29–35. doi: 10.1001/2013.jamainternmed.744
240. Bardai A, Blom MT, van Hoeijen DA, van Deutekom HW, Brouwer HJ, Tan HL. Atrial fibrillation is an independent risk factor for ventricular fibrillation: a large-scale population-based case-control study. *Circ Arrhythm Electrophysiol.* 2014;7:1033–1039. doi: 10.1161/CIRCEP.114.002094
241. Rattanawong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2018;51:91–104. doi: 10.1007/s10840-017-0308-9
242. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J.* 2016;37:1591–1602. doi: 10.1093/eurheartj/ehw007
243. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm.* 2017;14:801–807. doi: 10.1016/j.hrthm.2017.01.038
244. Al-Kawaz M, Omran SS, Parikh NS, Elkind MSV, Soliman EZ, Kamel H. Comparative risks of ischemic stroke in atrial flutter versus atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2018;27:839–844. doi: 10.1016/j.jstrokecerebrovasdis.2017.10.025
245. Lin YS, Chen TH, Chi CC, Lin MS, Tung TH, Liu CH, Chen YL, Chen MC. Different implications of heart failure, ischemic stroke, and mortality between nonvalvular atrial fibrillation and atrial flutter-a view from a national cohort study. *J Am Heart Assoc.* 2017;6:e006406. doi: 10.1161/JAHA.117.006406
246. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
247. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
248. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
249. Jackson SL, Tong X, Yin X, George MG, Ritchey MD. Emergency department, hospital inpatient, and mortality burden of atrial fibrillation in the United States, 2006 to 2014. *Am J Cardiol.* 2017;120:1966–1973. doi: 10.1016/j.amjcard.2017.08.017
250. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes.* 2011;4:313–320. doi: 10.1161/CIRCOUTCOMES.110.958165
251. Turakhia MP, Shafrin J, Bognar K, Goldman DP, Mendys PM, Abdulsattar Y, Wiederkehr D, Trocio J. Economic burden of undiagnosed nonvalvular atrial fibrillation in the United States. *Am J Cardiol.* 2015;116:733–739. doi: 10.1016/j.amjcard.2015.05.045
252. Li X, Tse VC, Au-Doung LW, Wong ICK, Chan EW. The impact of ischaemic stroke on atrial fibrillation-related healthcare cost: a systematic review. *Europace.* 2017;19:937–947. doi: 10.1093/europace/euw093
253. Johnsen SP, Dalby LW, Täckström T, Olsen J, Fraschke A. Cost of illness of atrial fibrillation: a nationwide study of societal impact. *BMC Health Serv Res.* 2017;17:714. doi: 10.1186/s12913-017-2652-y
254. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119
255. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
256. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, et al; RE-LY Atrial Fibrillation Registry and Cohort Study Investigators. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study [published correction appears in *Lancet*. 2017;389:602]. *Lancet.* 2016;388:1161–1169. doi: 10.1016/S0140-6736(16)30968-0

17. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

See Tables 17-1 through 17-7 and Charts 17-1 through 17-4

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Cardiac Arrest (Including VF and Ventricular Flutter)

ICD-9 427.4, 427.5; *ICD-10* I46.0, I46.1, I46.9, I49.0.

2017: Mortality—18 835. Any-mention mortality—379 133.

Abbreviations Used in Chapter 17

ACS	acute coronary syndrome
AED	automated external defibrillator
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
ARVC	arrhythmogenic right ventricular cardiomyopathy
AV	atrioventricular
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CARES	Cardiac Arrest Registry to Enhance Survival
CASQ2	calsequestrin 2
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CLRD	chronic lower respiratory disease
CPC	Cerebral Performance Index
CPR	cardiopulmonary resuscitation
CPVT	catecholaminergic polymorphic ventricular tachycardia
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	diabetes mellitus
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMS	emergency medical services
ERP	early repolarization pattern
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio

(*Continued*)

Abbreviations Used in Chapter 17 Continued

ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IQR	interquartile range
IRR	incidence rate ratio
LQTS	long-QT syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
METs	metabolic equivalents
MI	myocardial infarction
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PA	physical activity
PE	pulmonary embolism
PEA	pulseless electrical activity
PVC	premature ventricular contraction
PVT	polymorphic ventricular tachycardia
QTc	corrected QT interval
ROC	Resuscitation Outcomes Consortium
RR	relative risk
RV	right ventricular
RYR2	ryanodine receptor 2
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SD	standard deviation
STEMI	ST-segment–elevation myocardial infarction
SUDS	Sudden Unexpected Death Study
TdP	torsade de pointes
VF	ventricular fibrillation
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

Tachycardia

ICD-9 427.0, 427.1, 427.2; *ICD-10* I47.1, I47.2, I47.9.

2017: Mortality—997. Any-mention mortality—8035.

Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.[1] An operational definition of SCA is unexpected cardiac arrest that results in attempts to restore circulation. If resuscitation attempts are unsuccessful, this situation is referred to as SCD. SCA results from many disease processes; a consensus statement by the International Liaison Committee on Resuscitation recommends categorizing cardiac arrest into events with external causes (drowning, trauma, asphyxia, electrocution, and drug overdose) or medical causes.[2] Because of fundamental differences in underlying pathogenesis

and the system of care, epidemiological data for OHCA and IHCA are collected and reported separately. For similar reasons, data for infants (<1 year of age), children (1–18 years of age), and adults are reported separately.

- In a Swedish registry of 70 846 OHCAs from 1992 to 2014, 92% of cases had medical causes. Among nonmedical cases, trauma was the most common cause.[3]
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW syndrome (6.8%). and LQTS (6.0%).[4]

Incidence (See Tables 17-1 through 17-3)

- The ROC clinical trial network maintained a registry of EMS-assessed and EMS-treated OHCA in multiple regions of the United States from 2005 to 2015 (Table 17-1).
- The ongoing CARES registry[5] estimates the incidence of EMS-treated OHCA among individuals of any age in >1400 EMS agencies in the United States (Table 17-1).
- Incidence of EMS-assessed OHCA for 2015 in people of any age is 110.8 individuals per 100 000 population (95% CI, 108.9–112.6), or 356 461 people (quasi CI, 350 349–362 252), based on extrapolation from the ROC registry of OHCA (ROC Investigators, unpublished data, July 7, 2016) to the total population of the United States (325 193 000 as of June 9, 2017).[6]
- Incidence of EMS-treated OHCA in people of any age is 57 individuals per 100 000 population based on the 2013 CARES registry of EMS-treated OHCA and 63.8 individuals per 100 000 population based on the 2013 ROC registry.[7]
- Incidence of EMS-treated OHCA in people of any age is 74.3 individuals per 100 000 population based on the 2018 CARES registry, with >2-fold variation between states (range, 51.6–128.3; Table 17-2).
- Of the 3 686 296 hospital discharges from academic medical centers in 2012, 33 700 (0.91%) included a cardiac arrest diagnosis.[8]
- In the NIS for 2016:
  - "Cardiac arrest" or "VF/flutter" was included in 273 295 hospital discharges (rate of 84.6 per 100 000 people). For 9.5% (26 040) this was the principal diagnosis for hospital admission.
  - *ICD-10* codes for CPR or defibrillation were included in 286 945 hospital discharges (rate of 88.8 per 100 000 people).[9]
- In the NEDS for 2016:
  - The weighted national estimate of ED visits with a principal diagnosis of "cardiac arrest" or "VF/flutter" was 183 629 (rate of 56.8 per 100 000 people). Of these, 15.8% (29 096) were admitted to the same hospital or transferred to another hospital (Table 17-3).
  - "Cardiac arrest" or "VF/flutter" was estimated at 404 691 visits among all listed diagnoses, but this larger number may include patients with cardiac arrest after hospital admission (Table 17-3).
  - The weighted national estimate of ED visits including *ICD-10* codes for CPR or defibrillation was 187 097 (rate of 57.9 per 100 000 people; unpublished tabulation using HCUP,[9] 2016).

OHCA: Adults (See Table 17-4)

- Incidence of EMS-assessed OHCA for 2015 in adults was 140.7 individuals per 100 000 population (95% CI, 138.3–143.1), or 347 322 adults (95% CI, 341 397–353 246) based on extrapolation from the ROC registry of OHCA to the total population of the United States (ROC Investigators, unpublished data, July 7, 2016).[6]
- Incidence of EMS-treated OHCA in adults for 2015 was 73.0 individuals per 100 000 population (95% CI, 71.2–74.7), or 180 202 adults (95% CI, 175 759–184 399) in the ROC registry. Approximately 52% of EMS-assessed adult OHCA had resuscitation attempted (ROC Investigators, unpublished data, July 7, 2016).
- In 2015, the incidence of EMS-treated OHCA in adults was 66 per 100 000. Incidence of EMS-treated OHCA with initial shockable rhythm was 13.5 per 100 000 (ROC Investigators, unpublished data, July 7, 2016).
- Ten ambulance services serving almost 54 000 000 residents of England attended 28 729 EMS-treated cardiac arrests in 2014 (annual incidence 53 per 100 000 residents).[10]
- In 2018, location of OHCA in adults was most often a home or residence (69.8%), followed by public settings (18.8%) and nursing homes (11.5%; Table 17-4). OHCA in adults was witnessed by a layperson in 37.7% of cases or by an EMS provider in 12.7% of cases. For 49.6% of cases, collapse was not witnessed.[5]
- Initial recorded cardiac rhythm was VF or VT or shockable by an AED in 18.7% of EMS-treated OHCAs in 2018 (Table 17-4).

- Of 4729 patients with STEMI in Los Angeles County, CA, from 2011 to 2014, 422 (9%) had OHCA.[11]
- In a clinical trial of a wearable defibrillator in 2302 patients with reduced EF (<35%) after AMI, 44 patients (1.9%) had arrhythmic sudden death, 21 (0.9%) had appropriate defibrillator shock, and 86 (3.7%) had death attributable to any cause during the first 90 days.[12]

IHCA: Adults (See Table 17-4)

- Incidence of adult IHCA was a mean of 10.16 (SD, 26.08) per 1000 hospital admissions and 1.99 (SD, 1.57) per 1000 inpatient days in the 2018 GWTG data (GWTG–Resuscitation, unpublished data, 2019).
- Incidence of IHCA was 4.0 per 1000 hospitalizations (range, 1.4–11.8 per 1000 hospitalizations) based on 2 205 123 hospitalizations at 101 Veterans Health Administration hospitals between 2008 and 2012.[13]
- Incidence of IHCA was 1.7 per 1000 hospital admissions based on 18 069 patients with IHCA in the Swedish Register of CPR.[14]
- Incidence of IHCA was 1.6 per 1000 hospital admissions, with a median across hospitals of 1.5 (IQR, 1.2–2.2) in the UK National Cardiac Arrest Audit database between 2011 and 2013 (144 hospitals and 22 628 patients ≥16 years of age).[15]
- According to 2018 GWTG data, location of adult IHCA was 54.2% in the ICU, operating room, or ED and 45.8% in noncritical care areas among 26 742 events at 319 hospitals (Table 17-4).
- Initial recorded cardiac rhythm was VF or VT or shockable in 15.3% of adult IHCAs in 2018 GWTG data (GWTG–Resuscitation, unpublished data, 2019; Table 17-4).

OHCA: Children

- Incidence of EMS-assessed OHCA in children in 2015 was 7037 (quasi CI, 6214–7861) in the United States based on extrapolation from ROC for individuals <18 years of age (ROC Investigators, unpublished data, July 7, 2016).
- In 2018, location of EMS-treated OHCA was at home for 92.1% of children ≤1 year old, 81.2% of children 1 to 12 years of age, and 75.7% of children 13 to 18 years of age in the CARES 2018 data. Location was in a public place for 7.8% of children ≤1 year old, 18.8% of children 1 to 12 years of age, and 23.1% of children 13 to 18 years of age.[5]
- Annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.[16]

Sports-Related SCA/SCD

- Sports-related SCA accounted for 39% of SCAs among those ≤18 years of age, 13% for those 19 to 25 years of age, and 7% for those 25 to 34 years of age in a prospective registry of 3775 SCAs in Portland, OR, between 2002 and 2015 that included 186 SCAs in young people (5–34 years of age).[17]
- Incidence of SCA or SCD was 1 per 44 832 athlete-years for males and 1 per 237 510 athlete-years for females based on a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes.[18]
- Incidence of SCA during competitive sports in people 12 to 45 years of age was 0.76 per 100 000 athlete-years in a population-based registry of all paramedic responses in Toronto, Canada, from 2009 to 2014.[19]
- Studies that included >14 million participants in long-distance or marathon running events from 1976 to 2009 reported race-related incidence of SCA or SCD ranging from 0.6 to 1.9 per 100 000 runners using various methods to ascertain events.[20] Only 2 deaths were reported among 1 156 271 participants in half or full marathons in Sweden from 2007 to 2016, yielding an estimated SCD incidence of 0.24 (95% CI, 0.04–0.79) per 100 000 runners.[21]
- In a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes, adjudication revealed a cause of death in 50 cases (73%): idiopathic LVH or possible cardiomyopathy (26%), autopsy-negative sudden unexplained death (18%), HCM (14%), and myocarditis (14%).[18]
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW (6.8%), and LQTS (6.0%).[4]
- Among 55 patients admitted to 8 Spanish hospitals with SCA during or within 1 hour of vigorous sport activities between 2007 and 2016, 90.9% were male, mean (SD) age was 47 (15) years, and 96.4% presented with shockable rhythm. The cause of SCA varied by age: 25% cardiomyopathy, 63% idiopathic VF, and 13% AMI for those <35 years of age; 9% cardiomyopathy, 18% idiopathic VF, 67% AMI, and 7% unknown for those ≥35 years of age.[22]
- Preparticipation screening of 5169 middle and high-school students (mean [SD] age 13.06 [1.78] years) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.[23] Anatomic findings included DCM (n=11), nonobstructive HCM (n=3), and anomalous coronary artery origins (n=23). Electrocardiographic findings included WPW (n=4), prolonged QT intervals (n=34), and Brugada pattern (n=1).

IHCA: Children (See Table 17-4)

- Incidence of IHCA for children (30 days to 18 years of age) was a mean 12.66 (SD, 41.04) per 1000 admissions and 1.89 (SD, 4.99) per 1000 inpatient days for 810 events from 92 hospitals per 2018 GWTG data (GWTG–Resuscitation, unpublished data, 2019).
- Of 810 events of IHCA in children (30 days to 18 years of age) at 92 hospitals, 87% occurred in the ICU, operating room, or ED and 13% in noncritical care areas per 2018 GWTG data (Table 17-4).
- Incidence of IHCA was 1.8 CPR events per 100 pediatric (<18 years of age) ICU admissions (sites ranged from 0.6 to 2.3 per 100 ICU admissions) in the Collaborative Pediatric Critical Care Research Network data set of 10 078 pediatric ICU admissions from 2011 to 2013.[24]
- In a registry of 23 cardiac ICUs in the Pediatric Critical Care Consortium that included 15 098 children between 2014 and 2016, 3.1% of children in ICUs had a cardiac arrest, with substantial variation between centers (range, 1%–5.5%), for a mean incidence of 4.8 cardiac arrests per 1000 cardiac ICU days (range, 1.1–10.4 per 1000 cardiac ICU days).[25]
- Initial recorded cardiac arrest rhythm was VF or VT or shockable in 9.0% of 571 events at 90 hospitals in GWTG–Resuscitation in 2018 (Table 17-4).

Lifetime Risk and Cumulative Incidence (See Table 17-5 and Chart 17-1)

- SCD appeared among the multiple causes of death on 13.5% of death certificates in 2017 (379 133 of 2 813 503), which suggests that 1 of every 7.4 people in the United States died of SCD (Table 17-5). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2017, infants had a higher incidence of SCD (11.2 per 100 000) than older children (1.2–2.2 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 35 to 39 years of age (13.3 per 100 000; Chart 17-1).
- Of 2656 Finnish males 42 to 60 years of age randomly selected from 1984 to 1989 and prospectively followed up until 2008, a total of 193 (7.3%) had SCD.[26]

Secular Trends (See Table 17-1 and Charts 17-2 and 17-3)

- Incidence of EMS-treated OHCA increased from 47 per 100 000 to 66 per 100 000 between 2008 and 2015 in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016; Table 17-1).
- The annual rate of SCD among patients with HF with reduced EF has declined from 6.5% to 3.3%, based on analysis of 3583 cases of SCD among 40 195 patients enrolled in 12 clinical trials in which enrollment started between 1995 and 2010.[27] This analysis estimates the current cumulative incidence of SCD in patients with HF with reduced EF is 1% by 3 months, <2% by 6 months, and 8.8% by 3 years.
- Incidence of pediatric OHCA declined from 1997 to 2014 in Perth, Western Australia, particularly among children <1 year old.[16]
- Incidence of pediatric (<16 years of age) OHCA that was EMS attended (6.7 per 100 000) or EMS treated (4.9 per 100 000) did not change from 2000 to 2016 in Victoria, Australia.[28] Survival to hospital discharge increased from 9.4% to 17.7%.
- Age-adjusted death rates for any mention of SCD declined from 138 per 100 000 person-years in 1999 to 97.1 per 100 000 person-years by 2017 (Chart 17-2).
- Unadjusted survival to hospital discharge after EMS-treated OHCA increased from 10.2% in 2006 to 12.4% in 2015 in the ROC Epistry (Table 17-1).
- Survival after IHCA increased from 28.5% to 53.8% between 2000 and 2016 and then declined to 48.7% by 2018 in GWTG data (Chart 17-3).
- A national database of 120 365 adult, medical OHCAs in the Republic of Korea from 2006 to 2015 reported increases over time in layperson CPR (1.2% to 17.0%), age- and sex-adjusted survival (3.0% to 8.0%), and good functional recovery (0.9% to 5.8%).[29] Layperson CPR rates increased more in the highest socioeconomic quintile (1.6% to 32.5%) than in the lowest socioeconomic quintile (1.6% to 15.3%)

Risk Factors (See Charts 17-1 and 17-4)

- SCA and SCD result from many different disease processes, each of which can have different risk factors. Among patients with OHCA resuscitated and hospitalized from 2012 to 2016, ACS and other cardiac causes accounted for the largest proportion of causes. Among patients with IHCA, respiratory failure was the most common cause (Chart 17-4).[30]

Age

- In 2017, mortality rates for any mention of SCD decreased for those from 0 to 9 years of age, stayed stable from 10 to 14 years of age, and increased from 15 years of age onward (Chart 17-1).

Sex

- According to multiple studies, females with OHCA are older, less likely to present with shockable rhythms, and less likely to collapse in public.

Despite these factors that would reduce survival, females have equivalent or higher rates of survival to hospital discharge or to 30 days relative to males.[31]

- In an EMS-based registry of 3862 OHCAs from 2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).[32] Females were older, collapsed unwitnessed at home, were considered to have a noncardiac cause, presented in a nonshockable rhythm, and less often received layperson CPR. There was no difference between sexes in survival of the event or 30-day survival after adjustment for age, rhythm, location of arrest, and witnessed collapse.
- In a registry that included 40159 OHCAs from 2009 to 2012 in Singapore, Japan, Republic of Korea, Malaysia, Thailand, Taiwan, and United Arab Emirates, OHCA was more common in males (60%) than females (40%).[33] Females were older, more often presented in a nonshockable rhythm, and more often received layperson CPR, but less often collapsed in public. There was no difference between sexes in survival of the event or survival to hospital discharge after adjustment for these factors.

Race

- In patients with implanted defibrillators, rate of first ventricular dysrhythmia or death within 4 years was higher among black patients (42%) than whites (34%; adjusted HR, 1.60 [95% CI, 1.18–2.17]).[34]
- A study in New York, NY, found the age-adjusted incidence of OHCA per 10000 adults was 10.1 among blacks, 6.5 among Hispanics, and 5.8 among whites.[35]

Socioeconomic Factors

- OHCA rates were higher in census tracts from the lowest socioeconomic quartile relative to the highest socioeconomic quartile (IRR, 1.9 [95% CI, 1.8–2.0]) in 9235 cases from the ROC Epistry (from 2006 to 2007).[36]
- In King County, WA, SCA was more common in census tracts with more pharmacies or other medical facilities (OR 1.28 [95% CI, 1.03–1.59]).[37]
- In a national database of 120365 adult, medical OHCAs in the Republic of Korea from 2006 to 2015, there were differences from the lowest to highest socioeconomic quintiles for layperson CPR (5.5% to 11.4%), survival to hospital discharge (3.8% to 6.1%), and good functional recovery (1.9% to 2.9%).[29]

HD, Cardiac Risk Factors, and Other Comorbidities

- Among 2656 Finnish males 42 to 60 years of age randomly selected from 1984 to 1989 and prospectively followed up until 2008, the hazard for SCD increased with below-median (7.9 METs) baseline cardiopulmonary fitness (HR, 1.6 [95% CI, 1.1–2.3]) and below-median (191 kcal/d) leisure-time PA (HR, 1.4 [95% CI, 1.0–2.0]).[26]
- In a cohort of 233970 patients from the United Kingdom, resting heart rate >90 beats per minute was associated an increased hazard of SCD or cardiac arrest as initial presentation of HD (adjusted HR, 2.71 [95% CI, 190–3.83]).[38]
- In a cohort of 1937360 patients from the United Kingdom registered between 1997 and 2010, smoking was not associated with hazard of SCD or cardiac arrest as the initial presentation of HD (age-adjusted HR, 1.04 [95% CI, 0.91–1.09]), but it was associated with increased risk of unheralded death caused by CHD (age-adjusted HR, 2.70 [95% CI, 2.27–3.21]), a phenotype that may overlap with SCD.[39]
- In a cohort of 1937360 patients from the United Kingdom registered between 1997 and 2010, heavy drinking (adjusted HR, 1.50 [95% CI, 1.26–1.77]) and former drinking (adjusted HR, 1.37 [95% CI, 1.12 -1.67]) were associated with increased hazard of SCD or cardiac arrest as the initial presentation of HD.[40]
- Among 7011 patients admitted to the hospital with acute HF, the 30-day rate of SCD, SCA, or VT/VF was 1.8% (n=121).[41] Events were associated with male sex (adjusted OR, 1.73 [95% CI, 1.07–2.49]), history of VT (adjusted OR, 2.11 [95% CI, 1.30–3.42]), chronic obstructive pulmonary disease (adjusted OR, 1.63 [95% CI, 1.07–2.49]), or prolonged QRS interval (adjusted OR, 1.10 [95% CI, 1.03–1.17] per 10% increase from baseline).
- Analysis of 76009 patients including 8401 with AF from 21 studies between 1991 and 2017 found that patients with AF had higher risk of incident SCD/SCA or VF/VT (RR, 2.04 [95% CI, 1.77–2.35]).[42]
- Among 21105 patients with AF followed up for a median of 2.8 years, SCD accounted for 31.7% of all deaths, with an incidence of 12.9 per 1000 patient-years.[43]
- Risk of SCD in prospective cohorts who were initially free of CVD when recruited in 1987 to 1993 was associated with male sex, black race, DM, current smoking, and SBP.[44]
- A logistic model incorporating age, sex, race, current smoking, SBP, use of antihypertensive medication, DM, serum potassium, serum albumin, HDL-C, eGFR, and QTc interval, derived in 13677 adults, correctly stratified 10-year risk of SCD in a separate cohort of 4207 adults (C statistic, 0.820 in ARIC and 0.745 in CHS).[44]

- A meta-analysis of 24 trials of statins in patients with HF, which included a total of 11 463 patients, concluded that statins did not reduce the risk of SCD (RR, 0.92 [95% CI, 0.70–1.21]).[45]
- In a registry of 2119 SCAs in Portland, OR, from 2002 to 2015, prior syncope was present in 6.8% of cases, and history of syncope was associated with increased risk of SCA relative to 746 geographically matched control subjects (OR, 2.8 [95% CI, 1.68–4.85]).[46]
- In a cohort of 5211 Finnish people >30 years of age in 2000 to 2001 followed up for a median of 13.2 years, high baseline thyroid-stimulating hormone was independently associated with greater risk of SCD (HR, 2.28 [95% CI, 1.13–4.60]).[47]
- In a meta-analysis that included 17 studies with 118 954 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), and specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).[48]

Risk Prediction

Prodromal Symptoms

- Abnormal vital signs during the 4 hours preceding IHCA occurred in 59.4% and at least 1 severely abnormal vital sign occurred in 13.4% of 7851 patients in the 2007 to 2010 GWTG data.[49]
- Early warning score systems using both clinical criteria and vital signs identified hospital patients with a higher risk of IHCA.[50]
- A comparison using receiver-operator curves of early warning score accuracy for predicting risk of IHCA and other serious events for individual patients in the hospital had areas under the curve of 0.663 to 0.801.[51]
- Among 1352 surgical patients with postoperative IHCA within 30 days, 746 (55%) had developed a postoperative complication (acute kidney injury, acute respiratory failure, DVT/PE, MI, sepsis/septic shock, stroke, transfusion) before the arrest.[52]

ECG Abnormalities

- Among 12 241 subjects from the ARIC study, in which 346 subjects had SCD during a median follow-up of 23.6 years, prolongation of the QT interval at baseline was associated with risk of SCD (HR, 1.49 [95% CI, 1.01–2.18]), and this association was driven specifically by the T-wave onset to T-peak component of the total interval.[53]
- In a cohort of 4176 subjects with no known HD, 687 (16.5%) had early repolarization with terminal J wave, but this pattern had no association with cardiac deaths (0.8%) over 6 years of follow-up compared with matched control subjects.[54]
- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years of age, 1.3% had ERP, with higher prevalence in males (2.6%) than females (0.2%).[55]
- In an Italian public health screening project, 24% of 13 016 students 16 to 19 years of age had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats, AV block, Brugada-like ECG pattern, left anterior/posterior fascicular block, LVH/RV hypertrophy, long/short QT interval, left atrial enlargement, right atrial enlargement, short PQ interval, and ventricular pre-excitation WPW syndrome.[56]

Genetics and Family History Associated With SCD

- Age- and sex-adjusted prevalence of electrocardiographic abnormalities associated with SCD was 0.6% to 1.1% in a sample of 7889 Spanish citizens ≥40 years of age, including Brugada syndrome in 0.13%, QTc <340 ms in 0.18%, and QTc ≥480 ms in 0.42%.[57]
- Exome sequencing in younger (<51 years of age) decedents who died of sudden unexplained death or suspected arrhythmic death revealed likely pathogenic variants in channelopathy- or cardiomyopathy-related genes for 29% to 34% of cases.[58,59] Among children with exertion-related deaths, pathogenic mutations were present in 10 of 11 decedents (91%) 1 to 10 years of age and 4 of 21 decedents (19%) 11 to 19 years of age.[60]
- Screening of 398 first-degree relatives of 186 unexplained SCA and 212 unexplained SCD probands revealed cardiac abnormalities in 30.2%: LQTS (13%), CPVT (4%), ARVC (4%), and Brugada syndrome (3%).[61]
- In a registry of 109 families of probands with unexplained SCD from 2007 to 2012, screening of 411 relatives revealed a diagnosis in 18% of families: LQTS (15%), Brugada syndrome (3%), and CPVT (1%).[62]
- In a registry of families of probands with unexplained SCD before 45 years of age from 2009 to 2014, screening of 230 people from 64 families revealed a diagnosis in 25% of families: Brugada syndrome (11%), LQTS (7.8%), DCM (3.1%), and HCM (3.1%).[63]
- Screening of 292 relatives of 56 probands with SCD revealed a diagnosis in 47 (16.1%) relatives: LQTS (12.7%), CPVT (0.3%), DCM (0.7%), ARVC (0.3%), and thoracic aortic dilation (0.3%). Among relatives completing follow-up, 3.3% had a cardiac event within 3 years and 7.2% within 5 years.[64]
- Prevalence of genetic HD declines with increasing age according to a screening of 180 survivors of

SCA, who represented 5.9% of 3037 referrals to a genetic heart rhythm clinic from 1999 to 2017.[65] Among 127 adults, diagnoses included idiopathic VF (44.1%), arrhythmogenic bileaflet mitral valve (14.2%), acquired LQTS (9.4%), LQTS (7.9%), and J-wave syndromes such as Brugada (3.9%). Among 53 children, diagnoses included LQTS (28.3%), CPVT (20.8%), idiopathic VF (20.8%), HCM (5.7%), and triadin knockout syndrome (5.7%).

Genome-Wide Association Studies

- GWASs on cases of arrhythmic death attempt to identify previously unidentified genetic variants and biological pathways associated with potentially lethal ventricular arrhythmias and risk of sudden death. Limitations of these studies are the small number of samples available for analysis and the heterogeneity of case definition. The number of loci uniquely associated with SCD is much smaller than for other complex diseases. For example, a recent GWAS of 3939 cases with SCA found no variants associated with SCD at genomewide significance, which suggests that common genetic variation is not a significant risk factor for SCD.[66]
- In addition, studies do not consistently identify the same variants. A pooled analysis of case-control and cohort GWASs identified a rare (1.4% minor allele frequency) novel marker at the *BAZ2B* locus (bromodomain adjacent zinc finger domain 2B) that was associated with a risk of arrhythmic death (OR, 1.9 [95% CI, 1.6–2.3]), but inconsistent relationships for alleles associated with QRS and QT prolongation.[67]

Long-QT Syndrome

- Hereditary LQTS is a genetic channelopathy characterized by prolongation of the QT interval (QTc typically >460 ms) and susceptibility to ventricular tachyarrhythmias that lead to syncope and SCD. Investigators have identified mutations in 15 genes leading to this phenotype (*LQT1* through *LQT15*).[68,69] *LQT1 (KCNQ1)*, *LQT2 (KCNH2)*, and *LQT3 (SCN5A)* mutations account for the majority (≈80%) of the typed mutations.[70,71]
- Approximately 5% of sudden infant death syndrome and some cases of intrauterine fetal death could be attributable to LQTS.[72,73]
- Acquired prolongation of the QT interval is common. Prevalence of prolonged QTc was 115 of 412 (27.9%) among adults admitted to an ICU from 2014 to 2016 in Brazil.[74] At least 1 drug known to prolong QT interval was present in 70.4% of these cases.
- Prevalence of prolonged QTc interval was 251 of 900 patients (27.9%) admitted to a cardiac care unit from 2008 to 2009.[75]
- Prevalence of prolonged QTc interval was 50 of 712 patients (7%) admitted to a short-stay medical unit in the United Kingdom.[76]
- Prevalence of prolonged QTc interval was 95 of 7522 patients (1.9%) with ECG in the ED from 2010 to 2011, and these prolongations were attributable individually or in combination to electrolyte disturbances (51%), QT-prolonging medical conditions (56%), or QT-prolonging medications (77%).[77]

Short-QT Syndrome

Prevalence and Incidence

- Short-QT syndrome is an inherited mendelian condition characterized by shortening of the QT interval (typically QT <320 ms) and predisposition to AF, ventricular tachyarrhythmias, and sudden death. Mutations in 5 ion channel genes have been described (*SQT1–SQT5*).[78]
- Prevalence of a QTc interval shorter than 320 ms in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,[79] which was identical to prevalence from a Portugal sudden death registry.[80]
- Prevalence of QT interval ≤320 ms in 18 825 apparently healthy people from the United Kingdom 14 to 35 years of age between 2005 and 2013 was 0.1%.[81] Short QT intervals were associated with male sex and Afro-Caribbean ethnicity.
- Prevalence of QT interval ≤340 ms in 99 380 unique patients ≤21 years of age at Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.[82] Of these children, 15 of 45 (33%) were symptomatic.[82]
- In an international case series of 15 centers that included 25 patients ≤21 years of age with short-QT syndrome who were followed up for 5.9 years (IQR, 4–7.1 years), 6 patients had aborted sudden death (24%) and 4 (16%) had syncope.[83] Sixteen patients (84%) had a familial or personal history of cardiac arrest. A gene mutation associated with short-QT syndrome was identified in 5 of 21 probands (24%).

Brugada Syndrome

Prevalence and Incidence

- Brugada syndrome is an acquired or inherited channelopathy characterized by persistent ST-segment elevation in the precordial leads (V_1–V_3), right bundle-branch block, and susceptibility to ventricular arrhythmias and SCD.[84] Brugada syndrome is associated with mutations in at least 12 ion channel–related genes.[84,85]
- In a meta-analysis of 24 studies, prevalence was estimated at 0.4% worldwide, with regional

prevalence of 0.9%, 0.3%, and 0.2% in Asia, Europe, and North America, respectively.[86] Prevalence was higher in males (0.9%) than in females (0.1%).[84,87–89]

Complications

- Cardiac event rates for Brugada syndrome patients followed up prospectively in Northern Europe (31.9 months) and Japan (48.7 months) were similar: 8% to 10% in patients with prior aborted sudden death, 1% to 2% in those with history of syncope, and 0.5% in asymptomatic patients. Predictors of poor outcome included clinical history of syncope or ventricular tachyarrhythmias, family history of sudden death, and a spontaneous ERP on ECG.[87,90,91]
- Among patients with Brugada syndrome, first-degree AV block, syncope, and spontaneous type 1 ST-segment elevation were independently associated with risk of sudden death or implantable cardioverter-defibrillator–appropriate therapies.[92,93]
- Among 678 patients with Brugada syndrome from 23 centers in 14 countries, patients whose first documented arrhythmic event was SCA had a mean (SD) age of 39 (15) years, whereas patients with prophylactic defibrillator implantation first documented arrhythmic event was 46 (13) years.[94]

Catecholaminergic PVT

Prevalence and Incidence

- CPVT is a familial condition characterized by adrenergically induced ventricular arrhythmias associated with syncope and sudden death. Arrhythmias include frequent ectopy, bidirectional VT, and PVT with exercise or catecholaminergic stimulation (such as emotion, or medicines such as isoproterenol). Mutations in genes encoding RYR2 (*CPVT1*) are found in the majority of patients and result in a dominant pattern of inheritance.[95] Mutations in genes encoding CASQ2 (*CPVT2*) are found in a small minority and result in a recessive pattern of inheritance. Mutations have also been described in *KCNJ2* (*CPVT3*), *TRDN*, *ANK2*, and *CALM1*.[95]
- Prevalence of CPVT is estimated at 1:5000 to 1:10 000, but this could be an underestimate, because childhood cases were excluded.[95]
- Analysis of 171 probands with CPVT who were <19 years of age and 65 adult relatives described clinical presentations and prevalence of genotypes.[96] The presenting symptom was cardiac arrest for 28% of cases and syncope/seizure in 58%. Genetic testing of 194 subjects identified variants in *RYR2* (60%), *CASQ2* (5%), *KCNJ2* (1%), and >1 gene in 17 cases (9%). For 23 cases (12%), no genetic variant was identified.

Complications

- Risk factors for cardiac events included younger age at diagnosis and absence of β-blocker therapy. A history of aborted cardiac arrest and absence of β-blocker therapy were risk factors for fatal or near-fatal events.[97]
- In a cohort of 34 patients with CPVT, 20.6% developed fatal cardiac events during 7.4 years of follow up.[98]
- Incidence of SCA in children with ≥2 CPVT gene variants was 11 of 15 (73%).[99] VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

Arrhythmogenic RV Dysplasia/ Cardiomyopathy

Complications

- During a median follow-up of 100 patients with arrhythmogenic RV dysplasia for 6 years, 47 patients received an implantable cardioverter-defibrillator, 29 of whom received appropriate implantable cardioverter-defibrillator shocks. At the end of follow-up, 66 patients were alive. Twenty-three patients died at study entry, and 11 died during follow-up (91% of deaths were attributable to SCA).[100] Similarly, the annual mortality rate was 2.3% for 130 patients with ARVC from Paris, France, who were followed up for a mean of 8.1 years.[101]
- In a cohort of 301 patients with ARVC from a single center in Italy, probability of a first life-threatening arrhythmic event was 14% at 5 years, 23% at 10 years, and 30% at 15 years.[102]
- In a cohort of 502 patients with ARVC, younger patients (<50 years of age versus >50 years of age) were more likely to present with SCA (5% versus 2%) or SCD (7% versus 6%).[103]

Hypertrophic Cardiomyopathy

(Please refer to Chapter 20, Cardiomyopathy and Heart Failure, for statistics regarding the general epidemiology of HCM.)

Complications

- Among 1436 SCA cases in individuals 5 to 59 years of age between 2002 and 2015, HCM was present in 3.2% of those 5 to 34 years of age and 2.2% of those 35 to 59 years of age. This study noted the difficulty of distinguishing HCM from secondary LVH in older patients, who were excluded from the analysis.[104]

Early Repolarization Syndrome

Prevalence and Incidence

- There is no single electrocardiographic definition or set of criteria for ERP. Studies have used a range of criteria including ST elevation, terminal QRS slurring, terminal QRS notching, J-point elevation, J waves, and other variations. Although the Brugada ECG pattern is considered an early repolarization variant, it is generally not included in epidemiology assessments of ERP or early repolarization syndrome.[105]
- ERP was observed in 4% to 19% of the population (more commonly in young males and in athletes) and conventionally has been considered a benign finding.[105–109]
- In CARDIA, 18.6% of 5069 participants had early repolarization restricted to the inferior and lateral leads at baseline; by year 20, only 4.8% exhibited an ERP.[109] Younger age, black race, male sex, longer exercise duration and QRS duration, and lower BMI, heart rate, QT index, and Cornell voltage were associated with the presence of baseline early repolarization. Persistence of the electrocardiographic pattern from baseline to year 20 was associated with black race (OR, 2.62 [95% CI, 1.61–4.25]), BMI (OR, 0.62 per 1 SD [95% CI, 0.40–0.94]), serum triglyceride levels (OR, 0.66 per 1 SD [95% CI, 0.45–0.98]), and QRS duration (OR, 1.68 per 1 SD [95% CI, 1.37–2.06]) at baseline.[109]

Complications

- Shocks from an automatic implantable cardioverter-defibrillator occur more often and earlier in survivors of idiopathic VF with inferolateral early repolarization syndrome.[110,111]
- In an analysis of the Social Insurance Institution's Coronary Disease Study in Finland, J-point elevation was identified in 5.8% of 10 864 people.[108] Those with inferior lead J-point elevation more often were male and more often were smokers; had a lower resting heart rate, lower BMI, lower BP, shorter QTc, and longer QRS duration; and were more likely to have electrocardiographic evidence of CAD. Those with lateral J-point elevation were more likely to have LVH. Before and after multivariable adjustment, subjects with J-point elevation ≥1 mm in the inferior leads (n=384) had a higher risk of cardiac death (adjusted RR, 1.28 [95% CI, 1.04–1.59]) and arrhythmic death (adjusted RR, 1.43 [95% CI, 1.06–1.94]); however, these patients did not have a significantly higher rate of all-cause mortality. Before and after multivariable adjustment, subjects with J-point elevation >2 mm (n=36) had an increased risk of cardiac death (adjusted RR, 2.98 [95% CI, 1.85–4.92]), arrhythmic death (adjusted RR, 3.94 [95% CI, 1.96–7.90]), and death of any cause (adjusted RR, 1.54 [95% CI, 1.06–2.24]).
- Evidence from families with a high penetrance of the early repolarization syndrome associated with a high risk of sudden death suggests that the syndrome can be inherited in an autosomal dominant fashion.[112]

Premature Ventricular Contractions

- In a study of 1139 older adults in the CHS without HF or systolic dysfunction studied by Holter monitor (median duration, 22.2 hours), 0.011% of all heartbeats were PVCs, and 5.5% of participants had nonsustained VT. Over follow-up, the highest quartile of ambulatory ECG PVC burden was associated with an adjusted odds of decreased LVEF (OR, 1.13 [95% CI, 1.05–1.21]) and incident HF (HR, 1.06 [95% CI, 1.02–1.09]) and death (HR, 1.04 [95% CI, 1.02–1.06]).[113] Although PVC ablation has been shown to improve cardiomyopathy, the association with death may be complex, representing both a potential cause and a noncausal marker for coronary or structural HD.
- Among 698 patients with cardiac resynchronization therapy, 3-year risk of VT/VF was higher in patients with >10 PVCs/h (24%) than in patients with <10 PVCs /h (8%; adjusted HR, 2.79 [95% CI, 1.69–4.58]).[114]

Monomorphic VT

Prevalence and Incidence

- Among 2099 subjects (mean age 52 years; 52.2% male) without known CVD, exercise-induced nonsustained VT occurred in 3.7% and was not independently associated with total mortality.[115]

Polymorphic VT

Prevalence and Incidence

- In the setting of AMI, the prevalence of PVT was 4.4%.[116]

Complications

- In the setting of AMI, PVT is associated with increased mortality (17.8%).[116]

Risk Factors

- PVT in the setting of a normal QT interval is most frequently seen in the context of acute ischemia or MI.[117]

Torsade de Pointes

Prevalence and Incidence

- Among 14 756 patients exposed to QT-prolonging drugs in 36 studies, 6.3% developed QT prolongation, and 0.33% developed TdP.[118]

- A prospective, active surveillance, Berlin-based registry of 51 hospitals observed that the annual incidence of symptomatic drug-induced QT prolongation in adults was 2.5 per million males and 4.0 per million females. The authors reported 42 potentially associated drugs, including metoclopramide, amiodarone, melperone, citalopram, and levomethadone. The mean age of patients with QT prolongation/TdP was 57±20 years, and the majority of the cases occurred in females (66%) and out of the hospital (60%).[119]
- The prevalence of drug-induced prolongation of QT interval and TdP is 2 to 3 times higher in females than in males.[120,121]

Complications

- In a cohort of 459 614 Medicaid and Medicaid-Medicare enrollees 30 to 75 years of age who were taking antipsychotic medications, the incidence of sudden death was 3.4 per 1000 person-years, and the incidence of ventricular arrhythmia was 35.1 per 1000 person-years.[122]

Risk Factors

- An up-to-date list of drugs with the potential to cause TdP is available at a website maintained by the University of Arizona Center for Education and Research on Therapeutics.[123]
- Specific risk factors for drug-induced TdP include prolonged QT interval, female sex, advanced age, bradycardia, hypokalemia, hypomagnesemia, LV systolic dysfunction, and conditions that lead to elevated plasma concentrations of causative drugs, such as kidney disease, liver disease, drug interactions, or some combination of these.[121,124,125]
- Drug-induced TdP rarely occurs in patients without concomitant risk factors. An analysis of 144 published articles describing TdP associated with noncardiac drugs revealed that 100% of the patients had at least 1 risk factor, and 71% had at least 2 risk factors.[121]

Awareness and Treatment (See Table 17-1)

- Median annual CPR training rate for US counties was 2.39% (25th–75th percentiles, 0.88%–5.31%) based on training data from the AHA, the American Red Cross, and the Health & Safety Institute, the largest providers of CPR training in the United States.[126] Training rates were lower in rural areas, counties with high proportions of black or Hispanic residents, and counties with lower median household income.
- Prevalence of reported current training in CPR was 18% and prevalence of having CPR training at some point was 65% in a survey of 9022 people in the United States in 2015.[127] The prevalence of CPR training was lower in Hispanic/Latino people, older people, people with less formal education, and lower-income groups.
- Those with prior CPR training include 90% of citizens in Norway,[128] 68% of citizens in Victoria, Australia,[129] 61.1% of laypeople in the United Kingdom,[130] and 49% of people in the Republic of Korea,[131] according to surveys.
- Laypeople with knowledge of AEDs include 69.3% of people in the United Kingdom, 66% in Philadelphia, PA, and 32.6% in the Republic of Korea.[130–132] A total of 58% of Philadelphia respondents[132] but only 2.1% of UK respondents[130] reported that they would actually use an AED during a cardiac arrest.
- A survey of 5456 households in Beijing, China, Shanghai, China, and Bangalore, India, found that 26%, 15%, and 3% of respondents, respectively, were trained in CPR.[133]
- A survey of 501 inhabitants of Vienna, Austria, found that 52% would recognize cardiac arrest, 50% were willing to use an AED, and 33% were willing to do CPR.[134]
- Laypeople in the United States initiated CPR in 39.2% of OHCAs in CARES 2018 data (Table 17-1).
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.[135]
- Laypeople in the United States were less likely to initiate CPR for people with OHCA in low-income black neighborhoods (OR, 0.49 [95% CI, 0.41–0.58])[136] or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income white neighborhoods.[137]
- Laypeople from Hispanic and Latino neighborhoods in Denver, CO, reported that barriers to learning or providing CPR include lack of recognition of cardiac arrest events and lack of understanding about what a cardiac arrest is and how CPR can save a life, as well as fear of becoming involved with law enforcement.[138]

Mortality (See Tables 17-2 and 17-5 and Chart 17-1)

- In 2017, primary-cause SCD mortality was 18 835, and any-mention SCD mortality in the United States was 379 133 (Table 17-5). The any-mention age-adjusted annual rate is 97.1 (95% CI, 96.8–97.4) SCDs per 100 000 population.[139]
- Survival of hospitalization after cardiac arrest varied between academic medical centers and was higher in hospitals with higher cardiac arrest volume, higher surgical volume, greater availability of invasive cardiac services, and more affluent catchment areas.[8]

- Survival after OHCA varied between US regions (4.2%–19.8%) in the ROC Epistry from 2011 to 2015.[140] This variation was more marked at the level of EMS agencies (0%–28.9%) and persisted after adjustment for multiple patient, resuscitation, and hospital variables.[141]
- Survival after EMS-treated OHCA was 10.4% in the 2018 CARES registry, with variation between states reporting data (range, 7.8%–15.3%; Table 17-2).
- Of 1 452 808 death certificates from 1999 to 2015 for US residents 1 to 34 years of age, 31 492 listed SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100 000 individuals.[142]
  - SCD rate varied by age, from 0.49 per 100 000 (1–10 years) to 2.76 per 100 000 (26–34 years).
  - The rate of SCD declined from 1999 to 2015, from 1.48 to 1.13 per 100 000 individuals.
- Mortality rates for any mention of SCD by age are provided in Chart 17-1.

OHCA: Adults (See Tables 17-1 and 17-6)

- Survival to hospital discharge after EMS-treated OHCA was 10.4%, and survival with good functional status was 8.2% based on 73 910 cases in CARES for 2018.[5]
- Survival to hospital discharge after EMS-treated cardiac arrest in 2018 was 10.4% for patients of any age and 10.4% for adults in the CARES registry (Tables 17-1 and 17-6).
- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2018 was 28.2% for all presentations, with higher survival rates in public places (40.9%) and lower survival rates in homes/residences (26.4%) and nursing homes (18.5%) in the 2018 CARES registry (Table 17-6).
- Survival to hospital discharge varied between regions of the United States, being higher in the Midwest (adjusted OR, 1.16 [95% CI, 1.02–1.32]) and the South (adjusted OR, 1.24 [95% CI, 1.09–1.40]) relative to the Northeast, in 154 177 patients hospitalized after OHCA in the NIS (2002–2013).[143]
- Survival at 1, 5, 10, and 15 years, respectively, was 92.2%, 81.4%, 70.1%, and 62.3% among 3449 patients surviving to hospital discharge after OHCA from 2000 to 2014 in Victoria, Australia.[144]
- Patients with STEMI who had OHCA had higher in-hospital mortality (38%) than STEMI patients without OHCA (6%) in a Los Angeles, CA, registry of 4729 STEMI patients from 2011 to 2014.[11]
- Survival to 30 days was lower for 2516 patients in nursing homes (1.7% [95% CI, 1.2%–2.2%]) than for 24 483 patients in private homes (4.9% [95% CI, 4.6%–5.2%]) in a national database in Denmark from 2001 to 2014.[145]

Sports-Related SCA/SCD

- In a population-based registry of all paramedic responses for SCA from 2009 to 2014, 43.8% of athletes with SCA during competitive sports survived to hospital discharge.[19]

IHCA: Adults (See Table 17-4 and Chart 17-3)

- Survival to hospital discharge was 25.8% of 26 742 adult IHCAs at 319 hospitals in GWTG 2018 data (Table 17-4, Chart 17-3). Among survivors, 82% had good functional status (cerebral performance category 1 or 2) at hospital discharge.
- Unadjusted survival rate after IHCA was 18.4% in the UK National Cardiac Arrest Audit database between 2011 and 2013. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.[15]
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18 069 patients from 66 hospitals between 2006 and 2015 in the Swedish Register of CPR.[14]
- Survival to hospital discharge after IHCA was lower for males than for females (adjusted OR, 0.90 [95% CI, 0.83–0.99]) in a Swedish registry of 14 933 cases of IHCA from 2007 to 2014.[146]
- Mortality was lower among 348 368 patients with IHCA managed in teaching hospitals (55.3%) than among 376 035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (adjusted OR, 0.92 [95% CI, 0.90–0.94]).[147]

OHCA: Children (See Table 17-7)

- Survival to hospital discharge after EMS-treated nontraumatic cardiac arrest in 2015 was 13.2% (95% CI, 7.0%–19.4%) for children in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016).
- Survival to hospital discharge was 6.7% for 1280 children ≤1 year old, 16.2% for 560 children 1 to 12 years of age, and 19.2% for 416 children 13 to 18 years of age in CARES 2018 data (Table 17-7).
- Mortality was lower in teaching hospitals (OR, 0.57 [95% CI, 0.50–0.66), trauma centers (OR, 0.76 [95% CI, 0.67–0.86]), and urban hospitals (OR, 0.78 [95% CI, 0.63–0.97]) relative to nonteaching, nontrauma, or rural hospitals, respectively, among 42 036 presentations of children 0 to 18 years of age for cardiac or respiratory failure in the HCUP NEDS.[148]
- In a registry including 974 children with OHCA from 2009 to 2012 in Singapore, Japan, Republic

of Korea, Malaysia, Thailand, Taiwan, and United Arab Emirates, 8.6% (range, 0%–9.7%) of children survived to hospital discharge.[149]

IHCA: Children (See Table 17-4)

- Survival to hospital discharge after pulseless IHCA was 41.1% in 571 children 0 to 18 years of age and 38.2% in 159 neonates (0–30 days old) per 2018 GWTG data (Table 17-4).
- Survival to hospital discharge for children with IHCA in the ICU was 45% in the Collaborative Pediatric Critical Care Research Network from 2011 to 2013.[24]

Complications (See Tables 17-6 and 17-7)

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficits (Tables 17-6 and 17-7).
- Functional impairments are associated with reduced function, reduced quality of life, and shortened lifespan.[150,151]
- Functional recovery continues over at least the first 12 months after OHCA in children and over the first 6 to 12 months after OHCA in adults.[152,153]
- Among 366 patients discharged after IHCA in a Veterans Administration hospital between 2014 and 2015, 55 (15%) endorsed suicidal ideation during the first 12 months.[154]
- Serial testing in a cohort of 141 people who survived hospitalization after SCA revealed severe cognitive deficits in 14 (13%), anxiety and depression in 16 (15%), posttraumatic stress symptoms in 29 (28%), and severe fatigue in 55 (52%).[155] Subjective symptoms declined over time after SCA, although 10% to 22% had cognitive impairments at 12 months, with executive functioning being most affected.[156]
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.[155]
- Of 287 people who survived hospitalization after OHCA, 47% had reduced participation in premorbid activities, and 27% of those who were working before the OHCA were on sick leave at 6 months.[157]
- Of 153 survivors of OHCA 18 to 65 years of age in Paris, France, between 2000 and 2013, 96 (63%) returned to work after a mean (SD) of 714 (1013) days.[158] Younger patients with a higher-level job and for whom cardiac arrest occurred in the workplace were more likely to return to work.
- Of 206 patients who survived to 1 year after OHCA in Finland, 188 (91.3%) were living at home.[159] Among 95 patients who were employed before the arrest, 69 (72.6%) had returned to work, whereas 23 (24.2) had stopped work specifically because of their medical condition.
- Among 195 family caregivers of cardiac arrest survivors, anxiety was present in 33 caregivers (25%) and depression in 18 caregivers (14%) at 12 months.[160]
- Among 57 437 patients discharged from the hospital after cardiac arrest identified from 2008 to 2015 Medicare claims data, unadjusted annual incidence of seizures was 1.26% (95% CI, 1.20%–1.33%), which is higher than for other Medicare patients (0.61% [95% CI, 0.61%–0.62%]).[161] Cardiac arrest survivors had no increased hazard for seizures after adjustment for demographics and comorbidities (HR, 0.9 [95% CI, 0.9–1.0]).

Healthcare Utilization and Cost

- In the Oregon SUDS, the estimated societal burden of SCD in the United States was 2 million years of potential life lost for males and 1.3 million years of potential life lost for females, accounting for 40% to 50% of the years of potential life lost from all cardiac disease.[162]
- Among 138 children surviving IHCA, caregiver burden increased at baseline and at 3 and 12 months as measured by the Infant Toddler Quality of Life Questionnaire (<5 years) or the Child Health Questionnaire (children >5 years).[163]
- Among males, estimated deaths attributable to SCD exceeded all other individual causes of death, including lung cancer, accidents, CLRD, cerebrovascular disease, DM, prostate cancer, and colorectal cancer.[162]

Global Burden

- International comparisons of cardiac arrest epidemiology must take into account differences in case ascertainment. OHCA usually is identified through EMS systems, and regional and cultural differences in use of EMS affect results.[164]
- A systematic review of the international epidemiology of OHCA from 1991 to 2007 included 30 studies from Europe, 24 from North America, 7 from Asia, and 6 from Australia.[165] Estimated incidence per 100 000 population of EMS-assessed OHCA was 86.4 in Europe, 98.1 in North America, 52.5 in Asia, and 112.9 in Australia. Estimated incidence per 100 000 population of EMS-treated OHCA was 40.6 in Europe, 47.3 in North America, 45.9 in Asia, and 51.1 in Australia. The proportion of cases

with VF was highest in Europe (35.2%) and lowest in Asia (11.2%).

- A prospective data collection concerning 10 682 OHCA cases from 27 European countries in October 2014 found an incidence of 84 per 100 000 people, with CPR attempted in 19 to 104 cases per 100 000 people.[166] Return of pulse occurred in 28.6% (range for countries, 9%–50%), with 10.3% (range, 1.1%–30.8%) of people on whom CPR was attempted surviving to hospital discharge or 30 days.
- Western Australia reports an age- and sex-adjusted incidence of 65.9 EMS-attended cardiac arrests per 100 000 population, with resuscitation attempted in 43%.[167] Survival to hospital discharge was 8.7%. Among children (<18 years of age), crude incidence was 5.6 per 100 000.[16]
- Hospitals in Beijing, China, reported IHCA incidence of 17.5 events per 1000 admissions.[168]
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.[169]

Table 17-1. Trends in Layperson Response and Outcomes for EMS-Treated OHCA, 2006 to 2018

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Survival to hospital discharge													
ROC	10.2	10.1	11.9	10.3	11.1	11.3	12.4	11.9	12.7	12.4	…	…	…
CARES	…	…	…	…	…	10.5	10	10.6	10.8	10.6	10.8	10.5	10.4
Survival if first rhythm shockable													
ROC	25.9	29	33.6	27.8	30.1	30.9	34.1	32.7	33.5	30.2	…	…	…
CARES	…	…	…	…	…	…	…	…	29.3	29.1	29.5	29.3	29.5
First rhythm shockable													
ROC	23.7	21.7	21.9	20.9	20.8	21.4	21.7	20.2	20.8	21.3	…	…	…
CARES	…	…	…	…	…	23.2	23.1	23.2	20.4	20.1	19.8	18.4	18.4
Layperson-initiated CPR													
ROC	36.5	37.9	37.4	39.1	38.6	38.6	42.8	43	44.5	43.6	…	…	…
CARES	…	…	…	…	…	38	37.8	40.4	40.4	40.6	40.7	39.4	39.2
Layperson use of AED													
ROC	3.2	3.3	3.9	4.5	4	3.9	5.1	6	6.6	6.7	…	…	…
CARES	…	…	…	…	…	4.4	4	4.6	4.9	5.4	5.7	6.0	7.3
AED shock by layperson													
ROC	2	1.6	1.8	1.8	2	1.8	2	2.2	2.2	2.3	…	…	…
CARES	…	…	…	…	…	1.7	1.6	1.6	1.6	1.7	1.7	1.6	1.7

Values are percentages. AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; ellipses (…), data not available; EMS, emergency medical services, OHCA, out-of-hospital cardiac arrest; and ROC, Resuscitation Outcomes Consortium.

Source: Data reported by ROC (ROC Investigators, unpublished data, July 7, 2016) and CARES.[5]

Table 17-2. Regional Variation in EMS-Treated OHCA, 2018

	Percent of Population Reporting Data	EMS-Treated OHCA Cases	Rate per 100 000 persons	Layperson-Initiated CPR, %	Public Use of AED, %	Survival to Hospital Discharge if Witnessed Collapse and Shockable Rhythm, %	Overall Survival to Hospital Discharge, %
United States	33.7	81 864	74.3	39.2	11.9	33.3	10.4
Alaska	83.2	410	66.8	70.7	14.9	35.1	12.9
District of Columbia	100.0	793	112.9	31.4	8.5	37.5	7.8
Delaware	100.0	1241	128.3	32.1	9.0	32.5	14.3
Hawaii	100.0	1348	94.9	47.8	9.9	33.2	10.7
Michigan	81.9	7451	91.0	37.6	14.5	29.9	8.4
Minnesota	85.6	2478	51.6	37.4	13.0	36.2	13.1
Montana	60.5	375	58.4	50.3	9.1	27.5	11.5
North Carolina	68.9	5420	75.7	36.3	11.8	34.7	12.5
Oregon	85.6	2300	64.1	55.0	13.3	39.0	14.5
Pennsylvania	70.4	7254	80.5	33.3	12.9	33.9	9.4
Vermont	100.0	507	81.0	46.2	9.2	25.6	11.6
Washington	84.4	4051	63.7	57.3	14.5	42.1	15.3

Population reporting data indicates percentage of region's population within geographic footprint of EMS agencies contributing data. Layperson CPR rate excludes EMS witnessed, nursing home, and healthcare facility events. Public AED use rate excludes EMS witnessed, home/residence, nursing home, and healthcare facility events. AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services, and OHCA, out-of-hospital cardiac arrest.

Source: Cardiac Arrest Registry to Enhance Survival 2018 data from states with ≥50% population reporting data and voluntarily sharing data.[5]

Table 17-3. SCA Diagnoses Among ED Visits in the United States, 2016

	Adult (≥18 y)	Child (1–17 y)	Infant (<1 y)	Total	Rate per 100 000 People
Any listed diagnosis, n	393 872	6510	3961	404 691	125.2
CPR or defibrillation procedure code, n	185 509	969	559	187 097	88.8
Principal diagnosis, n	177 052	3406	3027	183 629	56.8
Died in ED, %	77.1	70.0	80.8	77.0	…
Transferred to another hospital, %	5.1	15.0	8.4	5.3	…
Admitted to same hospital, %	10.8	5.2	2.1	10.5	…
Died in same hospital, %	5.6	2.1	1.9	5.5	…
Discharged from same hospital, %	4.9	2.7	…	5.0	…

CPR indicates cardiopulmonary resuscitation; ED, emergency department; ellipses (…), data not reported; and SCA, sudden cardiac arrest.

Source: Unpublished tabulation using Healthcare Cost and Utilization Project, 2016.[9]

Table 17-4. Characteristics of and Outcomes for OHCA and IHCA, 2018

	OHCA		IHCA	
	Adults	Children	Adults	Children
Survival to hospital discharge	10.4	11.4	25.8	41.1
Good functional status at hospital discharge	8.2	9.2	21.2	14.2
VF/VT/shockable	18.7	7.6	15.3	9.0
PEA	…	…	53.9	48.4
Asystole	…	…	22.7	28.5
Unknown	…	…	8.1	14.2
Public setting	18.8	13.3	…	…
Home	69.8	86.4	…	…
Nursing home	11.5	0.3	…	…
Arrest in ICU, operating room, or ED	…	…	54.2	87.0
Noncritical care area	…	…	45.8	13.0

Values are percentages. ED indicates emergency department; ellipses (…), data not available; EMS, emergency medical services; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Source: OHCA data derived from the Cardiac Arrest Registry to Enhance Survival,[5] based on 79356 EMS-treated OHCA adult cases and 2256 EMS-treated OHCA child cases in 2018. IHCA data are from Get With The Guidelines (unpublished AHA tabulation) 2018, based on 26742 pulseless adult IHCAs in 319 hospitals and 571 pulseless child IHCAs in 90 hospitals.

Table 17-5. SCA Mortality, 2017 (*ICD-10* Codes 146.0, 146.1, 146.9, 149.0)

Population Group	Number of Deaths as Underlying Cause, 2017, All Ages	Number of Deaths as Any-Mention Cause, 2017, All Ages
Both sexes	18835	379133
Males	10144	195227
Females	8691	183906
NH white males	7623	140039
NH white females	6554	130378
NH black males	1748	26213
NH black females	1506	26815
Hispanic males	456	18823
Hispanic females	355	17596
NH Asian/Pacific Islander males	252	7913
NH Asian/Pacific Islander females	220	7416
NH American Indian/Alaska Natives	87	2502

Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses. *ICD-10* indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and SCA, sudden cardiac arrest.

Sources: Underlying cause data derived from unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017.[170] Any-mention cause data derived from unpublished NHLBI tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database, 2017.[139]

Table 17-6. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (Age ≥18 Years), CARES, 2018

Presenting Characteristics (N)	Survival to Hospital Admission	Survival to Hospital Discharge	Survival With Good Neurological Function (CPC 1 or 2)	In-Hospital Mortality*
All presentations (79356)	28.2	10.4	8.2	63.3
Home/residence (55358)	26.4	8.5	6.6	67.9
Nursing home (9105)	18.5	4.3	1.9	76.9
Public setting (14893)	40.9	21.0	18.1	48.7
Unwitnessed (39378)	17.9	4.4	3.2	75.4
Bystander witnessed (29887)	37.3	15.6	12.7	58.1
EMS provider witnessed (10089)	41.7	17.9	14.3	57.1
Shockable presenting rhythm (14867)	48.2	29.2	25.7	39.3
Nonshockable presenting rhythm (64477)	23.6	6.0	4.1	74.7
Layperson CPR (22707)	31.2	13.6	11.6	56.2
No layperson CPR (35706)	24.6	7.3	5.5	70.5

Values are percentages. CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Index; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to hospital who died before hospital discharge.

Source: Data derived from CARES.[5]

Table 17-7. Outcomes of EMS-Treated Nontraumatic OHCA in Children, CARES, 2018

Age Group (N)	Survival to Hospital Admission	Survival to Hospital Discharge	Survival With Good Neurological Function (CPC 1 or 2)	In-Hospital Mortality*
<1 y (1280)	19.2	6.7	4.9	65.0
1–12 y (560)	37.9	16.2	13.2	57.1
13–18 y (416)	41.1	19.2	17.1	53.2

Values are percentages. CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

*Percentage of patients admitted to hospital who died before hospital discharge.

Source: Data derived from CARES.[5]

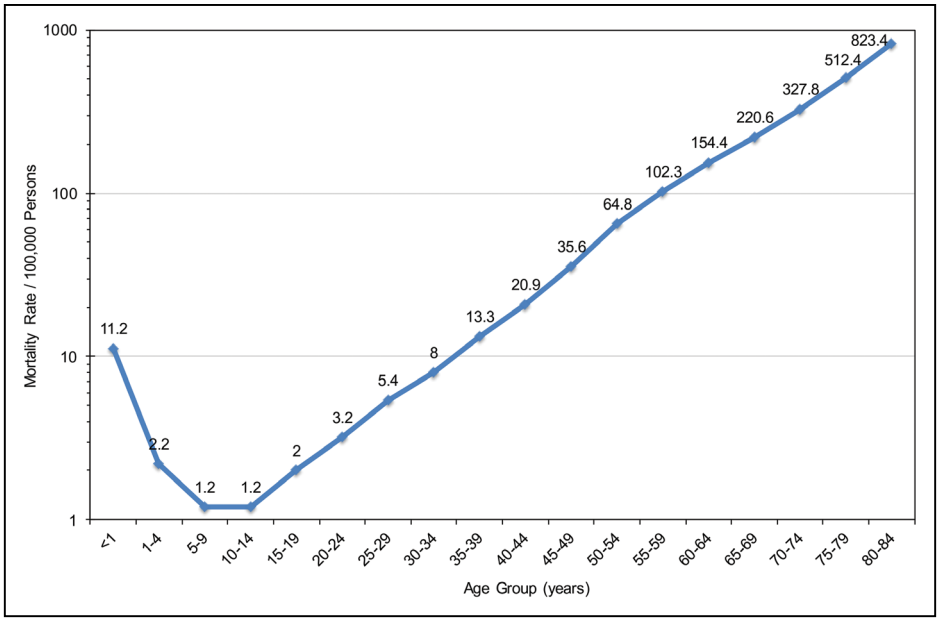

Chart 17-1. Age-specific mortality rates for any mention of sudden cardiac death by age, United States, 2017.
Source: Data derived from Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database. Accessed June 7, 2018.[139]

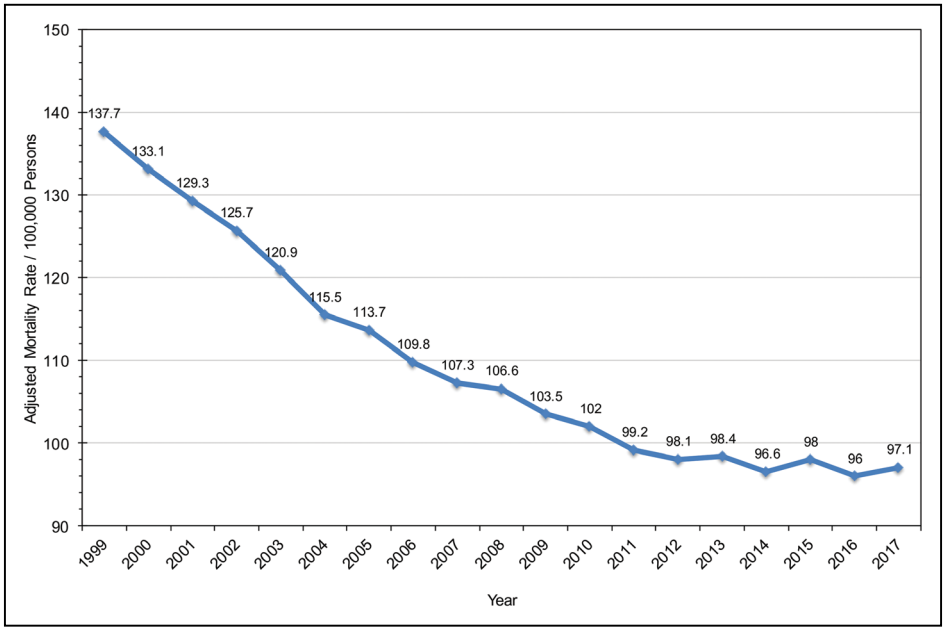

Chart 17-2. Age-adjusted mortality rates for any mention of sudden cardiac death, United States, 1999 to 2017.
Source: Data derived from Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research. Accessed June 7, 2018.[139]

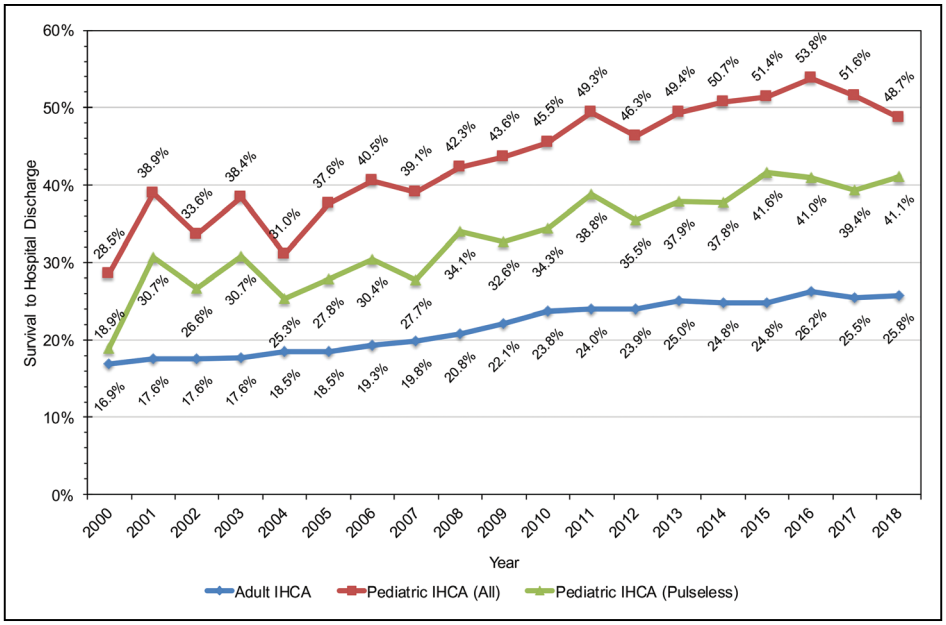

Chart 17-3. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG–Resuscitation from 2000 to 2018.
GWTG indicates Get With The Guidelines; and IHCA, in-hospital cardiac arrest.
Source: GWTG–Resuscitation; unpublished American Heart Association data, 2017.

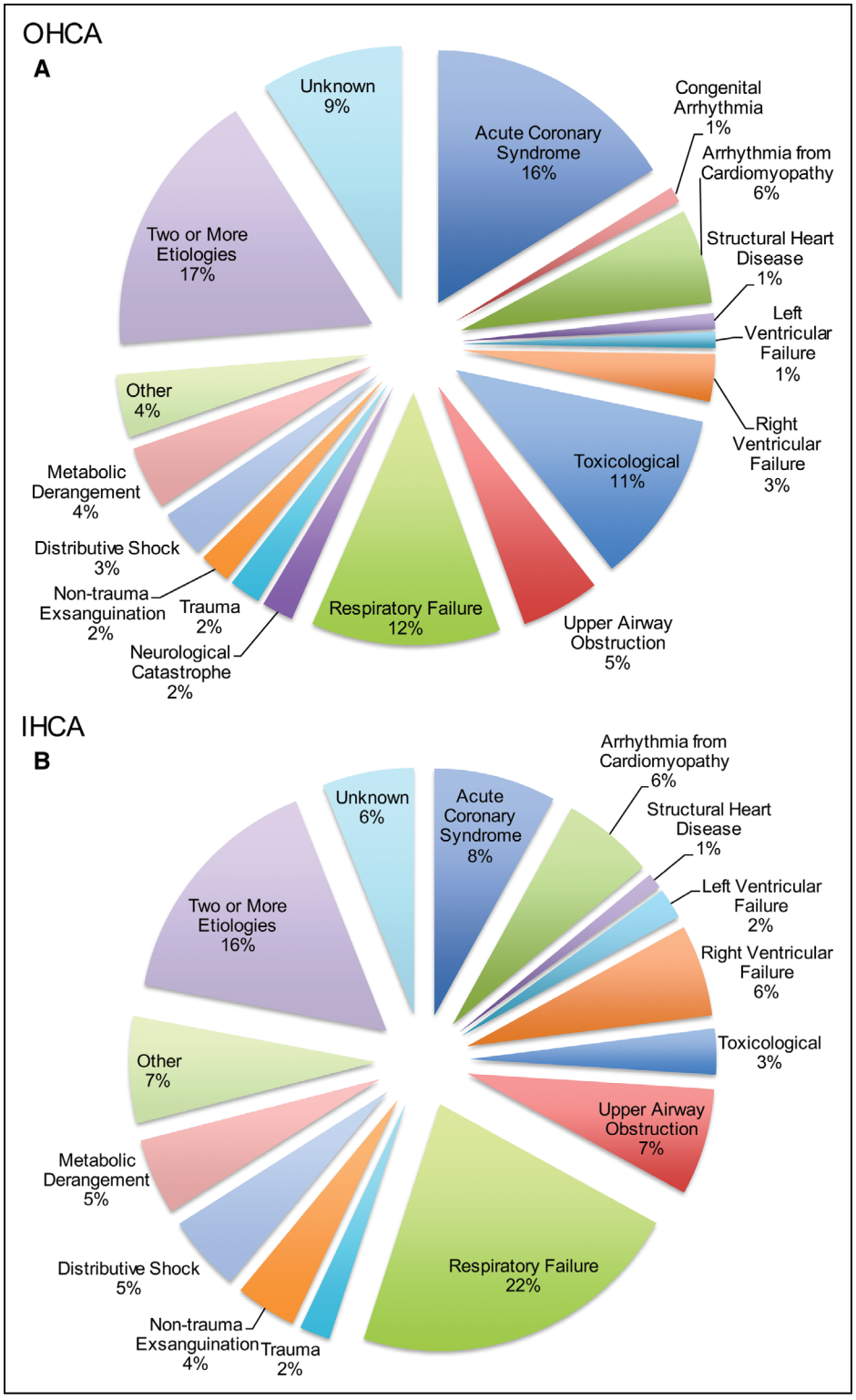

Chart 17-4. Detailed causes of OHCA and IHCA among patients surviving to hospital admission.
A, Proportion of hospitalized patients with each cause after OHCA. **B**, Proportion of hospitalized patients with each cause after IHCA. Pathogenesis based on testing and evaluation in the hospital. "Other" corresponds to all other causes. IHCA, in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.
Source: Data derived from Chen et al.[30]

REFERENCES

1. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, et al; on behalf of the International Liaison Committee on Resuscitation; American Heart Association; European Resuscitation Council; Australian Resuscitation Council; New Zealand Resuscitation Council; Heart and Stroke Foundation of Canada; InterAmerican Heart Foundation; Resuscitation Councils of Southern Africa; ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385–3397. doi: 10.1161/01.CIR.0000147236.85306.15
2. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, et al; on behalf of the Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation [published correction appears in *Circulation*. 2015;132:e168–e169]. *Circulation*. 2015;132:1286–1300. doi: 10.1161/CIR.0000000000000144
3. Claesson A, Djarv T, Nordberg P, Ringh M, Hollenberg J, Axelsson C, Ravn-Fischer A, Stromsoe A. Medical versus non medical etiology in out-of-hospital cardiac arrest: changes in outcome in relation to the revised Utstein template. *Resuscitation*. 2017;110:48–55. doi: 10.1016/j.resuscitation.2016.10.019
4. Peterson DF, Siebert DM, Kucera KL, Thomas LC, Maleszewski JJ, Lopez-Anderson M, Suchsland MZ, Harmon KG, Drezner JA. Etiology of sudden cardiac arrest and death in US competitive athletes: a 2-year prospective surveillance study [published online April 9, 2018]. *Clin J Sport Med*. 2018. doi: 10.1097/JSM.0000000000000598. https://insights.ovid.com/crossref?an=00042752-900000000-99312
5. Cardiac Arrest Registry to Enhance Survival website. https://mycares.net. Accessed April 1, 2019.
6. US population data (population clock). United States Census Bureau website. www.census.gov/popclock. Accessed June 8, 2019.
7. Graham RM, McCoy MA, Shchultz AM. eds. *Strategies to Improve Cardiac Arrest Survival: A Time to Act*. Washington, DC: National Academies Press; 2015.
8. Kurz MC, Donnelly JP, Wang HE. Variations in survival after cardiac arrest among academic medical center-affiliated hospitals. *PLoS One*. 2017;12:e0178793. doi: 10.1371/journal.pone.0178793
9. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
10. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, Cooke MW, Deakin CD, Gale CP, Fothergill R, et al; OHCAO Collaborators. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation*. 2017;110:133–140. doi: 10.1016/j.resuscitation.2016.10.030
11. Shavelle DM, Bosson N, Thomas JL, Kaji AH, Sung G, French WJ, Niemann JT. Outcomes of ST elevation myocardial infarction complicated by out-of-hospital cardiac arrest (from the Los Angeles County Regional System). *Am J Cardiol*. 2017;120:729–733. doi: 10.1016/j.amjcard.2017.06.010
12. Olgin JE, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, Zweibel S, Buxton AE, Elayi CS, Chung EH, et al; VEST Investigators. Wearable cardioverter-defibrillator after myocardial infarction. *N Engl J Med*. 2018;379:1205–1215. doi: 10.1056/NEJMoa1800781
13. Bradley SM, Kaboli P, Kamphuis LA, Chan PS, Iwashyna TJ, Nallamothu BK. Temporal trends and hospital-level variation of inhospital cardiac arrest incidence and outcomes in the Veterans Health Administration. *Am Heart J*. 2017;193:117–123. doi: 10.1016/j.ahj.2017.05.018
14. Hessulf F, Karlsson T, Lundgren P, Aune S, Strömsöe A, Södersved Källestedt ML, Djärv T, Herlitz J, Engdahl J. Factors of importance to 30-day survival after in-hospital cardiac arrest in Sweden: a population-based register study of more than 18,000 cases. *Int J Cardiol*. 2018;255:237–242. doi: 10.1016/j.ijcard.2017.12.068
15. Nolan JP, Soar J, Smith GB, Gwinnutt C, Parrott F, Power S, Harrison DA, Nixon E, Rowan K; National Cardiac Arrest Audit. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation*. 2014;85:987–992. doi: 10.1016/j.resuscitation.2014.04.002
16. Inoue M, Tohira H, Williams T, Bailey P, Borland M, McKenzie N, Brink D, Finn J. Incidence, characteristics and survival outcomes of out-of-hospital cardiac arrest in children and adolescents between 1997 and 2014 in Perth, Western Australia. *Emerg Med Australas*. 2017;29:69–76. doi: 10.1111/1742-6723.12657
17. Jayaraman R, Reinier K, Nair S, Aro AL, Uy-Evanado A, Rusinaru C, Stecker EC, Gunson K, Jui J, Chugh SS. Risk factors of sudden cardiac death in the young: multiple-year community-wide assessment. *Circulation*. 2018;137:1561–1570. doi: 10.1161/CIRCULATIONAHA.117.031262
18. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ, et al. Incidence and etiology of sudden cardiac arrest and death in high school athletes in the United States. *Mayo Clin Proc*. 2016;91:1493–1502. doi: 10.1016/j.mayocp.2016.07.021
19. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P; Rescu Investigators. Sudden cardiac arrest during participation in competitive sports. *N Engl J Med*. 2017;377:1943–1953. doi: 10.1056/NEJMoa1615710
20. Waite O, Smith A, Madge L, Spring H, Noret N. Sudden cardiac death in marathons: a systematic review. *Phys Sportsmed*. 2016;44:79–84. doi: 10.1080/00913847.2016.1135036
21. Nilson F, Börjesson M. Mortality in long-distance running races in Sweden: 2007-2016. *PLoS One*. 2018;13:e0195626. doi: 10.1371/journal.pone.0195626
22. Vicent L, Ariza-Solé A, González-Juanatey JR, Uribarri A, Ortiz J, López de Sá E, Sans-Roselló J, Querol CT, Codina P, Sousa-Casasnovas I, et al; Cardiac Arrest and Myocardial Infarction Notified After Marathon Or Similar effort (CAMINAMOS) registry. Exercise-related severe cardiac events. *Scand J Med Sci Sports*. 2018;28:1404–1411. doi: 10.1111/sms.13037
23. Angelini P, Cheong BY, Lenge De Rosen VV, Lopez A, Uribe C, Masso AH, Ali SW, Davis BR, Muthupillai R, Willerson JT. High-risk cardiovascular conditions in sports-related sudden death: prevalence in 5,169 schoolchildren screened via cardiac magnetic resonance. *Tex Heart Inst J*. 2018;45:205–213. doi: 10.14503/THIJ-18-6645
24. Berg RA, Nadkarni VM, Clark AE, Moler F, Meert K, Harrison RE, Newth CJ, Sutton RM, Wessel DL, Berger JT, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med*. 2016;44:798–808. doi: 10.1097/CCM.0000000000001484
25. Alten JA, Klugman D, Raymond TT, Cooper DS, Donohue JE, Zhang W, Pasquali SK, Gaies MG. Epidemiology and outcomes of cardiac arrest in pediatric cardiac ICUs. *Pediatr Crit Care Med*. 2017;18:935–943. doi: 10.1097/PCC.0000000000001273
26. Hagnäs MJ, Lakka TA, Mäkikallio TH, Kurl S, Savonen K, Rauramaa R, Laukkanen JA. High leisure-time physical activity is associated with reduced risk of sudden cardiac death among men with low cardiorespiratory fitness. *Can J Cardiol*. 2018;34:288–294. doi: 10.1016/j.cjca.2017.12.003
27. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Køber L, et al. Declining risk of sudden death in heart failure. *N Engl J Med*. 2017;377:41–51. doi: 10.1056/NEJMoa1609758
28. Nehme Z, Namachivayam S, Forrest A, Butt W, Bernard S, Smith K. Trends in the incidence and outcome of paediatric out-of-hospital cardiac arrest: a 17-year observational study. *Resuscitation*. 2018;128:43–50. doi: 10.1016/j.resuscitation.2018.04.030
29. Lee SY, Song KJ, Shin SD, Ro YS, Hong KJ, Kim YT, Hong SO, Park JH, Lee SC. A disparity in outcomes of out-of-hospital cardiac arrest by community socioeconomic status: a ten-year observational study. *Resuscitation*. 2018;126:130–136. doi: 10.1016/j.resuscitation.2018.02.025
30. Chen N, Callaway CW, Guyette FX, Rittenberger JC, Doshi AA, Dezfulian C, Elmer J; Pittsburgh Post-Cardiac Arrest Service. Arrest etiology among patients resuscitated from cardiac arrest. *Resuscitation*. 2018;130:33–40. doi: 10.1016/j.resuscitation.2018.06.024

31. Bougouin W, Mustafic H, Marijon E, Murad MH, Dumas F, Barbouttis A, Jabre P, Beganton F, Empana JP, Celermajer DS, et al. Gender and survival after sudden cardiac arrest: a systematic review and meta-analysis. *Resuscitation.* 2015;94:55–60. doi: 10.1016/j.resuscitation.2015.06.018
32. Dicker B, Conaglen K, Howie G. Gender and survival from out-of-hospital cardiac arrest: a New Zealand registry study. *Emerg Med J.* 2018;35:367–371. doi: 10.1136/emermed-2017-207176
33. Ng YY, Wah W, Liu N, Zhou SA, Ho AF, Pek PP, Shin SD, Tanaka H, Khunkhlai N, Lin CH, et al; PAROS Clinical Research Network. Associations between gender and cardiac arrest outcomes in Pan-Asian out-of-hospital cardiac arrest patients. *Resuscitation.* 2016;102:116–121. doi: 10.1016/j.resuscitation.2016.03.002
34. Sabbag A, Goldenberg I, Moss AJ, McNitt S, Glikson M, Biton Y, Jackson L, Polonsky B, Zareba W, Kutyifa V. Predictors and risk of ventricular tachyarrhythmias or death in black and white cardiac patients: a MADIT-CRT Trial Substudy. *JACC Clin Electrophysiol.* 2016;2:448–455. doi: 10.1016/j.jacep.2016.03.003
35. Galea S, Blaney S, Nandi A, Silverman R, Vlahov D, Foltin G, Kusick M, Tunik M, Richmond N. Explaining racial disparities in incidence of and survival from out-of-hospital cardiac arrest. *Am J Epidemiol.* 2007;166:534–543. doi: 10.1093/aje/kwm102
36. Reinier K, Thomas E, Andrusiek DL, Aufderheide TP, Brooks SC, Callaway CW, Pepe PE, Rea TD, Schmicker RH, Vaillancourt C, et al; Resuscitation Outcomes Consortium Investigators. Socioeconomic status and incidence of sudden cardiac arrest. *CMAJ.* 2011;183:1705–1712. doi: 10.1503/cmaj.101512
37. Goh CE, Mooney SJ, Siscovick DS, Lemaitre RN, Hurvitz P, Sotoodehnia N, Kaufman TK, Zulaika G, Lovasi GS. Medical facilities in the neighborhood and incidence of sudden cardiac arrest. *Resuscitation.* 2018;130:118–123. doi: 10.1016/j.resuscitation.2018.07.005
38. Archangelidi O, Pujades-Rodriguez M, Timmis A, Jouven X, Denaxas S, Hemingway H. Clinically recorded heart rate and incidence of 12 coronary, cardiac, cerebrovascular and peripheral arterial diseases in 233,970 men and women: a linked electronic health record study. *Eur J Prev Cardiol.* 2018;25:1485–1495. doi: 10.1177/2047487318785228
39. Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, Smeeth L, Timmis A, Hemingway H. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1937360 people in England: lifetime risks and implications for risk prediction. *Int J Epidemiol.* 2015;44:129–141. doi: 10.1093/ije/dyu218
40. Bell S, Daskalopoulou M, Rapsomaniki E, George J, Britton A, Bobak M, Casas JP, Dale CE, Denaxas S, Shah AD, et al. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ.* 2017;356:j909. doi: 10.1136/bmj.j909
41. Pokorney SD, Al-Khatib SM, Sun JL, Schulte P, O'Connor CM, Teerlink JR, Armstrong PW, Ezekowitz JA, Starling RC, Voors AA, et al. Sudden cardiac death after acute heart failure hospital admission: insights from ASCEND-HF. *Eur J Heart Fail.* 2018;20:525–532. doi: 10.1002/ejhf.1078
42. Rattanawong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, Chung EH. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2018;51:91–104. doi: 10.1007/s10840-017-0308-9
43. Eisen A, Ruff CT, Braunwald E, Nordio F, Corbalan R, Dalby A, Dorobantu M, Mercuri M, Lanz H, Rutman H, et al. Sudden cardiac death in patients with atrial fibrillation: insights from the ENGAGE AF-TIMI 48 Trial. *J Am Heart Assoc.* 2016;5:e003735. doi: 10.1161/JAHA.116.003735
44. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, Kestenbaum B, Chen LY, Heckbert SR, Folsom AR, et al. Development and validation of a sudden cardiac death prediction model for the general population. *Circulation.* 2016;134:806–816. doi: 10.1161/CIRCULATIONAHA.116.023042
45. Al-Gobari M, Le HH, Fall M, Gueyffier F, Burnand B. No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: a meta-analysis of randomized controlled trials. *PLoS One.* 2017;12:e0171168. doi: 10.1371/journal.pone.0171168
46. Aro AL, Rusinaru C, Uy-Evanado A, Reinier K, Phan D, Gunson K, Jui J, Chugh SS. Syncope and risk of sudden cardiac arrest in coronary artery disease. *Int J Cardiol.* 2017;231:26–30. doi: 10.1016/j.ijcard.2016.12.021
47. Langén VL, Niiranen TJ, Puukka P, Lehtonen AO, Hernesniemi JA, Sundvall J, Salomaa V, Jula AM. Thyroid-stimulating hormone and risk of sudden cardiac death, total mortality and cardiovascular morbidity. *Clin Endocrinol (Oxf).* 2018;88:105–113. doi: 10.1111/cen.13472
48. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. *Psychosom Med.* 2017;79:153–161. doi: 10.1097/PSY.0000000000000382
49. Andersen LW, Kim WY, Chase M, Berg KM, Mortensen SJ, Moskowitz A, Novack V, Cocchi MN, Donnino MW; American Heart Association's Get With the Guidelines–Resuscitation Investigators. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. *Resuscitation.* 2016;98:112–117. doi: 10.1016/j.resuscitation.2015.08.016
50. Smith GB, Prytherch DR, Jarvis S, Kovacs C, Meredith P, Schmidt PE, Briggs J. A comparison of the ability of the physiologic components of medical emergency team criteria and the U.K. National Early Warning Score to discriminate patients at risk of a range of adverse clinical outcomes. *Crit Care Med.* 2016;44:2171–2181. doi: 10.1097/CCM.0000000000002000
51. Green M, Lander H, Snyder A, Hudson P, Churpek M, Edelson D. Comparison of the Between the Flags calling criteria to the MEWS, NEWS and the electronic Cardiac Arrest Risk Triage (eCART) score for the identification of deteriorating ward patients. *Resuscitation.* 2018;123:86–91. doi: 10.1016/j.resuscitation.2017.10.028
52. Kim M, Li G. Postoperative complications affecting survival after cardiac arrest in general surgery patients. *Anesth Analg.* 2018;126:858–864. doi: 10.1213/ANE.0000000000002460
53. O'Neal WT, Singleton MJ, Roberts JD, Tereshchenko LG, Sotoodehnia N, Chen LY, Marcus GM, Soliman EZ. Association between QT-interval components and sudden cardiac death: the ARIC Study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol.* 2017;10:e005485. doi: 10.1161/CIRCEP.117.005485
54. Lanza GA, Argirò A, Mollo R, De Vita A, Spera F, Golino M, Rota E, Filice M, Crea F. Six-year outcome of subjects without overt heart disease with an early repolarization/J wave electrocardiographic pattern. *Am J Cardiol.* 2017;120:2073–2077. doi: 10.1016/j.amjcard.2017.08.028
55. Sun GZ, Ye N, Chen YT, Zhou Y, Li Z, Sun YX. Early repolarization pattern in the general population: prevalence and associated factors. *Int J Cardiol.* 2017;230:614–618. doi: 10.1016/j.ijcard.2016.12.045
56. De Lazzari C, Genuini I, Gatto MC, Cinque A, Mancone M, D'Ambrosi A, Silvetti E, Fusto A, Pisanelli DM, Fedele F. Screening high school students in Italy for sudden cardiac death prevention by using a telecardiology device: a retrospective observational study. *Cardiol Young.* 2017;27:74–81. doi: 10.1017/S1047951116000147
57. Awamleh Garcia P, Alonso Martin JJ, Graupner Abad C, Jimenez Hernandez RM, Curcio Ruigomez A, Talavera Calle P, Cristobal Varela C, Serrano Antolin J, Muniz J, Gomez Doblas JJ, et al. Prevalence of electrocardiographic patterns associated with sudden cardiac death in the Spanish population aged 40 years or older: results of the OFRECE Study. *Rev Esp Cardiol (Engl Ed).* 2017;70:801–807.
58. Christiansen SL, Hertz CL, Ferrero-Miliani L, Dahl M, Weeke PE, LuCamp, Ottesen GL, Frank-Hansen R, Bundgaard H, Morling N. Genetic investigation of 100 heart genes in sudden unexplained death victims in a forensic setting. *Eur J Hum Genet.* 2016;24:1797–1802. doi: 10.1038/ejhg.2016.118
59. Nunn LM, Lopes LR, Syrris P, Murphy C, Plagnol V, Firman E, Dalageorgou C, Zorio E, Domingo D, Murday V, et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *Europace.* 2016;18:888–896. doi: 10.1093/europace/euv285
60. Anderson JH, Tester DJ, Will ML, Ackerman MJ. Whole-exome molecular autopsy after exertion-related sudden unexplained death in the young. *Circ Cardiovasc Genet.* 2016;9:259–265. doi: 10.1161/CIRCGENETICS.115.001370
61. Steinberg C, Padfield GJ, Champagne J, Sanatani S, Angaran P, Andrade JG, Roberts JD, Healey JS, Chauhan VS, Birnie DH, et al. Cardiac abnormalities in first-degree relatives of unexplained cardiac arrest victims: a report from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythm Electrophysiol.* 2016;9:e004274. doi: 10.1161/CIRCEP.115.004274
62. Kumar S, Peters S, Thompson T, Morgan N, Maccicoca I, Trainer A, Zentner D, Kalman JM, Winship I, Vohra JK. Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. *Heart Rhythm.* 2013;10:1653–1660. doi: 10.1016/j.hrthm.2013.08.022
63. Quenin P, Kyndt F, Mabo P, Mansourati J, Babuty D, Thollet A, Guyomarch B, Redon R, Barc J, Schott JJ, et al. Clinical yield of familial screening after sudden death in young subjects: the French experience. *Circ Arrhythm Electrophysiol.* 2017;10:e005236. doi: 10.1161/CIRCEP.117.005236

64. Müllertz KM, Christiansen MK, Broendberg AK, Pedersen LN, Jensen HK. Outcome of clinical management in relatives of sudden cardiac death victims. *Int J Cardiol.* 2018;262:45–50. doi: 10.1016/j.ijcard.2018.03.022
65. Giudicessi JR, Ackerman MJ. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. *Int J Cardiol.* 2018;270:214–220. doi: 10.1016/j.ijcard.2018.05.100
66. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Müller-Nurasyid M, Moes A, Meitinger T, Mak A, Huikuri H, et al. A comprehensive evaluation of the genetic architecture of sudden cardiac arrest. *Eur Heart J.* 2018;39:3961–3969. doi: 10.1093/eurheartj/ehy474
67. Arking DE, Junttila MJ, Goyette P, Huertas-Vazquez A, Eijgelsheim M, Blom MT, Newton-Cheh C, Reinier K, Teodorescu C, Uy-Evanado A, et al. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. *PLoS Genet.* 2011;7:e1002158. doi: 10.1371/journal.pgen.1002158
68. Bezzina CR, Lahrouchi N, Priori SG. Genetics of sudden cardiac death. *Circ Res.* 2015;116:1919–1936. doi: 10.1161/CIRCRESAHA.116.304030
69. Nakano Y, Shimizu W. Genetics of long-QT syndrome. *J Hum Genet.* 2016;61:51–55. doi: 10.1038/jhg.2015.74
70. Goldenberg I, Zareba W, Moss AJ. Long QT syndrome. *Curr Probl Cardiol.* 2008;33:629–694. doi: 10.1016/j.cpcardiol.2008.07.002
71. Wedekind H, Burde D, Zumhagen S, Debus V, Burkhardtsmaier G, Mönnig G, Breithardt G, Schulze-Bahr E. QT interval prolongation and risk for cardiac events in genotyped LQTS-index children. *Eur J Pediatr.* 2009;168:1107–1115. doi: 10.1007/s00431-008-0896-6
72. Crotti L, Tester DJ, White WM, Bartos DC, Insolia R, Besana A, Kunic JD, Will ML, Velasco EJ, Bair JJ, et al. Long QT syndrome-associated mutations in intrauterine fetal death. *JAMA.* 2013;309:1473–1482. doi: 10.1001/jama.2013.3219
73. Tester DJ, Wong LCH, Chanana P, Jaye A, Evans JM, FitzPatrick DR, Evans MJ, Fleming P, Jeffrey I, Cohen MC, et al. Cardiac genetic predisposition in sudden infant death syndrome. *J Am Coll Cardiol.* 2018;71:1217–1227. doi: 10.1016/j.jacc.2018.01.030
74. Fernandes FM, Silva EP, Martins RR, Oliveira AG. QTc interval prolongation in critically ill patients: prevalence, risk factors and associated medications. *PLoS One.* 2018;13:e0199028. doi: 10.1371/journal.pone.0199028
75. Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, Kovacs RJ. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US. *Drug Saf.* 2012;35:459–470. doi: 10.2165/11598160-000000000-00000
76. Mahmud R, Gray A, Nabeebaccus A, Whyte MB. Incidence and outcomes of long QTc in acute medical admissions. *Int J Clin Pract.* 2018;72:e13250. doi: 10.1111/ijcp.13250
77. Anderson HN, Bos JM, Haugaa KH, Morlan BW, Tarrell RF, Caraballo PJ, Ackerman MJ. Prevalence and outcome of high-risk QT prolongation recorded in the emergency department from an institution-wide QT alert system. *J Emerg Med.* 2018;54:8–15. doi: 10.1016/j.jemermed.2017.08.073
78. Cross B, Homoud M, Link M, Foote C, Garlitski AC, Weinstock J, Estes NA 3rd. The short QT syndrome. *J Interv Card Electrophysiol.* 2011;31:25–31. doi: 10.1007/s10840-011-9566-0
79. Kobza R, Roos M, Niggli B, Abächerli R, Lupi GA, Frey F, Schmid JJ, Erne P. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. *Heart Rhythm.* 2009;6:652–657. doi: 10.1016/j.hrthm.2009.01.009
80. Providência R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal Ferreira MJ, Gonçalves L, Marijon E, Lambiase PD. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. *Heart.* 2018;104:502–508. doi: 10.1136/heartjnl-2017-311673
81. Dhutia H, Malhotra A, Parpia S, Gabus V, Finocchiaro G, Mellor G, Merghani A, Millar L, Narain R, Sheikh N, et al. The prevalence and significance of a short QT interval in 18,825 low-risk individuals including athletes. *Br J Sports Med.* 2016;50:124–129. doi: 10.1136/bjsports-2015-094827
82. Guerrier K, Kwiatkowski D, Czosek RJ, Spar DS, Anderson JB, Knilans TK. Short QT interval prevalence and clinical outcomes in a pediatric population. *Circ Arrhythm Electrophysiol.* 2015;8:1460–1464. doi: 10.1161/CIRCEP.115.003256
83. Villafañe J, Atallah J, Gollob MH, Maury P, Wolpert C, Gebauer R, Watanabe H, Horie M, Anttonen O, Kannankeril P, et al. Long-term follow-up of a pediatric cohort with short QT syndrome. *J Am Coll Cardiol.* 2013;61:1183–1191. doi: 10.1016/j.jacc.2012.12.025
84. Benito B, Brugada J, Brugada R, Brugada P. Brugada syndrome [published correction appears in *Rev Esp Cardiol*. 2010;63:620]. *Rev Esp Cardiol.* 2009;62:1297–1315. doi: 10.1016/s1885-5857(09)73357-2
85. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, et al; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) [published correction appears in *Europace*. 2012;14:277]. *Europace.* 2011;13:1077–1109. doi: 10.1093/europace/eur245
86. Quan XQ, Li S, Liu R, Zheng K, Wu XF, Tang Q. A meta-analytic review of prevalence for Brugada ECG patterns and the risk for death. *Medicine (Baltimore).* 2016;95:e5643. doi: 10.1097/MD.0000000000005643
87. Baron RC, Thacker SB, Gorelkin L, Vernon AA, Taylor WR, Choi K. Sudden death among Southeast Asian refugees: an unexplained nocturnal phenomenon. *JAMA.* 1983;250:2947–2951.
88. Gilbert J, Gold RL, Haffajee CI, Alpert JS. Sudden cardiac death in a southeast Asian immigrant: clinical, electrophysiologic, and biopsy characteristics. *Pacing Clin Electrophysiol.* 1986;9:912–914. doi: 10.1111/j.1540-8159.1986.tb06640.x
89. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol.* 2000;86:91–94. doi: 10.1016/s0002-9149(00)00835-3
90. Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, Matsumoto N, Iwasaka T. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. *J Am Coll Cardiol.* 2001;38:771–774. doi: 10.1016/s0735-1097(01)01419-x
91. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, et al; on behalf of the Brugada Syndrome Investigators in Japan. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. *Circ Arrhythm Electrophysiol.* 2009;2:495–503. doi: 10.1161/CIRCEP.108.816892
92. Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, Pasquié JL, Duparc A, Mondoly P, Cardin C, Delay M, et al. Prevalence and prognostic role of various conduction disturbances in patients with the Brugada syndrome. *Am J Cardiol.* 2013;112:1384–1389. doi: 10.1016/j.amjcard.2013.06.033
93. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. *Circulation.* 2010;121:635–643. doi: 10.1161/CIRCULATIONAHA.109.887026
94. Milman A, Andorin A, Gourraud JB, Postema PG, Sacher F, Mabo P, Kim SH, Juang JJM, Maeda S, Takahashi Y, et al. Profile of patients with Brugada syndrome presenting with their first documented arrhythmic event: data from the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS). *Heart Rhythm.* 2018;15:716–724. doi: 10.1016/j.hrthm.2018.01.014
95. Lieve KV, Wilde AA. Inherited ion channel diseases: a brief review. *Europace.* 2015;17(suppl 2):ii1–ii6. doi: 10.1093/europace/euv105
96. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, Potts JE, Maginot KR, Salerno JC, Cohen MI, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace.* 2018;20:541–547. doi: 10.1093/europace/euw389
97. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, Klug D, Hayashi M, Takatsuki S, Villain E, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation.* 2009;119:2426–2434. doi: 10.1161/CIRCULATIONAHA.108.829267
98. Kawata H, Ohno S, Aiba T, Sakaguchi H, Miyazaki A, Sumitomo N, Kamakura T, Nakajima I, Inoue YY, Miyamoto K, et al. Catecholaminergic polymorphic ventricular tachycardia (CPVT) associated with ryanodine receptor (RyR2) gene mutations: long-term prognosis after initiation of medical treatment. *Circ J.* 2016;80:1907–1915. doi: 10.1253/circj.CJ-16-0250
99. Roston TM, Haji-Ghassemi O, LaPage MJ, Batra AS, Bar-Cohen Y, Anderson C, Lau YR, Maginot K, Gebauer RA, Etheridge SP, et al. Catecholaminergic polymorphic ventricular tachycardia patients with multiple genetic variants in the PACES CPVT Registry. *PLoS One.* 2018;13:e0205925. doi: 10.1371/journal.pone.0205925
100. Dalal D, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, Roguin A, Tichnell C, James C, Russell SD, et al. Arrhythmogenic right ventricular

dysplasia: a United States experience. *Circulation.* 2005;112:3823–3832. doi: 10.1161/CIRCULATIONAHA.105.542266
101. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation.* 2004;110:1879–1884. doi: 10.1161/01.CIR.0000143375.93288.82
102. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, Monteforte N, Memmi M, Gambelli P, Novelli V, et al. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol.* 2016;68:2540–2550. doi: 10.1016/j.jacc.2016.09.951
103. Bhonsale A, Te Riele ASJM, Sawant AC, Groeneweg JA, James CA, Murray B, Tichnell C, Mast TP, van der Pols MJ, Cramer MJM, et al. Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation. *Heart Rhythm.* 2017;14:883–891. doi: 10.1016/j.hrthm.2017.02.013
104. Aro AL, Nair SG, Reinier K, Jayaraman R, Stecker EC, Uy-Evanado A, Rusinaru C, Jui J, Chugh SS. Population burden of sudden death associated with hypertrophic cardiomyopathy. *Circulation.* 2017;136:1665–1667. doi: 10.1161/CIRCULATIONAHA.117.030616
105. Patton KK, Ellinor PT, Ezekowitz M, Kowey P, Lubitz SA, Perez M, Piccini J, Turakhia M, Wang P, Viskin S; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology and Council on Functional Genomics and Translational Biology. Electrocardiographic early repolarization: a scientific statement from the American Heart Association. *Circulation.* 2016;133:1520–1529. doi: 10.1161/CIR.0000000000000388
106. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med.* 2008;358:2016–2023. doi: 10.1056/NEJMoa071968
107. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol.* 2008;52:1231–1238. doi: 10.1016/j.jacc.2008.07.010
108. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med.* 2009;361:2529–2537. doi: 10.1056/NEJMoa0907589
109. Walsh JA 3rd, Ilkhanoff L, Soliman EZ, Prineas R, Liu K, Ning H, Lloyd-Jones DM. Natural history of the early repolarization pattern in a biracial cohort: CARDIA (Coronary Artery Risk Development in Young Adults) Study. *J Am Coll Cardiol.* 2013;61:863–869. doi: 10.1016/j.jacc.2012.11.053
110. Kamakura T, Kawata H, Nakajima I, Yamada Y, Miyamoto K, Okamura H, Noda T, Satomi K, Aiba T, Takaki H, et al. Significance of non-type 1 anterior early repolarization in patients with inferolateral early repolarization syndrome. *J Am Coll Cardiol.* 2013;62:1610–1618. doi: 10.1016/j.jacc.2013.05.081
111. Siebermair J, Sinner MF, Beckmann BM, Laubender RP, Martens E, Sattler S, Fichtner S, Estner HL, Kääb S, Wakili R. Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace.* 2016;18:718–725. doi: 10.1093/europace/euv301
112. Gourraud JB, Le Scouarnec S, Sacher F, Chatel S, Derval N, Portero V, Chavernac P, Sandoval JE, Mabo P, Redon R, et al. Identification of large families in early repolarization syndrome. *J Am Coll Cardiol.* 2013;61:164–172. doi: 10.1016/j.jacc.2012.09.040
113. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, Sotoodehnia N, Gottdiener JS, et al. Ventricular ectopy as a predictor of heart failure and death. *J Am Coll Cardiol.* 2015;66:101–109. doi: 10.1016/j.jacc.2015.04.062
114. Ruwald AC, Aktas MK, Ruwald MH, Kutyifa V, McNitt S, Jons C, Mittal S, Steinberg JS, Daubert JP, Moss AJ, et al. Postimplantation ventricular ectopic burden and clinical outcomes in cardiac resynchronization therapy-defibrillator patients: a MADIT-CRT substudy. *Ann Noninvasive Electrocardiol.* 2018;23:e12491. doi: 10.1111/anec.12491
115. Marine JE, Shetty V, Chow GV, Wright JG, Gerstenblith G, Najjar SS, Lakatta EG, Fleg JL. Prevalence and prognostic significance of exercise-induced nonsustained ventricular tachycardia in asymptomatic volunteers: BLSA (Baltimore Longitudinal Study of Aging). *J Am Coll Cardiol.* 2013;62:595–600. doi: 10.1016/j.jacc.2013.05.026
116. Hai JJ, Un KC, Wong CK, Wong KL, Zhang ZY, Chan PH, Lau CP, Siu CW, Tse HF. Prognostic implications of early monomorphic and non-monomorphic tachyarrhythmias in patients discharged with acute coronary syndrome. *Heart Rhythm.* 2018;15:822–829. doi: 10.1016/j.hrthm.2018.02.016
117. Choudhuri I, Pinninti M, Marwali MR, Sra J, Akhtar M. Polymorphic ventricular tachycardia, part I: structural heart disease and acquired causes. *Curr Probl Cardiol.* 2013;38:463–496. doi: 10.1016/j.cpcardiol.2013.07.001
118. Arunachalam K, Lakshmanan S, Maan A, Kumar N, Dominic P. Impact of drug induced long QT syndrome: a systematic review. *J Clin Med Res.* 2018;10:384–390. doi: 10.14740/jocmr3338w
119. Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and torsade de pointes in Germany. *Europace.* 2014;16:101–108. doi: 10.1093/europace/eut214
120. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA.* 1993;270:2590–2597. doi: 10.1001/jama.270.21.2590
121. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. *Medicine (Baltimore).* 2003;82:282–290. doi: 10.1097/01.md.0000085057.63483.9b
122. Leonard CE, Freeman CP, Newcomb CW, Bilker WB, Kimmel SE, Strom BL, Hennessy S. Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *J Clin Exp Cardiolog.* 2013;(suppl 10):1–9. doi: 10.4172/2155-9880.S10-006
123. Arizona Center for Education and Research on Therapeutics. QTDrugs list. Credible Meds website. https://crediblemeds.org/healthcare-providers/. Accessed April 1, 2019.
124. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W; on behalf of the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular Nursing; American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation [published correction appears in *Circulation*. 2010;122:e440]. *Circulation.* 2010;121:1047–1060. doi: 10.1161/CIRCULATIONAHA.109.192704
125. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J.* 2007;153:891–899. doi: 10.1016/j.ahj.2007.01.040
126. Anderson ML, Cox M, Al-Khatib SM, Nichol G, Thomas KL, Chan PS, Saha-Chaudhuri P, Fosbol EL, Eigel B, Clendenen B, et al. Rates of cardiopulmonary resuscitation training in the United States. *JAMA Intern Med.* 2014;174:194–201. doi: 10.1001/jamainternmed.2013.11320
127. Blewer A, Ibrahim S, Leary M, Dutwin D, McNally B, Anderson M, Morrison L, Aufderheide T, Daya M, Idris A, et al. Cardiopulmonary resuscitation training disparities in the United States. *J Am Heart Assoc.* 2017;6:e006124. doi: 10.1161/JAHA.117.006124
128. Bakke HK, Steinvik T, Angell J, Wisborg T. A nationwide survey of first aid training and encounters in Norway. *BMC Emerg Med.* 2017;17:6. doi: 10.1186/s12873-017-0116-7
129. Bray JE, Smith K, Case R, Cartledge S, Straney L, Finn J. Public cardiopulmonary resuscitation training rates and awareness of hands-only cardiopulmonary resuscitation: a cross-sectional survey of Victorians. *Emerg Med Australas.* 2017;29:158–164. doi: 10.1111/1742-6723.12720
130. Brooks B, Chan S, Lander P, Adamson R, Hodgetts GA, Deakin CD. Public knowledge and confidence in the use of public access defibrillation. *Heart.* 2015;101:967–971. doi: 10.1136/heartjnl-2015-307624
131. Lee MJ, Hwang SO, Cha KC, Cho GC, Yang HJ, Rho TH. Influence of nationwide policy on citizens' awareness and willingness to perform bystander cardiopulmonary resuscitation. *Resuscitation.* 2013;84:889–894. doi: 10.1016/j.resuscitation.2013.01.009
132. Gonzalez M, Leary M, Blewer AL, Cinousis M, Sheak K, Ward M, Merchant RM, Becker LB, Abella BS. Public knowledge of automatic external defibrillators in a large U.S. urban community. *Resuscitation.* 2015;92:101–106. doi: 10.1016/j.resuscitation.2015.04.022
133. Duber HC, McNellan CR, Wollum A, Phillips B, Allen K, Brown JC, Bryant M, Guptam RB, Li Y, Majumdar P, et al. Public knowledge of cardiovascular disease and response to acute cardiac events in three cities in China and India. *Heart.* 2018;104:67–72. doi: 10.1136/heartjnl-2017-311388
134. Krammel M, Schnaubelt S, Weidenauer D, Winnisch M, Steininger M, Eichelter J, Hamp T, van Tulder R, Sulzgruber P. Gender and age-specific aspects of awareness and knowledge in basic life support. *PLoS One.* 2018;13:e0198918. doi: 10.1371/journal.pone.0198918
135. Ong ME, Shin SD, De Souza NN, Tanaka H, Nishiuchi T, Song KJ, Ko PC, Leong BS, Khunkhlai N, Naroo GY, et al; PAROS Clinical Research Network. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia:

the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation.* 2015;96:100–108. doi: 10.1016/j.resuscitation.2015.07.026
136. Sasson C, Magid DJ, Chan P, Root ED, McNally BF, Kellermann AL, Haukoos JS; CARES Surveillance Group. Association of neighborhood characteristics with bystander-initiated CPR. *N Engl J Med*. 2012;367:1607–1615. doi: 10.1056/NEJMoa1110700
137. Moon S, Bobrow BJ, Vadeboncoeur TF, Kortuem W, Kisakye M, Sasson C, Stolz U, Spaite DW. Disparities in bystander CPR provision and survival from out-of-hospital cardiac arrest according to neighborhood ethnicity. *Am J Emerg Med.* 2014;32:1041–1045. doi: 10.1016/j.ajem.2014.06.019
138. Sasson C, Haukoos JS, Ben-Youssef L, Ramirez L, Bull S, Eigel B, Magid DJ, Padilla R. Barriers to calling 911 and learning and performing cardiopulmonary resuscitation for residents of primarily Latino, high-risk neighborhoods in Denver, Colorado. *Ann Emerg Med.* 2015;65:545–552.e2. doi: 10.1016/j.annemergmed.2014.10.028
139. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
140. Zive DM, Schmicker R, Daya M, Kudenchuk P, Nichol G, Rittenberger JC, Aufderheide T, Vilke GM, Christenson J, Buick JE, et al; ROC Investigators. Survival and variability over time from out of hospital cardiac arrest across large geographically diverse communities participating in the Resuscitation Outcomes Consortium. *Resuscitation.* 2018;131:74–82. doi: 10.1016/j.resuscitation.2018.07.023
141. Okubo M, Schmicker RH, Wallace DJ, Idris AH, Nichol G, Austin MA, Grunau B, Wittwer LK, Richmond N, Morrison LJ, et al; Resuscitation Outcomes Consortium Investigators. Variation in survival after out-of-hospital cardiac arrest between emergency medical services agencies. *JAMA Cardiol.* 2018;3:989–999. doi: 10.1001/jamacardio.2018.3037
142. El-Assaad I, Al-Kindi SG, Aziz PF. Trends of out-of-hospital sudden cardiac death among children and young adults. *Pediatrics*. 2017;140:e20171438. doi: 10.1542/peds.2017-1438
143. Albaeni A, Beydoun MA, Beydoun HA, Akinyele B, RaghavaKurup L, Chandra-Strobos N, Eid SM. Regional variation in outcomes of hospitalized patients having out-of-hospital cardiac arrest. *Am J Cardiol.* 2017;120:421–427. doi: 10.1016/j.amjcard.2017.04.045
144. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-of-hospital cardiac arrest. *Heart.* 2017;103:1104–1110. doi: 10.1136/heartjnl-2016-310485
145. Pape M, Rajan S, Hansen SM, Mortensen RN, Riddersholm S, Folke F, Karlsson L, Lippert F, Køber L, Gislason G, et al. Survival after out-of-hospital cardiac arrest in nursing homes: a nationwide study. *Resuscitation.* 2018;125:90–98. doi: 10.1016/j.resuscitation.2018.02.004
146. Al-Dury N, Rawshani A, Israelsson J, Strömsöe A, Aune S, Agerström J, Karlsson T, Ravn-Fischer A, Herlitz J. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: a nationwide study with the emphasis on gender and age. *Am J Emerg Med.* 2017;35:1839–1844. doi: 10.1016/j.ajem.2017.06.012
147. Dolmatova EV, Moazzami K, Klapholz M, Kothari N, Feurdean M, Waller AH. Impact of hospital teaching status on mortality, length of stay and cost among patients with cardiac arrest in the United States. *Am J Cardiol.* 2016;118:668–672. doi: 10.1016/j.amjcard.2016.05.062
148. Hansen M, Fleischman R, Meckler G, Newgard CD. The association between hospital type and mortality among critically ill children in US EDs. *Resuscitation.* 2013;84:488–491. doi: 10.1016/j.resuscitation.2012.07.032
149. Tham LP, Wah W, Phillips R, Shahidah N, Ng YY, Shin SD, Nishiuchi T, Wong KD, Ko PC, Khunklai N, et al. Epidemiology and outcome of paediatric out-of-hospital cardiac arrests: a paediatric sub-study of the Pan-Asian Resuscitation Outcomes Study (PAROS). *Resuscitation.* 2018;125:111–117. doi: 10.1016/j.resuscitation.2018.01.040
150. Geri G, Dumas F, Bonnetain F, Bougouin W, Champigneulle B, Arnaout M, Carli P, Marijon E, Varenne O, Mira JP, et al. Predictors of long-term functional outcome and health-related quality of life after out-of-hospital cardiac arrest. *Resuscitation.* 2017;113:77–82. doi: 10.1016/j.resuscitation.2017.01.028
151. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW; Pittsburgh Post-Cardiac Arrest Service. Long-term survival benefit from treatment at a specialty center after cardiac arrest. *Resuscitation.* 2016;108:48–53. doi: 10.1016/j.resuscitation.2016.09.008
152. Silverstein FS, Slomine BS, Christensen J, Holubkov R, Page K, Dean JM, Moler FW; Therapeutic Hypothermia to Improve Survival After Cardiac Arrest Trial Group. Functional outcome trajectories after out-of-hospital pediatric cardiac arrest. *Crit Care Med.* 2016;44:e1165–e1174. doi: 10.1097/CCM.0000000000002003
153. Tong JT, Eyngorn I, Mlynash M, Albers GW, Hirsch KG. Functional neurologic outcomes change over the first 6 months after cardiac arrest. *Crit Care Med.* 2016;44:e1202–e1207. doi: 10.1097/CCM.0000000000001963
154. Bucy RA, Hanisko KA, Kamphuis LA, Nallamothu BK, Iwashyna TJ, Pfeiffer PN. Suicide risk management protocol in post-cardiac arrest survivors: development, feasibility, and outcomes. *Ann Am Thorac Soc.* 2017;14:363–367. doi: 10.1513/AnnalsATS.201609-694BC
155. Moulaert VRM, van Heugten CM, Gorgels TPM, Wade DT, Verbunt JA. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. *Neurorehabil Neural Repair.* 2017;31:530–539. doi: 10.1177/1545968317697032
156. Steinbusch CVM, van Heugten CM, Rasquin SMC, Verbunt JA, Moulaert VRM. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: a prospective longitudinal cohort study. *Resuscitation.* 2017;120:132–137. doi: 10.1016/j.resuscitation.2017.08.007
157. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, Horn J, Insorsi A, Kjaergaard J, Nilsson F, et al. Return to work and participation in society after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes.* 2018;11:e003566. doi: 10.1161/CIRCOUTCOMES.117.003566
158. Descatha A, Dumas F, Bougouin W, Cariou A, Geri G. Work factors associated with return to work in out-of-hospital cardiac arrest survivors. *Resuscitation.* 2018;128:170–174. doi: 10.1016/j.resuscitation.2018.05.021
159. Tiainen M, Vaahersalo J, Skrifvars MB, Hästbacka J, Grönlund J, Pettilä V. Surviving out-of-hospital cardiac arrest: the neurological and functional outcome and health-related quality of life one year later. *Resuscitation.* 2018;129:19–23. doi: 10.1016/j.resuscitation.2018.05.011
160. van Wijnen HG, Rasquin SM, van Heugten CM, Verbunt JA, Moulaert VR. The impact of cardiac arrest on the long-term wellbeing and caregiver burden of family caregivers: a prospective cohort study. *Clin Rehabil.* 2017;31:1267–1275. doi: 10.1177/0269215516686155
161. Morris NA, May TL, Motta M, Agarwal S, Kamel H. Long-term risk of seizures among cardiac arrest survivors. *Resuscitation.* 2018;129:94–96. doi: 10.1016/j.resuscitation.2018.06.019
162. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Public health burden of sudden cardiac death in the United States. *Circ Arrhythm Electrophysiol.* 2014;7:212–217. doi: 10.1161/CIRCEP.113.001034
163. Meert K, Slomine BS, Christensen JR, Telford R, Holubkov R, Dean JM, Moler FW. Burden of caregiving after a child's in-hospital cardiac arrest. *Resuscitation.* 2018;127:44–50. doi: 10.1016/j.resuscitation.2018.03.034
164. Nishiyama C, Brown SP, May S, Iwami T, Koster RW, Beesems SG, Kuisma M, Salo A, Jacobs I, Finn J, et al. Apples to apples or apples to oranges? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation.* 2014;85:1599–1609. doi: 10.1016/j.resuscitation.2014.06.031
165. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation.* 2010;81:1479–1487. doi: 10.1016/j.resuscitation.2010.08.006
166. Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, et al; EuReCa ONE Collaborators. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation.* 2016;105:188–195. doi: 10.1016/j.resuscitation.2016.06.004
167. Bray JE, Di Palma S, Jacobs I, Straney L, Finn J. Trends in the incidence of presumed cardiac out-of-hospital cardiac arrest in Perth, Western Australia, 1997-2010. *Resuscitation.* 2014;85:757–761. doi: 10.1016/j.resuscitation.2014.02.017
168. Shao F, Li CS, Liang LR, Qin J, Ding N, Fu Y, Yang K, Zhang GQ, Zhao L, Zhao B, et al. Incidence and outcome of adult in-hospital cardiac arrest in Beijing, China. *Resuscitation.* 2016;102:51–56. doi: 10.1016/j.resuscitation.2016.02.002
169. Ngunga LM, Yonga G, Wachira B, Ezekowitz JA. Initial rhythm and resuscitation outcomes for patients developing cardiac arrest in hospital: data from low-middle income country. *Glob Heart.* 2018;13:255–260. doi: 10.1016/j.gheart.2018.07.001
170. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death microdata files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.

18. SUBCLINICAL ATHEROSCLEROSIS

See Charts 18-1 through 18-4

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Multiple complementary imaging modalities allow detection and quantification of atherosclerosis through its stages in different vascular beds. Early identification of subclinical atherosclerosis can guide preventive care, including lifestyle modifications and medical treatment (eg, aspirin, antihypertensive therapy, lipid-lowering therapy) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Several modalities can be used for imaging atherosclerosis, including CT of the chest for evaluation of CAC, B-mode ultrasound of the neck for evaluation of carotid artery IMT or plaque, brachial artery reactivity testing, aortic and carotid MRI, and tonometric methods of measuring vascular compliance or microvascular reactivity. Among these modalities, the role of CAC in cardiovascular risk assessment is particularly well defined. According to the 2018 Cholesterol Clinical Practice Guideline[1] and the 2019 CVD Primary Prevention Clinical Practice Guidelines,[2] in intermediate-risk or selected borderline-risk adults, if the decision about statin therapy remains uncertain after 10-year ASCVD risk calculation and after accounting for risk enhancers, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.[1]

Abbreviations Used in Chapter 18

ABI	ankle-brachial index
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
ASCVD	atherosclerotic cardiovascular disease
AWHS	Aragon Workers' Health Study
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry
CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
EF	ejection fraction
ESRD	end-stage renal disease
FHS	Framingham Heart Study
FMD	flow-mediated dilation
FRS	Framingham Risk Score
HANDLS	Healthy Aging in Neighborhoods of Diversity Across the Life Span
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
IMPROVE	Carotid Intima Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High Risk European Population
IMT	intima-media thickness
JHS	Jackson Heart Study
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)

(*Continued*)

Abbreviations Used in Chapter 18 Continued

LV	left ventricular
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular events
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	metabolic syndrome
MI	myocardial infarction
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NHLBI	National Heart, Lung, and Blood Institute
NNT_5	5-year number needed to treat
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PESA	Progression of Early Subclinical Atherosclerosis
PREDIMED	Prevención con Dieta Mediterránea
PWV	pulse-wave velocity
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SWAN	Study of Women's Health Across the Nation
TC	total cholesterol
TIA	transient ischemic attack
TIPS	The Indian Polycap Study

Coronary Artery Calcification

Background

- CAC measures the burden of atherosclerosis in the coronary arteries by CT. Other components of the atherosclerotic plaque, including fatty (eg, cholesterol-rich components) and fibrotic components, often accompany CAC and can be present even in the absence of CAC.
- The presence of any CAC, which indicates that at least some atherosclerotic plaque is present, is defined by an Agatston score >0. The Agatston score is calculated as a sum of scores for each calcification in a coronary artery, assigning a weighted

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value to the highest density of calcification and multiplying this by the area of calcification. Scores can be reported in both age, sex, and race percentile units and in absolute units; absolute CAC cutoffs offer more prognostic information across all age groups in both males and females.[3] An absolute score of 1 to 99 may favor statin therapy, especially among individuals ≥55 years of age, and a score of ≥100 is a stronger indication for statin therapy, with the choice made in the context of shared decision making.[1,2]

Prevalence and Risk Factors (See Charts 18-1 through 18-3)

- The NHLBI's FHS reported CAC measured in 3238 white adults in age groups ranging from <45 to ≥75 years of age.[4]
  - Overall, 32.0% of females and 52.9% of males had prevalent CAC.
  - Among participants at intermediate risk according to the FRS, 58% of females and 67% of males had prevalent CAC.
- The NHLBI's CARDIA study measured CAC in 3043 black and white adults 33 to 45 years of age (at the CARDIA year 15 examination).[5]
  - Overall, 15.0% of males, 5.1% of females, 5.5% of those 33 to 39 years of age, and 13.3% of those 40 to 45 years of age had prevalent CAC. Overall, 1.6% of participants had an Agatston score >100.
- Chart 18-1 shows the prevalence of CAC by ethnicity and sex in adults 33 to 45 years of age. The prevalence of CAC was lower in black versus white males but was similar in black versus white females at these ages.
- The NHLBI's JHS assessed the prevalence of elevated CAC in 4416 black participants (mean age 54 years; 64% females).[6]
  - CAC >100 was noted in 14% of those without any MetS or DM, 26% of those with MetS, and 41% of those with DM.
- The NHLBI's MESA, a study of white, black, Chinese, and Hispanic adults, measured CAC in 6814 participants 45 to 84 years of age (mean 63 years), including white (n=2619), black (n=1898), Hispanic (n=1494), and Chinese (n=803) males and females.[7]
  - The overall prevalence of CAC in these 4 ethnic groups was 70.4%, 52.1%, 56.5%, and 59.2%, respectively, among men and was 44.6%, 36.5%, 34.9%, and 41.9%, respectively, among women.
  - The prevalence and 75th percentile levels of CAC were highest in white males and lowest in black and Hispanic females. Significant ethnic differences persisted after adjustment for risk factors, with the prevalence of coronary calcium being 22% lower in blacks, 15% lower in Hispanics, and 8% lower in Chinese than in whites.
- Compared with MESA, the MASALA study is a community-based cohort of South Asians in the United States and on average 5 years younger than in MESA.[8]
  - The age-adjusted prevalence of CAC was similar among white (68.8%) and South Asian (67.9%) males, with these groups having a greater prevalence of CAC than Chinese (57.8%), black (51.2%), and Hispanic (57.9%) males.
  - In contrast, the age-adjusted prevalence of CAC was lower in South Asian females (36.8%) than in white females (42.6%) and females of other races/ethnicities.
- Further illustrating the variability of CAC based on population and habits, a forager-horticulturalist population of 705 individuals living in the Bolivian Amazon had the lowest reported levels of CAC of any population recorded to date.[9]
  - Overall in the population (mean age 58 years; 50% females), 85% of individuals were free from any CAC, and even in individuals >75 years of age, 65% remained free of CAC. These unique data indicate that coronary atherosclerosis can typically be avoided by maintaining a low lifetime burden of CAD risk factors.[9]
- The prevalence of CAC varies according to baseline traditional risk factor profile. In recent studies from MESA, the prevalence of CAC in those with no lipid abnormalities was 42% versus 50% in those with 3 lipid abnormalities,[10] and 32% of people in MESA with no known traditional CVD risk factors had presence of CAC versus 65% of those with 3 risk factors.[11]
- The duration of risk factor exposure is associated with CAC, as exemplified in an analysis of exposure to DM and prediabetes in 3628 participants in CARDIA.[12]
  - For each additional 5 years of exposure to DM and prediabetes, the adjusted HR for CAC was 1.15 (95% CI, 1.06–1.25) and 1.07 (95% CI, 1.01–1.13), respectively.
- Beyond traditional cardiovascular risk factors, recent studies have identified obesity, NAFLD, and elevated Lp(a) as being associated with CAC.
  - Considering 1585 participants free of CHD and free of MetS, those who were obese had a higher prevalence of CAC than individuals with a normal weight, with a prevalence ratio of 1.59 (95% CI, 1.38–1.84).[13]

- In a meta-analysis of 42 410 individuals, including 16 883 with NAFLD, CAC scores were higher in those with NAFLD (OR, 1.64 [95% CI, 1.42–1.89]).[14]
- In 937 apparently healthy asymptomatic family members of individuals with premature ASCVD, high Lp(a) levels were associated with CAC ≥100 (OR, 1.79 [95% CI, 1.13–2.83]).[15]
- In a cohort of 428 HIV-positive and 276 HIV-negative individuals concurrently referred for clinically indicated cardiac CT, those who were HIV positive had less calcified plaque than those who were HIV negative (adjusted OR, 0.57 [95% CI, 0.40–0.82]).[16]

- The 10-year trends in CAC among individuals without clinical CVD in MESA were assessed (Chart 18-2).
  - The mean age at the baseline examination was 67 years, with 47.4% men. Detectable CAC was evaluated in whites, African American, Hispanic, and Chinese participants, with >50% prevalence at baseline.
  - Ten-year trends in CAC prevalence among the 4 racial/ethnic groups revealed a significant trend toward increased prevalence of CAC in blacks but not in any other group (Chart 18-2). Among blacks, the CAC prevalence ratio (year 10 versus baseline) was 1.27 (P<0.001 for test for trend).[17]
  - The severity of CAC was also evaluated at baseline and 10 years (Chart 18-3). After adjustment for age, sex, ethnicity, and type of CT scanner, the proportion of participants with no CAC decreased over time from 40.7% to 32.6% (P=0.007), and the proportions increased from 29.9% to 37.0% (P=0.01) for those with a CAC score ranging from 1 to 99 and from 14.7% to 17.7% (P=0.14) for those with a CAC score of 100 to 399, whereas the proportion with a CAC score ≥400 decreased from 9.1% to 7.2% (P=0.11).

CAC and Incidence of ASCVD Events (CHD and Stroke)
(See Chart 18-4)

- In a landmark study, the NHLBI's MESA reported on the association of CAC scores with first CHD events over a median follow-up of 3.9 years among a population-based sample of 6722 individuals (39% white, 27% black, 22% Hispanic, and 12% Chinese).[18]
  - Chart 18-4 shows the HRs associated with CAC scores of 1 to 100, 101 to 300, and >300 compared with those without CAC (score=0), after adjustment for standard risk factors. People with CAC scores of 1 to 100 had ≈4 times greater risk and those with CAC scores >100 were 7 to 10 times more likely to experience a coronary event than those without CAC.
  - CAC provided similar predictive value for coronary events in whites, Chinese, blacks, and Hispanics (HRs ranging from 1.15–1.39 for each doubling of coronary calcium).
- In a more recent MESA analysis with 12-year follow-up, machine learning was used to assess predictors of cardiovascular events.
  - Among 735 variables from imaging and noninvasive tests, questionnaires, and biomarker panels, CAC emerged as the strongest predictor of CHD and ASCVD events.[19]
- CAC was highly predictive of CHD event risk in both young and elderly MESA participants in a follow-up that extended to 8.5 years, which suggests that once CAC is known, chronological age has less importance.[20]
  - Compared with a CAC score of 0, CAC >100 was associated with an increased multivariable-adjusted CHD event risk in the younger individuals (45–54 years of age), with an HR of 12.4 (95% CI, 5.1–30.0).
  - The respective risk was similar even in the very elderly (75–84 years of age), with an HR of 12.1 (95% CI, 2.9–50.2).
- The prospective Dallas Heart Study reported the prognostic value of CAC scores in a relatively younger cohort (44.4±9.0 years of age) of 2084 participants who were followed up for a median of 9 years.[21]
  - Compared with individuals with CAC=0, those with CAC scores of 10 to 100 and >100 were associated with an HR of 3.43 (95% CI, 1.36–8.56) and 5.64 (95% CI, 2.28–13.97) for CHD events, respectively.
  - The addition of CAC to the traditional risk factor model resulted in significant improvement in the C statistic (Δ=0.03; P=0.003), as well as a net correct reclassification of 22%.
- In the Heinz Nixdorf Recall Study of 4180 individuals, CAC independently predicted stroke during a mean follow-up of 7.9 years.[22] Cox proportional hazards regressions were used to examine CAC as a predictor of stroke in addition to established vascular risk factors (age, sex, SBP, LDL-C, HDL-C, DM, smoking, and AF).
  - Study participants who had a stroke had significantly higher CAC values at baseline than the remaining participants (median 104.8 [quartile 1, 14.0; quartile 3, 482.2] versus 11.2 [quartile 1, 0; quartile 3, 106.2]; P<0.001).
  - In a multivariable Cox regression, log10(CAC +1) was a stroke predictor (HR, 1.52 [95% CI,

1.19–1.92]; *P*=0.001) independent of traditional risk factors in low- and intermediate-risk individuals.

- A recent meta-analysis that pooled data from 3 studies evaluated 13 262 asymptomatic individuals (mean age 60 years, 50% males) without apparent CVD.[23]
  - During a mean follow-up of 7.2 years, the pooled RR of incident stroke with CAC >0 was 2.95 (95% CI, 2.18–4.01; *P*<0.001) compared with CAC=0.
  - Furthermore, there was an increasing risk with higher CAC score (0.12% per year for CAC=0, 0.26% per year for CAC 1–99, 0.41% per year for CAC 100–399, and 0.70% per year for CAC ≥400).

CAC and Incidence of HF, AF, and Noncardiovascular Outcomes

- In the Rotterdam Study, CAC independently predicted incident HF during a median follow-up of 6.8 years.[24]
  - After adjustment for risk factors, those with severe CAC (>400) had a 4.1-fold higher risk (95% CI, 1.7–10.1) of HF than those with CAC scores of 0 to 10.
  - In addition, CAC substantially improved the risk classification (net reclassification index, 34.0%).
- A recent MESA analysis examining prediction of HF with preserved EF found that CAC >300 was a significant independent predictor in females (HR, 2.82 [95% CI, 1.32–6.00]) but not in males (HR, 0.91 [95% CI, 0.46–1.82]).[25]
- In MESA, during a median follow-up of 8.5 years, after accounting for risk factors, higher CAC scores were associated with increased risk for AF (CAC=0: HR, 1.0 [referent]; CAC=1–100: HR, 1.4 [95% CI, 1.01–2.0]; CAC=101–300: HR, 1.6 [95% CI, 1.1–2.4]; CAC >300: HR, 2.1 [95% CI, 1.4–2.9]).[26] The addition of CAC to a risk score yielded relative integrated discrimination improvement of 0.10 (95% CI, 0.061–0.15).
- A MESA analysis also showed that a higher CAC burden was associated with noncardiovascular outcomes.[27]
  - During a median follow-up of 10.2 years, accounting for demographics and traditional risk factors, participants with severe CAC (>400) were at an increased risk of cancer (HR, 1.53 [95% CI, 1.18–1.99]), CKD (HR, 1.70 [95% CI, 1.21–2.39]), pneumonia (HR, 1.97 [95% CI, 1.37–2.82]), chronic obstructive pulmonary disease (HR, 2.71 [95% CI, 1.60–4.57]), and hip fracture (HR, 4.29 [95% CI, 1.47–12.50]) compared with those with CAC=0.

CAC Progression and Risk

- Data from 6778 people in MESA showed annual CAC progression averaged 25±65 Agatston units, and among those without CAC at baseline, a 5-U annual change in CAC was associated with HRs of 1.4 and 1.5 for total and hard CHD events, respectively.[28]
  - Among those with CAC >0 at baseline, HRs per 100-U annual change in CAC were 1.2 and 1.3, respectively, and for those with annual progression ≥300 versus no progression, HRs were 3.8 and 6.3, respectively.
- Furthermore, in MESA, CAC progression was associated with incident AF. Presence of any CAC progression (>0 per year) in the 5-year follow-up was associated with 1.55-fold higher risk for AF (95% CI, 1.10–2.19).[26]
  - The risk of AF increased with higher levels of CAC progression: (1–100 per year: HR, 1.47 [95% CI, 1.03–2.09]; 101–300 per year: HR, 1.92 [95% CI, 1.15–3.20]; >300 per year: HR, 3.23 [95% CI, 1.48–7.05]).
- In a MESA study of 2759 postmenopausal females, despite no association between sex hormones and prevalent CAC, an association emerged between sex hormones and CAC progression over a median of 4.7 years.[29]
  - Females with higher free testosterone showed greater CAC progression (RR, 1.26 [95% CI, 1.01–1.56]), and those with higher sex hormone binding globulin had lower progression (0.80 [5% CI, 0.64–0.99]).

Social Determinants of CAC

- Addressing individuals living in the rural United States, a study reported the distribution of CAC scores among 1607 (mean age 56 years; 56% females) community-dwelling asymptomatic individuals from central Appalachia.[30]
  - Overall, 44% had a CAC score of 0, whereas the prevalence of those with mild (1–99), moderate (100–399), and severe (≥400) CAC was 29%, 15%, and 11%, respectively.
- Schmidt et al[31] examined the interaction of SES and a common variant in chromosome 9p21.3 in association with CAC and incident events in the Heinz Nixdorf Recall Study. In the 4116 participants in the analysis, SES was examined by education and income.
  - Genotype-income interaction, but not genotype-education interaction, was observed for CAC and events.
  - The lowest tertile of income had the strongest genetic effect, a 53.1% (95% CI, 30.6%–79.6%; $P=1.8\times10^{-7}$) increase in CAC and an HR of 1.44 (95% CI, 1.01–2.07;

P=0.049) for incident coronary events per additional risk allele.
— This suggests that lower income may be a determinant of increased expression of genetic susceptibility to CAD.

Carotid IMT

Background

- Carotid IMT measures the thickness of 2 layers (the intima and media) of the wall of the carotid arteries, the largest conduits of blood going to the brain. Carotid IMT is thought to be an earlier manifestation of atherosclerosis than CAC, because thickening precedes the development of frank atherosclerotic plaque. Carotid IMT methods may vary by part of the artery measured (common carotid, internal carotid, or bulb), measurement of near and far walls, and reporting of average (more common) or maximum thickness.
- Carotid IMT is greater with age and in males. Thus, high-risk levels of thickening might be considered as those in the highest quartile or quintile for one's age and sex, or ≥1 mm. Carotid ultrasound can also detect plaques and percent stenosis, although primary prevention guidelines have not recommended screening of asymptomatic people using either the presence of atherosclerotic plaque or carotid IMT to quantify atherosclerosis or predict risk.[32,33]
- In the CHS, mean maximal common carotid IMT was 1.03±0.20 mm, and mean internal carotid IMT was 1.37±0.55 mm.[34]

Risk Factors

- In participants in the Bogalusa Heart Study (mean age of 32±3 years), after adjustment for age, race, and sex, carotid IMT was associated significantly and positively with waist circumference, SBP, DBP, and LDL-C. Carotid IMT was inversely correlated with HDL-C levels. Participants with greater numbers of adverse risk factors (0, 1, 2, 3, or more) had stepwise increases in mean carotid IMT levels.[35]
- Additionally, the Bogalusa Heart Study investigated the association between risk factors measured in childhood with carotid IMT measured in these young adults.[36] Higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for being >75th percentile for carotid IMT in young adulthood. Higher SBP and LDL-C and lower HDL-C in young adulthood were also associated with having high carotid IMT.
- A similar pattern of association between risk factors at a younger age and carotid IMT in adulthood was demonstrated in a large Finnish cohort study.[37] These data highlight the importance of adverse risk factor levels in early childhood and young adulthood in the early development of atherosclerosis.
- Two large, population-based prospective studies have investigated the association of carotid ultrasound findings with outcomes with shared pathogenesis of atherosclerosis.[38,39]
  — In 1243 FHS participants (57±9 years of age; 53% females), the degree of carotid stenotic burden on carotid ultrasound was predictive of cerebral microbleeds on brain MRI, a marker of stroke and dementia. Carotid stenosis ≥25% was associated with a 2.2-fold (95% CI, 1.10–4.40) increased risk of cerebral microbleed, whereas no association was noted with carotid IMT.[38]
  — Among 13 197 individuals 45 to 64 years of age (26% blacks, 56% females) followed up for a median of 22.7 years, mean carotid IMT in the fourth quartile (≥0.81 mm) versus first quartile (<0.62) was significantly associated with ESRD.[39]
- Recent evidence suggests that sleep patterns and duration, which are associated with CVD, are associated with subclinical atherosclerosis.[40] In nearly 4000 asymptomatic middle-aged individuals in the PESA Study, individuals with very short (<6 hours) sleep and highest quintile of sleep fragmentation had the greatest odds of subclinical atherosclerosis defined by carotid and femoral ultrasound imaging.[40] Compared with those who slept 7 to 8 hours per night, and with adjustment for conventional risk factors, those who slept <6 hours per night had a 1.27 greater odds of noncoronary atherosclerosis.
- In the Bogalusa Heart Study,[35] carotid IMT was measured in 518 black and white males and females at a mean age of 32±3 years. These males and females were healthy but overweight.
  — Males had significantly higher carotid IMT in all segments than females, and blacks had higher common carotid and carotid bulb IMT than whites.
- Updates from an individual-participant meta-analysis involving 15 population-based cohorts worldwide that included 60 211 individuals (46 788 whites, 7200 blacks, 3816 Asians, and 2407 Hispanics) demonstrated differing associations between risk factors and burden of carotid IMT according to racial/ethnic groups.[41] Specifically, the association between age and carotid IMT was weaker in blacks and Hispanics, SBP was more strongly associated with carotid IMT in Asians, and HDL-C and smoking were less associated with carotid IMT in blacks.
- Among both females and males in the NHLBI's MESA, blacks had the highest common carotid

IMT, but they were similar to whites and Hispanics in internal carotid IMT. Chinese participants had the lowest carotid IMT, in particular in the internal carotid, of the 4 ethnic groups.[42]

- In MESA, carotid IMT and CAC were found to be commonly associated, but patterns of association differed somewhat by sex and race.[42]
  - Common and internal carotid IMT were greater in females and males who had CAC than in those who did not, regardless of ethnicity.
  - Overall, CAC prevalence and scores were associated with carotid IMT, but associations were somewhat weaker in blacks than in other ethnic groups.
  - In general, blacks had the thickest carotid IMT of all 4 ethnic groups, regardless of the presence of CAC.
  - Common carotid IMT differed little by race/ethnicity in females with any CAC, but among females with no CAC, IMT was higher among blacks (0.86 mm) than in the other 3 groups (0.76–0.80 mm).

Social Determinants of Carotid IMT and Vascular Disease

- The IMPROVE study cohort of 3703 Europeans studied the relation of SES with carotid IMT. Manual laborers had higher carotid IMT than white collar workers, a finding that was independent of sex, age groups, and education and was only partially mediated by risk factors.[43]
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race × SES effect whereby blacks with high (rather than low) SES had higher carotid IMT and PWV (aortic stiffness) than other groups, suggesting a group with greater subclinical CVD.[44]
- In the Young Finns Study of 1813 adults 27 to 39 years of age followed up for >20 years, SES indexed to education was inversely associated with CVD risk factors including obesity, glycemic level, and smoking and was directly associated with PA.[45] Individuals with higher education had lower progression in IMT in follow-up.

Risk Prediction

- A study from 3 population-based cohorts (ARIC, N=13 907; MESA, N=6640; and the Rotterdam Study, N=5220) demonstrated that both a higher carotid IMT and presence of carotid plaque were independently associated with an increased risk of incident AF.[46] In this study, a 1-SD increase in carotid IMT and presence of carotid plaque were associated with a meta-analyzed HR of 1.12 (95% CI, 1.08–1.16) and 1.30 (95% CI, 1.19–1.42), respectively.
- The CHS reported follow-up of 4476 males and females ≥65 years of age (mean age 72 years) who were free of CVD at baseline.[34] After a mean follow-up of 6.2 years, those with maximal combined carotid IMT in the highest quintile had a 4-fold greater risk for incident heart attack or stroke than those in the bottom quintile. After adjustment for other risk factors, a 3-fold greater risk for the top versus the bottom quintile remained.
- In one of the largest studies to date evaluating both prediction and reclassification from carotid IMT and presence of carotid plaque, ARIC investigators found that the addition of carotid IMT and plaque to traditional risk factors improved prediction of CHD risk.[47] In particular, among 13 145 participants (5682 men, 7463 women), ≈23% were reclassified by adding carotid IMT and plaque data to traditional risk factors. The area under the curve improved from 0.742 to 0.755 (95% CI for difference in adjusted area under the curve, 0.008–0.017).
- In MESA, during a median follow-up of 3.3 years, an IMT rate of change of 0.5 mm per year was associated with an HR of 1.23 (95% CI, 1.02–1.48) for incident stroke.[48] The upper quartile of IMT rate of change had an HR of 2.18 (95% CI, 1.07–4.46) compared with the lower 3 quartiles combined.
- Despite this evidence, conflicting data have been reported on the contribution of carotid IMT to risk prediction. A consortium of 14 population-based cohorts consisting of 45 828 individuals followed up for a median of 11 years demonstrated little additive value of common carotid IMT to FRS for purposes of discrimination and reclassification of incident MI and stroke (95% CI, 2.7%–4.6%).[49] The C statistics of the model with FRS alone (0.757 [95% CI, 0.749–0.764]) and with addition of common carotid IMT (0.759 [95% CI, 0.752–0.766]) were similar. The net reclassification improvement with the addition of common carotid IMT was small (0.8% [95% CI, 0.1%–1.6%]). In those at intermediate risk, the net reclassification improvement was 3.6% among all individuals.
- Interestingly, the ability of carotid IMT to predict incident CVD events might also depend on how the data are modeled. In MESA, the use of an age-, sex-, and race-adjusted carotid IMT score that combined data from both the internal and common carotid artery resulted in a significant improvement in the net reclassification improvement of 4.9% (P=0.024), with a particularly higher impact in individuals with an intermediate FRS, in whom the net reclassification improvement was 11.5%.[50]
- Among 13 590 participants in ARIC who were 45 to 64 years of age, each 1-SD increase in carotid

IMT was associated with incident HF (HR, 1.20 [95% CI, 1.16–1.25]) in a 20-year follow-up after accounting for major CVD risk factors and CHD.[51] Similar associations were also noted across all race and sex groups. This relationship was found to be much stronger among those without established DM.

- A study from a consortium of population-based cohorts reported no added value of measurement of mean common carotid IMT in individuals with high BP for improving cardiovascular risk prediction.[52] For those at intermediate risk, the addition of mean common carotid IMT to an existing cardiovascular risk score resulted in a small but statistically significant improvement in risk prediction.
- In a recent study, however, carotid plaque burden measured via 3-dimensional carotid ultrasound showed promise in improving CVD risk prediction.[53] The prospective BioImage Study enrolled 5808 asymptomatic US adults (mean age 69 years; 56.5% females). Carotid plaque areas from both carotid arteries were summed as the carotid plaque burden. The primary end point was the composite of MACE (cardiovascular death, MI, and ischemic stroke). After adjustment for risk factors, the HRs for MACE were 1.45 (95% CI, 0.67–3.14) and 2.36 (95% CI, 1.13–4.92) with increasing carotid plaque burden tertile. Net reclassification improved significantly with carotid plaque burden (0.23).
- To date, few studies have comprehensively studied the association of carotid IMT progression with CVD outcomes. Data from a comprehensive meta-analysis of individual participant data demonstrated that common carotid artery IMT progression in people with DM ranged between –0.09 and 0.04 mm per year in a follow-up of 3.6 years; however, this change was not associated with cardiovascular outcomes.[54] The HR for a 1-SD increase in common carotid artery IMT progression was 0.99 (95% CI, 0.91–1.08).

CAC, Carotid IMT, CT Angiography, and Risk Prediction

- In MESA, the investigators reported on follow-up of 6779 males and females in 4 ethnic groups over 9.5 years and compared the predictive utility of carotid IMT, carotid plaque, and CAC (presence and burden).[55]
  - CAC presence was a stronger predictor of incident CVD and CHD than carotid ultrasound measures.
  - Mean IMT ≥75th percentile (for age, sex, and race) alone did not predict events. Compared with traditional risk factors, C statistics for CVD (C=0.756) and CHD (C=0.752) increased the most by the addition of CAC presence (CVD, C=0.776; CHD, C=0.784; *P*<0.001), followed by carotid plaque presence (CVD, C=0.760; CHD, C=0.757; *P*<0.05).
  - Compared with risk factors (C=0.782), carotid plaque presence (C=0.787; *P*=0.045) but not CAC (C=0.785; *P*=0.438) improved prediction of stroke/TIA.
- Investigators from the NHLBI's CARDIA and MESA studies examined the burden and progression of subclinical atherosclerosis among adults <50 years of age.[56] Ten-year and lifetime risks for CVD were estimated for each participant, and the participants were stratified into 3 groups of predicted CVD risk: (1) low 10-year (<10%)/low lifetime (<39%) risk; (2) low 10-year (<10%)/high lifetime (≥39%) risk; and (3) high 10-year risk (>10%). The final group had the highest burden and greatest progression of subclinical atherosclerosis. Given the young age of those studied, ≈90% of participants were at low 10-year risk, but of these, half had high predicted lifetime risk. Compared with those with low short-term/low lifetime predicted risks, those with low short-term/high lifetime predicted risk had significantly greater burden and progression of CAC and significantly greater burden of carotid IMT, even at these younger ages. These data confirm the importance of early exposure to risk factors for the onset and progression of subclinical atherosclerosis.
- Although CAC and carotid ultrasound have been used more commonly in epidemiological studies, CT angiography has been examined for its potential role in detection, quantitation, and characterization of atherosclerotic coronary plaques that might make them prone to rupture, such as positive remodeling, low attenuation, and spotty calcifications.[57]
- However, limited impact on the prediction of outcomes in asymptomatic individuals has been shown, and thus, guidelines have not recommended its use as a screening tool for assessment of cardiovascular risk in asymptomatic individuals.[2,32,33,58] In the CONFIRM study, although CT angiography presence, extent, and severity of CAD improved risk prediction over traditional risk factors, no additional prognostic value for all-cause death was conferred once traditional risk factors and CAC scores were included in the model.[59] In another analysis of the CONFIRM data, it was noted that coronary CT angiography only provided incremental prognostic utility for prediction of mortality and nonfatal MI for asymptomatic individuals with moderately high CAC scores, but not for those with lower or higher CAC scores.[60]

Genetics/Family History

- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that associate with CAC and carotid artery IMT in multiethnic and racial populations.[61–64] On the basis of the identified genes and variants, there are considerable shared genetic components to subclinical disease and other risk factors (such as blood lipids) and incident disease.
- Recently, investigators identified 8 unique genetic loci that contribute to carotid IMT in 71 128 individuals and 1 novel locus for carotid plaque in 48 434 individuals.[65] Genetic correlations with CHD and stroke using linkage disequilibrium score regression analysis were observed, which suggests the connection between genetic susceptibility to subclinical atherosclerosis and overt CVD.

Treatment: Healthy Lifestyle and Preventive Medications

- A healthy lifestyle is the foundation of preventive treatment. Diets high in vegetables and fruits are associated with lower risk for CVD. PREDIMED, a small, randomized cohort study, demonstrated delayed progression of carotid IMT and carotid plaque after a median of 2.4 years in those randomized to a Mediterranean diet with nuts versus controls.[66]
- Recently, a study examining the relation of different vegetables to carotid IMT in a cohort of older females showed that a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.[67] Consuming ≥3 servings of vegetables each day was associated with an ≈5% lower amount of carotid atherosclerosis compared with consuming <2 servings of vegetables.
- SWAN examined the association of a 10-component Healthy Lifestyle Score using self-reported data regarding smoking, diet, and PA with carotid atherosclerosis in females during midlife. After 14 years of follow up, individuals with a healthier lifestyle, particularly the abstinence of smoking, had lower carotid IMT, which emphasizes the role of optimal lifestyle habits on subclinical atherosclerosis.[68] Similar results of lifestyle habits including Mediterranean diet, abstinence from smoking, and moderate alcohol intake were associated with lower subclinical atherosclerosis in nearly 2000 individuals in the Spanish AWHS.[69]
- CAC has been examined in multiple studies for its potential to identify those most likely and not likely to benefit from pharmacological treatment for the primary prevention of CVD.
- A total of 950 participants from MESA who met JUPITER clinical trial entry criteria (risk factors plus LDL-C <130 mg/dL and high-sensitivity CRP ≥2 mg/L) were identified and stratified according to CAC scores of 0, 1 to 100, or >100; CHD event rates were calculated, and the NNT_5 was calculated by applying the benefit found in JUPITER to the event rates found in each of these groups.[70] For CHD, the predicted NNT_5 was 549 for those with CAC of 0, 94 for scores of 1 to 100, and 24 for scores >100.
- In a similar fashion, 2 studies extrapolated the NNT_5 for LDL-C lowering by statins, applying the 30% RR reduction associated with a 1 mmol/L (39 mg/dL) reduction in LDL-C from a Cochrane meta-analysis of statin therapy in primary prevention across the spectrum of lipid abnormalities (LDL-C ≥130 mg/dL, HDL-C <40 mg/dL for males or <50 mg/dL for females, and triglycerides ≥150 mg/dL), as well as across 10-year FRS categories (0%–6%, 6%–10%, 10%–20%, and >20%).[10,71]
  - The estimated NNT_5 for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC ≥100.[10] The NNT_5 was 30 in participants with no lipid abnormality and CAC >100, whereas it was 154 in those with 3 lipid abnormalities and CAC of 0. A very high NNT_5 of 186 and 222, respectively, was estimated to prevent 1 CHD event in the absence of CAC among those with 10-year FRS of 11% to 20% and >20%. The respective estimated NNT_5 was as low as 36 and 50 with the presence of a very high CAC score (>300) among those with 10-year FRS of 0% to 6% and 6% to 10%, respectively. These collective data show the utility of CAC in identifying those most likely to benefit from statin treatment across the spectrum of risk profiles with an appropriate NNT_5.
  - Similarly, CAC testing also identified appropriate candidates who might derive the highest benefit with aspirin therapy. In MESA, individuals with CAC ≥100 had an estimated net benefit with aspirin regardless of their traditional risk status; the estimated NNT_5 was 173 for individuals classified as having <10% FRS and 92 for individuals with ≥10% FRS, and the estimated 5-year number needed to harm was 442 for a major bleed.[71] Conversely, individuals with zero CAC had unfavorable estimates (estimated NNT_5 of 2036 for individuals with <10% FRS and 808 for individuals with ≥10% FRS; estimated 5-year number needed to harm of 442 for a major bleed). Sex-specific and age-stratified analyses showed similar results.
- A study from MESA also examined the role of CAC testing to define the target population to treat with a polypill.[72] The NNT_5 to prevent 1 event

was estimated by applying the expected 62% CHD event reduction associated with the use of the polypill (based on TIPS). The estimated NNT_5 to prevent 1 CHD event ranged from 170 to 269 for patients with CAC=0, from 58 to 79 for those with CAC scores from 1 to 100, and from 25 to 27 for those with CAC scores >100, which enabled significant reductions in the population considered for treatment with more selective use of the polypill and, as a result, avoidance of treatment of those who were unlikely to benefit.

- Within the scope of the 2013 ACC/AHA guideline on the treatment of blood cholesterol, data from MESA demonstrated that among those for whom statins were recommended, 41% had CAC=0 and had 5.2 ASCVD events per 1000 person-years.[73] Among 589 participants (12%) considered for moderate-intensity statin treatment, 338 (57%) had CAC=0, with an ASCVD event rate of 1.5 per 1000 person-years. Of participants eligible (recommended or considered) for statins, 44% (1316 of 2966) had CAC=0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1000 person-years. The study results highlighted that among the intermediate-risk range of 5% to 20%, nearly half (48%) had CAC=0, and their 10-year ASCVD risk was below the threshold recommended for statin therapy (4.5%).
- These findings were recently confirmed in the JHS.[74] Among 2812 black individuals 40 to 75 years of age without prevalent ASCVD followed up for a median of 10 years, participants who were statin eligible by the 2013 ACC/AHA guideline on the treatment of blood cholesterol experienced a 10-year ASCVD event rate of 8.1 per 1000 person-years. However, in the absence of CAC, the 10-year observed ASCVD risk was below the threshold of statin recommendation set by the guidelines, at 3.1 per 1000 person-years.

Measures of Vascular Function and Incident CVD Events

Background

- Measures of arterial tonometry (stiffness) are based on the concept that pulse pressure has been shown to be an important risk factor for CVD. Arterial tonometry offers the ability to directly and noninvasively measure central PWV in the thoracic and abdominal aorta.
- BP and its variability are related to CVD events. Greater home BP variability was associated with higher carotid IMT, aortic calcification, and lower ABI in 1033 Japanese males and females.[75]
- Brachial FMD is a marker for nitric oxide release from the endothelium that can be measured by ultrasound. Impaired FMD is an early marker of CVD.
- Recommendations have not been specific, however, as to which, if any, measures of vascular function might be useful for CVD risk stratification in selected patient subgroups. Because of the absence of significant prospective data relating these measures to outcomes, the guidelines do not recommend measuring either FMD or arterial stiffness for cardiovascular risk assessment in asymptomatic adults.[58]

Arterial Stiffness and CVD

- The Rotterdam Study measured arterial stiffness in 2835 elderly participants (mean age 71 years).[76] They found that as aortic PWV increased, the RR of CHD was 1.72 (second versus first tertile) and 2.45 (third versus first tertile). Results remained robust even after accounting for carotid IMT, ABI, and pulse pressure.
- A study from Denmark of 1678 individuals 40 to 70 years of age found that each 1-SD increment in aortic PWV (3.4 m/s) increased CVD risk by 16% to 20%.[77]
- The FHS studied several indices of arterial stiffness, including PWV, wave reflection, and central pulse pressure.[78] Higher PWV was associated with a 48% increased risk of incident CVD events, and PWV improved CVD risk prediction (integrated discrimination improvement of 0.7%, $P<0.05$).
- An analysis from the JHS suggested peripheral arterial tonometry is associated with LVH.[79] A total of 440 black participants (mean age 59±10 years, 60% females) underwent both peripheral arterial tonometry and cardiac MRI evaluations between 2007 and 2013. Age- and sex-adjusted Pearson correlation analysis suggested that natural log-transformed LV mass index measured by MRI was negatively correlated with reactive hyperemia index (coefficient –0.114; $P=0.02$) after accounting for age, sex, BMI, DM, hypertension, ratio of TC and HDL-C, smoking, and history of CVD.
- Evidence suggests that arterial stiffness has negative impacts on brain health across the life spectrum. In 5853 children in the Generation R study, DBP was related to nonverbal intelligence, and in 5187 adults in the Rotterdam study, cognition was linearly related to SBP, PWV, and pulse pressure, and nonlinearly with DBP.[80] In the ARIC–Neurocognitive and positron emission tomography study, higher arterial stiffness measured by heart-carotid PWV was associated with greater β-amyloid deposition in the brain defined by positron emission tomography imaging, and carotid femoral PWV was associated with lower brain volumes and with higher white matter hyperintensity burden.[81] FHS investigators also previously demonstrated findings of arterial stiffness with brain aging and similar brain structural abnormalities and progression of these abnormalities in regions implicated in Alzheimer disease.[82–86]

FMD and CVD

- A recent meta-analysis assessed the relation of FMD with CVD events. Thirteen studies involving 11516 individuals without established CVD, with a mean duration of 2 to 7.2 years and adjusted for age, sex, and risk factors, reported a multivariate RR of 0.93 (95% CI, 0.90–0.96) per 1% increase in brachial FMD.[87]

Comparison of Measures

- In MESA, a comparison of 6 risk markers—CAC, ABI, high-sensitivity CRP, carotid IMT, brachial FMD, and family history of CHD—and their clinical utility over FRS was evaluated in 1330 intermediate-risk individuals.[88] After 7.6 years of follow-up, CAC, ABI, high-sensitivity CRP, and family history were independently associated with incident CHD in multivariable analyses (HRs of 2.6, 0.79, 1.28, and 2.18, respectively), but carotid IMT and brachial FMD were not. CAC provided the highest incremental improvement over the FRS (0.784 for both CAC and FRS versus 0.623 for FRS alone), as well as the greatest net reclassification improvement (0.659).
- Additionally, in MESA, the values of 12 negative markers (CAC score of 0, carotid IMT <25th percentile, absence of carotid plaque, brachial FMD >5% change, ABI >0.9 and <1.3, high-sensitivity CRP <2 mg/L, homocysteine <10 μmol/L, N-terminal pro-BNP <100 pg/mL, no microalbuminuria, no family history of CHD [any/premature], absence of MetS, and healthy lifestyle) were compared for all and hard CHD and for all CVD events over the 10-year follow-up.[89] After accounting for CVD risk factors, absence of CAC had the strongest negative predictive value, with an adjusted mean diagnostic likelihood ratio of 0.41 (SD, 0.12) for all CHD and 0.54 (SD, 0.12) for CVD, followed by carotid IMT <25th percentile (diagnostic likelihood ratio, 0.65 [SD, 0.04] and 0.75 [SD, 0.04], respectively).
- Similar findings were also noted in the Rotterdam Study, in which among 12 CHD risk markers, improvements in FRS predictions were most statistically and clinically significant with the addition of CAC scores.[90]
- The pooled cohort ASCVD risk estimator was recently compared against the FRS for prediction of subclinical atherosclerosis measured by carotid IMT and vascular dysfunction measured by carotid femoral PWV, central pulse pressure, and augmentation index in a cohort of 1231 individuals free of prevalent CVD.[91] Not surprisingly, given that the FRS was based on individuals of northern European descent, the pooled cohort risk equations were suggested to better identify the significance of race in subclinical atherosclerosis and vascular dysfunction.

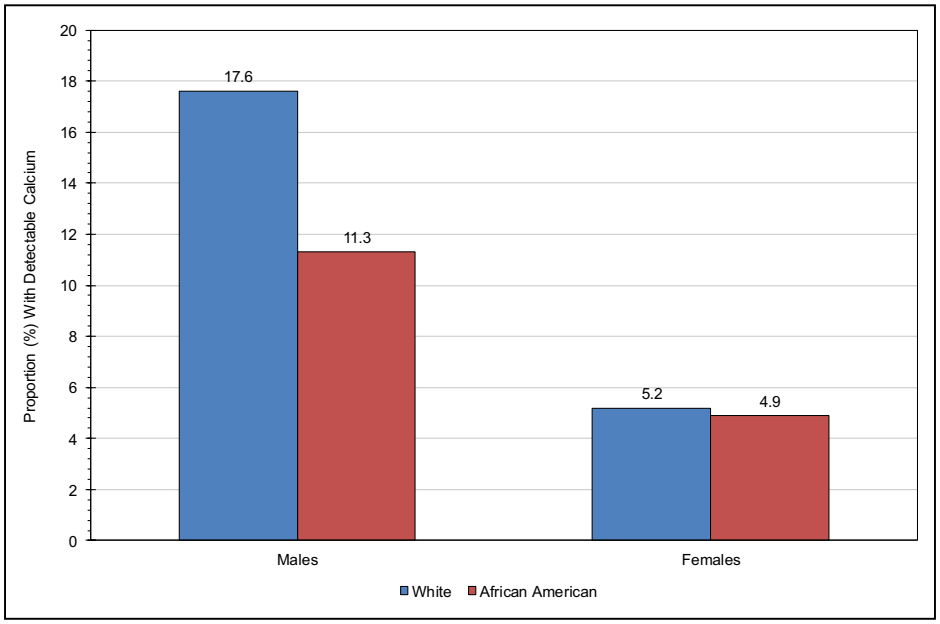

Chart 18-1. Prevalence (%) of detectable coronary calcium in the CARDIA study: US adults 33 to 45 years of age (2000 to 2001).
P<0.0001 across race-sex groups. CARDIA indicates Coronary Artery Risk Development in Young Adults.
Source: Data derived from Loria et al.[5]

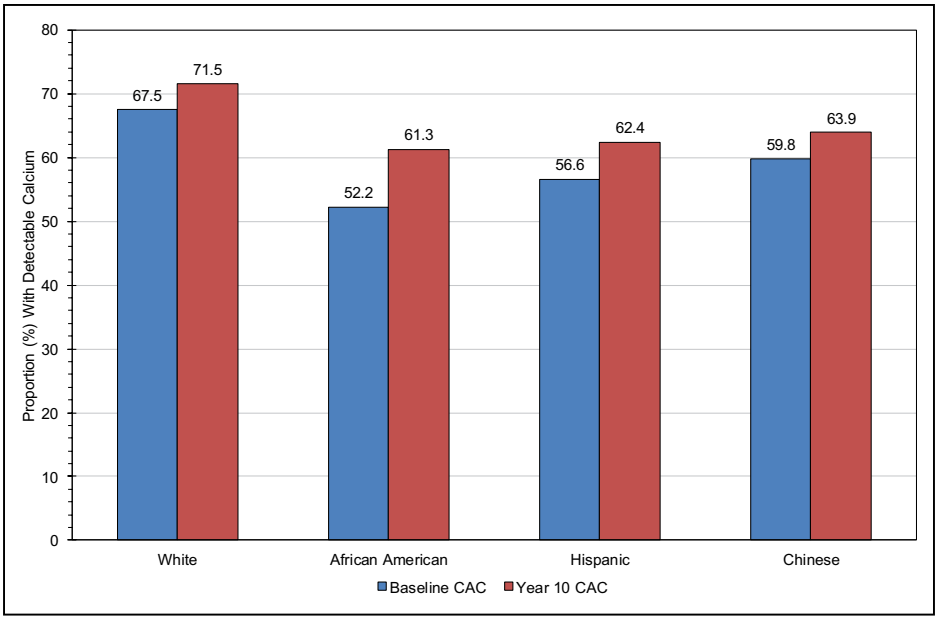

Chart 18-2. Prevalence by ethnicity of detectable CAC at baseline (2000–2002) and year 10 (2010–2012) among US adults 55 to 84 years of age without cardiovascular disease in MESA.

CAC indicates coronary artery calcification; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Data derived from Bild et al.[7,17]

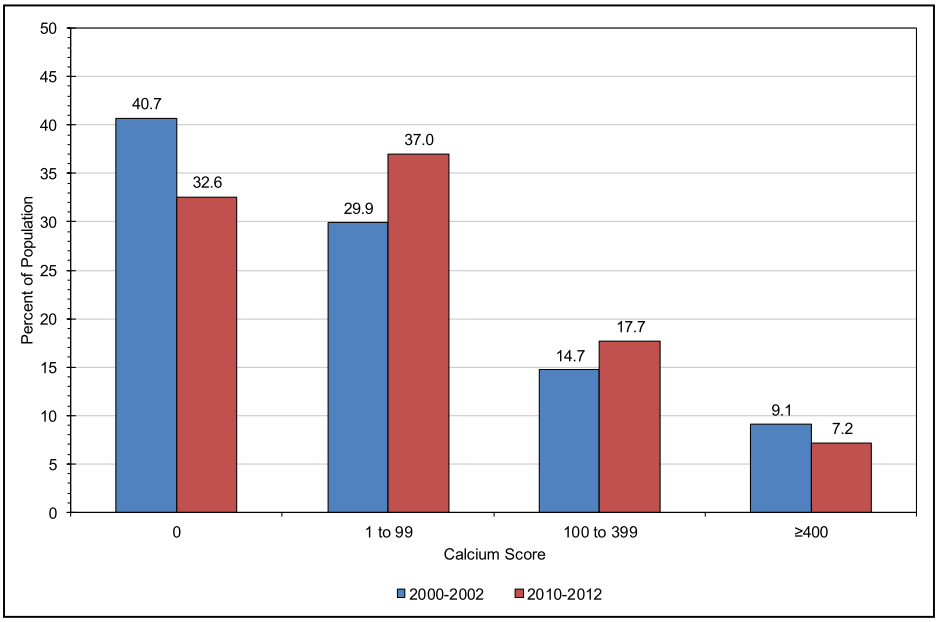

Chart 18-3. Ten-year trends in severity of coronary artery calcification in US individuals without clinical cardiovascular disease in MESA, baseline examination 2000 to 2002.

Data adjusted to the average baseline age (67 years), sex (47% male), race/ethnicity (39% white, 28% African American, 21% Hispanic, and 12% Chinese), and scanner (electron-beam computed tomography vs other). MESA indicates Multi-Ethnic Study of Atherosclerosis.

Source: Adapted from Bild et al.[17]

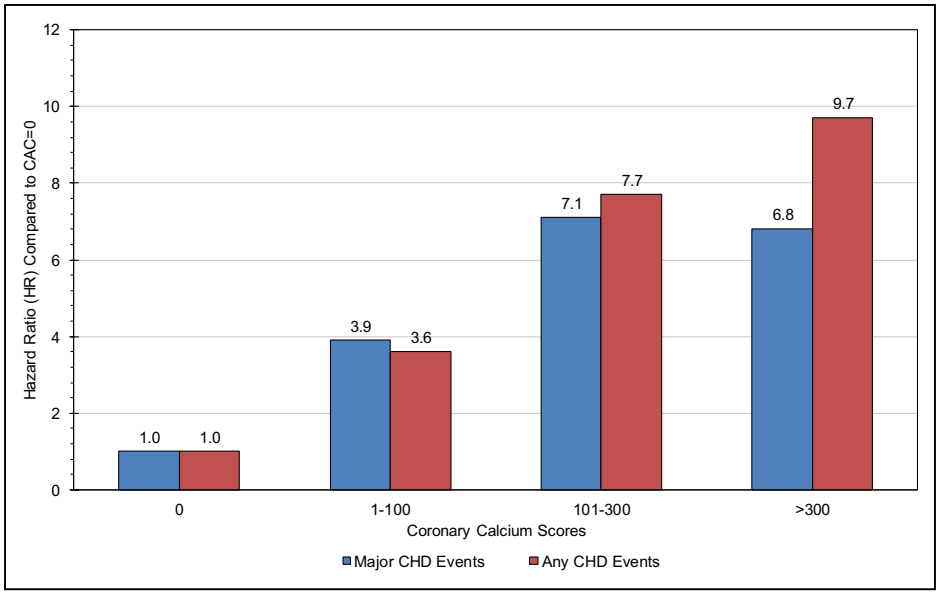

Chart 18-4. HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0) in MESA, baseline examination 2000 to 2002.

Baseline examination 2000 to 2002 with median of 3.9 years of follow-up (maximum 5.3 years). All HRs $P<0.0001$. Major CHD events included myocardial infarction and death attributable to CHD; any CHD events included major CHD events plus definite angina or definite or probable angina followed by revascularization. CAC indicates coronary artery calcification; CHD, coronary heart disease; HR, hazard ratio; and MESA, Multi-Ethnic Study of Atherosclerosis.
Source: Data derived from Detrano et al.[18]

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published correction appears in *Circulation*. 2019;139:e1182–e1186]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
2. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease [published correction appears in *Circulation*. 2019;140:e649–e650]. *Circulation*. 2019;140:e1e596–e646. doi: 10.1161/CIR.0000000000000678
3. Budoff MJ, Nasir K, McClelland RL, Detrano R, Wong N, Blumenthal RS, Kondos G, Kronmal RA. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis) [published correction appears in *J Am Coll Cardiol*. 2009;53:1474]. *J Am Coll Cardiol*. 2009;53:345–352. doi: 10.1016/j.jacc.2008.07.072
4. Hoffmann U, Massaro JM, Fox CS, Manders E, O'Donnell CJ. Defining normal distributions of coronary artery calcium in women and men (from the Framingham Heart Study). *Am J Cardiol*. 2008;102:1136–1141.e1. doi: 10.1016/j.amjcard.2008.06.038
5. Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, Williams OD, Bild DE, Detrano R. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. *J Am Coll Cardiol*. 2007;49:2013–2020. doi: 10.1016/j.jacc.2007.03.009
6. Xanthakis V, Sung JH, Samdarshi TE, Hill AN, Musani SK, Sims M, Ghraibeh KA, Liebson PR, Taylor HA, Vasan RS, et al. Relations between subclinical disease markers and type 2 diabetes, metabolic syndrome, and incident cardiovascular disease: the Jackson Heart Study. *Diabetes Care*. 2015;38:1082–1088. doi: 10.2337/dc14-2460
7. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005;111:1313–1320. doi: 10.1161/01.CIR.0000157730.94423.4B
8. Kanaya AM, Kandula NR, Ewing SK, Herrington D, Liu K, Blaha MJ, Srivastava S, Dave SS, Budoff MJ. Comparing coronary artery calcium among U.S. South Asians with four racial/ethnic groups: the MASALA and MESA studies [published correction appears in *Atherosclerosis*. 2014;235:36–37]. *Atherosclerosis*. 2014;234:102–107. doi: 10.1016/j.atherosclerosis.2014.02.017
9. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet*. 2017;389:1730–1739. doi: 10.1016/S0140-6736(17)30752-3
10. Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, Ouyang P, Jones SR, Blumenthal RS, Budoff MJ, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2014;129:77–86. doi: 10.1161/CIRCULATIONAHA.113.003625
11. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT, Agatston A, Blumenthal RS, Nasir K. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232–2241. doi: 10.1093/eurheartj/eht508
12. Reis JP, Allen NB, Bancks MP, Carr JJ, Lewis CE, Lima JA, Rana JS, Gidding SS, Schreiner PJ. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA Study. *Diabetes Care*. 2018;41:731–738. doi: 10.2337/dc17-2233
13. Kowall B, Lehmann N, Mahabadi AA, Moebus S, Erbel R, Jöckel KH, Stang A. Associations of metabolically healthy obesity with prevalence and progression of coronary artery calcification: results from the Heinz Nixdorf Recall Cohort Study. *Nutr Metab Cardiovasc Dis*. 2019;29:228–235. doi: 10.1016/j.numecd.2018.11.002
14. Kapuria D, Takyar VK, Etzion O, Surana P, O'Keefe JH, Koh C. Association of hepatic steatosis with subclinical atherosclerosis: systematic review and meta-analysis. *Hepatol Commun*. 2018;2:873–883. doi: 10.1002/hep4.1199
15. Verweij SL, de Ronde MWJ, Verbeek R, Boekholdt SM, Planken RN, Stroes ESG, Pinto-Sietsma SJ. Elevated lipoprotein(a) levels are associated with coronary artery calcium scores in asymptomatic individuals with a family history of premature atherosclerotic cardiovascular disease. *J Clin Lipidol*. 2018;12:597–603.e1. doi: 10.1016/j.jacl.2018.02.007
16. Tarr PE, Ledergerber B, Calmy A, Doco-Lecompte T, Marzel A, Weber R, Kaufmann PA, Nkoulou R, Buechel RR, Kovari H; Swiss HIV Cohort Study. Subclinical coronary artery disease in Swiss HIV-positive and HIV-negative persons. *Eur Heart J*. 2018;39:2147–2154. doi: 10.1093/eurheartj/ehy163
17. Bild DE, McClelland R, Kaufman JD, Blumenthal R, Burke GL, Carr JJ, Post WS, Register TC, Shea S, Szklo M. Ten-year trends in coronary calcification in individuals without clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis [published correction appears

in *PLoS One*. 2014;9:e103666]. *PLoS One.* 2014;9:e94916. doi: 10.1371/journal.pone.0094916
18. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008;358:1336–1345. doi: 10.1056/NEJMoa072100
19. Ambale-Venkatesh B, Yang X, Wu CO, Liu K, Hundley WG, McClelland R, Gomes AS, Folsom AR, Shea S, Guallar E, et al. Cardiovascular event prediction by machine learning: the Multi-Ethnic Study of Atherosclerosis. *Circ Res.* 2017;121:1092–1101. doi: 10.1161/CIRCRESAHA.117.311312
20. Tota-Maharaj R, Blaha MJ, Blankstein R, Silverman MG, Eng J, Shaw LJ, Blumenthal RS, Budoff MJ, Nasir K. Association of coronary artery calcium and coronary heart disease events in young and elderly participants in the Multi-Ethnic Study of Atherosclerosis: a secondary analysis of a prospective, population-based cohort. *Mayo Clin Proc.* 2014;89:1350–1359. doi: 10.1016/j.mayocp.2014.05.017
21. Paixao AR, Ayers CR, El Sabbagh A, Sanghavi M, Berry JD, Rohatgi A, Kumbhani DJ, McGuire DK, Das SR, de Lemos JA, et al. Coronary artery calcium improves risk classification in younger populations. *JACC Cardiovasc Imaging.* 2015;8:1285–1293. doi: 10.1016/j.jcmg.2015.06.015
22. Hermann DM, Gronewold J, Lehmann N, Moebus S, Jöckel KH, Bauer M, Erbel R; on behalf of the Heinz Nixdorf Recall Study Investigative Group. Coronary artery calcification is an independent stroke predictor in the general population. *Stroke.* 2013;44:1008–1013. doi: 10.1161/STROKEAHA.111.678078
23. Chaikriangkrai K, Jhun HY, Palamaner Subash Shantha G, Bin Abdulhak A, Sigurdsson G, Nabi F, Mahmarian JJ, Chang SM. Coronary artery calcium score as a predictor for incident stroke: systematic review and meta-analysis. *Int J Cardiol.* 2017;236:473–477. doi: 10.1016/j.ijcard.2017.01.132
24. Leening MJ, Elias-Smale SE, Kavousi M, Felix JF, Deckers JW, Vliegenthart R, Oudkerk M, Hofman A, Steyerberg EW, Stricker BH, et al. Coronary calcification and the risk of heart failure in the elderly: the Rotterdam Study. *JACC Cardiovasc Imaging.* 2012;5:874–880. doi: 10.1016/j.jcmg.2012.03.016
25. Sharma K, Al Rifai M, Ahmed HM, Dardari Z, Silverman MG, Yeboah J, Nasir K, Sklo M, Yancy C, Russell SD, et al. Usefulness of coronary artery calcium to predict heart failure with preserved ejection fraction in men versus women (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol.* 2017;120:1847–1853. doi: 10.1016/j.amjcard.2017.07.089
26. O'Neal WT, Efird JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR, Nazarian S, Soliman EZ. Coronary artery calcium progression and atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging.* 2015;8:e003786. doi: 10.1161/CIRCIMAGING.115.003786
27. Handy CE, Desai CS, Dardari ZA, Al-Mallah MH, Miedema MD, Ouyang P, Budoff MJ, Blumenthal RS, Nasir K, Blaha MJ. The association of coronary artery calcium with noncardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging.* 2016;9:568–576. doi: 10.1016/j.jcmg.2015.09.020
28. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2013;61:1231–1239. doi: 10.1016/j.jacc.2012.12.035
29. Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, Heckbert SR, Budoff MJ, Post WS, Michos ED. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Comput Tomogr.* 2019;13:41–47. doi: 10.1016/j.jcct.2018.09.010
30. Mamudu HM, Paul TK, Wang L, Veeranki SP, Panchal HB, Alamian A, Sarnosky K, Budoff M. The effects of multiple coronary artery disease risk factors on subclinical atherosclerosis in a rural population in the United States. *Prev Med.* 2016;88:140–146. doi: 10.1016/j.ypmed.2016.04.003
31. Schmidt B, Frolich S, Dragano N, Frank M, Eisele L, Pechlivanis S, Forstner AJ, Nothen MM, Mahabadi AA, Erbel R, et al. Socioeconomic status interacts with the genetic effect of a chromosome 9p21.3 common variant to influence coronary artery calcification and incident coronary events in the Heinz Nixdorf Recall Study (Risk Factors, Evaluation of Coronary Calcium, and Lifestyle). *Circ Cardiovasc Genet.* 2017;10:e001441. doi: 10.1161/CIRCGENETICS.116.001441
32. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al; on behalf of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129(suppl 2):S74–S75]. *Circulation.* 2014;129(suppl 2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
33. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, et al; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37:2315–2381. doi: 10.1093/eurheartj/ehw106
34. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; for the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med.* 1999;340:14–22. doi: 10.1056/NEJM199901073400103
35. Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS; Bogalusa Heart Study. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (the Bogalusa Heart Study). *Am J Cardiol.* 2002;90:953–958. doi: 10.1016/s0002-9149(02)02660-7
36. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study [published correction appears in *JAMA*. 2003;290:2943]. *JAMA.* 2003;290:2271–2276. doi: 10.1001/jama.290.17.2271
37. Juonala M, Viikari JS, Kähönen M, Taittonen L, Laitinen T, Hutri-Kähönen N, Lehtimäki T, Jula A, Pietikäinen M, Jokinen E, et al. Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study. *Eur Heart J.* 2010;31:1745–1751. doi: 10.1093/eurheartj/ehq141
38. Romero JR, Preis SR, Beiser A, DeCarli C, D'Agostino RB, Wolf PA, Vasan RS, Polak JF, Seshadri S. Carotid atherosclerosis and cerebral microbleeds: the Framingham Heart Study. *J Am Heart Assoc.* 2016;5:e002377. doi: 10.1161/JAHA.115.002377
39. Pang Y, Sang Y, Ballew SH, Grams ME, Heiss G, Coresh J, Matsushita K. Carotid intima-media thickness and incident ESRD: the Atherosclerosis Risk in Communities (ARIC) Study. *Clin J Am Soc Nephrol.* 2016;11:1197–1205. doi: 10.2215/CJN.11951115
40. Domínguez F, Fuster V, Fernández-Alvira JM, Fernández-Friera L, López-Melgar B, Blanco-Rojo R, Fernández-Ortiz A, García-Pavía P, Sanz J, Mendiguren JM, et al. Association of sleep duration and quality with subclinical atherosclerosis. *J Am Coll Cardiol.* 2019;73:134–144. doi: 10.1016/j.jacc.2018.10.060
41. Gijsberts CM, Groenewegen KA, Hoefer IE, Eijkemans MJ, Asselbergs FW, Anderson TJ, Britton AR, Dekker JM, Engström G, Evans GW, et al. Race/ethnic differences in the associations of the Framingham risk factors with carotid IMT and cardiovascular events. *PLoS One.* 2015;10:e0132321. doi: 10.1371/journal.pone.0132321
42. Manolio TA, Arnold AM, Post W, Bertoni AG, Schreiner PJ, Sacco RL, Saad MF, Detrano RL, Szklo M. Ethnic differences in the relationship of carotid atherosclerosis to coronary calcification: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis.* 2008;197:132–138. doi: 10.1016/j.atherosclerosis.2007.02.030
43. Tedesco CC, Veglia F, de Faire U, Kurl S, Smit AJ, Rauramaa R, Giral P, Amato M, Bonomi A, Ravani A, et al; IMPROVE Study Group. Association of lifelong occupation and educational level with subclinical atherosclerosis in different European regions: results from the IMPROVE study. *Atherosclerosis.* 2018;269:129–137. doi: 10.1016/j.atherosclerosis.2017.12.023
44. Wendell CR, Waldstein SR, Evans MK, Zonderman AB. Distributions of subclinical cardiovascular disease in a socioeconomically and racially diverse sample. *Stroke.* 2017;48:850–856. doi: 10.1161/STROKEAHA.116.015267
45. Kestilä P, Magnussen CG, Viikari JS, Kähönen M, Hutri-Kähönen N, Taittonen L, Jula A, Loo BM, Pietikäinen M, Jokinen E, et al. Socioeconomic status, cardiovascular risk factors, and subclinical atherosclerosis in young adults: the Cardiovascular Risk in Young Finns Study. *Arterioscler Thromb Vasc Biol.* 2012;32:815–821. doi: 10.1161/ATVBAHA.111.241182
46. Chen LY, Leening MJ, Norby FL, Roetker NS, Hofman A, Franco OH, Pan W, Polak JF, Witteman JC, Kronmal RA, et al. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the Atherosclerosis

Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. *J Am Heart Assoc*. 2016;5:e002907. doi: 10.1161/JAHA.115.002907

47. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607. doi: 10.1016/j.jacc.2009.11.075
48. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:3017–3021. doi: 10.1161/STROKEAHA.111.625186
49. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis [published correction appears in *JAMA*. 2013;310:1739]. *JAMA*. 2012;308:796–803. doi: 10.1001/jama.2012.9630
50. Polak JF, Szklo M, O'Leary DH. Carotid intima-media thickness score, positive coronary artery calcium score, and incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2017;6:e004612. doi: 10.1161/JAHA.116.004612
51. Effoe VS, McClendon EE, Rodriguez CJ, Wagenknecht LE, Evans GW, Chang PP, Bertoni AG. Diabetes status modifies the association between carotid intima-media thickness and incident heart failure: the Atherosclerosis Risk in Communities study. *Diabetes Res Clin Pract*. 2017;128:58–66. doi: 10.1016/j.diabres.2017.04.009
52. Bots ML, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, et al. Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. *Hypertension*. 2014;63:1173–1181. doi: 10.1161/HYPERTENSIONAHA.113.02683
53. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol*. 2015;65:1065–1074. doi: 10.1016/j.jacc.2015.01.017
54. Lorenz MW, Price JF, Robertson C, Bots ML, Polak JF, Poppert H, Kavousi M, Dörr M, Stensland E, Ducimetiere P, et al. Carotid intima-media thickness progression and risk of vascular events in people with diabetes: results from the PROG-IMT collaboration. *Diabetes Care*. 2015;38:1921–1929. doi: 10.2337/dc14-2732
55. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8:e002262. doi: 10.1161/CIRCIMAGING.114.002262
56. Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, Shea S, Sidney S, O'Leary DH, Chan C, et al. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the Coronary Artery Risk Development in Young Adults Study and Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2009;119:382–389. doi: 10.1161/CIRCULATIONAHA.108.800235
57. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49–57. doi: 10.1016/j.jacc.2009.02.068
58. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, et al; on behalf of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:e584–e636. doi: 10.1161/CIR.0b013e3182051b4c
59. Cho I, Al'Aref SJ, Berger A, Ó Hartaigh B, Gransar H, Valenti V, Lin FY, Achenbach S, Berman DS, Budoff MJ, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur Heart J*. 2018;39:934–941. doi: 10.1093/eurheartj/ehx774
60. Cho I, Chang HJ, Ó Hartaigh B, Shin S, Sung JM, Lin FY, Achenbach S, Heo R, Berman DS, Budoff MJ, et al. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study [published correction appears in *Eur Heart J*. 2015;36:3287]. *Eur Heart J*. 2015;36:501–508. doi: 10.1093/eurheartj/ehu358
61. Natarajan P, Bis JC, Bielak LF, Cox AJ, Dörr M, Feitosa MF, Franceschini N, Guo X, Hwang SJ, Isaacs A, et al; CHARGE Consortium. Multiethnic exome-wide association study of subclinical atherosclerosis. *Circ Cardiovasc Genet*. 2016;9:511–520. doi: 10.1161/CIRCGENETICS.116.001572
62. Divers J, Palmer ND, Langefeld CD, Brown WM, Lu L, Hicks PJ, Smith SC, Xu J, Terry JG, Register TC, et al. Genome-wide association study of coronary artery calcified atherosclerotic plaque in African Americans with type 2 diabetes. *BMC Genet*. 2017;18:105. doi: 10.1186/s12863-017-0572-9
63. Wojczynski MK, Li M, Bielak LF, Kerr KF, Reiner AP, Wong ND, Yanek LR, Qu L, White CC, Lange LA, et al. Genetics of coronary artery calcification among African Americans, a meta-analysis. *BMC Med Genet*. 2013;14:75. doi: 10.1186/1471-2350-14-75
64. Vargas JD, Manichaikul A, Wang XQ, Rich SS, Rotter JI, Post WS, Polak JF, Budoff MJ, Bluemke DA. Common genetic variants and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2016;245:230–236. doi: 10.1016/j.atherosclerosis.2015.11.034
65. Franceschini N, Giambartolomei C, de Vries PS, Finan C, Bis JC, Huntley RP, Lovering RC, Tajuddin SM, Winkler TW, Graff M, et al; MEGASTROKE Consortium. GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes. *Nat Commun*. 2018;9:5141. doi: 10.1038/s41467-018-07340-5
66. Sala-Vila A, Romero-Mamani ES, Gilabert R, Núñez I, de la Torre R, Corella D, Ruiz-Gutiérrez V, López-Sabater MC, Pintó X, Rekondo J, et al. Changes in ultrasound-assessed carotid intima-media thickness and plaque with a Mediterranean diet: a substudy of the PREDIMED trial. *Arterioscler Thromb Vasc Biol*. 2014;34:439–445. doi: 10.1161/ATVBAHA.113.302327
67. Blekkenhorst LC, Bondonno CP, Lewis JR, Woodman RJ, Devine A, Bondonno NP, Lim WH, Zhu K, Beilin LJ, Thompson PL, et al. Cruciferous and total vegetable intakes are inversely associated with subclinical atherosclerosis in older adult women. *J Am Heart Assoc*. 2018;7:1–13. doi: 10.1161/JAHA.117.008391
68. Wang D, Jackson EA, Karvonen-Gutierrez CA, Elliott MR, Harlow SD, Hood MM, Derby CA, Sternfeld B, Janssen I, Crawford SL, et al. Healthy lifestyle during the midlife is prospectively associated with less subclinical carotid atherosclerosis: the Study of Women's Health Across the Nation [published correction appears in *J Am Heart Assoc*. 2019;8:e002260]. *J Am Heart Assoc*. 2018;7:e010405. doi: 10.1161/JAHA.118.010405
69. Uzhova I, Mateo-Gallego R, Moreno-Franco B, Molina-Montes E, Leon-Latre M, Casasnovas Lenguas JA, Civeira F, Peñalvo JL. The additive effect of adherence to multiple healthy lifestyles on subclinical atherosclerosis: insights from the AWHS. *J Clin Lipidol*. 2018;12:615–625. doi: 10.1016/j.jacl.2018.03.081
70. Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ, Agatston A, O'Leary DH, Lima J, Blumenthal RS, Nasir K. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011;378:684–692. doi: 10.1016/S0140-6736(11)60784-8
71. Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silverman MG, Blankstein R, Budoff MJ, Greenland P, Folsom AR. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Qual Outcomes*. 2014;7:453–460. doi: 10.1161/CIRCOUTCOMES.113.000690
72. Bittencourt MS, Blaha MJ, Blankstein R, Budoff M, Vargas JD, Blumenthal RS, Agatston AS, Nasir K. Polypill therapy, subclinical atherosclerosis, and cardiovascular events-implications for the use of preventive pharmacotherapy: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2014;63:434–443. doi: 10.1016/j.jacc.2013.08.1640
73. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Miemdema MD, Sibley CT, Shaw LJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2015;66:1657–1668. doi: 10.1016/j.jacc.2015.07.066
74. Shah RV, Spahillari A, Mwasongwe S, Carr JJ, Terry JG, Mentz RJ, Addison D, Hoffmann U, Reis J, Freedman JE, et al. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: the Jackson Heart Study. *JAMA Cardiol*. 2017;2:644-652. doi: 10.1001/jamacardio.2017.0944

75. Takashi H, Katsuyuki M, Takayoshi O, Hisatomi A, Akira F, Atsushi S, Aya K, Maryam Z, Naoyuki T, Seiko O, et al. Home blood pressure variability and subclinical atherosclerosis in multiple vascular beds: a population-based study. *J Hypertens*. 2018;36:2193–2203. doi: 10.1097/HJH.0000000000001810
76. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–663. doi: 10.1161/CIRCULATIONAHA.105.555235
77. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113:664–670. doi: 10.1161/CIRCULATIONAHA.105.579342
78. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655
79. Tripathi A, Benjamin EJ, Musani SK, Hamburg NM, Tsao CW, Saraswat A, Vasan RS, Mitchell GF, Fox ER. The association of endothelial function and tone by digital arterial tonometry with MRI left ventricular mass in African Americans: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:258–264. doi: 10.1016/j.jash.2017.03.005
80. Lamballais S, Sajjad A, Leening MJG, Gaillard R, Franco OH, Mattace-Raso FUS, Jaddoe VWV, Roza SJ, Tiemeier H, Ikram MA. Association of blood pressure and arterial stiffness with cognition in 2 population-based child and adult cohorts. *J Am Heart Assoc*. 2018;7:e009847. doi: 10.1161/JAHA.118.009847
81. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256. doi: 10.1212/WNL.0000000000005259
82 Cooper LL, Himali JJ, Torjesen A, Tsao CW, Beiser A, Hamburg NM, DeCarli C, Vasan RS, Seshadri S, Pase MP, et al. Inter-relations of orthostatic blood pressure change, aortic stiffness, and brain structure and function in young adults. *J Am Heart Assoc*. 2017;6:e006206. doi: 10.1161/JAHA.117.006206
83. Maillard P, Mitchell GF, Himali JJ, Beiser A, Fletcher E, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, et al. Aortic stiffness, increased white matter free water, and altered microstructural integrity: a continuum of injury. *Stroke*. 2017;48:1567–1573. doi: 10.1161/STROKEAHA.116.016321
84. Maillard P, Mitchell GF, Himali JJ, Beiser A, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, DeCarli C. Effects of arterial stiffness on brain integrity in young adults from the Framingham Heart Study. *Stroke*. 2016;47:1030–1036. doi: 10.1161/STROKEAHA.116.012949
85. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, Mitchell GF, Seshadri S. Association of arterial stiffness with progression of subclinical brain and cognitive disease. *Neurology*. 2016;86:619–626. doi: 10.1212/WNL.0000000000002368
86. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, Himali JJ, Hamburg NM, Vita JA, Levy D, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. *Neurology*. 2013;81:984–991. doi: 10.1212/WNL.0b013e3182a43e1c
87. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014;15:736–746. doi: 10.1093/ehjci/jet256
88. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795. doi: 10.1001/jama.2012.9624
89. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, Dardari Z, Sibley CT, Burke GL, Kronmal RA, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2016;133:849–858. doi: 10.1161/CIRCULATIONAHA.115.018524
90. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med*. 2012;156:438–444. doi: 10.7326/0003-4819-156-6-201203200-00006
91. Topel ML, Shen J, Morris AA, Al Mheid I, Sher S, Dunbar SB, Vaccarino V, Sperling LS, Gibbons GH, Martin GS, et al. Comparisons of the Framingham and pooled cohort equation risk scores for detecting subclinical vascular disease in blacks versus whites. *Am J Cardiol*. 2018;121:564–569. doi: 10.1016/j.amjcard.2017.11.031

19. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

See Tables 19-1 through 19-3 and Charts 19-1 through 19-11

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Coronary Heart Disease

ICD-9 410 to 414, 429.2; *ICD-10* I20 to I25 (includes MI *ICD-10* I21 to I22).

Prevalence

(See Tables 19-1 and 19-2 and Charts 19-1 through 19-4)

- On the basis of data from NHANES 2013 to 2016,[1] an estimated 18.2 million Americans ≥20 years of age have CHD (Table 19-1). The prevalence of CHD was higher for males than females ≥60 years of age (Chart 19-1).

Abbreviations Used in Chapter 19

ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AHA	American Heart Association
AMI	acute myocardial infarction
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCVD	atherosclerotic cardiovascular disease
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease
BRFSS	Behavioral Risk Factor Surveillance System
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CARDIoGRAM	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis
CARDIoGRAMplusC4D	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM) plus the Coronary Artery Disease Genetics (C4D)
CARE	Cholesterol and Recurrent Events
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CMS	Centers for Medicare & Medicaid Services

(*Continued*)

Abbreviations Used in Chapter 19 Continued

CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patient Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
EMS	emergency medical services
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FINRISK	Finnish population survey on risk factors for chronic, noncommunicable diseases
FRS	Framingham Risk Score
GBD	Global Burden of Disease
GRS	genetic risk score
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HDL-C	high-density lipoprotein cholesterol
HD	heart disease
HF	heart failure
HR	hazard ratio
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
IHD	ischemic heart disease
JHS	Jackson Heart Study
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MI-GENES	Myocardial Infarction Genes Study
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Study
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
NYHA	New York Heart Association
OR	odds ratio
PCI	percutaneous coronary intervention

(*Continued*)

Abbreviations Used in Chapter 19 Continued

PHS	Physicians' Health Study
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus Stents in Patients With Left Main Coronary Artery Disease
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SES	socioeconomic status
SHS	Strong Heart Study
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TC	total cholesterol
TRACE-CORE	Transitions, Risks, and Actions in Coronary Events–Center for Outcomes Research and Education
UA	unstable angina
UI	uncertainty interval
WHI	Women's Health Initiative
WHS	Women's Health Study

- Total CHD prevalence is 6.7% in US adults ≥20 years of age. CHD prevalence is 7.4% for males and 6.2% for females. CHD prevalence by sex and ethnicity is shown in Table 19-1.
- On the basis of data from the 2017 NHIS, the CHD prevalence estimates are 5.6% among whites, 5.9% among blacks, 2.7% among American Indian/Alaska Natives, and 4.3% among Asians ≥18 years of age.[2]
- According to data from NHANES 2013 to 2016 (unpublished NHLBI tabulation),[1] the overall prevalence for MI is 3.0% in US adults ≥20 years of age. Males have a higher prevalence of MI than females for all age groups except 20 to 39 years (Chart 19-2). MI prevalence is 4.0% for males and 2.3% for females. MI prevalence by sex and ethnicity is shown in Table 19-1.
- According to data from NHANES 2013 to 2016,[1] the overall prevalence for angina is 3.6% in US adults ≥20 years of age (Table 19-2).
- According to data from NHANES for the period 1988 to 2012, angina prevalence declined substantially in NH whites (from 4.0% to 2.1%) but not in NH blacks (from 4.9% to 4.4%). Angina prevalence declined in both males and females ≥65 years of age (males from 5.1% to 2.9%, females from 5.6% to 2.4%).[3]
- Data from the BRFSS 2017 survey indicated that 4.2% of respondents had been told that they had had an MI. The highest prevalence was in West Virginia (6.0%) and the lowest was in Hawaii (2.6%; age-adjusted; Chart 19-3).[4]
- In the same survey, 3.9% of respondents had been told that they had angina or CHD. The highest prevalence was in Puerto Rico (6.6%) and West Virginia (6.0%), and the lowest was in the District of Columbia (2.1%) and Hawaii (2.2%; age-adjusted; Chart 19-4).[4]

Incidence
(See Charts 19-5 through 19-7)

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI[5]).
- On the basis of data tabulated by NHLBI from the 2005 to 2014 ARIC study of the NHLBI[5]:
  - This year, ≈720 000 Americans will have a new coronary event (defined as first hospitalized MI or CHD death), and ≈335 000 will have a recurrent event.
  - The estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks. Of these 805 000 first and recurrent events, it is estimated that 170 000 are silent.
  - Average age at first MI is 65.6 years for males and 72.0 years for females.
- In the REGARDS study, 37% of adjudicated MIs had a primary hospital discharge diagnosis of MI, whereas 63% had a primary hospital discharge diagnosis other than MI, which suggests that most MIs that result in hospitalization might be occurring during hospitalization for other acute illnesses.[6]
- Self-reported income and education were associated with incident CHD (defined as definite or probable MI or acute CHD death) in the REGARDS study. Those reporting low income and low education had twice the incidence of CHD as those reporting high income and high education (10.1 versus 5.2 per 1000 person-years, respectively).[7]
- Annual numbers for MI or fatal CHD in the NHLBI-sponsored ARIC study and the CHS stratified by age and sex are displayed in Chart 19-5. Incidence of heart attacks or fatal CHD stratified by age, race, and sex is displayed in Chart 19-6.
- Incidence of MI by age, sex, and race in the NHLBI-sponsored ARIC study is displayed in Chart 19-7. Black males have a higher incidence of MI in all age groups.
- HRs for incident fatal CHD were higher for black males than for white males 45 to 65 years of age

(ARIC: 2.09 [95% CI, 1.42–3.06]; REGARDS: 2.11 [95% CI, 1.32–3.38]). Nonfatal CHD risk was lower (ARIC: 0.82 [95% CI, 0.64–1.05]; REGARDS: 0.94 [95% CI, 0.69–1.28]). However, after adjustment for social determinants of health and cardiovascular risk factors, black males and females have similar risk for fatal CHD but lower risk for nonfatal CHD.[8]

- In 9498 participants in the ARIC study, whites had a higher rate of clinically recognized MI than blacks (5.04 versus 3.24 per 1000 person-years, *P*=0.002).[9]

Secular Trends

- The overall body of literature suggests that the incidence of MI in the United States has declined significantly over time.[10]
- In Olmsted County, MN, between 1995 and 2012, the population rate of MI declined 3.3% per year; however, these declines varied among types of MI, with the greatest declines occurring for prehospital fatal MI.[11]
- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 person-years. The rates of MI as the primary reason for hospitalization decreased over time (from 1063 to 677 per 100 000 person-years between 2002 and 2011), whereas the rates of MI as a secondary reason for hospitalization increased (from 190 to 245 per 100 000 person-years). The percentage of MIs that were attributable to a secondary diagnosis increased from 28% to 40%.[12]
- Among Medicare beneficiaries, the rates of primary hospitalization for MI between 2002 and 2011 declined by 36.6% among NH whites (from 1057 to 670 per 100 000 person-years between 2002 and 2011) and by 26.4% among NH blacks (from 966 to 711 per 100 000 person-years between 2002 and 2011).[13]

Social Determinants

- In an analysis of a population-based register sample of adults 40 to 60 years of age in Finland in 1995 (N=302 885) followed up until the end of 2007, MI incidence and mortality were examined in relation to living arrangements (living with a marital partner was contrasted to 3 alternatives: cohabiting with nonmarital partner, coresidence with people other than a partner, and living alone). Living arrangements were strong determinants for survival after MI independent of other sociodemographic factors. The results demonstrated greater fatality associated with living alone in males (HR, 1.50 [95% CI, 1.29–1.75]) and suggested that cohabitation in midlife might be associated with a greater fatality risk in females (HR, 2.00 [95% CI 1.26–3.17]).[14]
- In an analysis of nationally representative longitudinal register data in Finnish adults (N = 94 501) for the period 1988 to 2010, household crowding during childhood increased the risk of MI incidence in adulthood by 16% (95% CI, 5%–29%) in males and 25% (95% CI, 3%–50%) in females. Most aspects of childhood circumstances did not strongly influence long-term fatality risk. Income and education remained associated with MI incidence when adjusted for unobserved shared family factors in siblings. Low adult socioeconomic resources remained a strong determinant of MI incidence and fatality.[15]
- Among US adults 45 to 74 years of age in 2009 to 2013, factors accounting for the US county variation in CVD mortality included demographic composition (36% of the variation in county CVD); economic/social conditions (32%); and healthcare utilization, features of the environment, and health indicators (6%).[16]

Risk Prediction

- The percentage of US adults with a 10-year predicted ASCVD risk (using the Pooled Cohort risk equations) ≥20% decreased from 13.0% in 1999 to 2000 to 9.4% in 2011 to 2012. The proportion of US adults with 10-year predicted ASCVD risk of 7.5% to <20% was 23.9% in 1999 to 2000 and 26.8% in 2011 to 2012.[17]
- For adults with optimal risk factors (TC of 170 mg/dL, HDL-C of 50 mg/dL, SBP of 110 mm Hg without antihypertensive medication use, no DM, and not a smoker), 10-year CVD risk ≥7.5% will occur at 65 years of age for white males, 70 years of age for black males and females, and 75 years of age for white females.[18]
- The ASCVD tool might overestimate risk across all strata of risk compared with external contemporary cohorts (PHS, WHS, and WHI Observational Study), as well as in reanalysis of the original validation cohorts. However, some of the subsequent analyses were not conducted in comparable populations as the original study cohorts.[19]
- In 9066 participants 45 to 79 years of age from the REGARDS study, the observed and predicted ASCVD risk using the Pooled Cohort risk equations were similar in people with high social deprivation, although ASCVD risk was overestimated in those with low social deprivation.[20]
- In the WHI, although the risk of ASCVD was overestimated using the Pooled Cohort risk equations, adding additional ASCVD events identified through linkage with CMS claims that were not self-reported resulted in alignment of the observed and predicted risks.[21]

Genetics and Family History

Family History as a Risk Factor

- Among adults ≥20 years of age, 12.4% (SE, 0.5%) reported having a parent or sibling with a heart attack or angina before 50 years of age. The racial/ethnic breakdown from NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation)[1]:
  - For NH whites, 12.2% (SE 1.0%) for males, 15.0% (SE 0.9%) for females.
  - For NH blacks, 7.1% (SE 0.9%) for males, 14.0% (SE 1.3%) for females.
  - For Hispanics, 7.7% (SE 0.6%) for males, 10.7% (SE 0.5%) for females.
  - For NH Asians, 6.3% (SE 0.9%) for males, 4.6% (SE 0.8%) for females.
- HD occurs as people age, so the prevalence of family history will vary depending on the age at which it is assessed. The breakdown of reported family history of heart attack by age of survey respondent in the US population as measured by NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation)[1]:
  - 20 to 39 years of age, 8.5% (SE 1.0%) for males, 9.9% (SE 0.6%) for females.
  - 40 to 59 years of age, 11.4% (SE 1.4%) for males, 16.9% (SE 1.2%) for females.
  - 60 to 79 years of age, 13.6% (SE 1.7%) for males, 16.6% (SE 1.6%) for females.
  - ≥80 years of age, 12.5% (SE 2.7%) for males, 13.6% (SE 2.6%) for females.
- Family history of premature angina, MI, angioplasty, or bypass surgery increases lifetime risk by ≈50% for both HD (from 8.9% to 13.7%) and CVD mortality (from 14.1% to 21%).[22]
- In premature ACS (≤55 years of age), a greater percentage of females (28%) than males (20%) have a family history of CAD (P=0.008). Compared with patients without a family history, patients with a family history of CAD have a higher prevalence of traditional CVD risk factors.[23]
- Among patients with STEMI in the NIS between 2003 and 2011, those with a family history of CAD were more likely to undergo coronary intervention and had lower in-hospital mortality than patients without a family history (OR, 0.45 [95% CI, 0.43–0.47]; P<0.001).[24]

Genetic Predictors of CHD

- For the past decades, candidate gene studies have been conducted to identify the genetic variants underlying the heritability of CHD, but very few have identified consistent, replicated, and independent genetic variants, and all have had small effect sizes.
- Over the past decade, the application of GWASs to large cohorts of CHD case and control subjects has identified many consistent genetic variants associated with CHD. The total number of CAD-associated regions identified in GWASs is 73, with 15 novel CAD associations related to atherosclerosis and traditional risk factors but also highlighting the importance of key biological process in the arterial wall.[25]
- The first GWAS identified the now most consistently replicated genetic marker for CHD and MI in European-derived populations, on chromosome 9p21.3.[26] The frequency of the primary SNP is very common (50% of the white population is estimated to harbor 1 risk allele, and 23% harbors 2 risk alleles).[27]
  - The 10-year HD risk for a 65-year-old male with 2 risk alleles at 9p21.3 and no other traditional risk factors is ≈13.2%, whereas a similar male with 0 alleles would have a 10-year risk of ≈9.2%. The 10-year HD risk for a 40-year-old female with 2 alleles and no other traditional risk factors is ≈2.4%, whereas a similar female with 0 alleles would have a 10-year risk of ≈1.7%.[27]
- The association of SNPs with incident CHD was investigated in a large multiethnic study of multiple cohorts in the United States (including NHANES, WHI, the Multiethnic Cohort Study, CHS, ARIC, CARDIA, HCHS/SOL, and SHS). SNPs, including in 9p21, *APOE*, and *LPL*, were associated with incident CHD in individuals of European ancestry but not blacks. Effect sizes were greater for those ≤55 years of age and in females.[28]
- More recently, genetic studies of CHD have focused on the coding regions of the genome (exons) and have identified additional genes and SNPs for CHD, including loss-of-function mutations in the angiopoietin-like 4 gene (*ANGPTL4*), which is an inhibitor of lipoprotein lipase. These mutations are associated with low plasma triglycerides and high HDL-C.[29]
- In a discovery analysis of common SNPs (minor allele frequency of >5%) on an exome array, 6 new loci associated with CAD were identified, including SNPs on the *KCNJ13-GIGYF2*, *C2*, *MRVI1-CTR9*, *LRP1*, *SCARB1*, and *CETP* genes.[30]
- In the DiscovEHR study, loss-of-function variants in the angiopoietin-like 3 gene (*ANGPTL3*) were less common in patients with CAD than in control subjects (0.33% versus 0.45%) and were associated with 27% lower triglyceride levels, 9% lower LDL-C, and 4% lower HDL-C.[31]
- Protein-truncating variants at the *CETP* gene are associated with increased HDL-C and lower LDL-C and triglycerides. Compared with noncarriers, carriers of protein-truncating variants at *CETP* had a

lower risk of CHD (OR, 0.70 [95% CI, 0.54–0.90]; *P*=5.1×10–3).[32]

- Using a network mendelian randomization analysis, a 1-U longer genetically determined telomere length was associated with a lower risk of CHD in the CARDIoGRAM Consortium (OR, 0.79 [95% CI, 0.65–0.97]; *P*=0.016) and the CARDIoGRAMplusC4D 1000 Genome Consortium (OR, 0.89 [95% CI, 0.79–1.00]; *P*=0.052). Fasting insulin can partially mediate the association of telomere length with CHD, accounting for 18.4% of the effect of telomere length on CHD.[33]
- Whole-genome sequencing studies, which offer a deeper and more comprehensive coverage of the genome, have recently identified 13 variants with large effects on blood lipids. Five variants within *PCSK9*, *APOA1*, *ANGPTL4*, and *LDLR* are associated with CHD.[34]

Clinical Utility of Genetic Markers

- Recent advances have demonstrated the utility of genetics in CAD risk prediction. In 48 421 individuals enrolled in the Malmo Diet and Cancer Study and 2 primary prevention trials (JUPITER, ASCOT) and 2 secondary prevention trials of lipid lowering (CARE, PROVE IT-TIMI22), a GRS consisting of 27 variants of genetic risk for CAD improved risk prediction above models that incorporated traditional risk factors and family history.[35] In the Malmo Diet and Cancer Study, application of an additional 23 SNPs known to be associated with CAD resulted in greater discrimination and reclassification (both *P*<0.0001).[36]
- In the FINRISK and FHS cohorts, with a sample size of 16 082 individuals, a GRS incorporating 49 310 SNPs based on the CARDIoGRAMplusC4D Consortium data showed that the combination of GRS with the FRS improved 10-year cardiac risk prediction, particularly in those ≥60 years of age.[37]
- Studies have also shown that patients with early-onset MI have a higher proportion of very high polygenic GRS than of FH mutations; for example, ≈2% carry a rare FH genetic mutation, whereas ≈17% have a high polygenic risk score.[38]
- In the MI-GENES trial of intermediate-risk patients, patient knowledge of their GRS resulted in lower levels of LDL-C than in a control group managed by conventional risk factors alone, which suggests the influence of GRS in risk prevention.[39]
- Even in individuals with high genetic risk, prevention strategies have added benefit. For example, in 4 studies across 55 685 participants, genetic and lifestyle factors were independently associated with CHD, but even in participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower RR of CHD than was an unfavorable lifestyle.[40]
- A novel genomic risk score for CAD including 1.7 million genetic variants was associated with increased risk of CAD in the UK Biobank (HR, 1.71 [95% CI, 1.68–1.73] per SD increase in the score). Compared with individuals in the bottom quintile of the score, the HR of CAD for those in the top quintile was 4.17 (95% CI, 3.97–4.38). However, adding the genetic score to conventional risk factors only resulted in a small increase in predictive ability (C-statistic changing from 0.670 to 0.696).[41]

Awareness, Treatment, Control

Awareness of Warning Signs and Risk for HD

- In 2012, NH black and Hispanic females had lower awareness than white females that HD/heart attack is the leading cause of death for females.[42]
- The percentages of females in 2012 identifying warning signs for a heart attack were as follows: pain in the chest—56%; pain that spreads to the shoulder, neck, or arm—60%; shortness of breath—38%; chest tightness—17%; nausea—18%; and fatigue—10%.[42]
- Among online survey participants, 21% responded that their doctor had talked to them about HD risk. Rates were lower among Hispanic females (12%) than whites (22%) or blacks (22%) and increased with age from 6% (25–34 years) to 33% (≥65 years).[42]
- Among 2009 females and 976 males <55 years of age hospitalized for MI, only 48.7% of females and 52.9% of males reported having been told they were at risk for HD or a heart problem. Also, 50.3% of females and 59.7% of males reported their healthcare provider had discussed HD and things they could do to take care of their heart.[43] Data from the NHIS indicate that awareness of 5 common heart attack symptoms (jaw, neck, or back discomfort; weakness or lightheadedness; chest discomfort; arm or shoulder discomfort; and shortness of breath) increased from 39.6% in 2008 to 50.0% in 2014 and 50.2% in 2017. In 2017, knowledge of the 5 symptoms was higher in females than in males (54.4% versus 45.6%) and differed by race/ethnicity (whites, 54.8%; blacks, 43.1%; Asians, 33.5%; Hispanics, 38.9%).[44]

Time of Symptom Onset and Arrival at Hospital

- Data from Worcester, MA, indicate that the median time from symptom onset to hospital arrival did not improve from 2001 through 2011. In 2009 to 2011, 48.9% of patients reached the hospital within 2 hours of symptom onset, compared with 45.8% in 2001 to 2003.[45]
- A retrospective analysis of the NHAMCS data from 2004 to 2011 that reviewed 15 438 hospital visits

related to ACS symptoms suggested that blacks have a 30% longer waiting time than whites, the reasons for which are unclear.[46]

- The timing of hospital admission influences management of MI. A study of the NIS database from 2003 to 2011 indicated that admission on a weekend for NSTEMI was associated with a significantly reduced odds for coronary angiography (OR, 0.88 [95% CI, 0.89–0.90]; *P*<0.001) and early invasive strategy (OR, 0.48 [95% CI, 0.47–0.48]; *P*<0.001), resulting in greater mortality.[47]
- Among patients hospitalized for ACS between 2001 and 2011 in the NIS, those with STEMI admitted on the weekend versus on a weekday had a 3% higher odds of in-hospital mortality.[48]
- In a meta-analysis including 57 136 patients from 10 studies, door-to-balloon time of >90 minutes versus ≤90 minutes was associated with higher in-hospital or 30-day mortality (OR, 1.52 [95% CI, 1.40–1.65]). An increased risk of 6-month to 12-month mortality was also observed for >90 minute door-to-balloon delay in 14 261 patients from 8 studies (OR, 1.53 [95% CI, 1.13–2.06]).[49]

Operations and Procedures

- In 2014, an estimated 480 000 percutaneous transluminal coronary angioplasties, 371 000 inpatient bypass procedures, 1 016 000 inpatient diagnostic cardiac catheterizations, 86 000 carotid endarterectomies, and 351 000 pacemaker procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP[50]).
- In an analysis of the BEST, PRECOMBAT, and SYNTAX trials comparing individuals with MI and who had left main or multivessel CAD, the outcomes of CABG versus PCI were examined. CABG was associated with a lower risk of recurrent MI and repeat revascularizations.[51] In patients with multivessel CAD, CABG was associated with lower all-cause and cardiovascular mortality; however, no differences in all-cause and cardiovascular mortality between CABG and PCI were observed among patients with multivessel plus left main CAD.[52]
- In a meta-analysis of 6 randomized trials that included 4686 patients with unprotected left main CAD, no significant differences in all-cause and cardiovascular mortality or a composite outcome of death, MI, or stroke were observed between patients treated with PCI versus CABG. However, PCI was associated with a lower risk of the composite outcome within the first 30 days of follow-up (OR, 0.62 [95% CI, 0.45–0.86]).[53]
- In 5-year follow-up of the SYNTAX trial, greater MI-related death in PCI-treated patients was associated with the presence of DM, 3-vessel disease, or high SYNTAX scores.[54]
- At 5 years of follow-up in the SYNTAX and BEST randomized trials, among patients with multivessel CAD involving the proximal left anterior descending coronary artery, PCI was associated with increased composite outcome of all-cause death, MI, or stroke (HR, 1.43 [95% CI, 1.05–1.95]; *P*=0.026), cardiovascular death (HR, 2.17 [95% CI, 1.24–3.81]; *P*=0.007), and major adverse cardiovascular and cerebrovascular events (HR, 1.68 [95% CI, 1.31–2.15]; *P*<0.001).[55]
- In 27 840 STEMI patients transported via EMS to 744 hospitals in the ACTION registry, preactivation of the catheterization laboratory >10 minutes before hospital arrival compared with no preactivation was associated with shorter times to the catheterization laboratory (median of 17 minutes versus 28 minutes), shorter door-to-device time (median of 40 minutes versus 52 minutes), and lower in-hospital mortality (2.8% versus 3.4%; *P*=0.01).[56]
- In the NIS, isolated CABG procedures decreased by 25.4% from 2007 to 2011 (326 to 243 cases per million adults), particularly at higher-volume centers. Low-volume centers were associated with greater risk of all-cause in-hospital mortality in multivariable analysis (OR, 1.39 [95% CI, 1.24–1.56]; *P*<0.001).[57]
- According to the NIS, the number of PCI procedures declined by 38% between 2006 and 2011. Among patients with stable IHD, a 61% decline in PCI occurred over this time period.[58]
- In Washington State, the overall number of PCIs decreased by 6.8% between 2010 and 2013, with a 43% decline in the number of PCIs performed for elective indications.[59]
- Among Medicare fee-for-service beneficiaries, the total number of revascularization procedures performed peaked in 2010 and declined by >4% per year through 2012. In-hospital and 90-day mortality rates declined after CABG surgery overall, as well as among patients presenting for elective CABG or CABG after NSTEMI.[60]
- Between 2011 and 2014, the use of femoral access declined (from 88.8% to 74.5%) and radial access increased (from 10.9% to 25.2%).[61]
- In a meta-analysis of 13 observational studies and 3 RCTs, a transradial approach for PCI was associated with a reduction in vascular complications (OR, 0.36 [95% CI, 0.30–43]) and stroke (OR, 0.79 [95% CI, 0.64–0.97]) compared with a transfemoral approach. A transradial approach was also associated with a reduced risk of death (OR, 0.56 [95% CI, 0.45–0.69]), although this was driven by the observational studies, because no association with death was observed in the randomized trials.[62]

- In 2014, from the CathPCI registry, median door-to-balloon time for primary PCI for STEMI was 59 minutes for patients receiving PCI in the presenting hospital and 105 minutes for patients transferred from another facility for therapy.[61]
- The importance of adherence to optimal medical therapy was highlighted in an 8-hospital study of NSTEMI patients, in which medication nonadherence was associated with a composite outcome of all-cause mortality, nonfatal MI, and reintervention (HR, 2.79 [95% CI, 2.19–3.54]; *P*<0.001). In propensity-matched analysis, CABG outcomes were favorable compared with PCI in patients nonadherent to medical therapy (*P*=0.001), but outcomes were similar in medicine-adherent patients (*P*=0.574).[63]

Cardiac Rehabilitation

- In the NCDR ACTION Registry–GWTG, cardiac rehabilitation referral after patients were admitted with a primary diagnosis of STEMI or NSTEMI increased from 72.9% to 80.7% between 2007 and 2012.[64]
- In the NCDR between 2009 and 2012, 59% of individuals were referred to cardiac rehabilitation after PCI, with significant site-specific variation.[65]
- In the BRFSS from 2005 to 2015, <40% of patients self-reported participation in cardiac rehabilitation after AMI. Between 2011 and 2015, patients who declared participation in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]; *P*=0.002) or black (OR, 0.70 [95% CI, 0.53–0.93]; *P*=0.014); were less well educated (high school versus college graduate: OR, 0.69 [95% CI, 0.59–0.81]; *P*<0.001; less than high school versus college graduate: OR, 0.47 [95% CI 0.37–0.61]; *P*<0.001); and were more likely to be retired or self-employed (OR, 1.39 [95% CI, 1.24–1.73]; *P*=0.003) than patients who did not participate in cardiac rehabilitation.[66]
- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health interventions (consisting of an online and smartphone-based platform by which patients reported dietary and exercise habits and received educational information geared toward a healthy lifestyle) had more weight loss at 90 days than the control group (mean±SD of −5.1±6.5 kg versus −0.8±3.8 kg; *P*=0.02) and reduced cardiovascular-related rehospitalizations and ED visits at 180 days (8.1% versus 26.6%; RR, 0.30 [95% CI, 0.08–1.10]; *P*=0.054).[67]

Mortality (See Table 19-1)

- On the basis of 2017 mortality data[68]:
  - CHD mortality was 365 914, and CHD any-mention mortality was 541 008 (Table 19-1).
  - MI mortality was 110 346. MI any-mention mortality was 149 028 (Table 19-1).
- From 2007 to 2017, the annual death rate attributable to CHD declined 28.1% and the actual number of deaths declined 10.0% (unpublished NHLBI tabulation using CDC WONDER[69]).
- CHD age-adjusted death rates per 100 000 were 131.1 for NH white males, 142.2 for NH black males, and 93.9 for Hispanic males; for NH white females, the rate was 66.7; for NH black females, it was 81.8; and for Hispanic females, it was 52.4 (unpublished NHLBI tabulation using CDC WONDER[69]).
- 77% of CHD deaths occurred out of the hospital. According to US mortality data, 281 792 CHD deaths occur out of the hospital or in hospital EDs annually (unpublished NHLBI tabulation using CDC WONDER[69]).
- The estimated average number of years of life lost because of an MI death is 16.1 (unpublished NHLBI tabulation using CDC WONDER[69]).
- Approximately 35% of the people who experience a coronary event in a given year will die as a result of it, and ≈14% who experience an MI will die of it (unpublished NHLBI tabulation using ARIC Community Surveillance [2005–2014])[5].
- Life expectancy after AMI treated in hospitals with high performance on 30-day mortality measures compared with low-performing hospitals was on average between 0.74 and 1.14 years longer.[70]
- In-hospital mortality is higher in females than in males with STEMI (7.4% versus 4.6%) and NSTEMI (4.8% versus 3.9%).[71,72] Females experience longer door-to-balloon times and lower rates of guideline-directed medical therapy than males; however, a 4-step systems-based approach to minimize STEMI care variability at the Cleveland Clinic resulted in reduced sex disparities and improved care and outcomes in females.[73]
- Among 194 071 adults who were hospitalized for an AMI in the 2009 to 2010 NIS, in-hospital mortality for those <65 years of age was higher for Hispanic females (3.7%) than for black females (3.1%) and white females (2.5%). Differences were smaller for males <65 years of age. Among older adults (≥65 years), in-hospital mortality was 8.0% for white females and between 6% and 8% for other race-sex groups.[74]
- In a study using data from the Cooperative Cardiovascular Project, survival and life expectancy after AMI were higher in whites than in blacks (7.4% versus 5.7%). White patients living in high SES areas showed the longest life expectancy. Gaps in life expectancy between white and black patients were largest among high SES areas, with smaller differences in medium and low SES areas.

These differences were attenuated but did not disappear after adjustment for patient and treatment characteristics.[75]

- Among patients hospitalized for STEMI between 2003 and 2014 in the NIS database, lack of health insurance (OR, 1.77 [95% CI, 1.72–1.82]; *P*<0.001) and below-median income (OR, 1.08 [95% CI, 1.07–1.09]; *P*<0.001) were independent predictors of in-hospital mortality.[76]
- Compared with nonparticipants, participants in the Supplemental Nutrition Assistance Program have twice the risk of CVD mortality, which likely reflects differences in socioeconomic, environmental, and behavioral characteristics.[77]
- In the CRUSADE study including 22 295 patients ≥65 years of age treated for STEMI or NSTEMI at 344 hospitals in the United States between 2004 and 2006, in-hospital mortality was 7%. Mortality was 24% at 1 year, 51% at 5 years, and 65% at 8 years. Eight-year mortality was higher for NSTEMI (67%) than for STEMI (53%), although the difference was attenuated after adjustment for demographics and comorbidities (HR, 0.94 [95% CI, 0.88–1.00]).[78]
- Among Medicare fee-for-service beneficiaries, between 1999 and 2011, the 30-day mortality rate after hospitalized MI declined by 29.4%.[79]
- In a community-based study of Worcester, MA, the percentage of patients dying after cardiogenic shock during their hospitalization for MI declined from 47.1% in 2001 to 2003 to 28.6% in 2009 to 2011.[80]
- Between 2001 and 2011 in the NIS, in-hospital mortality did not change for patients with STEMI with a PCI (3.40% and 3.52% in 2001 and 2011, respectively) or CABG (5.79% and 5.70% in 2001 and 2011, respectively) and increased for patients with no intervention (12.43% and 14.91% in 2001 and 2011, respectively). In-hospital mortality declined for patients with NSTEMI undergoing CABG (from 4.97% to 2.91%) or no procedure (from 8.87% to 6.26%) but did not change for patients with NSTEMI undergoing PCI (1.73% and 1.45%).[81]
- Among US males <55 years of age, CHD mortality declined 5.5% per year between 1979 and 1989; a smaller decline was present in 1990 to 1999 (1.2% per year) and in 2000 to 2011 (1.8% per year). Among US females <55 years of age, CHD mortality declined 4.6% per year in 1979 to 1989, with no decline between 1990 and 1999 and a decline of 1.0% in 2000 to 2011.[82]
- Taking into account past trends in CHD mortality from 1980, and considering age period and cohort effects, CHD mortality is likely to continue its decades-long decline, with a reduction in deaths by 2030 of 27%; however, race disparities will persist.[83] Recent reports have suggested a slowing down of all CVD and HD mortality in recent years.[84,85]

Complications

- In a pooled analysis of individuals after PCI in 5 RCTs, those with STEMI had a greater risk of death within the first 30 days after PCI than those with stable IHD, whereas those with NSTEMI had a greater risk of death during the entire 2 years of follow up.[86]
- From the NCDR CathPCI registry, in 2014 the unadjusted rates of various events were as follows: acute kidney injury, 2.6% (versus 2.3% in 2011); blood transfusion, 1.4% (versus 1.9% in 2011); postprocedural stroke, 0.2% (versus 0.2% in 2011); emergency CABG surgery, 0.2% (versus 0.3% in 2011); and vascular access site injury, 1.3% (versus 1.2% in 2011).[61]
- STEMI confers greater in-hospital risks than NSTEMI, including death (6.4% for STEMI, 3.4% for NSTEMI), cardiogenic shock (4.4% versus 1.6%, respectively), and bleeding (8.5% versus 5.5%, respectively).[61] In the NCDR ACTION Registry–GWTG, a measure of neighborhood SES was associated with in-hospital deaths and major bleeding in patients with AMI. Compared with those in the highest quintile of neighborhood SES, those residing in the most disadvantaged quintile experienced higher rates of in-hospital death (OR, 1.10 [95% CI, 1.02–1.18]) and major bleeding (OR, 1.10 [95% CI, 1.05–1.15]).[87]
- Among females with AMI, those with spontaneous coronary artery dissection had higher odds of in-hospital mortality (6.8%) than females without spontaneous coronary artery dissection (3.8%; OR, 1.87 [95% CI, 1.65–2.11]; *P*<0.001).[88]
- In the NCDR ACTION Registry–GWTG, patients with STEMI or NSTEMI with nonobstructive coronary arteries (<50% stenosis) had lower in-hospital mortality than patients with obstructive CAD (1.1% versus 2.9%; *P*<0.001). Nonobstructive coronary arteries were more common in females than males (10.5% versus 3.4%; *P*<0.001), but no difference in in-hospital mortality was observed between females and males with nonobstructive coronary arteries (*P*=0.84).[89]
- Patients with LV thrombosis complicating anterior STEMI had longer hospital stays, higher hospitalization-related costs, and higher risk of thromboembolic events than those without LV thrombosis (7.3% versus 2.1%; OR, 3.65 [95% CI, 1.95–6.84]; *P*<0.001).[90]
- In a propensity score–matched analysis from the NIS HCUP that included discharges with MI as the

principal diagnosis from 2012 to 2014, patients with delirium had higher rates of in-hospital mortality than those without delirium (10.5% versus 7.6%; RR, 1.39 [95% CI, 1.2–1.6]; $P<0.001$).[91]

- Individuals with HF symptoms (NYHA functional class ≥2) within 30 days after PCI for STEMI experience increased risk of death or hospitalization for HF within 1 year compared with those without HF symptoms (HR, 3.78 [95% CI, 1.16–12.22]; $P=0.03$).[92]
- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 1 year after a first MI (unpublished NHLBI tabulation):
  - At ≥45 years of age, 18% of males and 23% of females will die.
  - At 45 to 64 years of age, 3% of white males, 5% of white females, 9% of black males, and 10% of black females will die.
  - At 65 to 74 years of age, 14% of white males, 18% of white females, 22% of black males, and 21% of black females will die.
  - At ≥75 years of age, 27% of white males, 29% of white females, 19% of black males, and 31% of black females will die.
- In part because females have MIs at older ages than males, they are more likely to die of MI within a few weeks.
- Within 5 years after a first MI:
  - At ≥45 years of age, 36% of males and 47% of females will die.
  - At 45 to 64 years of age, 11% of white males, 17% of white females, 16% of black males, and 28% of black females will die.
  - At 65 to 74 years of age, 25% of white males, 30% of white females, 33% of black males, and 44% of black females will die.
  - At ≥75 years of age, 55% of white males, 60% of white females, 61% of black males, and 64% of black females will die.
- Of those who have a first MI, the percentage with a recurrent MI or fatal CHD within 5 years is as follows:
  - At ≥45 years of age, 17% of males and 21% of females.
  - At 45 to 64 years of age, 11% of white males, 15% of white females, 22% of black males, and 32% of black females.
  - At 65 to 74 years of age, 12% of white males, 17% of white females, 30% of black males, and 30% of black females.
  - At ≥75 years of age, 21% of white males, 20% of white females, 45% of black males, and 20% of black females.
- The percentage of people with a first MI who will have HF in 5 years is as follows:
  - At ≥45 years of age, 16% of males and 22% of females.
  - At 45 to 64 years of age, 6% of white males, 10% of white females, 13% of black males, and 25% of black females.
  - At 65 to 74 years of age, 12% of white males, 16% of white females, 20% of black males, and 32% of black females.
  - At ≥75 years of age, 25% of white males, 27% of white females, 23% of black males, and 19% of NH black females.
- The percentage of people with a first MI who will have an incident stroke within 5 years is as follows:
  - At ≥45 years of age, 4% of males and 7% of females.
  - At ≥45 years of age, 5% of white males, 6% of white females, 4% of black males, and 10% of black females.
- The median survival time (in years) after a first MI is as follows:
  - At ≥45 years of age, 8.2 for males and 5.5 for females.
  - At ≥45 years of age, 8.4 for white males, 5.6 for white females, 7.0 for black males, and 5.5 for black females.
- The burden of rehospitalizations for AMI may be substantial: A retrospective cohort study of 78 085 Medicare beneficiaries ≥66 years of age without recent CHD history who were hospitalized for AMI in 2000 to 2010 reported that 20.6% had at least 1 rehospitalization during the 10 years after the index MI. Among patients with a CHD rehospitalization, 35.9% had ≥2 CHD rehospitalizations. Males and patients ≥85 years of age had greater rate ratios for first rehospitalization.[93]
- A study of 3 250 194 Medicare beneficiaries admitted for PCI found that readmission rates declined slightly from 16.1% in 2000 to 15.4% in 2012. The majority of readmissions were because of chronic IHD (26.6%), HF (12%), and chest pain/angina (7.9%). A minority (<8%) of total readmissions were for AMI, UA, or cardiac arrest/cardiogenic shock.[94]
- Rehospitalization can be influenced by clinical, psychosocial, and sociodemographic characteristics not accounted for in traditional CMS claims-based models, including prior PCI, CKD, low health literacy, lower serum sodium levels, and lack of cigarette smoking.[95]
- In a study of 3 central Massachusetts hospitals, the 90-day rehospitalization rate declined from 31.5% in 2001 to 2003 to 27.3% in 2009 to 2011.[96] Crude 30-day rehospitalization rates decreased from 20.5% in 2001 to 2003 to 15.8% in 2009 to 2011.[97]

Hospital Discharges and Ambulatory Care Visits (See Table 19-1 and Chart 19-8)

- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 857 000 to 1 045 000 (Table 19-1).
- From 1997 through 2016, the number of hospital discharges for CHD was higher for males than females (Chart 19-8).
- In 2016, there were 11 072 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS[98]). In 2016, there were 469 000 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using NHAMCS[99]).
- In the NIS, the mean length of hospital stay for STEMI patients with primary PCI declined from 3.3 days in 2005 to 2.7 days in 2014; the proportion of hospitalizations with length of stay >3 days declined from 31.9% in 2005 to 16.9% in 2014.[100]
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin, P2Y12 inhibitors, and statins, was high (89.1% in 2011 and 93.5% in 2014). However, in the ACTION-GWTG registry, metrics that were shown to need improvement were defect-free care (median hospital performance rate of 78.4% in 2014), P2Y12 inhibitor use in eligible medically treated patients with AMI (56.7%), and the use of aldosterone antagonists in patients with LV systolic dysfunction and either DM or HF (12.8%).[61]

Cost

- The estimated direct costs of HD in 2014 to 2015 (average annual) were $109.4 billion (MEPS,[101] unpublished NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2014 to 2015 (average annual) was $218.7 billion (MEPS,[101] unpublished NHLBI tabulation).
- MI ($12.1 billion) and CHD ($9.0 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2013.[102]
- In 642 105 Medicare beneficiaries hospitalized for AMI between 2011 and 2014, 30-day episode payments averaged $22 128 but varied 2-fold across hospitals. Median costs were $20 207 in the lowest quartile versus $24 174 in the highest quartile of hospitals.[103]
- In Medicare beneficiaries hospitalized with AMI, the 180-day expenditures increased from an average of $32 182 per person in 1999 to 2000 to $36 836 in 2008 and remained relatively stable thereafter, with expenditures of $36 668 in 2013 to 2014.[104]
- In a multipayer administrative claims database of patients with incident inpatient PCI admissions between 2008 and 2011, post-PCI angina and chest pain were common and costly ($32 437 versus $17 913; $P<0.001$ at 1 year comparing those with and without angina or chest pain).[105]
- Among Medicare beneficiaries linked to the NCDR CathPCI Registry with inpatient or outpatient PCI between July 2009 and December 2012, costs were $3502 (95% CI, $3347–$3648; $P<0.001$) lower for patients with same-day discharge than for those not discharged the same day. Although a minority of patients receive transradial intervention and same-day discharge (1.2%), a cost savings of $3689 (95% CI, $3486–$3902; $P<0.001$) was observed compared with patients with transfemoral intervention not discharged the same day.[106]

Global Burden (See Table 19-3 and Charts 19-9 and 19-10)

- The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[107] Globally, it is estimated that in 2017, 126.5 million people live with IHD, and it is more prevalent in males than in females (68.5 and 57.9 million people, respectively). The number of people with IHD increased by 74.9% from 1990 to 2017, although the age-standardized rate per 100 000 decreased 11.8% over the same time period (Table 19-3).
  - IHD mortality rates are generally lower than 150 per 100 000 for most of the world but exceed 280 per 100 000 in Eastern Europe and Central Asia (Chart 19-9).
  - Eastern Europe, North Africa, and the Middle East have the highest prevalence rates of IHD in the world (Chart 19-10).

Acute Coronary Syndrome
ICD-9 410, 411; *ICD-10* I20.0, I21, I22.

- In 2016, there were 661 000 ACS principal diagnosis discharges. Of these, an estimated 409 000 were males, and 252 000 were females. This estimate was derived by adding the principal diagnoses for MI (651 000) to those for UA (10 000; unpublished NHLBI tabulation using HCUP[50]).
- When all listed discharge diagnoses in 2016 were included, the corresponding number of inpatient hospital discharges was 1 045 000 unique hospitalizations for ACS; 615 000 were males, and 430 000 were females. Of the total, 1 022 000 were for MI alone, and 23 000 were for UA alone (HCUP,[50] unpublished NHLBI tabulation).
- In a study using the NIS and the State Inpatient Databases for the year 2009, mean charge per

ACS discharge was $63 578 (median $41 816). Mean charges, however, were greater for the first compared with the second admission ($71 336 versus $53 290, respectively).[108]

- On the basis of medical, pharmacy, and disability insurance claims data from 2007 to 2010, short-term productivity losses associated with ACS were estimated at $7943 per disability claim, with long-term productivity losses of $52 473 per disability claim. ACS also resulted in substantial wage losses, from $2263 to $20 609 per disability claim for short- and long-term disability, respectively.[109]
- According to data from the NIS, between 2001 and 2011, the use of PCI for patients with ACS declined by 15%.[58]
- In a report from the TRACE-CORE study, persons with recurrent ACS were more likely to report anxiety, depression, higher perceived stress, and lower mental and physical quality of life; were more likely to have impaired cognition; and had lower levels of health literacy and health numeracy than individuals with a first ACS.[110]
- In the NIS from 2012 to 2013, females with non–ST-elevation ACS treated with an early invasive strategy had lower in-hospital mortality than females treated conservatively (2.1% versus 3.8%). However, the survival advantage for invasive management was restricted to females with NSTEMI (OR, 0.52 [95% CI, 0.46–0.58]), and no differences in in-hospital survival for invasive versus conservative treatment were observed among females with UA.[111]
- In a meta-analysis of 8 randomized trials, the risk of long-term all-cause mortality at a mean of 10.3 years of follow-up was similar for non–ST-elevation ACS patients treated with a routine strategy (coronary angiography within 24 to 96 hours of presentation) versus a selective invasive strategy (medical stabilization with or without coronary angiography in those who demonstrated evidence of ischemia on noninvasive stress test or with ongoing symptoms), at 28.5% for both strategies.[112]

Stable AP

ICD-9 413; *ICD-10* I20.1 to I20.9.

Prevalence

(See Table 19-2 and Chart 19-11)

- According to data from NHANES 2013 to 2016, the prevalence of AP among adults (≥20 years of age) is 3.6% (9.4 million adults; Table 19-2).
- On the basis of NHANES 2013 to 2016, the prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >10% among males and females ≥80 years of age (Chart 19-11).
- On the basis of data from NHANES in 2009 to 2012, there were an average of 3.4 million people ≥40 years of age in the United States with angina each year, compared with 4 million in 1988 to 1994. Declines in angina symptoms have occurred for NH whites but not for NH blacks.[3]
- In Americans ≥40 years of age with health insurance, age-adjusted angina prevalence declined from 7.6% in 2001 to 2002 to 5.2% in 2011 to 2012 (*P* for trend<0.001), whereas in those without health insurance, there was an increase from 4.7% to 7.6% (*P* for trend=0.4).[113]
- Among patients with a history of CAD (ACS, prior coronary revascularization procedure, or stable angina), 32.7% self-reported at least 1 episode of angina over the past month. Of those reporting angina, 23.3% reported daily or weekly symptoms of angina, and 56.3% of these patients with daily or weekly angina were taking at least 2 antianginal medications.[114]

Table 19-1. CHD in the United States

Population Group	Prevalence, CHD, 2013–2016 Age ≥20 y	Prevalence, MI, 2013–2016 Age ≥20 y	New and Recurrent MI and Fatal CHD, 2005–2014 Age ≥35 y	New and Recurrent MI, 2005–2014 Age ≥35 y	Mortality,* CHD, 2017 All Ages	Mortality,* MI, 2017 All Ages	Hospital Discharges: CHD, 2016 All Ages
Both sexes	18 200 000 (6.7%)	8 400 000 (3.0%)	1 055 000	805 000	365 914	110 346	1 045 000
Males	9 400 000 (7.4%)	5 100 000 (4.0%)	610 000	470 000	213 295 (58.3%)†	64 436 (58.4%)†	664 000
Females	8 800 000 (6.2%)	3 300 000 (2.3%)	445 000	335 000	152 619 (41.7%)†	45 910 (41.6%)†	381 000
NH white males	7.7%	4.0%	520 000‡	…	168 868	51 155	…
NH white females	6.1%	2.2%	370 000‡	…	119 151	35 720	…
NH black males	7.2%	4.0%	90 000‡	…	22 167	6595	…
NH black females	6.5%	2.2%	75 000‡	…	18 055	5458	…
Hispanic males	6.0%	3.4%	…	…	14 195	4437	…
Hispanic females	6.0%	2.0%	…	…	10 041	3113	…
NH Asian males	4.8%	2.4%	…	…	5721	1693§	…
NH Asian females	3.2%	1.0%	…	…	4103	1271§	…
NH American Indian or Alaska Native	…	…	…	…	2032	593	…

CHD includes people who responded "yes" to at least 1 of the questions in "Has a doctor or other health professional ever told you that you had CHD, angina or angina pectoris, heart attack, or MI?" Those who answered "no" but were diagnosed with Rose angina are also included (the Rose questionnaire is only administered to survey participants >40 years of age). CHD indicates coronary heart disease; ellipses (…), data not available; MI, myocardial infarction; and NH, non-Hispanic.

*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total CHD and MI mortality that is for males vs females.

‡Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

§Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey 2013 to 2016.[1] Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities study (2005–2014),[5] unpublished tabulation by NHLBI, extrapolated to the 2014 US population. Mortality: unpublished NHLBI tabulation using National Vital Statistics System, 2017.[68] Mortality for NH Asians includes Pacific Islanders. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016[50] (data include those inpatients discharged alive, dead, or status unknown).

Table 19-2. AP* in the United States

Population Group	Prevalence, 2013–2016, Age ≥20 y	Hospital Discharges, 2016, All Ages
Both sexes	9 400 000 (3.6%)	18 000
Males	4 300 000 (3.5%)	9000
Females	5 100 000 (3.7%)	9000
NH white males	3.8%	…
NH white females	3.8%	…
NH black males	3.6%	…
NH black females	3.8%	…
Hispanic males	2.6%	…
Hispanic females	3.6%	…
NH Asian or Pacific Islander males	2.0%	…
NH Asian or Pacific Islander females	1.6%	…

AP includes people who either answered "yes" to the question of ever having angina or angina pectoris or who were diagnosed with Rose angina (the Rose questionnaire is only administered to survey participants >40 years of age). AP indicates angina pectoris; ellipses (…), data not available; and NH, non-Hispanic.

*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without myocardial infarction.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey (NHANES), 2013 to 2016.[1] Percentages for racial/ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2013 to 2016 were applied to 2016 population estimates (≥20 years of age). Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016[50]; data include those inpatients discharged alive, dead, or status unknown.

Table 19-3. Global Burden of IHD and Trends, 2017

	Both Sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions)	8.9 (8.8 to 9.1)	126.5 (118.6 to 134.7)	4.9 (4.8 to 5.0)	68.5 (64.3 to 73.2)	4.0 (3.9 to 4.1)	57.9 (54.3 to 61.9)
Percent change total number 1990 to 2017	52.3 (49.1 to 55.0)	74.9 (71.8 to 78.6)	58.3 (53.9 to 62.0)	73.6 (70.4 to 77.2)	45.5 (41.7 to 49.0)	76.6 (73.1 to 80.5)
Percent change total number 2007 to 2017	22.3 (20.6 to 23.8)	24.0 (21.7 to 26.5)	23.1 (21.1 to 25.2)	22.8 (20.5 to 25.4)	21.3 (19.1 to 23.4)	25.5 (23.3 to 27.9)
Rate per 100 000	116.9 (115.1 to 119.7)	1583.7 (1484.5 to 1691.1)	144.4 (141.5 to 147.9)	1835.8 (1720.7 to 1962.2)	93.3 (91.2 to 96.1)	1361.3 (1274.8 to 1453.4)
Percent change rate 2007 to 2017	−9.7 (−11.0 to −8.7)	−5.1 (−6.8 to −3.2)	−9.0 (−10.5 to −7.6)	−6.5 (−8.3 to −4.5)	−10.8 (−12.4 to −9.2)	−3.7 (−5.4 to −1.9)
Percent change rate 1990 to 2017	−30.0 (−31.3 to −28.8)	−11.8 (−13.5 to −9.9)	−27.8 (−29.7 to −26.2)	−14.3 (−16.0 to −12.5)	−33.2 (−34.9 to −31.6)	−9.8 (−11.5 to −7.8)

IHD indicates ischemic heart disease; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[107] Printed with permission. Copyright © 2018, University of Washington.

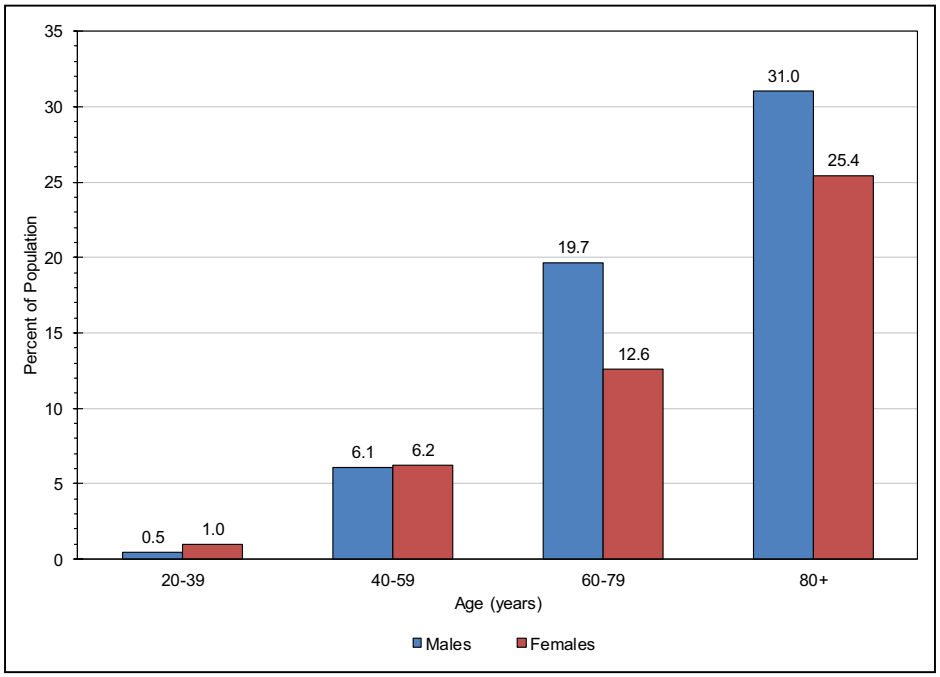

Chart 19-1. Prevalence of coronary heart disease by age and sex, United States (NHANES, 2013–2016).

NHANES indicates National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[1]

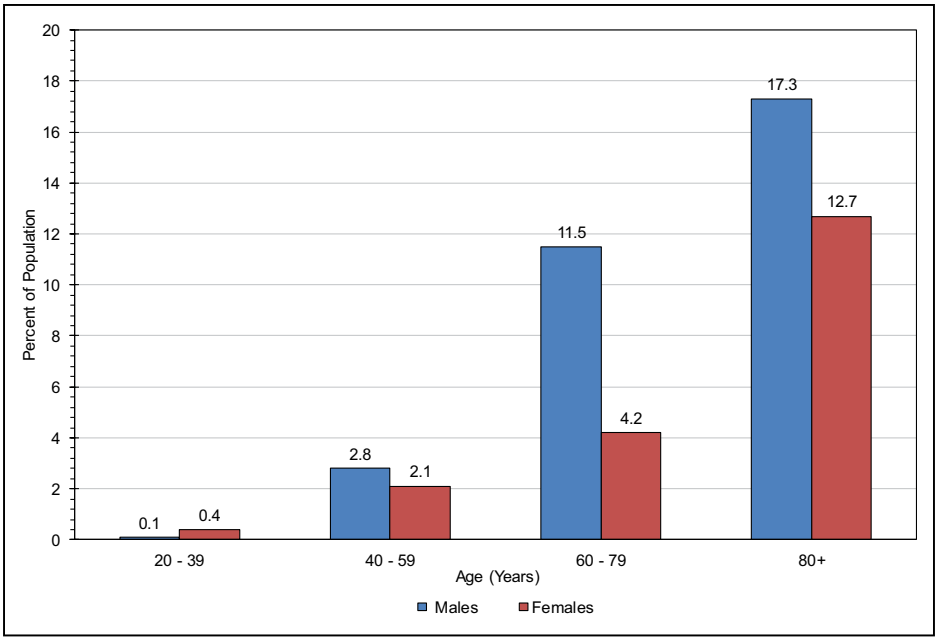

Chart 19-2. Prevalence of myocardial infarction (MI) by age and sex, United States (NHANES, 2013–2016).
MI includes people who answered "yes" to the question of ever having had a heart attack or MI.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[1]

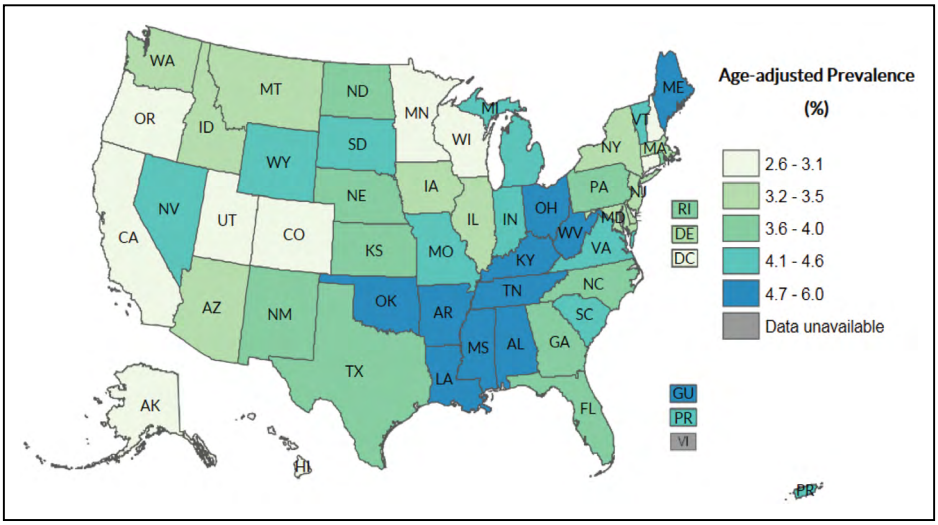

Chart 19-3. "Ever told you had a heart attack (myocardial infarction)?" Age-adjusted US prevalence by state (BRFSS Prevalence and Trends Data, 2017).
BRFSS indicates Behavioral Risk Factor Surveillance System.
Source: BRFSS Prevalence and Trends Data, 2017.[4]

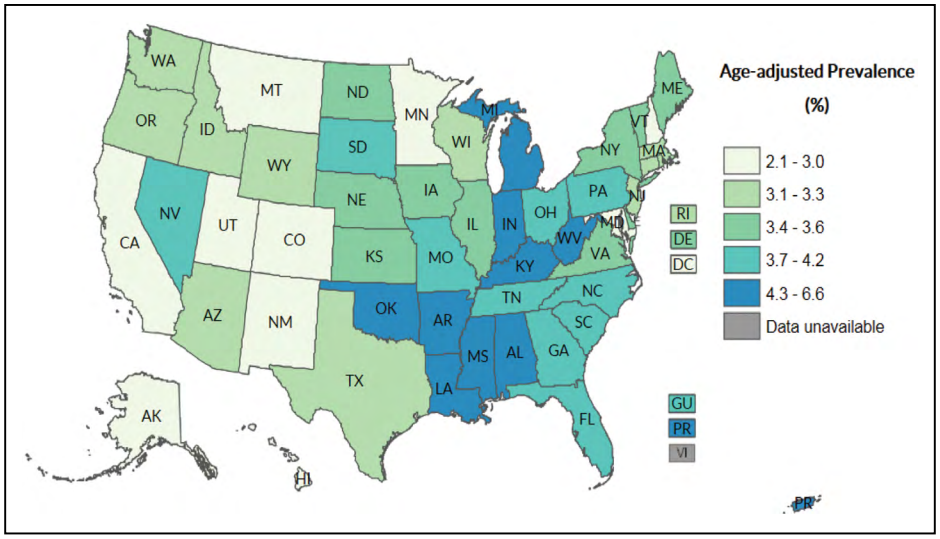

Chart 19-4. "Ever told you had angina or coronary heart disease?" Age-adjusted US prevalence by state (BRFSS Prevalence and Trends Data, 2017).
BRFSS indicates Behavioral Risk Factor Surveillance System.
Source: BRFSS Prevalence and Trends Data, 2017.[4]

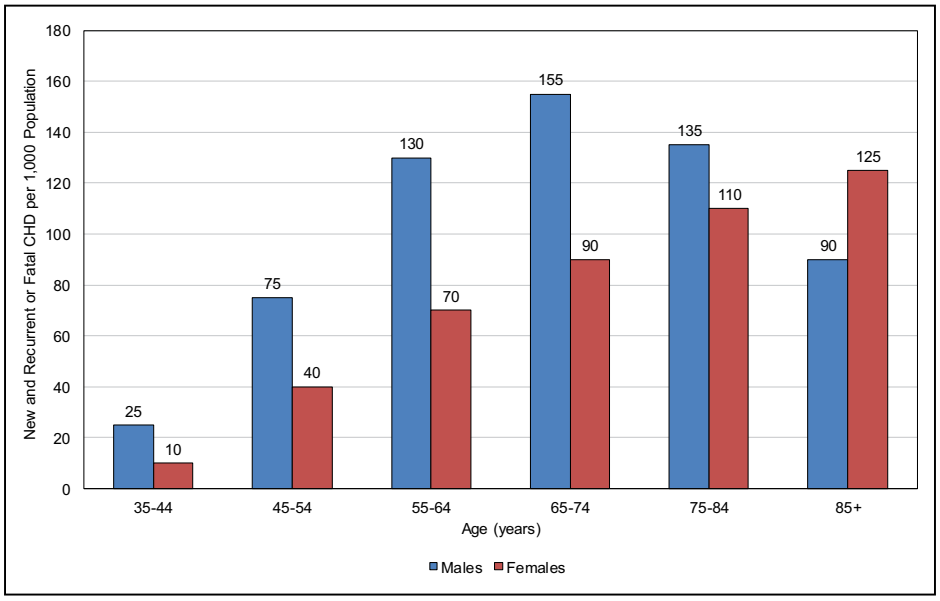

Chart 19-5. Annual number of US adults per 1000 having diagnosed heart attack or fatal CHD by age and sex (ARIC surveillance, 2005–2014 and CHS).
These data include myocardial infarction (MI) and fatal CHD but not silent MI.
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and CHS, Cardiovascular Health Study.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014[5] and CHS.[115]

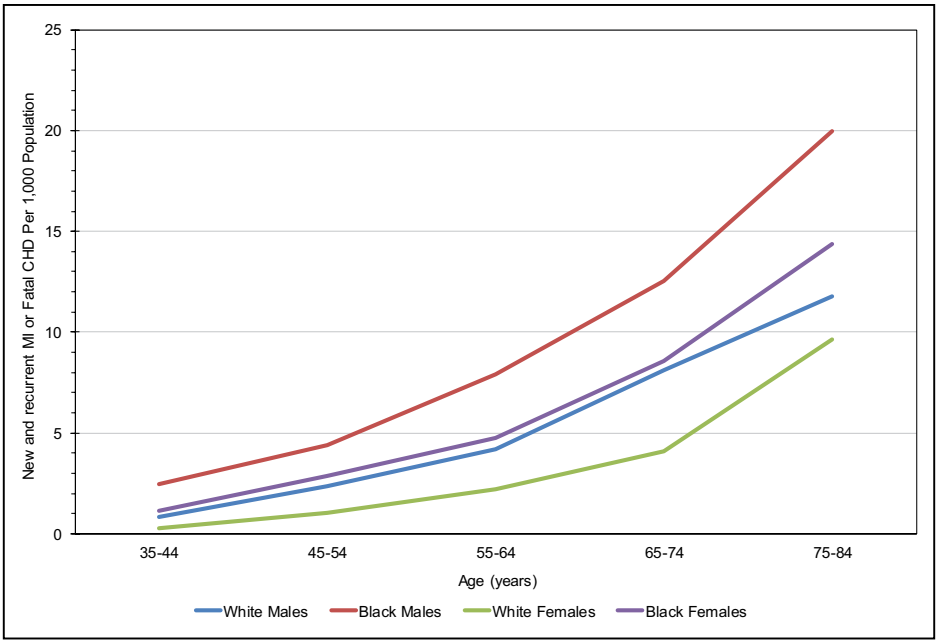

Chart 19-6. Incidence of heart attack or fatal CHD by age, sex, and race, United States (ARIC Surveillance, 2005–2014).
ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and MI, myocardial infarction.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014.[5]

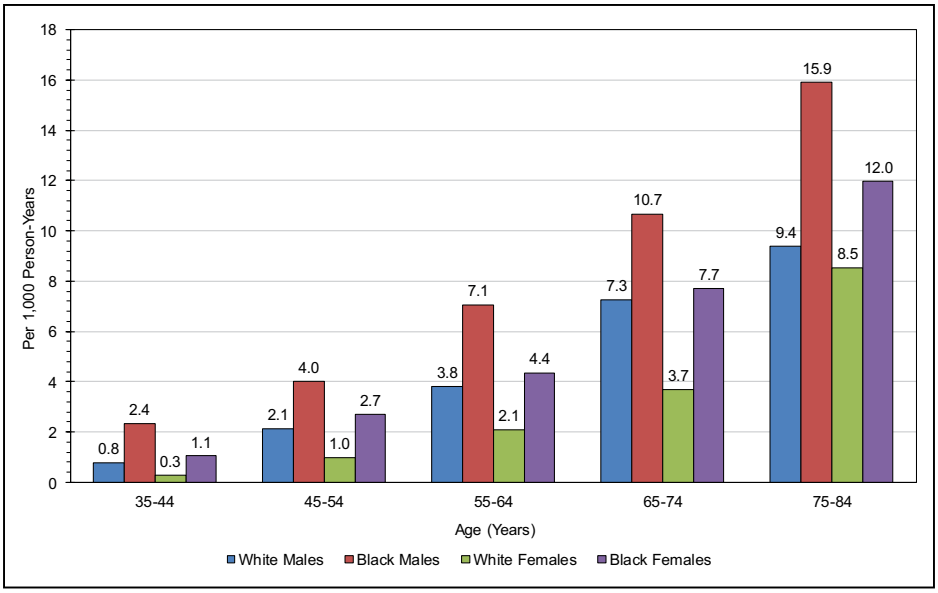

Chart 19-7. Incidence of myocardial infarction by age, sex, and race, United States (ARIC Surveillance, 2005–2014).
ARIC indicates Atherosclerosis Risk in Communities.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014.[5]

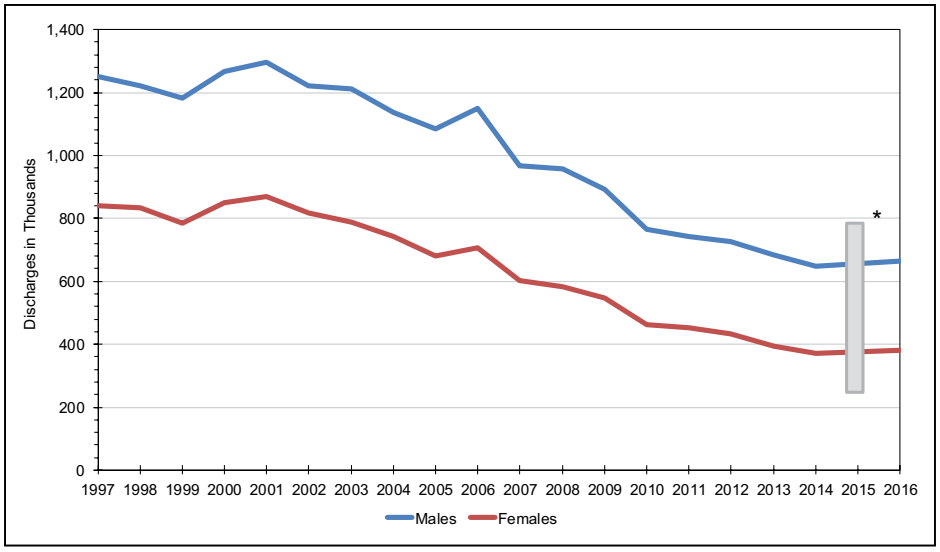

Chart 19-8. Hospital discharges for coronary heart disease by sex, United States (HCUP, 1997–2016).
Hospital discharges include people discharged alive, dead, and status unknown. HCUP indicates Healthcare Cost and Utilization Project.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.[50]

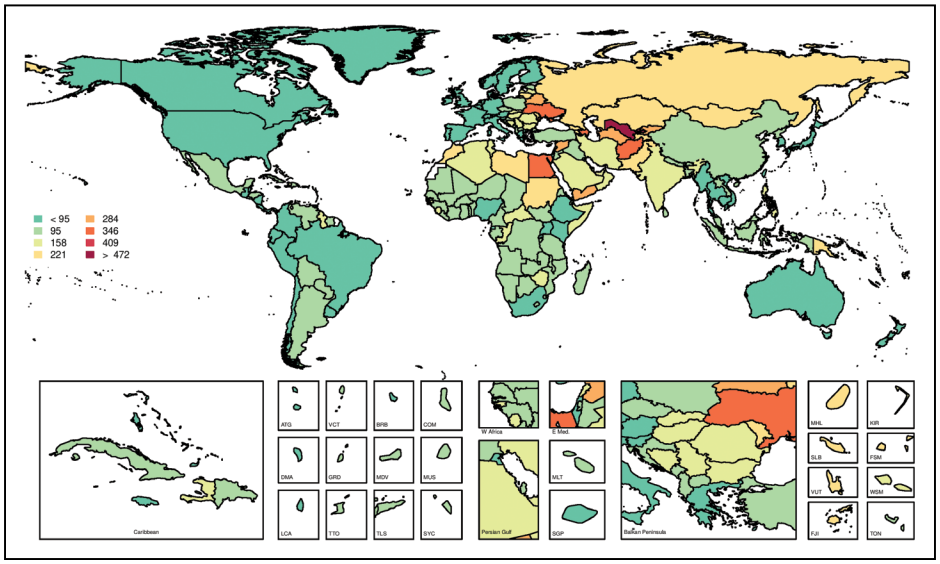

Chart 19-9. Age-standardized global mortality rates of ischemic heart disease (IHD) per 100 000, both sexes, 2017.
IHD mortality rates are generally lower than 150 per 100 000 for most of the world but exceed 280 per 100 000 in Eastern Europe and Central Asia.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. IHD indicates ischemic heart disease.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[107] Printed with permission. Copyright © 2018, University of Washington.

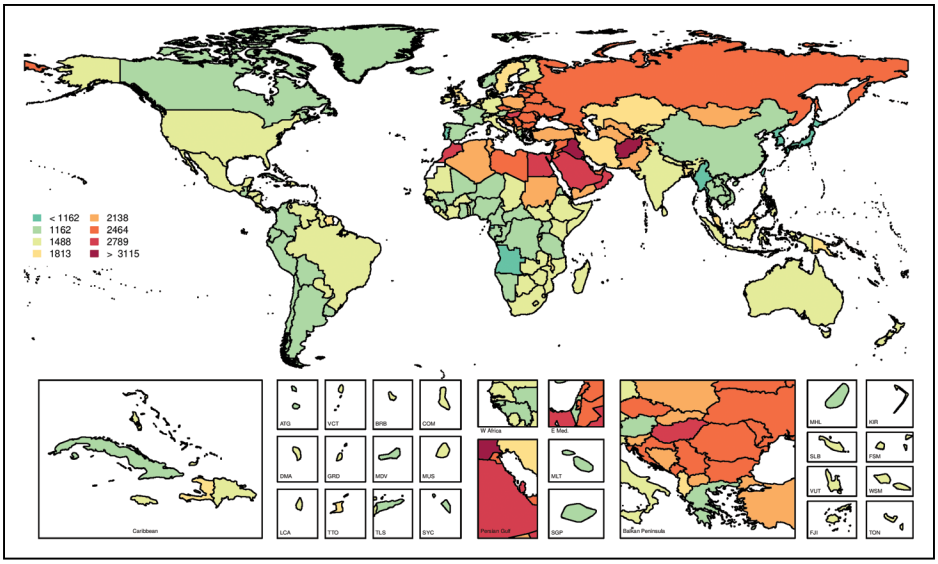

Chart 19-10. Age-standardized global prevalence rates of ischemic heart disease (IHD) per 100 000, both sexes, 2017.
Eastern Europe, North Africa, and the Middle East have the highest prevalence rates of IHD.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[107] Printed with permission. Copyright © 2018, University of Washington.

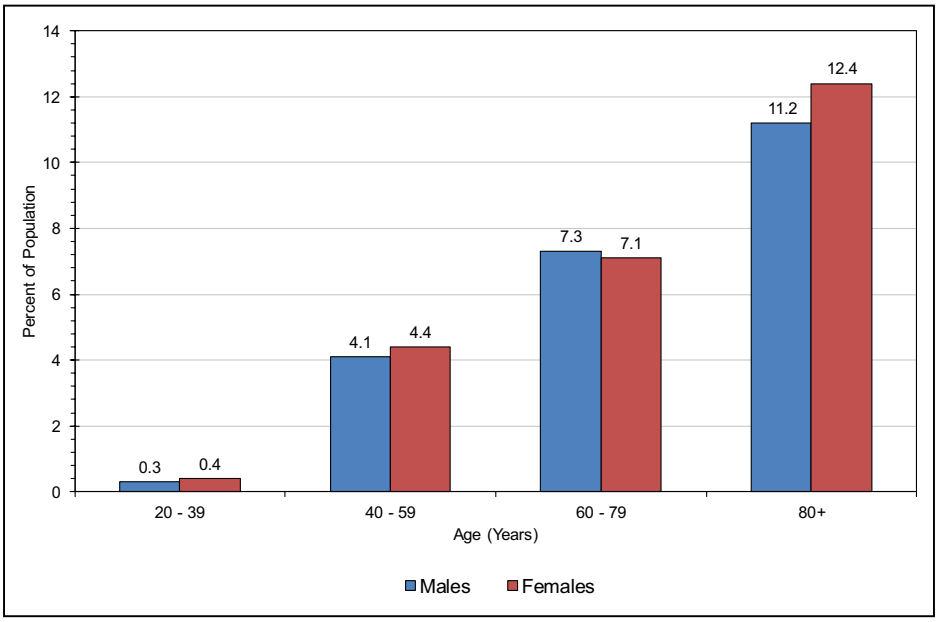

Chart 19-11. Prevalence of angina pectoris by age and sex (NHANES, 2013–2016).
Angina pectoris includes people who either answered "yes" to the question of ever having angina or angina pectoris or were diagnosed with Rose angina.
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[1]

REFERENCES

1. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
2. National Center for Health Statistics. Summary Health Statistics: National Health Interview Survey, 2017: Table A-1. Centers for Disease Control and Prevention website. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-1.pdf. Accessed March 25, 2019.
3. Will JC, Yuan K, Ford E. National trends in the prevalence and medical history of angina: 1988 to 2012. *Circ Cardiovasc Qual Outcomes.* 2014;7:407–413. doi: 10.1161/CIRCOUTCOMES.113.000779
4. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Behavioral Risk Factor Surveillance System (BRFSS). BRFSS prevalence & trends data [online] (2017). Centers for Disease Control and Prevention website. https://www.cdc.gov/brfss/brfssprevalence/. Accessed April 1, 2019.
5. Atherosclerosis Risk in Communities (ARIC) Study, Community Surveillance Component, 2005–2014. Collaborative Studies Coordinating Center website. https://sites.cscc.unc.edu/aric/. Accessed May 6, 2019.
6. Levitan EB, Olubowale OT, Gamboa CM, Rhodes JD, Brown TM, Muntner P, Deng L, Safford MM. Characteristics and prognosis of acute myocardial infarction by discharge diagnosis: the Reasons for Geographic and Racial Differences in Stroke study. *Ann Epidemiol.* 2015;25:499–504. e1. doi: 10.1016/j.annepidem.2015.02.004
7. Lewis MW, Khodneva Y, Redmond N, Durant RW, Judd SE, Wilkinson LL, Howard VJ, Safford MM. The impact of the combination of income and education on the incidence of coronary heart disease in the prospective Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study. *BMC Public Health.* 2015;15:1312. doi: 10.1186/s12889-015-2630-4
8. Colantonio LD, Gamboa CM, Richman JS, Levitan EB, Soliman EZ, Howard G, Safford MM. Black-white differences in incident fatal, nonfatal, and total coronary heart disease. *Circulation.* 2017;136:152–166. doi: 10.1161/CIRCULATIONAHA.116.025848
9. Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond WD, Kitzman D, Couper D, Soliman EZ. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 2016;133:2141–2148. doi: 10.1161/CIRCULATIONAHA.115.021177
10. Ford ES, Roger VL, Dunlay SM, Go AS, Rosamond WD. Challenges of ascertaining national trends in the incidence of coronary heart disease in the United States. *J Am Heart Assoc.* 2014;3:e001097. doi: 10.1161/JAHA.114.001097
11. Gerber Y, Weston SA, Jiang R, Roger VL. The changing epidemiology of myocardial infarction in Olmsted County, Minnesota, 1995-2012. *Am J Med.* 2015;128:144–151. doi: 10.1016/j.amjmed.2014.09.012
12. Sacks NC, Ash AS, Ghosh K, Rosen AK, Wong JB, Rosen AB. Trends in acute myocardial infarction hospitalizations: are we seeing the whole picture? *Am Heart J.* 2015;170:1211–1219. doi: 10.1016/j.ahj.2015.09.009
13. Sacks NC, Ash AS, Ghosh K, Rosen AK, Wong JB, Cutler DM, Rosen AB. Recent national trends in acute myocardial infarction hospitalizations in Medicare: shrinking declines and growing disparities. *Epidemiology.* 2015;26:e46–e47. doi: 10.1097/EDE.0000000000000298
14. Kilpi F, Konttinen H, Silventoinen K, Martikainen P. Living arrangements as determinants of myocardial infarction incidence and survival: a prospective register study of over 300,000 Finnish men and women. *Soc Sci Med.* 2015;133:93–100. doi: 10.1016/j.socscimed.2015.03.054
15. Kilpi F, Silventoinen K, Konttinen H, Martikainen P. Early-life and adult socioeconomic determinants of myocardial infarction incidence and fatality. *Soc Sci Med.* 2017;177:100–109. doi: 10.1016/j.socscimed.2017.01.055
16. Patel SA, Ali MK, Narayan KM, Mehta NK. County-level variation in cardiovascular disease mortality in the United States in 2009-2013: comparative assessment of contributing factors. *Am J Epidemiol.* 2016;184:933–942. doi: 10.1093/aje/kww081
17. Ford ES, Will JC, Mercado CI, Loustalot F. Trends in predicted risk for atherosclerotic cardiovascular disease using the Pooled Cohort risk equations among US adults from 1999 to 2012. *JAMA Intern Med.* 2015;175:299–302. doi: 10.1001/jamainternmed.2014.6403
18. Karmali KN, Goff DC Jr, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA Pooled Cohort risk assessment tool for atherosclerotic cardiovascular disease. *J Am Coll Cardiol.* 2014;64:959–968. doi: 10.1016/j.jacc.2014.06.1186
19. Cook NR, Ridker PM. Calibration of the Pooled Cohort equations for atherosclerotic cardiovascular disease: an update. *Ann Intern Med.* 2016;165:786–794. doi: 10.7326/M16-1739
20. Colantonio LD, Richman JS, Carson AP, Lloyd-Jones DM, Howard G, Deng L, Howard VJ, Safford MM, Muntner P, Goff DC Jr. Performance of the atherosclerotic cardiovascular disease Pooled Cohort risk equations by social deprivation status. *J Am Heart Assoc.* 2017;6:e005676. doi: 10.1161/JAHA.117.005676
21. Mora S, Wenger NK, Cook NR, Liu J, Howard BV, Limacher MC, Liu S, Margolis KL, Martin LW, Paynter NP, et al. Evaluation of the Pooled Cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. *JAMA Intern Med.* 2018;178:1231–1240. doi: 10.1001/jamainternmed.2018.2875
22. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. *Circulation.* 2012;125:3092–3098. doi: 10.1161/CIRCULATIONAHA.111.065490
23. Choi J, Daskalopoulou SS, Thanassoulis G, Karp I, Pelletier R, Behlouli H, Pilote L; GENESIS-PRAXY Investigators. Sex- and gender-related risk factor burden in patients with premature acute coronary syndrome. *Can J Cardiol.* 2014;30:109–117. doi: 10.1016/j.cjca.2013.07.674
24. Agarwal MA, Garg L, Lavie CJ, Reed GL, Khouzam RN. Impact of family history of coronary artery disease on in-hospital clinical outcomes in ST-segment myocardial infarction. *Ann Transl Med.* 2018;6:3. doi: 10.21037/atm.2017.09.27
25. Howson JMM, Zhao W, Barnes DR, Ho WK, Young R, Paul DS, Waite LL, Freitag DF, Fauman EB, Salfati EL, et al; CARDIoGRAMplusC4D; EPIC-CVD. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet.* 2017;49:1113–1119. doi: 10.1038/ng.3874
26. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science.* 2007;316:1491–1493. doi: 10.1126/science.1142842
27. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. *JAMA.* 2010;303:648–656. doi: 10.1001/jama.2010.118
28. Franceschini N, Carty C, Bůzková P, Reiner AP, Garrett T, Lin Y, Vöckler JS, Hindorff LA, Cole SA, Boerwinkle E, et al. Association of genetic variants and incident coronary heart disease in multiethnic cohorts: the PAGE study. *Circ Cardiovasc Genet.* 2011;4:661–672. doi: 10.1161/CIRCGENETICS.111.960096
29. Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Coding variation in ANGPTL4, LPL, and SVEP1 and the risk of coronary disease [published correction appears in *N Engl J Med.* 2016;374:1898]. *N Engl J Med.* 2016;374:1134–1144. doi: 10.1056/NEJMoa1507652
30. Webb TR, Erdmann J, Stirrups KE, Stitziel NO, Masca NG, Jansen H, Kanoni S, Nelson CP, Ferrario PG, König IR, et al; Wellcome Trust Case Control Consortium; MORGAM Investigators; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. *J Am Coll Cardiol.* 2017;69:823–836. doi: 10.1016/j.jacc.2016.11.056
31. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S, Van Hout CV, Bruse S, Dansky HM, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med.* 2017;377:211–221. doi: 10.1056/NEJMoa1612790
32. Nomura A, Won HH, Khera AV, Takeuchi F, Ito K, McCarthy S, Emdin CA, Klarin D, Natarajan P, Zekavat SM, et al. Protein-truncating variants at the cholesteryl ester transfer protein gene and risk for coronary heart disease. *Circ Res.* 2017;121:81–88. doi: 10.1161/CIRCRESAHA.117.311145
33. Zhan Y, Karlsson IK, Karlsson R, Tillander A, Reynolds CA, Pedersen NL, Hägg S. Exploring the causal pathway from telomere length to coronary heart disease: a network mendelian randomization study. *Circ Res.* 2017;121:214–219. doi: 10.1161/CIRCRESAHA.116.310517
34. Helgadottir A, Gretarsdottir S, Thorleifsson G, Hjartarson E, Sigurdsson A, Magnusdottir A, Jonasdottir A, Kristjansson H, Sulem P, Oddsson A, et al. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. *Nat Genet.* 2016;48:634–639. doi: 10.1038/ng.3561
35. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, Nordio F, Hyde C, Cannon CP, Sacks F, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet.* 2015;385:2264–2271. doi: 10.1016/S0140-6736(14)61730-X

36. Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ, Kathiresan S, Shiffman D. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. *Eur Heart J.* 2016;37:561–567. doi: 10.1093/eurheartj/ehv462
37. Abraham G, Havulinna AS, Bhalala OG, Byars SG, De Livera AM, Yetukuri L, Tikkanen E, Perola M, Schunkert H, Sijbrands EJ, et al. Genomic prediction of coronary heart disease. *Eur Heart J.* 2016;37:3267–3278. doi: 10.1093/eurheartj/ehw450
38. Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, Lichtman JH, D'Onofrio G, Mattera J, Dreyer R, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. *Circulation.* 2019;139:1593–1602. doi: 10.1161/CIRCULATIONAHA.118.035658
39. Kullo IJ, Jouni H, Austin EE, Brown SA, Kruisselbrink TM, Isseh IN, Haddad RA, Marroush TS, Shameer K, Olson JE, et al. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES Clinical Trial). *Circulation.* 2016;133:1181–1188. doi: 10.1161/CIRCULATIONAHA.115.020109
40. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med.* 2016;375:2349–2358. doi: 10.1056/NEJMoa1605086
41. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, et al; UK Biobank CardioMetabolic Consortium CHD Working Group. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. *J Am Coll Cardiol.* 2018;72:1883–1893. doi: 10.1016/j.jacc.2018.07.079
42. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA; on behalf of the American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on High Blood Pressure Research, and Council on Nutrition, Physical Activity and Metabolism. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. *Circulation.* 2013;127:1254–1263, e1–e29. doi: 10.1161/CIR.0b013e318287cf2f
43. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM, Lichtman JH. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO study. *J Am Coll Cardiol.* 2015;66:1949–1957. doi: 10.1016/j.jacc.2015.08.859
44. Fang J, Luncheon C, Ayala C, Odom E, Loustalot F. Awareness of heart attack symptoms and response among adults: United States, 2008, 2014, and 2017. *MMWR Morb Mortal Wkly Rep* 2019;68:101–106. doi: 10.15585/mmwr.mm6805a2
45. Makam RP, Erskine N, Yarzebski J, Lessard D, Lau J, Allison J, Gore JM, Gurwitz J, McManus DD, Goldberg RJ. Decade long trends (2001–2011) in duration of pre-hospital delay among elderly patients hospitalized for an acute myocardial infarction. *J Am Heart Assoc.* 2016;5:e002664. doi: 10.1161/JAHA.115.002664
46. Alrwisan A, Eworuke E. Are discrepancies in waiting time for chest pain at emergency departments between African Americans and whites improving over time? *J Emerg Med.* 2016;50:349–355. doi: 10.1016/j.jemermed.2015.07.033
47. Agrawal S, Garg L, Sharma A, Mohananey D, Bhatia N, Singh A, Shirani J, Dixon S. Comparison of inhospital mortality and frequency of coronary angiography on weekend versus weekday admissions in patients with non-ST-segment elevation acute myocardial infarction. *Am J Cardiol.* 2016;118:632–634. doi: 10.1016/j.amjcard.2016.06.022
48. Khoshchehreh M, Groves EM, Tehrani D, Amin A, Patel PM, Malik S. Changes in mortality on weekend versus weekday admissions for acute coronary syndrome in the United States over the past decade. *Int J Cardiol.* 2016;210:164–172. doi: 10.1016/j.ijcard.2016.02.087
49. Foo CY, Bonsu KO, Nallamothu BK, Reid CM, Dhippayom T, Reidpath DD, Chaiyakunapruk N. Coronary intervention door-to-balloon time and outcomes in ST-elevation myocardial infarction: a meta-analysis. *Heart.* 2018;104:1362–1369. doi: 10.1136/heartjnl-2017-312517
50. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
51. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Zeng Y, Park DW, Kang SJ, Lee SW, et al. Coronary artery bypass grafting versus drug-eluting stents implantation for previous myocardial infarction. *Am J Cardiol.* 2016;118:17–22. doi: 10.1016/j.amjcard.2016.04.009
52. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Park DW, Kang SJ, Lee SW, Kim YH, et al. Impact of multivessel coronary artery disease with versus without left main coronary artery disease on long-term mortality after coronary bypass grafting versus drug-eluting stent implantation. *Am J Cardiol.* 2017;119:225–230. doi: 10.1016/j.amjcard.2016.09.048
53. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, Christiansen EH, Holm NR, Thuesen L, Makikallio T, et al. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: a meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J.* 2017;190:54–63. doi: 10.1016/j.ahj.2017.05.005
54. Milojevic M, Head SJ, Parasca CA, Serruys PW, Mohr FW, Morice MC, Mack MJ, Ståhle E, Feldman TE, Dawkins KD, et al. Causes of death following PCI versus CABG in complex CAD: 5-year follow-up of SYNTAX. *J Am Coll Cardiol.* 2016;67:42–55. doi: 10.1016/j.jacc.2015.10.043
55. Cavalcante R, Sotomi Y, Zeng Y, Lee CW, Ahn JM, Collet C, Tenekecioglu E, Suwannasom P, Onuma Y, Park SJ, et al. Coronary bypass surgery versus stenting in multivessel disease involving the proximal left anterior descending coronary artery. *Heart.* 2017;103:428–433. doi: 10.1136/heartjnl-2016-309720
56. Shavadia JS, Roe MT, Chen AY, Lucas J, Fanaroff AC, Kochar A, Fordyce CB, Jollis JG, Tamis-Holland J, Henry TD, et al. Association between cardiac catheterization laboratory pre-activation and reperfusion timing metrics and outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a report from the ACTION Registry. *JACC Cardiovasc Interv.* 2018;11:1837–1847. doi: 10.1016/j.jcin.2018.07.020
57. Kim LK, Looser P, Swaminathan RV, Minutello RM, Wong SC, Girardi L, Feldman DN. Outcomes in patients undergoing coronary artery bypass graft surgery in the United States based on hospital volume, 2007 to 2011. *J Thorac Cardiovasc Surg.* 2016;151:1686–1692. doi: 10.1016/j.jtcvs.2016.01.050
58. Bangalore S, Gupta N, Généreux P, Guo Y, Pancholy S, Feit F. Trend in percutaneous coronary intervention volume following the COURAGE and BARI-2D trials: insight from over 8.1 million percutaneous coronary interventions. *Int J Cardiol.* 2015;183:6–10. doi: 10.1016/j.ijcard.2015.01.053
59. Bradley SM, Bohn CM, Malenka DJ, Graham MM, Bryson CL, McCabe JM, Curtis JP, Lambert-Kerzner A, Maynard C. Temporal trends in percutaneous coronary intervention appropriateness: insights from the Clinical Outcomes Assessment Program. *Circulation.* 2015;132:20–26. doi: 10.1161/CIRCULATIONAHA.114.015156
60. Culler SD, Kugelmass AD, Brown PP, Reynolds MR, Simon AW. Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012. *Circulation.* 2015;131:362–370. doi: 10.1161/CIRCULATIONAHA.114.012485
61. Masoudi FA, Ponirakis A, de Lemos JA, Jollis JG, Kremers M, Messenger JC, Moore JWM, Moussa I, Oetgen WJ, Varosy PD, et al. Trends in U.S. cardiovascular care: 2016 report from 4 ACC National Cardiovascular Data Registries. *J Am Coll Cardiol.* 2017;69:1427–1450. doi: 10.1016/j.jacc.2016.12.005
62. Alnasser SM, Bagai A, Jolly SS, Cantor WJ, Dehghani P, Rao SV, Cheema AN. Transradial approach for coronary angiography and intervention in the elderly: a meta-analysis of 777,841 patients. *Int J Cardiol.* 2017;228:45–51. doi: 10.1016/j.ijcard.2016.11.207
63. Kurlansky P, Herbert M, Prince S, Mack M. Coronary artery bypass graft versus percutaneous coronary intervention: meds matter: impact of adherence to medical therapy on comparative outcomes. *Circulation.* 2016;134:1238–1246. doi: 10.1161/CIRCULATIONAHA.115.021183
64. Beatty AL, Li S, Thomas L, Amsterdam EA, Alexander KP, Whooley MA. Trends in referral to cardiac rehabilitation after myocardial infarction: data from the National Cardiovascular Data Registry 2007 to 2012. *J Am Coll Cardiol.* 2014;63:2582–2583. doi: 10.1016/j.jacc.2014.03.030
65. Aragam KG, Dai D, Neely ML, Bhatt DL, Roe MT, Rumsfeld JS, Gurm HS. Gaps in referral to cardiac rehabilitation of patients undergoing percutaneous coronary intervention in the United States. *J Am Coll Cardiol.* 2015;65:2079–2088. doi: 10.1016/j.jacc.2015.02.063
66. Peters AE, Keeley EC. Trends and predictors of participation in cardiac rehabilitation following acute myocardial infarction: data from the Behavioral Risk Factor Surveillance System. *J Am Heart Assoc.* 2018;7:e007664. doi: 10.1161/JAHA.117.007664
67. Widmer RJ, Allison TG, Lennon R, Lopez-Jimenez F, Lerman LO, Lerman A. Digital health intervention during cardiac rehabilitation:

a randomized controlled trial. *Am Heart J.* 2017;188:65–72. doi: 10.1016/j.ahj.2017.02.016
68. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death microdata files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
69. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
70. Bucholz EM, Butala NM, Ma S, Normand ST, Krumholz HM. Life expectancy after myocardial infarction, according to hospital performance. *N Engl J Med.* 2016;375:1332–1342. doi: 10.1056/NEJMoa1513223
71. Langabeer JR 2nd, Henry TD, Fowler R, Champagne-Langabeer T, Kim J, Jacobs AK. Sex-based differences in discharge disposition and outcomes for ST-segment elevation myocardial infarction patients within a regional network. *J Womens Health (Larchmt).* 2018;27:1001–1006. doi: 10.1089/jwh.2017.6553
72. Langabeer JR 2nd, Champagne-Langabeer T, Fowler R, Henry T. Gender-based outcome differences for emergency department presentation of non-STEMI acute coronary syndrome. *Am J Emerg Med.* 2019;37:179–182. doi: 10.1016/j.ajem.2018.05.005
73. Huded CP, Johnson M, Kravitz K, Menon V, Abdallah M, Gullett TC, Hantz S, Ellis SG, Podolsky SR, Meldon SW, et al. 4-Step protocol for disparities in STEMI care and outcomes in women. *J Am Coll Cardiol.* 2018;71:2122–2132. doi: 10.1016/j.jacc.2018.02.039
74. Rodriguez F, Foody JM, Wang Y, López L. Young Hispanic women experience higher in-hospital mortality following an acute myocardial infarction. *J Am Heart Assoc.* 2015;4:e002089. doi: 10.1161/JAHA.115.002089
75. Bucholz EM, Ma S, Normand SL, Krumholz HM. Race, socioeconomic status, and life expectancy after acute myocardial infarction. *Circulation.* 2015;132:1338–1346. doi: 10.1161/CIRCULATIONAHA.115.017009
76. Pancholy S, Patel G, Pancholy M, Nanavaty S, Coppola J, Kwan T, Patel T. Association between health insurance status and in-hospital outcomes after ST-segment elevation myocardial infarction. *Am J Cardiol.* 2017;120:1049–1054. doi: 10.1016/j.amjcard.2017.06.041
77. Conrad Z, Rehm CD, Wilde P, Mozaffarian D. Cardiometabolic mortality by Supplemental Nutrition Assistance Program participation and eligibility in the United States. *Am J Public Health.* 2017;107:466–474. doi: 10.2105/AJPH.2016.303608
78. Kochar A, Chen AY, Sharma PP, Pagidipati NJ, Fonarow GC, Cowper PA, Roe MT, Peterson ED, Wang TY. Long-term mortality of older patients with acute myocardial infarction treated in US clinical practice. *J Am Heart Assoc.* 2018;7:e007230. doi: 10.1161/JAHA.117.007230
79. Krumholz HM, Normand SL, Wang Y. Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999-2011. *Circulation.* 2014;130:966–975. doi: 10.1161/CIRCULATIONAHA.113.007787
80. Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D, Gore JM. Decade-long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes.* 2016;9:117–125. doi: 10.1161/CIRCOUTCOMES.115.002359
81. Sugiyama T, Hasegawa K, Kobayashi Y, Takahashi O, Fukui T, Tsugawa Y. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001-2011. *J Am Heart Assoc.* 2015;4:e001445. doi: 10.1161/JAHA.114.001445
82. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. *Circulation.* 2015;132:997–1002. doi: 10.1161/CIRCULATIONAHA.115.015293
83. Pearson-Stuttard J, Guzman-Castillo M, Penalvo JL, Rehm CD, Afshin A, Danaei G, Kypridemos C, Gaziano T, Mozaffarian D, Capewell S, et al. Modeling future cardiovascular disease mortality in the United States: national trends and racial and ethnic disparities. *Circulation.* 2016;133:967–978. doi: 10.1161/CIRCULATIONAHA.115.019904
84. Lloyd-Jones DM. Slowing progress in cardiovascular mortality rates: you reap what you sow. *JAMA Cardiol.* 2016;1:599–600. doi: 10.1001/jamacardio.2016.1348
85. Case A, Deaton A. Mortality and morbidity in the 21st century. *Brookings Pap Econ Act.* 2017;2017:397–476. doi: 10.1353/eca.2017.0005
86. Pilgrim T, Vranckx P, Valgimigli M, Stefanini GG, Piccolo R, Rat J, Rothenbühler M, Stortecky S, Räber L, Blöchlinger S, et al. Risk and timing of recurrent ischemic events among patients with stable ischemic heart disease, non-ST-segment elevation acute coronary syndrome, and ST-segment elevation myocardial infarction. *Am Heart J.* 2016;175:56–65. doi: 10.1016/j.ahj.2016.01.021
87. Udell JA, Desai NR, Li S, Thomas L, de Lemos JA, Wright-Slaughter P, Zhang W, Roe MT, Bhatt DL. Neighborhood socioeconomic disadvantage and care after myocardial infarction in the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004054. doi: 10.1161/CIRCOUTCOMES.117.004054
88. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M, Elgendy AY, Mojadidi MK, Omer M, Abuzaid A, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. *JACC Cardiovasc Interv.* 2018;11:80–90. doi: 10.1016/j.jcin.2017.08.016
89. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). *Circ Cardiovasc Qual Outcomes.* 2017;10:e003443. doi: 10.1161/CIRCOUTCOMES.116.003443
90. Ram P, Shah M, Sirinvaravong N, Lo KB, Patil S, Patel B, Tripathi B, Garg L, Figueredo V. Left ventricular thrombosis in acute anterior myocardial infarction: evaluation of hospital mortality, thromboembolism, and bleeding. *Clin Cardiol.* 2018;41:1289–1296. doi: 10.1002/clc.23039
91. Abdullah A, Eigbire G, Salama A, Wahab A, Awadalla M, Hoefen R, Alweis R. Impact of delirium on patients hospitalized for myocardial infarction: a propensity score analysis of the National Inpatient Sample. *Clin Cardiol.* 2018;41:910–915. doi: 10.1002/clc.22972
92. Giustino G, Redfors B, Brener SJ, Kirtane AJ, Généreux P, Maehara A, Dudek D, Neunteufl T, Metzger DC, Crowley A, et al. Correlates and prognostic impact of new-onset heart failure after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: insights from the INFUSE-AMI trial. *Eur Heart J Acute Cardiovasc Care.* 2018;7:339–347. doi: 10.1177/2048872617719649
93. Levitan EB, Muntner P, Chen L, Deng L, Kilgore ML, Becker D, Glasser SP, Safford MM, Howard G, Kilpatrick R, et al. Burden of coronary heart disease rehospitalizations following acute myocardial infarction in older adults. *Cardiovasc Drugs Ther.* 2016;30:323–331. doi: 10.1007/s10557-016-6653-6
94. McNeely C, Markwell S, Vassileva CM. Readmission after inpatient percutaneous coronary intervention in the Medicare population from 2000 to 2012. *Am Heart J.* 2016;179:195–203. doi: 10.1016/j.ahj.2016.07.002
95. McManus DD, Saczynski JS, Lessard D, Waring ME, Allison J, Parish DC, Goldberg RJ, Ash A, Kiefe CI; TRACE-CORE Investigators. Reliability of predicting early hospital readmission after discharge for an acute coronary syndrome using claims-based data. *Am J Cardiol.* 2016;117:501–507. doi: 10.1016/j.amjcard.2015.11.034
96. Chen HY, Tisminetzky M, Yarzebski J, Gore JM, Goldberg RJ. Decade-long trends in the frequency of 90-day rehospitalizations after hospital discharge for acute myocardial infarction. *Am J Cardiol.* 2016;117:743–748. doi: 10.1016/j.amjcard.2015.12.006
97. Chen HY, Tisminetzky M, Lapane KL, Yarzebski J, Person SD, Kiefe CI, Gore JM, Goldberg RJ. Decade-long trends in 30-day rehospitalization rates after acute myocardial infarction. *J Am Heart Assoc.* 2015;4:e002291. doi: 10.1161/JAHA.115.002291
98. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
99. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
100. Velagapudi P, Kolte D, Ather K, Khera S, Gupta T, Gordon PC, Aronow HD, Kirtane AJ, Abbott JD. Temporal trends and factors associated with prolonged length of stay in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol.* 2018;122:185–191. doi: 10.1016/j.amjcard.2018.03.365
101. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States, 1996–2015. Agency for Healthcare Research and

Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed June 17, 2019.
102. Torio C, Moore B. National inpatient hospital costs: the most expensive conditions by payer, 2013. HCUP Statistical Brief #204. May. Rockville, MD: Agency for Healthcare Research and Quality; May 2016. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.pdf. Accessed March 29, 2019.
103. Wadhera RK, Joynt Maddox KE, Wang Y, Shen C, Bhatt DL, Yeh RW. Association between 30-day episode payments and acute myocardial infarction outcomes among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004397. doi: 10.1161/CIRCOUTCOMES.117.004397
104. Likosky DS, Van Parys J, Zhou W, Borden WB, Weinstein MC, Skinner JS. Association between Medicare expenditure growth and mortality rates in patients with acute myocardial infarction: a comparison from 1999 through 2014. *JAMA Cardiol*. 2018;3:114–122. doi: 10.1001/jamacardio.2017.4771
105. Ben-Yehuda O, Kazi DS, Bonafede M, Wade SW, Machacz SF, Stephens LA, Hlatky MA, Hernandez JB. Angina and associated healthcare costs following percutaneous coronary intervention: a real-world analysis from a multi-payer database. *Catheter Cardiovasc Interv*. 2016;88:1017–1024. doi: 10.1002/ccd.26365
106. Amin AP, Patterson M, House JA, Giersiefen H, Spertus JA, Baklanov DV, Chhatriwalla AK, Safley DM, Cohen DJ, Rao SV, et al. Costs associated with access site and same-day discharge among Medicare beneficiaries undergoing percutaneous coronary intervention: an evaluation of the current percutaneous coronary intervention care pathways in the United States. *JACC Cardiovasc Interv*. 2017;10:342–351. doi: 10.1016/j.jcin.2016.11.049
107. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
108. LaMori JC, Shoheiber O, Dudash K, Crivera C, Mody SH. The economic impact of acute coronary syndrome on length of stay: an analysis using the Healthcare Cost and Utilization Project (HCUP) databases. *J Med Econ*. 2014;17:191–197. doi: 10.3111/13696998.2014.885907
109. Page RL 2nd, Ghushchyan V, Gifford B, Read RA, Raut M, Crivera C, Naim AB, Damaraju CV, Nair KV. The economic burden of acute coronary syndromes for employees and their dependents: medical and productivity costs. *J Occup Environ Med*. 2013;55:761–767. doi: 10.1097/JOM.0b013e318297323a
110. Goldberg RJ, Saczynski JS, McManus DD, Waring ME, McManus R, Allison J, Parish DC, Lessard D, Person S, Gore JM, et al; TRACE-CORE Investigators. Characteristics of contemporary patients discharged from the hospital after an acute coronary syndrome. *Am J Med*. 2015;128:1087–1093. doi: 10.1016/j.amjmed.2015.05.002
111. Elgendy IY, Mahmoud AN, Mansoor H, Bavry AA. Early invasive versus initial conservative strategies for women with non-ST-elevation acute coronary syndromes: a nationwide analysis. *Am J Med*. 2017;130:1059–1067. doi: 10.1016/j.amjmed.2017.01.049
112. Elgendy IY, Mahmoud AN, Wen X, Bavry AA. Meta-analysis of randomized trials of long-term all-cause mortality in patients with non-ST-elevation acute coronary syndrome managed with routine invasive versus selective invasive strategies. *Am J Cardiol*. 2017;119:560–564. doi: 10.1016/j.amjcard.2016.11.005
113. Yoon SS, Dillon CF, Illoh K, Carroll M. Trends in the prevalence of coronary heart disease in the U.S.: National Health and Nutrition Examination Survey, 2001–2012. *Am J Prev Med*. 2016;51:437-445. doi: 10.1016/j.amepre.2016.02.023
114. Kureshi F, Shafiq A, Arnold SV, Gosch K, Breeding T, Kumar AS, Jones PG, Spertus JA. The prevalence and management of angina among patients with chronic coronary artery disease across US outpatient cardiology practices: insights from the Angina Prevalence and Provider Evaluation of Angina Relief (APPEAR) study. *Clin Cardiol*. 2017;40:6–10. doi: 10.1002/clc.22628
115. Cardiovascular Health Study website. https://chs-nhlbi.org. Accessed July 10, 2019.

20. CARDIOMYOPATHY AND HEART FAILURE

See Tables 20-1 and 20-2 and Charts 20-1 through 20-7

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Cardiomyopathy
ICD-9 425; *ICD-10* I42.

2017: Mortality—21 427. Any-mention mortality—42 937.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually. Using HCUP data[1] for cardiomyopathy in 2016, there were 19 000 inpatient hospitalizations for which cardiomyopathy was the principal diagnosis (11 000 for men; 8000 for women) and 994 000 where it was included among all-listed diagnoses (NHLBI unpublished tabulation).

Abbreviations Used in Chapter 20

ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults Study
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CRP	C-reactive protein
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	diabetes mellitus
ED	emergency department
EF	ejection fraction
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project

(*Continued*)

Abbreviations Used in Chapter 20 Continued

HD	heart disease
Health ABC	Health, Aging, and Body Composition
HF	heart failure
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IHD	ischemic heart disease
IL	interleukin
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MedaMACS	Medical Arm of Mechanically Assisted Circulatory Support
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity
PAR	population attributable risk
PHS	Physicians' Health Study
PPCM	peripartum cardiomyopathy
PVC	premature ventricular contraction
QALY	quality-adjusted life-year
ROADMAP	Randomized Olmesartan and Diabetes Microalbuminuria Prevention
RR	relative risk
RV	right ventricular
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
UI	uncertainty interval

Hypertrophic Cardiomyopathy

- The prevalence of unexplained LVH has been estimated at 0.2% and up to 1.4% in the community.[2]
- Of persons with unexplained LVH, ≈20% to 30% are likely to have a sarcomere mutation that suggests clinically expressed HCM; however, not all people with sarcomere mutations manifest clinical HCM, because of incomplete penetrance, even among members of the same family (see Family History and Genetics for more details).[3]

- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM, contributing >24 000 person-years of follow-up, and observed ≈3-fold higher mortality risk in patients with HCM compared with similarly aged individuals in the US general population. Risk for adverse events (ie, any ventricular arrhythmia, HF, AF, stroke, or death) was highest in patients diagnosed before 40 years of age versus after 60 years of age (77% [95% CI, 72%–80%] versus 32% [95% CI, 29%–36%] cumulative incidence). Adverse events were also 2-fold higher in patients with versus without sarcomere mutations. AF and HF accounted for a substantial proportion of the adverse events, despite not typically manifesting until years to decades after initial diagnosis.[4]

Dilated Cardiomyopathy

- Commonly recognized causes of chronic DCM are mutations in a diverse group of genes that are inherited in an autosomal dominant fashion with age-dependent penetrance and variable clinical expression (see Family History and Genetics for more details). Other causes of DCM of variable chronicity and reversibility include cardiomyopathies that can develop after an identifiable exposure such as tachyarrhythmia, stress, neurohormonal disorder, alcoholism, chemotherapy, infection, or pregnancy (see Peripartum Cardiomyopathy).[5] The annual incidence of chronic idiopathic DCM has been reported as between 5 and 8 cases per 100 000, although these estimates might be low because of underrecognition, especially in light of prevalent asymptomatic LV dysfunction observed in community-based studies (see LV Function).[6,7]

Peripartum Cardiomyopathy

- Data from the NIS databases indicate that the incidence of PPCM increased between 2004 and 2011 from 8.5 to 11.8 per 10 000 live births (P_{trend}<0.001), likely related to rising average maternal age and prevalence of PPCM risk factors such as obesity, hypertension, pregnancy-related hypertension, and DM.[8]
- The NIS data also show that maternal age has increased in all racial/ethnic groups, except Hispanics and Asians/Pacific Islanders, and across all census regions in the United States. When stratified by race/ethnicity, incidence of PPCM was lowest in Hispanics and highest in blacks. When stratified by region, incidence was lowest in the West (6.5 [95% CI, 6.3–6.7] per 10 000 live births) and highest in the South (13.1 [95% CI, 12.9–13.1] per 10 000 live births).[8]
- In females diagnosed with PPCM, data from a prospective cohort indicate that 13% had major events (death, cardiac transplantation, or implantation of an LVAD) or persistent severe cardiomyopathy at 12 months. Black females had worse LV dysfunction at presentation and at 6 and 12 months postpartum than nonblack females.[9]
- For a majority of females with PPCM (50%–80%), LVEF recovers to at least a near-normal range (≥50%), with many achieving this recovery within the first 6 months; however, a substantial proportion remain affected by overtly impaired cardiac function.[9–12]

Youth

- Since 1996, the NHLBI-sponsored Pediatric Cardiomyopathy Registry has collected data on children with newly diagnosed cardiomyopathy in New England and the central Southwest (Texas, Oklahoma, and Arkansas).[13]
  - The overall incidence of cardiomyopathy is 1.13 cases per 100 000 among children <18 years of age.
  - Among children <1 year of age, the incidence is 8.34, and among children 1 to 18 years of age, it is 0.70 per 100 000.
  - The annual incidence is higher in black children than in white children, in boys than in girls, and in New England (1.44 per 100 000) than in the central Southwest (0.98 per 100 000).
- The estimated annual incidence of HCM in children was 4.7 per 1 million children, with higher incidence in New England than in the central Southwest region and higher incidence in boys than in girls.[14] Long-term outcomes of children with HCM suggest that 9% progress to HF and 12% to SCD.[15] See Chapter 16 (Disorders of Heart Rhythm) for statistics regarding sudden death in HCM.
- The estimated annual incidence of DCM in children <18 years of age is 0.57 per 100 000 overall, with higher incidence in boys than girls (0.66 versus 0.47 cases per 100 000, respectively) and blacks than whites (0.98 versus 0.46 cases per 100 000, respectively). The most commonly recognized causes of DCM were myocarditis (46%) and neuromuscular disease (26%).[16] The 5-year incidence rate of SCD is 3% among children <18 years of age at the time of DCM diagnosis.[17]
- Data from the Childhood Cancer Survivor Study cohort of 14 358 survivors of childhood or adolescent cancers show that these individuals are at 6-fold increased risk for future HF,[18] usually preceded by asymptomatic cardiomyopathy. This risk is especially pronounced for individuals who were treated with chest radiation or anthracycline chemotherapy and persists up to 30 years after the original cancer diagnosis.

Global Burden of Cardiomyopathy (See Table 20-1 and Charts 20-1 through 20-3)

- Chart 20-1 shows temporal trends in the incidence of PPCM in the United States.
- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[19]
  - Between 1990 and 2017, the global number of deaths attributable to cardiomyopathy and myocarditis increased 54.5%. In 2017, the age-adjusted death rate was 4.8 per 100 000, a 25.8% decrease in the rate from 1990 (Table 20-1).
  - The highest age-standardized mortality rates attributable to cardiomyopathy and myocarditis are in Eastern Europe (Chart 20-2).
  - Age-standardized prevalence of cardiomyopathy and myocarditis is highest in Central Europe (Chart 20-3).

Heart Failure
ICD-9 428; *ICD-10* I50.

2017: Mortality—80 480. Any-mention mortality—352 119. 2016: Hospital discharges—809 000.

Prevalence (See Table 20-2 and Chart 20-4)

- Based on data from NHANES 2013 to 2016, an estimated 6.2 million Americans ≥20 years of age had HF (Table 20-2; Chart 20-4). This represents an increase from an estimated 5.7 million US adults with HF based on NHANES 2009 to 2012 (NHLBI unpublished tabulation using NHANES[20]).
- Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF. Additionally, the total percentage of the population with HF is predicted to increase from 2.42% in 2012 to 2.97% in 2030.[21]

Incidence (See Table 20-2 and Chart 20-5)

- Based on ARIC Community Surveillance data, the incidence of HF in persons ≥55 years of age was ≈1 000 000 in 2014, with a slightly higher number of new-onset cases observed in women than in men (Table 20-2) and a greater burden seen in blacks than in whites (Chart 20-5).
- Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicate that HF incidence approaches 21 per 1000 population after 65 years of age.[22]
- Data from Kaiser Permanente indicated a 14% increase in the incidence of HF among the elderly (from the 1970s to the 1990s) along with improved HF survival, which resulted in increased HF prevalence, with both trends being more pronounced in males.[23]
- Data from Olmsted County, MN, indicate that the age- and sex-adjusted incidence of HF declined substantially, from 315.8 per 100 000 in 2000 to 219.3 per 100 000 in 2010, with a greater rate reduction for HF with reduced EF (–45.1% [95% CI, –33.0% to –55.0%]) than for HF with preserved EF (–27.9% [95% CI, –12.9% to –40.3%]).[24]
- In the CARDIA study, HF before 50 years of age was more common among blacks than whites. Hypertension, obesity, and systolic dysfunction were important risk factors that may be targets for prevention.[25]
- In MESA, blacks had the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans (4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively). This higher risk reflected differences in the prevalence of hypertension, DM, and low SES.[26] Blacks had the highest proportion of incident HF not preceded by clinical MI (75%).[26]
- Data from the 2005 to 2014 community surveillance component of the ARIC study indicate that rates of hospitalizations for HF are increasing over time, apparently driven by rises in HF with preserved EF. Overall events included 50% HF with reduced EF and 39% HF with preserved EF, where the former was more common in black males and white males and the latter was most common in white females. Other events may be attributable to intermediate or recovered EF. Age-adjusted rates of HF hospitalization were highest in blacks (38 per 1000 black males, 31 per 1000 black females).[27]

Lifetime Risk

- Because most forms of HF tend to present in older age, lifetime risk for HF in the community is high with an aging population. Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicated the following[22]:
  - Overall, at 45 years of age through 95 years of age, lifetime risks for HF were high (20%–45%).
  - Lifetime risks for HF were 30% to 42% in white males, 20% to 29% in black males, 32% to 39% in white females, and 24% to 46% in black females. The lower lifetime risk in black males appears likely to be attributable to competing risks.
  - Lifetime risk for HF was higher with higher BP and BMI at all ages.

— The lifetime risk of HF occurring for people with BMI ≥30 kg/m^2 was approximately double that of those with BMI <25 kg/m^2.
— The lifetime risk of HF occurring for people with BP >160/90 mm Hg was 1.6 times that of those with BP <120/90 mm Hg.

Risk Factors

- Traditional factors account for a considerable proportion of HF risk. Data from Olmsted County, MN, indicate that CHD, hypertension, DM, obesity, and smoking are responsible for 52% of incident HF cases in the population, with ORs or RRs and their PARs as follows[28]: CHD OR, 3.1 and overall PAR, 20% (highest in males, 23% versus 16% in females); cigarette smoking RR, 1.4 and PAR, 14%; hypertension RR, 1.4 and PAR, 20% (highest in females, 28% versus 13% in males); obesity RR, 2.0 and PAR, 12%; and DM OR, 2.7 and PAR, 12%.
- Traditional risk factors for HF are common in the US adult population. Data from NHANES indicate that at least 1 HF risk factor is present in up to one-third of the US adult population.[29]
- Racial disparities in risks for HF persist, as shown in the Health ABC Study, a US cohort of 2934 adults 70 to 79 years of age followed up for 7 years.[30] Among blacks, a greater proportion of HF risk (68% versus 49% among whites) was attributable to modifiable risk factors, including elevated SBP, elevated fasting glucose level, CHD, LVH, and smoking. LVH was 3-fold more prevalent in blacks than in whites. CHD (PAR, 23.9% for white participants, 29.5% for black participants) and uncontrolled BP (PAR, 21.3% for white participants, 30.1% for black participants) had the highest PARs in both races.[30] Hispanics carry a predominance of HF risk factors and healthcare disparities, which suggests a relatively elevated HF risk in this population as well.[31]
- Risk factors appear to differ by HF subtype. As a group, patients with HF with preserved EF are older, are more likely to be female, and have greater prevalence of hypertension, obesity, and anemia than those with HF with reduced EF.[32]
- Dietary and lifestyle factors also impact HF risk. Among 20 900 male physicians in the PHS, the lifetime risk of HF was higher in males with hypertension, whereas healthy lifestyle factors (normal weight, not smoking, regular PA, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were related to lower risk of HF.[33]
- In the ARIC study, greater adherence to the AHA's Life's Simple 7 guidelines (better profiles in smoking, BMI, PA, diet, cholesterol, BP, and glucose) was associated with a lower lifetime risk of HF, as well as more optimal echocardiographic parameters of cardiac structure and function.[34]
- Multiple nontraditional risk factors for HF have been identified.
  — In the FHS, circulating BNP, urinary ACR, elevated serum γ-glutamyl transferase, and higher levels of hematocrit were identified as risk factors for incident HF.[35–37] Circulating concentrations of resistin were also associated with incident HF independent of prevalent coronary disease, obesity, insulin resistance, and inflammation.[38] Circulating adiponectin concentrations were also related to incident HF, with a J-shaped relationship.[39] Inflammatory markers (IL-6 and tumor necrosis factor-α), serum albumin levels, and cigarette smoking exposure additionally were associated with increased HF risk.[40–42]
  — In the CHS, baseline cardiac high-sensitivity troponin and changes in high-sensitivity troponin levels were significantly associated with incident HF.[43] Conversely, circulating individual and total omega-3 fatty acid concentrations were associated with lower incidence of HF.[44]
  — In the ARIC study, white blood cell count, CRP, albuminuria, HbA_{1c} among individuals without DM, cardiac troponin, PVCs, and socioeconomic position over the life course were all identified as risk factors for HF.[45–50]
  — In MESA, plasma N-terminal pro-BNP provided incremental prognostic information beyond the traditional risk factors and the MRI-determined LV mass index for incident symptomatic HF.[51]
  — In the FHS, measures of major organ system dysfunction (higher serum creatinine, lower ratios of forced expiratory volume in 1 second to forced vital capacity, and lower hemoglobin concentrations) were also associated with an adjusted increased risk of new-onset HF.[52]

LV Function

- Measures of impaired systolic or diastolic LV function are common precursors to clinical HF.
  — In the FHS, the prevalence of asymptomatic LV systolic dysfunction was 5% and that of diastolic dysfunction was 36%. LV systolic and diastolic dysfunction were associated with increased risk of incident HF.
  — In Olmsted County, MN, diastolic dysfunction (HR, 1.81 [95% CI, 1.01–3.48]) was observed to progress with advancing age and was associated with an increased risk of incident clinical HF during 6 years of subsequent follow-up

after adjustment for age, hypertension, DM, and CAD.[53]
  - With respect to variation by race/ethnicity, presence of asymptomatic LV systolic dysfunction in MESA was higher in blacks than in whites, Chinese, and Hispanics (1.7% overall and 2.7% in blacks). After 9 years of follow-up, asymptomatic LV dysfunction was associated with increased risk of overt HF (HR, 8.69 [95% CI, 4.89–15.45]), as well as CVD and all-cause mortality.[6]
  - In the Echocardiographic Study of Hispanic/Latinos, almost half (49.7%) of middle-aged or older Hispanics had some form of cardiac dysfunction (systolic, diastolic, or both), although fewer than 1 in 20 Hispanic/Latinos had symptomatic or clinically recognized HF.[54]
- LV function is variably abnormal in the setting of clinically overt HF.
  - GWTG-HF data from 2005 to 2010 indicate that of 110 621 patients hospitalized with HF, half had a reduced EF (<40%), 14% had an EF that was ≥40% and <50%, and 36% had an EF of ≥50%.[32]
  - Data collected between 1985 and 2014 from 12 857 person-observations in the FHS showed that the frequency of HF with reduced EF (EF <40%) decreased over time, whereas HF with mid-range EF (40%–<50%) remained stable, and HF with preserved EF (EF ≥50%) increased over time. These findings appeared attributable to trends in risk factors, especially a decrease in prevalent CHD among people with HF.[55]

Family History and Genetics

- HCM and familial DCM are the most common mendelian cardiomyopathies, with autosomal dominant or recessive transmission, in addition to X-linked and mitochondrial inheritance.
- Familial DCM accounts for up to 50% of cases of DCM, with a prevalence of 1 in 2500, but is likely underestimated.[56] Familial DCM often displays an age-dependent penetrance.[57] Up to 40% of cases have an identifiable genetic cause.[56]
- Given the heterogeneous nature of the underlying genetics, manifestation of the disease is highly variable, even in cases for which the causal mutation has been identified.[58] Variants in the β-myosin heavy chain gene (*MYH7*) were some of the earliest to be associated with familial HCM,[59,60] with >30 other genes implicated since, each accounting for <5% of cases, as reviewed elsewhere.[57,61,62] The considerable variability in the penetrance and pathogenicity of specific mutations makes clinical interpretation of sequence data particularly challenging.
- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy,[63] as well as to DCM, with incomplete penetrance in the general population.[63] Analysis of sequence data in 7855 cardiomyopathy case subjects and >60 000 control subjects revealed the variance in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.[64]
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results,[57,60] highlighting a small number of putative loci, including *HSPB7*[65–67] and *CACNB4*.[68] Given the heterogeneous multifactorial nature of common HF, identification of causal genetic loci remains a challenge.
- Genetic variation within subjects with HF may determine outcomes, with a locus on chromosome 5q22 associated with mortality in HF patients.[69] A large meta-analysis of >73 000 subjects identified 52 loci associated with myocardial mass.[70] The clinical utility of genetic testing for variants associated with common HF and related phenotypes remains unclear.
- HCM is a monogenic disorder with primarily autosomal dominant inheritance and is caused by one of hundreds of mutations in up to 18 genes that primarily encode components of the sarcomere, with mutations in *MYH7* and cardiac myosin-binding protein C (*MYBPC3*) being the most common, with each having 40 HCM cases attributed to it.[71] A mutation is identifiable in 50% to 75% of cases of familial HCM.
- Clinical genetic testing is recommended for patients with DCM with significant conduction system disease or a family history of SCD, as well as in patients with a strong clinical index of suspicion for HCM. It can be considered in other forms of DCM and restrictive cardiomyopathy and in LV noncompaction.[72]
- Genetic testing is also recommended in family members of patients with DCM, HCM, restrictive cardiomyopathy, and LV noncompaction.[72]

Mortality (See Table 20-2)

- Survival after the onset of HF in older adults has improved, as indicated by data from Kaiser Permanente[23]; however, improvements in HF survival have not been even across all demographics. Among Medicare beneficiaries, the overall 1-year HF mortality rate declined slightly from 1998 to

2008 but remained high at 29.6%, and rates of decline were uneven across states.[73,74] In the NHLBI's ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively, and blacks had a greater 5-year case fatality rate than whites ($P<0.05$).[75]

- Observed mortality declines have been primarily attributed to evidence-based approaches to treat HF risk factors and the implementation of treatment with ACE inhibitors, β-blockers, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapies.[76] Contemporary evidence from the GWTG-HF registry suggests that ≈47% of individuals admitted to the hospital with HF should have had initiation of ≥1 new medication on discharge; ≈24% need to start ≥1 new medication and ≈14% need to start ≥3 new medications to be in compliance with current guidelines.[77]
- In a large Swedish registry of patients with HF with preserved EF, statins improved 1-year cardiovascular hospitalization, mortality, and cardiovascular mortality.[78] Accordingly, 5-year survival of HF diagnosis after an MI in Olmsted County, MN, improved in 2001 to 2010 versus 1990 to 2000, from 54% to 61%.[79]
- Some data suggest that improvements in survival could be leveling off over time. Data from the Rochester Epidemiology Project in Olmsted County, MN, showed improved survival after HF diagnosis between 1979 and 2000[80]; however, 5-year mortality did not decline from 2000 to 2010 and remained high at ≈50% (52.6% overall; 24.4% for 60-year-olds and 54.4% for 80-year-olds), Importantly, mortality was more frequently ascribed to noncardiovascular causes (54.3%), and the risk of noncardiovascular death was greater in HF with preserved EF than in HF with reduced EF.[24]
- Given improvements in HF survival overall, the number of individuals carrying a diagnosis of HF at death has increased. Mortality associated with HF is substantial, such that 1 in 8 deaths has HF mentioned on the death certificate (unpublished NHLBI tabulation).[81]
- In 2017, HF was the underlying cause in 80 480 deaths (36 824 males and 43 656 females; Table 20-2). Table 20-2 shows the numbers of these deaths that were coded for HF as the underlying cause.
- The number of underlying causes of deaths attributable to HF was 42.3% higher in 2017 (80 480) than it was in 2007 (56 565; unpublished NHLBI tabulation using NVSS[81]).
- In 2017, the overall any-mention age-adjusted death rate for HF was 89.7 per 100 000, with variation across racial/ethnic groups: in males, the rates were 111.3 for NH whites, 118.2 for NH blacks, 46.9 for NH Asians or Pacific Islanders, 95.0 for NH American Indians or Alaska Natives, and 69.2 for Hispanics; in females, the respective rates were 80.4 for NH whites, 86.0 for NH blacks, 34.7 for NH Asians or Pacific Islanders, 80.6 for NH American Indians or Alaska Natives, and 49.7 for Hispanics (unpublished NHLBI tabulation using CDC WONDER[82]).

Healthcare Utilization: Hospital Discharges/ Ambulatory Care Visits (See Table 20-2 and Chart 20-6)

- Hospital discharges for HF (including discharged alive, dead, and status unknown) are shown for the United States (1997–2016) by sex in Chart 20-6. Discharges for HF decreased from 2006 to 2016, with principal diagnosis discharges of 1 020 000 and 809 000, respectively (Table 20-2).
- In 2016, there were 1 932 000 physician office visits with a primary diagnosis of HF (NAMCS,[83] unpublished NHLBI tabulation). In 2016, there were 414 000 ED visits for HF (NHAMCS,[84] NHLBI unpublished tabulation).
- Among 1077 patients with HF in Olmsted County, MN, hospitalizations were common after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than one-half of all hospitalizations were related to noncardiovascular causes.[85]
- Among Medicare beneficiaries, the overall HF hospitalization rate declined substantially from 1998 to 2008 but at a lower rate for black males,[74] and the temporal trend findings were uneven across states.
- In the GWTG-HF Registry, only one-tenth of eligible HF patients received cardiac rehabilitation referral at discharge after hospitalization for HF.[86]
- Among Medicare part D coverage beneficiaries, HF medication adherence (ACE inhibitors/angiotensin receptor blockers, β-blockers, and diuretic agents) after HF hospitalization discharge decreased over 2 to 4 months after discharge, followed by a plateau over the subsequent year for all 3 medication classes.[87]
- Rates of HF rehospitalization or cardiovascular death were greatest for those previously hospitalized for HF.[88]
- Although Hispanic patients hospitalized with HF were significantly younger than NH whites, the prevalence of DM, hypertension, and overweight/obesity was higher among them. In multivariate analysis, a 45% lower in-hospital mortality risk was

observed among Hispanics with HF with preserved EF compared with NH whites but not among those with HF with reduced EF.[89]

- On the basis of data from the community surveillance component of the ARIC study of the NHLBI[90]:
  - The average incidence of hospitalized HF for those ≥55 years of age was 11.6 per 1000 people per year; incidence of recurrent hospitalized HF was 6.6 per 1000 people per year.
  - Age-adjusted annual hospitalized HF incidence was highest for black males (15.7 per 1000), followed by black females (13.3 per 1000), white males (12.3 per 1000), and white females (9.9 per 1000).
  - Of incident hospitalized HF events, 53% had HF with reduced EF and 47% had preserved EF. Black males had the highest proportion of hospitalized HF with reduced EF (70%); white females had the highest proportion of hospitalized HF with preserved EF (59%).
  - Age-adjusted 28-day and 1-year case fatality after hospitalized HF was 10.4% and 29.5%, respectively, and did not differ by race or sex.
- Data from the Health and Retirement Study from 1998 to 2014 show racial/ethnic differences in hospitalization trajectories over 24 months after HF diagnosis.[91] Compared with NH males, Hispanic males have declines in hospitalization after initial diagnosis but then increases in hospitalizations in later stages of disease. Among females, compared with whites, blacks had significantly more hospitalizations throughout the follow-up period.
- Data from Olmsted County, MN, indicate that among those with HF, hospitalizations were particularly common among males and did not differ by HF with reduced EF versus preserved EF, with 63% of hospitalizations for noncardiovascular causes. Among those with HF, hospitalization rates for cardiovascular causes did not change over time, whereas those for noncardiovascular causes increased from 2000 to 2010.[24]

Cost

The overall cost of HF continues to rise. See Chapter 26 (Economic Cost of Cardiovascular Disease) for further statistics.

- In 2012, total cost for HF was estimated to be $30.7 billion (2010$), of which more than two-thirds was attributable to direct medical costs.[21] Projections suggest that by 2030, the total cost of HF will increase by 127%, to $69.8 billion, amounting to ≈$244 for every US adult.[21]
- Implantable cardioverter-defibrillators could be cost-effective in the guideline-recommended groups of individuals with HF with reduced EF; however, the benefit might not be as great in those with high overall mortality risk (eg, age ≥75 years, New York Heart Association functional class III, LVEF ≤20%, BNP ≥700 pg/mL, SBP ≤120 mm Hg, AF, DM, chronic lung disease, and CKD).[92,93]
- The costs associated with treating HF comorbidities and HF exacerbations in youths are significant, totaling nearly $1 billion in inpatient costs, and may be rising. The associated cost burden of HF is anticipated to constitute a large portion of total pediatric healthcare costs.[94]

Open Heart Transplantation and Mechanical Circulatory Support Device Placement in the United States (See Chart 20-7)

From September 1987 to December 2012, 40 253 people were waiting for heart transplants, with a median survival of 2.3 years; 26 943 received transplants, with median survival of 9.5 years. Life-years saved were 465 296; life-years saved per patient were 5.0.[95]

- Among other causes, heart transplant patients die of SCD at a rate of 1.3% per year, particularly those with a history of allograft vasculopathy, although other risk factors have been described in a meta-analysis of >47 000 individuals.[96]
- According to a study based on the NIS, the outcomes after admission for HF are similar in patients with a prior history of heart transplant and those without previous transplants.[97]
- In the MedaMACS study, from May 2013 to October 2015, 161 patients with advanced HF were included, and 47% died within 2 years of follow-up. Although survival was similar to that of patients with an LVAD in the overall INTERMACS cohort, in individuals with HF of greater severity, survival was lower in the INTERMACS cohort.[98]
- In the ROADMAP study, among 195 patients with advanced ambulatory non–inotrope-dependent HF, only those with higher severity of HF (defined as INTERMACS profile 4) benefitted from LVAD implantation compared with optimal medical management, despite increased complications. In individuals with INTERMACS profiles 5 through 7, no benefit of LVADs was noted.[99]
- In 2019, INTERMACS reported >25 000 mechanical circulatory support device implantations from June 2006 to December 2017, of which >20 000 were primary left mechanical circulatory support devices, including total artificial hearts (339), pulsatile-flow LVADs (923), and continuous-flow LVADs (19 206), including axial and centrifugal pumps. This includes both isolated LVAD and combined left and right ventricular assist devices. As of 2017, 51% of the LVADs were centrifugal and 49% were axial-flow devices.[100]

- The 1-year LVAD survival rate has now reached 83%, with a median survival of 5 years among patients with isolated continuous-flow LVADs. When an additional RV assist device is needed, the 1-year survival is only 58% and the median survival is limited to 31%.[100]
- The proportion of LVADs implanted as destination therapy increased from 2% in 2008 to 49% in 2017 for continuous-flow LVADs, with an overall decline in those in whom the LVAD was implanted as a bridge to decision or transplantation over this time period (Chart 20-7).[100] However, a substantial difference in indications exists across device type, with 73% of axial-flow pump–type LVADs being used as destination therapy in 2017 versus only 27% of centrifugal-flow LVADs.
- The 1-year survival of individuals with an LVAD implanted as a bridge to transplantation was 88%; for those with a bridge-to-decision implantation, survival was 85%; and for those with an LVAD as destination therapy, survival was 80%.[100]
- From 2006 to April 2017, 450 individuals in INTERMACS underwent a total artificial heart implantation. Among those, 266 underwent transplantation and 162 died on support. The 1-year survival rate was 53%, with most deaths occurring because of multiorgan failure. At 12 months, 52% of the patients had undergone transplantation, 34% had died, and 13% were still alive and with the device.[101]
- According to an NIS study, there is no difference in outcomes after ventricular assist device implantation across geographic areas in the United States, despite differences in cost and length of stay.[102]
- In 2011, in-hospital mortality with LVAD implantation decreased significantly, from 47.2% in 2005 to 12.7%, among Medicare beneficiaries. An inflection point was seen, with a sharp rise in LVAD implantation and decrease in the in-hospital mortality rate in 2008. Average hospital length of stay decreased from the pulsatile LVAD (pre-2008) to the continuous-flow LVAD (2008–2011) eras.[103] The mean cost of LVAD-related hospitalization increased from $194 380 in 2005 to $234 808 in 2011.[104]
- In a comparable cost-effectiveness analysis in the French healthcare system, LVAD implants were associated with improved survival at a high cost, exceeding €100 000 per QALY, and were not considered cost-effective.[105]
- In a meta-analysis of 8 studies (7957 patients total) comparing mortality rates in patients treated with heart transplantation versus bridge-to-transplantation LVAD or LVAD as destination therapy, there was no difference in late (>6 months) all-cause mortality between heart transplantation and LVAD (pooled OR, 0.91 [95% CI, 0.62–1.32] for transplantation versus bridge-to-transplantation LVAD; pooled OR, 1.49 [95% CI, 0.48–4.66] for transplantation versus destination therapy LVAD).[106]
- In a Markov model analysis, LVADs in patients with non–inotrope-dependent HF improved quality of life, at a substantial increase in costs, mostly attributable to frequent readmissions and cost of follow-up care. The gain in quality of life was from 2.67 to 4.41 QALYs. However, the incremental cost-effectiveness ratio was US $209 400 per QALY gained and US $597 400 per life-year gained. Moreover, those results were sensitive to readmission rates and outpatient care costs.[107]
- Elevated LVAD index admission costs could be related to procurement costs and length of stay. Hospital readmissions also contribute significantly to overall cost of LVAD therapy: in a retrospective study with continuous-flow LVAD, 44% of patients were readmitted within 30 days of discharge, with a median cost of $7546. The most common causes of readmission were gastrointestinal bleeding, infection, and stroke, with device malfunction and arrhythmias the costliest causes of readmission. There was no difference in survival between patients who were and were not readmitted, although median follow-up was only 11 months.[108]
- In a study that used the United Network for Organ Sharing registry between 2006 and 2015 and addressed insurance status, among those with bridge-to-transplantation LVADs, Medicaid insurance was associated with worse survival of patients on the heart transplant waiting list compared with patients with private insurance, although access to transplantation was not different.[109]
- Among Medicare beneficiaries undergoing LVAD implantation, the outcomes vary widely according to the presence of ESRD. During a median follow-up of 762 days, 82% of individuals with ESRD died, whereas only 36% of those without ESRD died. Even after adjustment for confounding, the OR for mortality was 36.3 for the presence of ESRD.

LVAD and Open-Heart Transplantation Disparities

- The 2019 INTERMACS report did not specifically address the influence of sex or race/ethnicity on mortality after LVAD procedures, although a higher mortality was seen in females in prior reports (HR, 1.16; *P*=0.005).[110]
- In a study that included 111 patients with ventricular assist devices, SES was not associated with adverse prognosis or complications after implantation.[111]
- In the United Network for Organ Sharing database of 18 085 patients who had open heart

transplantation performed at 102 centers, blacks had a higher adjusted 1-year mortality, particularly at poor-performing centers (observed-to-expected mortality ratio >1.2; OR, 1.37 [95% CI, 1.12–1.69]; *P*=0.002).[112] Compared with whites and Hispanics, a higher proportion of blacks were treated at centers with higher than expected mortality, which persisted after adjustment for insurance type and education level.

Global Burden of HF

- HF prevalence was lowest in west sub-Saharan Africa (0.74 [95% CI, 0.58–0.98] per 1000 in males and 0.57 [95% CI, 0.44–0.76] per 1000 in females).[113] HF made the largest contribution to age-standardized years lived with disability among males in high-income North America, Oceania, Eastern and Western Europe, southern Latin America, and Central Asia.[113]
- HF risk factors vary substantially across world regions, with hypertension being highly associated with HF in all regions but most commonly in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa, and with a minimal association of IHD with HF in sub-Saharan Africa.[114] IHD prevalence among HF patients is highest in Europe and North America but rare in sub-Saharan Africa, whereas hypertension prevalence among HF patients was highest in Eastern Europe and sub-Saharan Africa; valvular and rheumatic HD prevalence among HF patients was highest in East Asia and Asia-Pacific countries.[114] Follow-up from a multiethnic cohort composed of individuals from low- to middle-income countries in Africa, Asia, the Middle East, and South America will provide additional data regarding the global burden of HF.[115] HF is common throughout sub-Saharan Africa. According to a meta-analysis, the most common pathogenesis is hypertensive HD in 39.2% (95% CI, 32.6%–45.9%), followed by cardiomyopathies in 21.4% (95% CI, 16.0%–27.2%) and rheumatic HD in 14.1% (95% CI, 10.0%–18.8%), whereas IHD was reported in only 7.2% of cases (95% CI, 4.1%–11.0%). However, there was important variability in the prevalence according to the region of the continent.[116]
- The prevalence estimates for HF across Asia range from 1.26% to 6.7%. Rheumatic HD is a major contributor to HF in certain parts of South Asia, such as India, but recently, trends toward an ischemic cause for HF have been observed in Asia, such as in China and Japan.[117]
- Ischemic HF prevalence in 2010 was highest (>5 per 1000) in high-income North America, Oceania, and Eastern Europe. In particular, HF prevalence in 2010 was highest in Oceania (4.53 [95% CI, 3.19–6.29] per 1000 in females; 5.22 [95% CI, 3.84–7.08] per 1000 in males), followed by high-income North America and North Africa/Middle East.[113]

Table 20-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, 2017

	Both Sexes Combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	0.4 (0.3 to 0.4)	5.4 (4.7 to 6.3)	0.2 (0.2 to 0.2)	2.7 (2.4 to 3.2)	0.2 (0.1 to 0.2)	2.7 (2.3 to 3.1)
Percent change total number, 1990 to 2017	54.5 (46.4 to 64.1)	57.5 (52.5 to 63.0)	74.9 (62.3 to 92.2)	65.9 (60.0 to 73.1)	33.2 (26.5 to 43.4)	49.8 (44.7 to 55.3)
Percent change total number, 2007 to 2017	8.1 (3.8 to 18.2)	24.5 (22.5 to 26.5)	6.7 (0.7 to 23.9)	26.1 (23.5 to 28.8)	10.0 (7.0 to 14.3)	22.8 (20.3 to 25.3)
Rate per 100 000	4.8 (4.5 to 5.0)	68.7 (59.6 to 79.1)	6.0 (5.2 to 6.4)	74.0 (64.0 to 85.4)	3.7 (3.5 to 3.9)	63.4 (54.8 to 72.9)
Percent change rate, 2007 to 2017	−16.6 (−19.8 to −9.4)	−5.8 (−7.1 to −4.5)	−15.9 (−20.3 to −2.8)	−4.2 (−6.1 to −2.5)	−17.1 (−19.3 to −14.0)	−6.9 (−8.6 to −5.2)
Percent change rate, 1990 to 2017	−25.8 (−29.4 to −20.6)	−21.7 (−24.1 to −19.2)	−16.0 (−21.8 to 0.6)	−17.2 (−19.9 to −14.0)	−36.1 (−38.9 to −31.9)	−25.0 (−27.5 to −22.5)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[19] Printed with permission.

Table 20-2. HF in the United States

Population Group	Prevalence, 2013–2016, Age ≥20 y	Incidence, 2014, Age ≥55 y	Mortality, 2017, All Ages*	Hospital Discharges, 2016, All Ages	Cost, 2012†
Both sexes	6 200 000 (2.2%)	1 000 000	80 480	809 000	$30.7 billion
Males	3 000 000 (2.4%)	495 000	36 824 (45.8%)‡	415 000	…
Females	3 200 000 (2.1%)	505 000	43 656 (54.2%)‡	394 000	…
NH white males	2.2%	430 000§	30 076	…	…
NH white females	1.9%	425 000§	36 004	…	…
NH black males	3.5%	65 000§	4068	…	…
NH black females	3.9%	80 000§	4683	…	…
Hispanic males	2.5%	…	1820	…	…
Hispanic females	2.1%	…	1960	…	…
NH Asian males	1.7%	…	633‖	…	…
NH Asian females	0.7%	…	752‖	…	…
NH American Indian or Alaska Native	…	…	339	…	…

HF includes people who answered "yes" to the question of ever having congestive heart failure. Ellipses (…) indicates data not available; HF, heart failure; and NH, non-Hispanic.

*Mortality data for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†Cost data are from Heidenreich et al.[21]

‡These percentages represent the portion of total mortality attributable to HF that is for males vs females.

§Estimates for whites include other nonblack races.

‖Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey 2013 to 2016.[20] Percentages are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Unpublished NHLBI tabulation using Atherosclerosis Risk in Communities study Community Surveillance, 2005 to 2014.[118] Mortality: Unpublished NHLBI tabulation using National Vital Statistics System, 2017.[81] Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016 (data include those inpatients discharged alive, dead, or status unknown).[1]

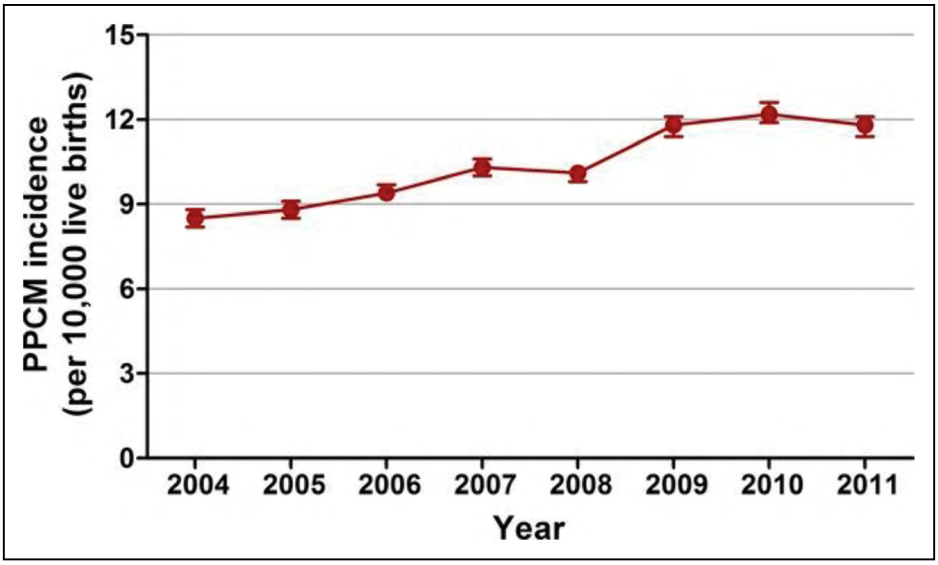

Chart 20-1. Temporal trends in PPCM incidence rate per 10 000 live births, United States, 2004 to 2011.

PPCM incidence rate per 10 000 live births per calendar year was calculated with the numerator representing the number of women 15 to 54 years of age with PPCM in that calendar year and the denominator representing the number of live births in women 15 to 54 years of age for the same calendar year. P_{trend}<0.001. Error bars represent 95% CI.

PPCM indicates peripartum cardiomyopathy.

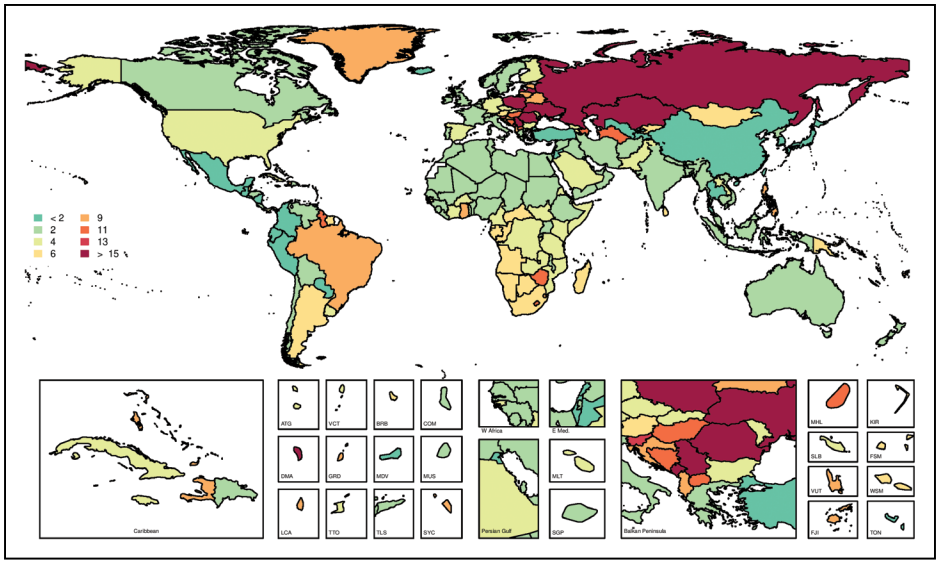

Chart 20-2. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2017.
The highest age-standardized mortality rates attributable to cardiomyopathy and myocarditis are in Eastern Europe.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[19] Printed with permission. Copyright © 2018, University of Washington.

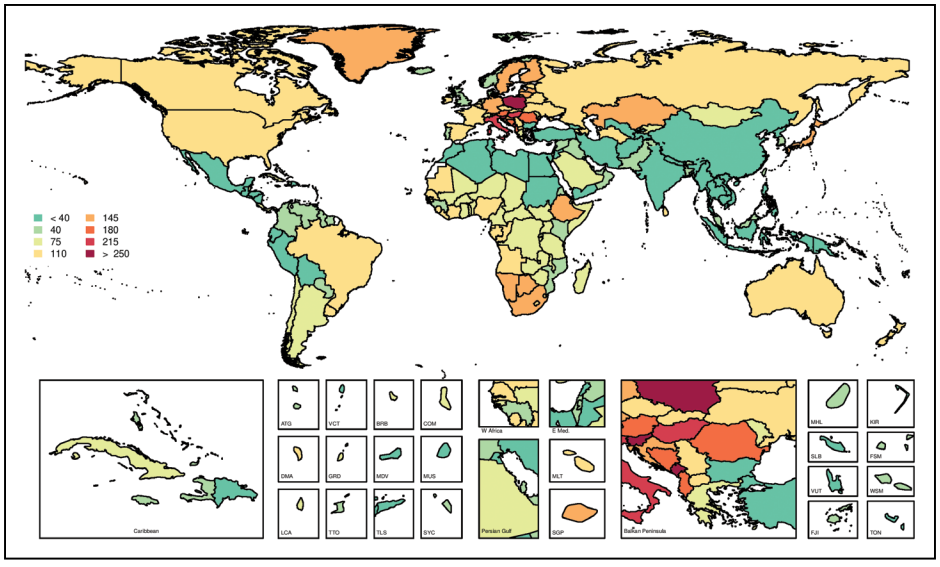

Chart 20-3. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2017.
Age-standardized prevalence of cardiomyopathy and myocarditis is highest in Central Europe.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[19] Printed with permission. Copyright © 2018, University of Washington.

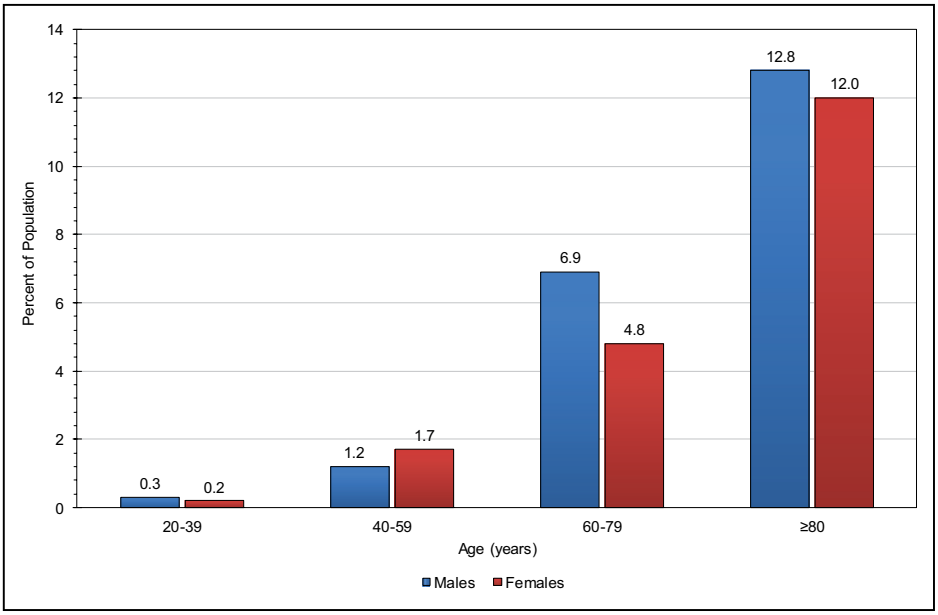

Chart 20-4. Prevalence of heart failure among US adults ≥20 years of age, by sex and age (NHANES, 2013–2016).
NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.[20]

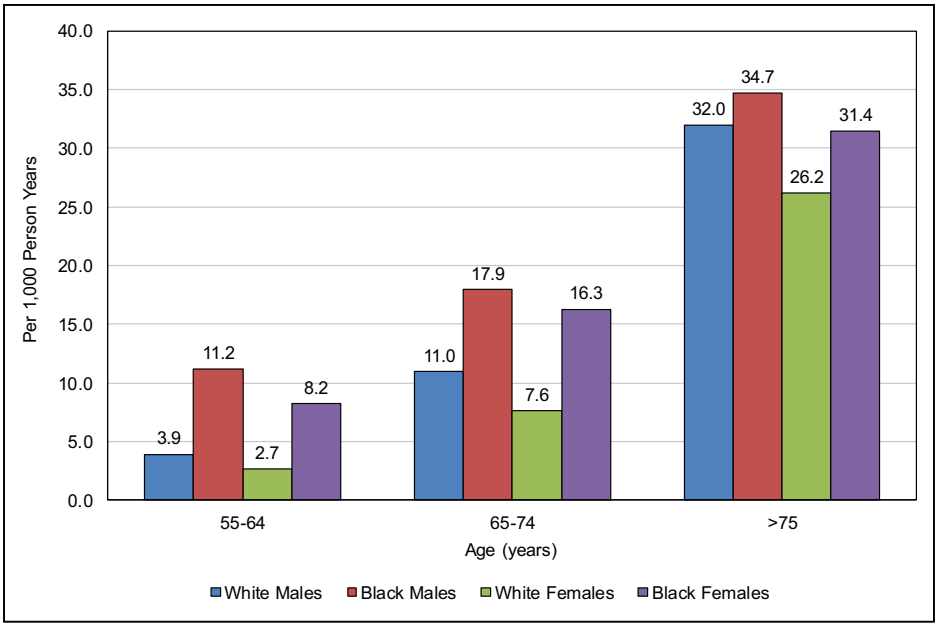

Chart 20-5. First acute decompensated heart failure annual event rates per 1000 from ARIC Community Surveillance by sex and race, United States, 2005 to 2014.
ARIC indicates Atherosclerosis Risk in Communities.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC Community Surveillance, 2005 to 2014.[118]

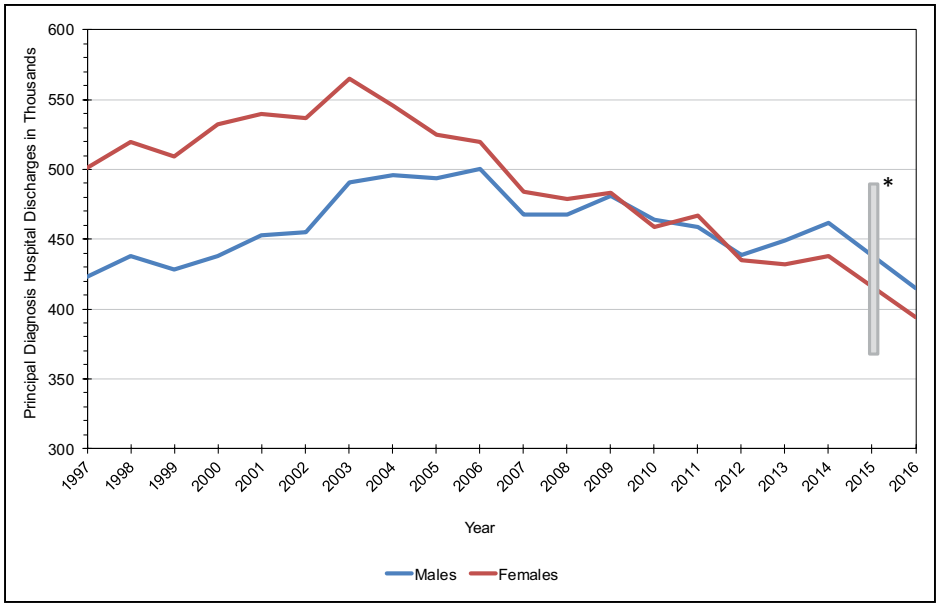

Chart 20-6. Hospital discharges for heart failure by sex, United States, 1997 to 2016.
Hospital discharges include people discharged alive, dead, and status unknown.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 1997 to 2016.[1]

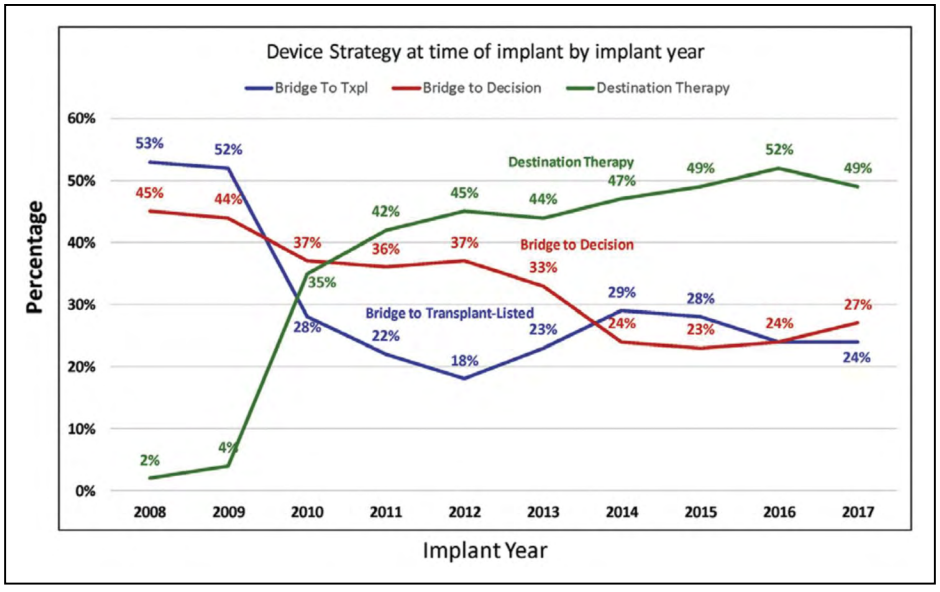

Chart 20-7. Device strategy at the time of implantation by year, United States, 2008 to 2017.
Implantations are continuous-flow left ventricular assist devices, April 2008 to December 2017. N=18 359.
Txpl indicates transplant.
Source: Reprinted from Kormos et al[100] with permission from The Society of Thoracic Surgeons. Copyright © 2019, The Society of Thoracic Surgeons. Published by Elsevier Inc. on behalf of International Society for Heart and Lung Transplantation.

REFERENCES

1. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
2. Massera D, McClelland RL, Ambale-Venkatesh B, Gomes AS, Hundley WG, Kawel-Boehm N, Yoneyama K, Owens DS, Garcia MJ, Sherrid MV, et al. Prevalence of unexplained left ventricular hypertrophy by cardiac magnetic resonance imaging in MESA. *J Am Heart Assoc.* 2019;8:e012250. doi: 10.1161/JAHA.119.012250
3. Bick AG, Flannick J, Ito K, Cheng S, Vasan RS, Parfenov MG, Herman DS, DePalma SR, Gupta N, Gabriel SB, et al. Burden of rare sarcomere gene variants in the Framingham and Jackson Heart Study cohorts. *Am J Hum Genet.* 2012;91:513–519. doi: 10.1016/j.ajhg.2012.07.017
4. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation.* 2018;138:1387–1398. doi: 10.1161/CIRCULATIONAHA.117.033200
5. Givertz MM, Mann DL. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. *Curr Heart Fail Rep.* 2013;10:321–330. doi: 10.1007/s11897-013-0157-5
6. Yeboah J, Rodriguez CJ, Stacey B, Lima JA, Liu S, Carr JJ, Hundley WG, Herrington DM. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2012;126:2713–2719. doi: 10.1161/CIRCULATIONAHA.112.112201
7. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med.* 1994;331:1564–1575. doi: 10.1056/NEJM199412083312307
8. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, Jain D, Gass A, Ahmed A, Panza JA, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. *J Am Heart Assoc.* 2014;3:e001056. doi: 10.1161/JAHA.114.001056
9. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexis JD, Ramani GV, Semigran MJ, et al; IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol.* 2015;66:905–914. doi: 10.1016/j.jacc.2015.06.1309
10. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, Shotan A. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation.* 2005;111:2050–2055. doi: 10.1161/01.CIR.0000162478.36652.7E
11. Irizarry OC, Levine LD, Lewey J, Boyer T, Riis V, Elovitz MA, Arany Z. Comparison of clinical characteristics and outcomes of peripartum cardiomyopathy between African American and non-African American women. *JAMA Cardiol.* 2017;2:1256–1260. doi: 10.1001/jamacardio.2017.3574
12. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J.* 2006;152:509–513. doi: 10.1016/j.ahj.2006.02.008
13. Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, et al. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. *Heart Fail Clin.* 2010;6:401–413, vii. doi: 10.1016/j.hfc.2010.05.002
14. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation.* 2007;115:773–781. doi: 10.1161/CIRCULATIONAHA.106.621185
15. Ziółkowska L, Turska-Kmieć A, Petryka J, Kawalec W. Predictors of long-term outcome in children with hypertrophic cardiomyopathy. *Pediatr Cardiol.* 2016;37:448–458. doi: 10.1007/s00246-015-1298-y
16. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA.* 2006;296:1867–1876. doi: 10.1001/jama.296.15.1867
17. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, et al; Pediatric Cardiomyopathy Registry Investigators. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol.* 2012;59:607–615. doi: 10.1016/j.jacc.2011.10.878
18. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ.* 2009;339:b4606. doi: 10.1136/bmj.b4606
19. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
20. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nhanes/. Accessed April 1, 2019.
21. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, et al; on behalf of the American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6:606–619. doi: 10.1161/HHF.0b013e318291329a
22. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML, Lloyd-Jones DM. Lifetime risk for heart failure among white and black Americans: Cardiovascular Lifetime Risk Pooling Project. *J Am Coll Cardiol.* 2013;61:1510–1517. doi: 10.1016/j.jacc.2013.01.022
23. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. *Circulation.* 2006;113:799–805. doi: 10.1161/CIRCULATIONAHA.104.492033
24. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med.* 2015;175:996–1004. doi: 10.1001/jamainternmed.2015.0924
25. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM, Arynchyn A, Lewis CE, Williams OD, Hulley SB. Racial differences in incident heart failure among young adults. *N Engl J Med.* 2009;360:1179–1190. doi: 10.1056/NEJMoa0807265
26. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, Burke GL, Lima JA. Differences in the incidence of congestive heart failure by ethnicity: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med.* 2008;168:2138–2145. doi: 10.1001/archinte.168.19.2138
27. Chang PP, Wruck LM, Shahar E, Rossi JS, Loehr LR, Russell SD, Agarwal SK, Konety SH, Rodriguez CJ, Rosamond WD. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005-2014): ARIC Study Community Surveillance. *Circulation.* 2018;138:12–24. doi: 10.1161/CIRCULATIONAHA.117.027551
28. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med.* 2009;122:1023–1028. doi: 10.1016/j.amjmed.2009.04.022
29. Kovell LC, Juraschek SP, Russell SD. Stage A heart failure is not adequately recognized in US adults: analysis of the National Health and Nutrition Examination Surveys, 2007-2010. *PLoS One.* 2015;10:e0132228. doi: 10.1371/journal.pone.0132228
30. Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, Rodondi N, Satterfield S, Bauer DC, Bibbins-Domingo K, et al. Epidemiology of incident heart failure in a contemporary elderly cohort: the Health, Aging, and Body Composition study. *Arch Intern Med.* 2009;169:708–715. doi: 10.1001/archinternmed.2009.40
31. Vivo RP, Krim SR, Cevik C, Witteles RM. Heart failure in Hispanics. *J Am Coll Cardiol.* 2009;53:1167–1175. doi: 10.1016/j.jacc.2008.12.037
32. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; for the Get With the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation.* 2012;126:65–75. doi: 10.1161/CIRCULATIONAHA.111.080770
33. Djoussé L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA.* 2009;302:394–400. doi: 10.1001/jama.2009.1062
34. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med.* 2015;128:970–976.e2. doi: 10.1016/j.amjmed.2015.03.027
35. Dhingra R, Gona P, Wang TJ, Fox CS, D'Agostino RB Sr, Vasan RS. Serum gamma-glutamyl transferase and risk of heart failure in the community. *Arterioscler Thromb Vasc Biol.* 2010;30:1855–1860. doi: 10.1161/ATVBAHA.110.207340

36. Coglianese EE, Qureshi MM, Vasan RS, Wang TJ, Moore LL. Usefulness of the blood hematocrit level to predict development of heart failure in a community. *Am J Cardiol.* 2012;109:241–245. doi: 10.1016/j.amjcard.2011.08.037
37. Velagaleti RS, Gona P, Larson MG, Wang TJ, Levy D, Benjamin EJ, Selhub J, Jacques PF, Meigs JB, Tofler GH, et al. Multimarker approach for the prediction of heart failure incidence in the community. *Circulation.* 2010;122:1700–1706. doi: 10.1161/CIRCULATIONAHA.109.929661
38. Frankel DS, Vasan RS, D'Agostino RB Sr, Benjamin EJ, Levy D, Wang TJ, Meigs JB. Resistin, adiponectin, and risk of heart failure: the Framingham Offspring study. *J Am Coll Cardiol.* 2009;53:754–762. doi: 10.1016/j.jacc.2008.07.073
39. Djoussé L, Wilk JB, Hanson NQ, Glynn RJ, Tsai MY, Gaziano JM. Association between adiponectin and heart failure risk in the Physicians' Health Study. *Obesity (Silver Spring).* 2013;21:831–834. doi: 10.1002/oby.20260
40. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Tang WW, Methvin A, Smith AL, Bauer DC, Newman AB, Kim L, Harris TB, et al; Health ABC Study. Serum albumin concentration and heart failure risk: the Health, Aging, and Body Composition study. *Am Heart J.* 2010;160:279–285. doi: 10.1016/j.ahj.2010.05.022
41. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, Kim L, Bibbins-Domingo K, Tindle H, Harris TB, et al. Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition Study. *Am Heart J.* 2012;164:236–242. doi: 10.1016/j.ahj.2012.05.013
42. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, Liu Y, Hoffmann U, Bauer DC, Newman AB, et al; Health ABC Study Investigators. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol.* 2010;55:2129–2137. doi: 10.1016/j.jacc.2009.12.045
43. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA.* 2010;304:2494–2502. doi: 10.1001/jama.2010.1708
44. Mozaffarian D, Lemaitre RN, King IB, Song X, Spiegelman D, Sacks FM, Rimm EB, Siscovick DS. Circulating long-chain ω-3 fatty acids and incidence of congestive heart failure in older adults: the Cardiovascular Health Study: a cohort study. *Ann Intern Med.* 2011;155:160–170. doi: 10.7326/0003-4819-155-3-201108020-00006
45. Agarwal SK, Simpson RJ Jr, Rautaharju P, Alonso A, Shahar E, Massing M, Saba S, Heiss G. Relation of ventricular premature complexes to heart failure (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol.* 2012;109:105–109. doi: 10.1016/j.amjcard.2011.08.009
46. Bekwelem W, Lutsey PL, Loehr LR, Agarwal SK, Astor BC, Guild C, Ballantyne CM, Folsom AR. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol.* 2011;21:739–748. doi: 10.1016/j.annepidem.2011.06.005
47. Blecker S, Matsushita K, Köttgen A, Loehr LR, Bertoni AG, Boulware LE, Coresh J. High-normal albuminuria and risk of heart failure in the community. *Am J Kidney Dis.* 2011;58:47–55. doi: 10.1053/j.ajkd.2011.02.391
48. Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, Selvin E. The association of hemoglobin A1c with incident heart failure among people without diabetes: the Atherosclerosis Risk in Communities study. *Diabetes.* 2010;59:2020–2026. doi: 10.2337/db10-0165
49. Roberts CB, Couper DJ, Chang PP, James SA, Rosamond WD, Heiss G. Influence of life-course socioeconomic position on incident heart failure in blacks and whites: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol.* 2010;172:717–727. doi: 10.1093/aje/kwq193
50. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation.* 2011;123:1367–1376. doi: 10.1161/CIRCULATIONAHA.110.005264
51. Choi EY, Bahrami H, Wu CO, Greenland P, Cushman M, Daniels LB, Almeida AL, Yoneyama K, Opdahl A, Jain A, et al. N-terminal pro-B-type natriuretic peptide, left ventricular mass, and incident heart failure: Multi-Ethnic Study of Atherosclerosis. *Circ Heart Fail.* 2012;5:727–734. doi: 10.1161/CIRCHEARTFAILURE.112.968701
52. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community [published correction appears in *Circulation*. 2011;124:e458]. *Circulation.* 2011;124:24–30. doi: 10.1161/CIRCULATIONAHA.110.979203
53. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA.* 2011;306:856–863. doi: 10.1001/jama.2011.1201
54. Mehta H, Armstrong A, Swett K, Shah SJ, Allison MA, Hurwitz B, Bangdiwala S, Dadhania R, Kitzman DW, Arguelles W, et al. Burden of systolic and diastolic left ventricular dysfunction among Hispanics in the United States: insights from the Echocardiographic Study of Latinos. *Circ Heart Fail.* 2016;9:e002733. doi: 10.1161/CIRCHEARTFAILURE.115.002733
55. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, Aragam J, Benjamin EJ, Larson MG. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. *JACC Cardiovasc Imaging.* 2018;11:1–11. doi: 10.1016/j.jcmg.2017.08.007
56. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol.* 2013;10:531–547. doi: 10.1038/nrcardio.2013.105
57. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol.* 2011;57:1641–1649. doi: 10.1016/j.jacc.2011.01.015
58. Page SP, Kounas S, Syrris P, Christiansen M, Frank-Hansen R, Andersen PS, Elliott PM, McKenna WJ. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. *Circ Cardiovasc Genet.* 2012;5:156–166. doi: 10.1161/CIRCGENETICS.111.960831
59. Marian AJ, Yu QT, Mares A Jr, Hill R, Roberts R, Perryman MB. Detection of a new mutation in the beta-myosin heavy chain gene in an individual with hypertrophic cardiomyopathy. *J Clin Invest.* 1992;90:2156–2165. doi: 10.1172/JCI116101
60. Perryman MB, Yu QT, Marian AJ, Mares A Jr, Czernuszewicz G, Ifegwu J, Hill R, Roberts R. Expression of a missense mutation in the messenger RNA for beta-myosin heavy chain in myocardial tissue in hypertrophic cardiomyopathy. *J Clin Invest.* 1992;90:271–277. doi: 10.1172/JCI115848
61. Cahill TJ, Ashrafian H, Watkins H. Genetic cardiomyopathies causing heart failure. *Circ Res.* 2013;113:660–675. doi: 10.1161/CIRCRESAHA.113.300282
62. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. *Genome Med.* 2017;9:20. doi: 10.1186/s13073-017-0410-8
63. Hastings R, de Villiers CP, Hooper C, Ormondroyd L, Pagnamenta A, Lise S, Salatino S, Knight SJ, Taylor JC, Thomson KL, et al. Combination of whole genome sequencing, linkage, and functional studies implicates a missense mutation in titin as a cause of autosomal dominant cardiomyopathy with features of left ventricular noncompaction. *Circ Cardiovasc Genet.* 2016;9:426–435. doi: 10.1161/CIRCGENETICS.116.001431
64. Walsh R, Thomson KL, Ware JS, Funke BH, Woodley J, McGuire KJ, Mazzarotto F, Blair E, Seller A, Taylor JC, et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. *Genet Med.* 2017;19:192–203. doi: 10.1038/gim.2016.90
65. Cappola TP, Li M, He J, Ky B, Gilmore J, Qu L, Keating B, Reilly M, Kim CE, Glessner J, et al. Common variants in HSPB7 and FRMD4B associated with advanced heart failure. *Circ Cardiovasc Genet.* 2010;3:147–154. doi: 10.1161/CIRCGENETICS.109.898395
66. Matkovich SJ, Van Booven DJ, Hindes A, Kang MY, Druley TE, Vallania FL, Mitra RD, Reilly MP, Cappola TP, Dorn GW 2nd. Cardiac signaling genes exhibit unexpected sequence diversity in sporadic cardiomyopathy, revealing HSPB7 polymorphisms associated with disease. *J Clin Invest.* 2010;120:280–289. doi: 10.1172/JCI39085
67. Stark K, Esslinger UB, Reinhard W, Petrov G, Winkler T, Komajda M, Isnard R, Charron P, Villard E, Cambien F, et al. Genetic association study identifies HSPB7 as a risk gene for idiopathic dilated cardiomyopathy. *PLoS Genet.* 2010;6:e1001167. doi: 10.1371/journal.pgen.1001167
68. Xu H, Dorn GWII, Shetty A, Parihar A, Dave T, Robinson SW, Gottlieb SS, Donahue MP, Tomaselli GF, Kraus WE, et al. A genome-wide association study of idiopathic dilated cardiomyopathy in African Americans. *J Pers Med.* 2018;8:E11. doi: 10.3390/jpm8010011
69. Smith NL, Felix JF, Morrison AC, Demissie S, Glazer NL, Loehr LR, Cupples LA, Dehghan A, Lumley T, Rosamond WD, et al. Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the Cohorts for Heart and Aging Research in Genomic Epidemiology

(CHARGE) consortium. *Circ Cardiovasc Genet.* 2010;3:256–266. doi: 10.1161/CIRCGENETICS.109.895763
70. van der Harst P, van Setten J, Verweij N, Vogler G, Franke L, Maurano MT, Wang X, Mateo Leach I, Eijgelsheim M, Sotoodehnia N, et al. 52 Genetic loci influencing myocardial mass. *J Am Coll Cardiol.* 2016;68:1435–1448. doi: 10.1016/j.jacc.2016.07.729
71. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *N Engl J Med.* 2011;364:1643–1656. doi: 10.1056/NEJMra0902923
72. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, et al; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) [published correction appears in *Europace*. 2012;14:277]. *Europace.* 2011;13:1077–1109. doi: 10.1093/europace/eur245
73. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
74. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. *JAMA.* 2011;306:1669–1678. doi: 10.1001/jama.2011.1474
75. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol.* 2008;101:1016–1022. doi: 10.1016/j.amjcard.2007.11.061
76. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A, Sinagra G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail.* 2014;16:317–324. doi: 10.1002/ejhf.16
77. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, Ho PM, Eapen ZJ, Hernandez AF, Heidenreich PA, et al. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. *Circulation.* 2015;132:1347–1353. doi: 10.1161/CIRCULATIONAHA.115.014281
78. Alehagen U, Benson L, Edner M, Dahlström U, Lund LH. Association between use of statins and mortality in patients with heart failure and ejection fraction of ≥50. *Circ Heart Fail.* 2015;8:862–870. doi: 10.1161/CIRCHEARTFAILURE.115.002143
79. Gerber Y, Weston SA, Enriquez-Sarano M, Berardi C, Chamberlain AM, Manemann SM, Jiang R, Dunlay SM, Roger VL. Mortality associated with heart failure after myocardial infarction: a contemporary community perspective. *Circ Heart Fail.* 2016;9:e002460. doi: 10.1161/CIRCHEARTFAILURE.115.002460
80. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA.* 2004;292:344–350. doi: 10.1001/jama.292.3.344
81. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
82. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
83. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
84. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
85. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations after heart failure diagnosis a community perspective. *J Am Coll Cardiol.* 2009;54:1695–1702. doi: 10.1016/j.jacc.2009.08.019
86. Golwala H, Pandey A, Ju C, Butler J, Yancy C, Bhatt DL, Hernandez AF, Fonarow GC. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: findings from Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol.* 2015;66:917–926. doi: 10.1016/j.jacc.2015.06.1089
87. Sueta CA, Rodgers JE, Chang PP, Zhou L, Thudium EM, Kucharska-Newton AM, Stearns SC. Medication adherence based on Part D claims for patients with heart failure after hospitalization (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol.* 2015;116:413–419. doi: 10.1016/j.amjcard.2015.04.058
88. Bello NA, Claggett B, Desai AS, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Solomon SD. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. *Circ Heart Fail.* 2014;7:590–595. doi: 10.1161/CIRCHEARTFAILURE.113.001281
89. Vivo RP, Krim SR, Krim NR, Zhao X, Hernandez AF, Peterson ED, Pina IL, Bhatt DL, Schwamm LH, Fonarow GC. Care and outcomes of Hispanic patients admitted with heart failure with preserved or reduced ejection fraction: findings from Get With The Guidelines-Heart Failure. *Circ Heart Fail.* 2012;5:167–175. doi: 10.1161/CIRCHEARTFAILURE.111.963546
90. Chang PP, Chambless LE, Shahar E, Bertoni AG, Russell SD, Ni H, He M, Mosley TH, Wagenknecht LE, Samdarshi TE, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol.* 2014;113:504–510. doi: 10.1016/j.amjcard.2013.10.032
91. Dupre ME, Gu D, Xu H, Willis J, Curtis LH, Peterson ED. Racial and ethnic differences in trajectories of hospitalization in US men and women with heart failure. *J Am Heart Assoc.* 2017;6:e006290. doi: 10.1161/JAHA.117.006290
92. Bilchick KC, Stukenborg GJ, Kamath S, Cheng A. Prediction of mortality in clinical practice for Medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. *J Am Coll Cardiol.* 2012;60:1647–1655. doi: 10.1016/j.jacc.2012.07.028
93. Heidenreich PA, Tsai V, Curtis J, Wang Y, Turakhia MP, Masoudi FA, Varosy PD, Goldstein MK. A validated risk model for 1-year mortality after primary prevention implantable cardioverter defibrillator placement. *Am Heart J.* 2015;170:281–289.e2. doi: 10.1016/j.ahj.2014.12.013
94. Nandi D, Rossano JW. Epidemiology and cost of heart failure in children. *Cardiol Young.* 2015;25:1460–1468. doi: 10.1017/S1047951115002280
95. Rana A, Gruessner A, Agopian VG, Khalpey Z, Riaz IB, Kaplan B, Halazun KJ, Busuttil RW, Gruessner RW. Survival benefit of solid-organ transplant in the United States. *JAMA Surg.* 2015;150:252–259. doi: 10.1001/jamasurg.2014.2038
96. Alba AC, Foroutan F, Ng Fat Hing NKV, Fan CS, Manlhiot C, Ross HJ. Incidence and predictors of sudden cardiac death after heart transplantation: a systematic review and meta-analysis. *Clin Transplant.* 2018;32:e13206. doi: 10.1111/ctr.13206
97. Basnet S, Dhital R, Tharu B, Poudel DR, Donato A. Comparison of outcomes after hospitalization among heart failure patients with and without history of heart transplantation. *Transplant Proc.* 2018;50:3720–3722. doi: 10.1016/j.transproceed.2018.08.048
98. Ambardekar AV, Forde-McLean RC, Kittleson MM, Stewart GC, Palardy M, Thibodeau JT, DeVore AD, Mountis MM, Cadaret L, Teuteberg JJ, et al. High early event rates in patients with questionable eligibility for advanced heart failure therapies: results from the Medical Arm of Mechanically Assisted Circulatory Support (Medamacs) Registry. *J Heart Lung Transplant.* 2016;35:722–730. doi: 10.1016/j.healun.2016.01.014
99. Shah KB, Starling RC, Rogers JG, Horstmanshof DA, Long JW, Kasirajan V, Stehlik J, Chuang J, Farrar DJ, Estep JD; ROADMAP Investigators. Left ventricular assist devices versus medical management in ambulatory heart failure patients: an analysis of INTERMACS profiles 4 and 5 to 7 from the ROADMAP study. *J Heart Lung Transplant.* 2018;37:706–714. doi: 10.1016/j.healun.2017.12.003
100. Kormos RL, Cowger J, Pagani FD, Teuteberg JJ, Goldstein DJ, Jacobs JP, Higgins RS, Stevenson LW, Stehlik J, Atluri P, et al. The Society of Thoracic Surgeons INTERMACS database annual report: evolving indications, outcomes, and scientific partnerships. *J Heart Lung Transplant.* 2019;38:114–126. doi: 10.1016/j.healun.2018.11.013
101. Arabía FA, Cantor RS, Koehl DA, Kasirajan V, Gregoric I, Moriguchi JD, Esmailian F, Ramzy D, Chung JS, Czer LS, et al. Interagency registry for mechanically assisted circulatory support report on the total artificial heart. *J Heart Lung Transplant.* 2018;37:1304–1312. doi: 10.1016/j.healun.2018.04.004
102. Briasoulis A, Inampudi C, Akintoye E, Adegbala O, Asleh R, Alvarez P, Bhama J. Regional variation in mortality, major complications, and cost after left ventricular assist device implantation in the United States (2009 to 2014). *Am J Cardiol.* 2018;121:1575–1580. doi: 10.1016/j.amjcard.2018.02.047

103. Khazanie P, Hammill BG, Patel CB, Eapen ZJ, Peterson ED, Rogers JG, Milano CA, Curtis LH, Hernandez AF. Trends in the use and outcomes of ventricular assist devices among Medicare beneficiaries, 2006 through 2011. *J Am Coll Cardiol*. 2014;63:1395–1404. doi: 10.1016/j.jacc.2013.12.020
104. Miller LW, Guglin M, Rogers J. Cost of ventricular assist devices: can we afford the progress? *Circulation*. 2013;127:743–748. doi: 10.1161/CIRCULATIONAHA.112.139824
105. Tadmouri A, Blomkvist J, Landais C, Seymour J, Azmoun A. Cost-effectiveness of left ventricular assist devices for patients with end-stage heart failure: analysis of the French hospital discharge database. *ESC Heart Fail*. 2018;5:75–86. doi: 10.1002/ehf2.12194
106. Theochari CA, Michalopoulos G, Oikonomou EK, Giannopoulos S, Doulamis IP, Villela MA, Kokkinidis DG. Heart transplantation versus left ventricular assist devices as destination therapy or bridge to transplantation for 1-year mortality: a systematic review and meta-analysis. *Ann Cardiothorac Surg*. 2018;7:3–11. doi: 10.21037/acs.2017.09.18
107. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, Owens DK, Hlatky MA. Cost-effectiveness of left ventricular assist devices in ambulatory patients with advanced heart failure. *JACC Heart Fail*. 2017;5:110–119. doi: 10.1016/j.jchf.2016.09.008
108. Marasco SF, Summerhayes R, Quayle M, McGiffin D, Luthe M. Cost comparison of heart transplant vs. left ventricular assist device therapy at one year. *Clin Transplant*. 2016;30:598–605. doi: 10.1111/ctr.12725
109. Emani S, Tumin D, Foraker RE, Hayes D Jr, Smith SA. Impact of insurance status on heart transplant wait-list mortality for patients with left ventricular assist devices [published online December 19, 2016]. *Clin Transplant*. doi: 10.1111/ctr.12875. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5705048/.
110. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant*. 2015;34:1495–1504. doi: 10.1016/j.healun.2015.10.003
111. Ahmed MM, Magar SM Jr, Jeng EI, Arnaoutakis GJ, Beaver TM, Vilaro J, Klodell CT Jr, Aranda JM Jr. Effects of socioeconomic status on clinical outcomes with ventricular assist devices. *Clin Cardiol*. 2018;41:1463–1467. doi: 10.1002/clc.23070
112. Kilic A, Higgins RS, Whitson BA, Kilic A. Racial disparities in outcomes of adult heart transplantation. *Circulation*. 2015;131:882–889. doi: 10.1161/CIRCULATIONAHA.114.011676
113. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, Murray CJ, Naghavi M. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129:1493–1501. doi: 10.1161/CIRCULATIONAHA.113.004046
114. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: a systematic review and pooled analysis. *Int J Cardiol*. 2013;168:1186–1194. doi: 10.1016/j.ijcard.2012.11.065
115. Dokainish H, Teo K, Zhu J, Roy A, Al-Habib K, ElSayed A, Palileo L, Jaramillo PL, Karaye K, Yusoff K, et al. Heart failure in low- and middle-income countries: background, rationale, and design of the INTERnational Congestive Heart Failure Study (INTER-CHF). *Am Heart J*. 2015;170:627–634.e1. doi: 10.1016/j.ahj.2015.07.008
116. Agbor VN, Essouma M, Ntusi NAB, Nyaga UF, Bigna JJ, Noubiap JJ. Heart failure in sub-Saharan Africa: a contemporaneous systematic review and meta-analysis. *Int J Cardiol*. 2018;257:207–215. doi: 10.1016/j.ijcard.2017.12.048
117. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J*. 2013;77:2209–2217. doi: 10.1253/circj.cj-13-0971
118. Atherosclerosis Risk in Communities (ARIC) Study, Community Surveillance Component, 2005–2014. Collaborative Studies Coordinating Center website. https://sites.cscc.unc.edu/aric/. Accessed May 6, 2019.

21. VALVULAR DISEASES

See Tables 21-1 and 21-2 and Charts 21-1 through 21-6

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Mortality and any-mention mortality in this section are for 2017 based on unpublished NHLBI tabulations using the NVSS and CDC WONDER.[1,2] "Mortality" is the number of deaths in 2017 for the given underlying cause based on *ICD-10*. Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP[3] (2016); data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2016 are based on *ICD-10* codes.

Abbreviations Used in Chapter 21

ACC	American College of Cardiology
AF	atrial fibrillation
AGES	Age, Gene/Environment Susceptibility
AHA	American Heart Association
APAC	Asia-Pacific
CABG	coronary artery bypass graft
CALA	Caribbean and Latin America
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CER	cost-effectiveness ratio
CI	confidence interval
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
DALY	disability-adjusted life-year
DCM	dilated cardiomyopathy
DM	diabetes mellitus
EF	ejection fraction
EVEREST	Endovascular Valve Edge-to-Edge Repair
EVEREST II HRS	Endovascular Valve Edge-to-Edge Repair High-Risk Study
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GRS	genetic risk score
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICE-PCS	International Collaboration on Endocarditis–Prospective Cohort Study

(*Continued*)

Abbreviations Used in Chapter 21 Continued

ICE-PLUS	International Collaboration on Endocarditis–PLUS
IE	infective endocarditis
IHD	ischemic heart disease
IQR	interquartile range
iSAVR	isolated surgical aortic valve replacement
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
LV	left ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MITRA-FR	Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
MR	mitral regurgitation
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
NYHA	New York Heart Association
OR	odds ratio
PAR	population attributable risk
PARTNER	Placement of Aortic Transcatheter Valve
QALY	quality-adjusted life-year
REMEDY	Global Rheumatic Heart Disease Registry
RR	relative risk
RV	right ventricular
SAVR	surgical aortic valve replacement
SD	standard deviation
SNP	single-nucleotide polymorphism
STS	Society of Thoracic Surgeons
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
SVT	supraventricular tachycardia
TA	transapical
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack
TOF	tetralogy of Fallot
TV	transvascular
TVT	Transcatheter Valve Therapy
VT	ventricular tachycardia

Valvular Heart Disease *ICD-9* 424; *ICD-10* I34 to I38.

2017: Mortality—24 811. Any-mention mortality—52 939.
2016: Hospital discharges—120 000.

Prevalence

- Previously undiagnosed, predominantly mild valvular HD was found in 51% of 2500 individuals ≥65 years of age from a primary care population screened using transthoracic echocardiography.

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The prevalence of undiagnosed moderate or severe valvular HD was 6.4%.[4]

Incidence

- In a recent report using a Swedish nationwide register to identify all patients with a first diagnosis of valvular HD at Swedish hospitals between 2003 and 2010 (N=10 164 211), the incidence of valvular HD was 63.9 per 100 000 person-years, with aortic stenosis (47.2%), MR (24.2%), and aortic regurgitation (18.0%) contributing most of the valvular diagnoses. The majority of valvulopathies were diagnosed in the elderly (68.9% in subjects ≥65 years of age). Incidences of aortic regurgitation, aortic stenosis, and MR were higher in males, who were also more frequently diagnosed at an earlier age. Mitral stenosis incidence was higher in females.[5]

Aortic Valve Disorders (See Chart 21-1)
ICD-9 424.1; *ICD-10* I35.

2017: Mortality—16 827. Any-mention mortality 35 434.
2016: Hospital discharges—91 000.

Prevalence

- Prevalence of aortic stenosis by echocardiography was 4.3% among individuals ≥70 years of age in the Icelandic AGES-Reykjavik cohort.[6]
- In younger age groups, the most prevalent cause of aortic stenosis is bicuspid aortic valve, the most common form of congenital HD. In an Italian study of 817 primary school students, the prevalence of bicuspid aortic valve was 0.5% (95% CI, 0.13%–1.2%).[7]

Incidence

- Nationally representative data from Sweden demonstrate an age-adjusted incidence of aortic stenosis from 15.0 to 11.4 per 100 000 males and from 9.8 to 7.1 per 100 000 females, between the years 1989 to 1991 and 2007 to 2009.[8]
- In the Norwegian Tromsø study, the incidence of new aortic stenosis was 5 per 1000 per year, with the initial mean age of participants being 60 years.[9]
- In the Canadian CANHEART aortic stenosis study, absolute incidence of severe aortic stenosis among individuals >65 years of age was 144 per 100 000 person-years (169 and 127 per 100 000 person-years in males and females, respectively).[10]

Lifetime Risk and Cumulative Incidence

- The number of elderly patients with calcific aortic stenosis is projected to more than double by 2050 in both the United States and Europe based on a simulation model in 7 decision analysis studies. In the Icelandic AGES-Reykjavik study alone, projections suggest a doubling in prevalence among those with severe aortic stenosis who are ≥70 years of age by 2040 and a tripling by 2060.[6]

Risk Factors

- In the Canadian CANHEART study, among 1.12 million individuals >65 years of age followed up for a median of 13 years, 20 995 subjects developed severe aortic stenosis. Hypertension (adjusted HR, 1.71 [95% CI, 1.66–1.76]), DM (HR, 1.49 [95% CI, 1.44–1.54]), and dyslipidemia (HR, 1.17 [95% CI, 1.14–1.21]) were the strongest predictors of development of severe aortic stenosis (all $P<0.001$).[10]
- In a retrospective analysis of predictors of cardiac outcomes in 227 ambulatory adults with bicuspid aortic valve, independent predictors of the composite end point (need for surgery, death, aortic dissection, endocarditis, HF, arrhythmias, or IHD) were baseline moderate to severe aortic valve dysfunction (HR, 3.19 [95% CI, 1.35–7.54]; $P<0.01$) and aortic valve leaflet calcification (HR, 4.72 [95% CI, 1.91–11.64]; $P<0.005$).[11]

Genetics and Family History

- A GWAS in 6942 individuals identified an SNP located in an intron of the Lp(a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating Lp(a) levels, and the development of aortic stenosis.[12]
- Multiple SNPs that encode for LDL-C have been combined to form a GRS that has been associated with prevalent aortic valve calcification (OR, 1.38 [95% CI, 1.09–1.74] per GRS increment) and incident aortic valve stenosis (HR, 2.78 [95% CI, 1.22–6.37] per GRS increment) by use of a mendelian randomization design.[13]
- The heritability of bicuspid aortic valve has been estimated at 89% (0.89±0.06; $P<0.001$), which suggests that most cases are familial.[14] Bicuspid aortic valve has been linked to mutations of *NOTCH1, GATA5*, and more recently *GATA4*.[15–17]
- GWASs and transcriptome studies of aortic valve stenosis have identified several loci, including *LPA*, *PALMD*, and *TEX41*.[12,18,19]
- In a nationwide Swedish study comprising 6 117 263 siblings (13 442 with aortic stenosis), having at least 1 sibling with aortic stenosis was associated with an HR of 3.41 (95% CI, 2.23–5.21) for being diagnosed with aortic stenosis. These findings indicate an overall familial aggregation of this disease beyond bicuspid aortic valve alone.[20]

Awareness, Treatment, and Control

- After the US Food and Drug Administration approved TAVR for patients with severe aortic

stenosis at high surgical risk in 2011, implantation numbers have increased steeply. From 2011 through 2014, the STS/ACC TVT Registry recorded 26 414 TAVR procedures performed at 348 centers in 48 US states.[21] Sixty-eight percent of patients were ≥80 years of age, median STS risk was 6.7%, and 95% of patients were deemed to be at extreme or high risk. The number of patients receiving commercially approved devices from 2012 through 2015 increased to 54 782 in a recent report from the same registry.[22]

- Despite the increase in TAVR procedures, the percentage of black patients undergoing TAVR was 3.8% compared with 93% among Caucasians in the STS/ACC TVT Registry.[21,23]
- The 54 782 patients with TAVR who entered the STS/ACC TVT Registry between 2012 and 2015 demonstrated decreases in expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) from 7% to 6% and in TVT Registry–predicted risk of mortality from 4% to 3% (both $P<0.0001$) from 2012 to 2015. Observed in-hospital mortality decreased from 5.7% to 2.9%, and 1-year mortality decreased from 25.8% to 21.6%. However, 30-day postprocedure pacemaker insertion increased from 8.8% in 2013 to 12.0% in 2015.[22]
- In Germany, >15 000 TAVR procedures were performed in 2016, a number 3 times higher than in 2011 based on data from the German Institute for Quality Assurance and Transparency in Healthcare. Over the same period (2011 to 2016), the number of SAVR procedures remained relatively stable at ≈10 000 per year, a lower number than for TAVR (Chart 21-1). In the same European registry, mortality decreased continuously, with overall in-hospital mortality being similar for TAVR and SAVR (2.6% versus 2.9%, $P=0.19$, respectively) in 2016 despite the higher risk profile in TAVR patients (Chart 21-1).
- On the basis of a retrospective study of 8210 patients using the NIS (2012 to 2014), females with severe aortic stenosis undergoing TAVR experienced similar mortality (4.7% versus 3.9%, $P=0.15$) as males.; however, females had higher rates of stroke (3% versus 2%, $P=0.04$), hemorrhage requiring transfusion (28% versus 20%, $P<0.0001$), and pericardial complications (1.3% versus 0.5%, $P=0.0009$).[24]
- Two randomized controlled trials (PARTNER 1A and US CoreValve High Risk) using balloon-expandable and self-expanding devices, respectively, have shown that TAVR is able to compete with SAVR in terms of mortality in high-risk patients at 1 and 5 years.[25,26]
- In a cohort of 1746 patients with severe aortic stenosis at intermediate surgical risk in the SURTAVI trial, the estimated incidence of the primary end point (death attributable to any cause or debilitating stroke) was 12.6% in the TAVR group (in whom a balloon-expandable device was used) and 14.0% in the SAVR group (95% credible interval [bayesian analysis] for difference, −5.2 to 2.3%; posterior probability of noninferiority, >0.999) at 24 months. In the PARTNER 2 trial using a self-expanding device, the Kaplan-Meier event rates of the same end point were 19.3% in the TAVR group and 21.1% in the SAVR group (HR in the TAVR group, 0.89 [95% CI, 0.73–1.09]; $P=0.25$) at 2-year follow-up. These findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.[27,28]
- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial[29] to either balloon-expandable TAVR or SAVR, the Kaplan-Meier estimate of the rate of the primary composite end point (death, stroke, or rehospitalization) was significantly lower in the TAVR group than in the SAVR group (8.5% versus 15.1%; absolute difference, −6.6 percentage points [95% CI, −10.8 to −2.5]; $P<0.001$ for noninferiority; HR, 0.54 [95% CI, 0.37–0.79]; $P=0.001$ for superiority). Similar results were obtained in the Evolut Low Risk trial[30] using a self-expanding valve in low-risk patients with severe aortic stenosis. Among the 1403 patients randomized to either TAVR or SAVR, the 24-month incidence of composite death or disabling stroke was 5.3% in the TAVR group and 6.7% in the SAVR group (difference, −1.4 percentage points [95% Bayesian credible interval for difference, −4.9 to 2.1]; posterior probability of noninferiority >0.999).

Mortality

- On the basis of *ICD-10* (with data coded from 1999 to 2009), there were 146 304 deaths over 10 years in the aortic valve disease category in the United States. Of these, 82.7% were attributed to aortic stenosis, 4.0% to aortic insufficiency, and 0.6% to aortic stenosis with insufficiency, whereas 11.9% were unspecified or coded as attributed to other aortic valve disease and 0.7% to congenital aortic valve disease (assumed to be predominantly bicuspid aortic valve). The age- and sex-adjusted mortality rate increased over time by 1.56% (95% CI, 1.52%–1.61%; $P<0.001$) per year for nonrheumatic aortic valve disease.[31]
- In the community, morbidity related to bicuspid aortic valve is higher in males than in females, with a total combined risk of aortic regurgitation, surgery, and IE of 52±4% versus 35±6% in females ($P=0.01$).[32] Nevertheless, females have a

significantly higher RR of death in tertiary and surgical referral cohorts, with an age-adjusted relative death risk of 1.63 (95% CI, 1.40–1.89) for females versus 1.34 (95% CI, 1.22–1.47) for males (P=0.026).[32] The risk of death is independently associated with aortic regurgitation (P≤0.04).

Complications

- In a cohort of 416 community-based participants from Olmsted County, MN, with bicuspid aortic valve followed up for a mean (SD) of 16 (7) years, the incidence of aortic dissection in individuals ≥50 years of age at baseline was 17.4 (95% CI, 2.9–53.6) cases per 10 000 patient-years. For patients ≥50 years of age with a bicuspid valve and a baseline aortic aneurysm, the incidence of aortic dissection was 44.9 (95% CI, 7.5–138.5) cases per 10 000 patient-years. In the remaining participants without baseline aortic aneurysm, the incidence of aneurysm was 84.9 (95% CI, 63.3–110.9) cases per 10 000 patient-years, for an age-adjusted RR of 86.2 (95% CI, 65.1–114) compared with the general population.[33]

Cost

- Initial length of stay was an average of 4.4 days shorter for patients at high surgical risk who were treated with TAVR than for those who underwent SAVR. TAVR also reduced the need for rehabilitation services at discharge and was associated with improved 1-month quality of life. TAVR had higher index admission and projected lifetime costs than SAVR (differences of $11 260 and $17 849 per patient, respectively). However, TAVR was estimated to provide a lifetime gain of 0.32 QALYs (0.41) with 3% discounting. Lifetime incremental CERs were $55 090 per QALY gained and $43 114 per life-year gained. On the basis of sensitivity analyses, a reduction in the initial cost of TAVR by ≈$1650 was expected to lead to an incremental CER of <$50 000 per QALY gained.[34]
- In a European study of patients at intermediate surgical risk with severe aortic stenosis, TAVR was associated with an increase of 0.42 years and 0.41 QALYs and lifetime cost savings of €439 compared with SAVR.[35]

Mitral Valve Disorders
ICD-9 424.0; *ICD-10* I34.

2017: Mortality—2719. Any-mention mortality—6274.
2016: Hospital discharges—26 000.

Prevalence

- A systematic review by de Marchena et al[36] found that in the US population, the prevalence of MR according to the Carpentier functional classification system was as follows:
  - Type I (congenital MR [<10 per million] and endocarditis [3–7 per million]): <20 per 1 million
  - Type II (MR associated with mitral valve prolapse): 15 170.5 per 1 million
  - Type IIIa (rheumatic HD, systemic lupus erythematosus, antiphospholipid syndrome, and rare diseases): 10 520 per 1 million
  - Type IIIb (ischemic MR, LV dysfunction, DCM): 16 250 per 1 million
  - Unclassified: 9530 per 1 million

Primary MR includes Carpentier types I, II, and IIIa, with the most common cause being mitral valve prolapse (type II MR). Secondary MR is associated with ischemic cardiomyopathy, LV dysfunction, or DCM (type IIIb MR).

Subclinical Disease

- Milder, nondiagnostic forms of mitral valve prolapse, first described in the familial context, are also present in the community and are associated with higher likelihood of mitral valve prolapse in offspring (OR, 2.52 [95% CI, 1.25–5.10]; P=0.01). Up to 80% of nondiagnostic morphologies can progress to diagnostic mitral valve prolapse.[37–39]

Genetics and Family History

- Among 3679 generation 3 participants in the FHS (53% female; mean age 40±9 years) with available parental data, 49 (1%) had mitral valve prolapse. Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10/186 [5.4%]) compared with no parental mitral valve prolapse (39/3493 [1.1%]; adjusted OR, 4.51 [95% CI, 2.13–9.54]; P<0.0001).[40] A number of genetic variants have been identified for the rare X-linked valvular dystrophy and the most common form of autosomal dominant mitral valve prolapse through pedigree investigations and GWASs. Genes implicated in mitral valve prolapse include *FLNA*, *DCHS1*, *DZIP1*, *TNS1*, and *LMCD1*.[41–44]
- Familial clustering exists across different MR subtypes, including both primary (ie, related to mitral valve prolapse) and nonprimary MR. In a recent study, heritability of MR in the FHS was estimated at 15% (95% CI, 7%–23%), 12% (95% CI, 4%–20%) excluding mitral valve prolapse, and 44% (95% CI, 15%–73%) for moderate or greater MR only (all P<0.05).[45] In Sweden, sibling MR was associated with an HR of 3.57 (95% CI, 2.21–5.76; P<0.001) for development of MR.

Awareness, Treatment, and Control (See Charts 21-2 and 21-3)

- The treatment of mitral valve prolapse remains largely surgical and based on valve repair. Nevertheless, percutaneous mitral valve repair techniques are becoming a common treatment

option for high-risk patients not deemed candidates for surgical repair. Data from the STS/ACC TVT Registry on patients commercially treated with the MitraClip percutaneous mitral valve repair device showed the following: of 564 patients (56% male, median age 83 years), 473 (86%) were severely symptomatic. The median STS Predicted Risk of Mortality scores for mitral valve repair and replacement were 7.9% (IQR, 4.7%–12.2%) and 10% (IQR, 6.3%–14.5%), respectively.[46] Most of the patients undergoing transcatheter mitral valve repair (90.8%) had degenerative disease, and the procedure was successful in reducing MR to moderate levels in 93% of cases. In the EVEREST II trial, which included mostly primary MR (73%) and compared MitraClip with surgical mitral valve repair, the respective rates of the components of the primary end point at 12 months were as follows: death, 6% in each group; surgery for mitral valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%.[47]

- Worldwide, the number of MitraClip procedures has increased progressively since 2008, especially in Western Europe. In the United States, the commercial use of the MitraClip started in 2014, with a steadily growing number of procedures performed (Chart 21-2).
- The role of MitraClip in secondary MR has been investigated in 2 recently published randomized clinical trials with divergent results (Chart 21-3).[48-50] MITRA-FR included 304 patients with HF, severe secondary MR, and LVEF 15% to 40% on optimal medical therapy and cardiac resynchronization therapy as indicated. There was no difference in the combined end point of death or rehospitalization for HF at 12 months (83 of 152 patients or 54.6% versus 78 of 152 or 51.3% for interventional and conservative management, respectively). The COAPT trial included 614 patients with HF and moderate-severe or severe secondary MR who were symptomatic (NYHA functional class II–IV) despite optimal medical therapy and cardiac resynchronization therapy. There was a significant reduction of the primary end point of rehospitalization because of HF at 2 years (35.8% versus 67.9%; HR, 0.53 [95% CI, 0.40–0.70]; *P*<0.001). There was also a significant reduction of all-cause mortality at 2 years (29% versus 46.1%; HR, 0.62 [95% CI, 0.46–0.82]; *P*<0.001). The divergent results of the 2 trials may be related to differences in sample characteristics, sample size, duration of follow-up and primary end point. Further studies are needed to solve this controversy.
- In patients with severe chronic MR secondary to ischemic cardiomyopathy undergoing CABG surgery, survival rates were not significantly different after bypass alone compared with bypass combined with mitral valve repair (1-, 5-, and 10-year survival of 88%, 75%, and 47% versus 92%, 74%, and 39%, respectively; *P*=0.6).[51] In patients with moderate secondary MR, the rate of death was 6.7% in the combined-surgery group and 7.3% in the CABG-alone group (HR with mitral valve repair, 0.90 [95% CI, 0.38–2.12]; *P*=0.81).[52]
- Despite the poor prognosis associated with severe MR, only a small minority of affected patients meeting criteria for surgical intervention undergo mitral surgery (29% for mitral valve prolapse–related MR and 5% for secondary MR), even in the Olmsted County community with advanced and readily accessible means of diagnosis and treatment.[53]

Mortality

- Secondary MR (or Carpentier type IIIb) is associated with 47% mortality over 5 years in patients with HF and is a predictor of long-term mortality (HR, 1.61 [95% CI, 1.22–2.12], *P*=0.001 after adjustment for clinical variables, and HR, 1.38 [95% CI, 1.03–1.84], *P*=0.03 after adjustment for echocardiographic parameters).[54]

Complications

- In the Olmsted County, MN, population, characterized by a mixed spectrum of community-dwelling and referred patients, females were diagnosed with mitral valve prolapse more often than males and at a younger age[55]; however, females had fewer complications (flail leaflet occurred in 2% versus 8% in males and severe regurgitation in 10% versus 23%; all *P*<0.001). At 15 years of follow-up, females with no or mild MR had better survival than males (87% versus 77%; adjusted RR, 0.82 [95% CI, 0.76–0.89]). In contrast, in individuals with severe MR, females had worse survival than males (60% versus 68%; adjusted RR, 1.13 [95% CI, 1.01–1.26]). Survival 10 years after surgery was similar in females and males (77% versus 79%; *P*=0.14).[56]

Cost

- Lifetime costs, life-years, QALYs, and incremental cost per life-year and QALY gained were estimated for patients receiving MitraClip therapy compared with standard of care.[57] The EVEREST II HRS provided data on treatment-specific overall survival, risk of clinical events, quality of life, and resource utilization. The published literature was reviewed to obtain health utility and unit costs (Canadian 2013 dollars). The incremental cost per QALY gained was $23 433. On the basis of sensitivity analysis, MitraClip therapy had a 92% chance of being cost-effective compared with standard of care at a $50 000 per QALY willingness-to-pay threshold.

Pulmonary Valve Disorders
ICD-9 424.3; *ICD-10* I37.

2017: Mortality—19. Any-mention mortality—49.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.[58] Among 44 neonates with critical pulmonic stenosis who underwent balloon pulmonary valvuloplasty from 1990 to 2017, 15 (34.1%) needed reintervention. At a median follow-up of 8.2 years (IQR, 3.4–13.1 years), moderate or severe pulmonary regurgitation was seen in 22 children (half of the sample), 3 of whom required pulmonary valve repair/replacement.[59]
- The most common cause of severe pulmonic regurgitation is iatrogenic, caused by surgical valvotomy/valvectomy or balloon pulmonary valvuloplasty performed for RV outflow tract obstruction as part of TOF repair.[60] Percutaneous pulmonic valve implantation of either a Melody or a SAPIEN valve is an effective and relatively safe option in patients with prosthetic pulmonic valve regurgitation, including those with a pulmonary artery conduit with regurgitant prosthetic valve.[60–62] In a study using the NIS database and including 57 percutaneous pulmonic valve implantation procedures performed in 2012, vascular complications occurred in 8 (14%), but serious complications occurred only in 3 patients (1 died, and 2 required surgical intervention).[63] Surgical pulmonary valve replacement is preferred for native pulmonic valve regurgitation (caused by endocarditis, carcinoid, etc) and is associated with <1% periprocedural mortality and excellent long-term outcome, with >60% freedom from reoperation at 10 years.[64]
- In a large multicenter cohort of 977 patients with repaired TOF, those treated with a pulmonary valve replacement had a similar risk of (aborted) death and sustained VT (41 subjects; HR, 0.65 [95% CI, 0.31–1.36]; *P*=0.25) and combined HF, nonsustained VT, and sustained SVT (88 subjects; HR, 1.43 [95% CI, 0.83–2.46]; *P*=0.19) compared with those without surgical treatment at an average follow-up of 5.3 years.[65]

Tricuspid Valve Disorders
ICD-9 424.2; *ICD-10* I36.

2017: Mortality—71. Any-mention mortality—239.

- The frequency of tricuspid regurgitation and valvular pathology was evaluated in a study of 5223 adults (predominantly males, with a mean age of 67 years) who underwent echocardiography at 3 Veterans Affairs medical centers.[66] Moderate to severe tricuspid regurgitation was present in 819 (16%), but only 8% had primary tricuspid valve pathology. In the same study, moderate or greater tricuspid regurgitation was associated with increased mortality regardless of pulmonary artery systolic pressure (HR, 1.31 [95% CI, 1.16–1.49] for pulmonary artery systolic pressure >40 mm Hg; HR, 1.32 [95% CI, 1.05–1.62] for pulmonary artery systolic pressure ≤40 mm Hg) and LVEF (HR, 1.49 [95% CI, 1.34–1.66] for EF <50%; HR, 1.54 [95% CI, 1.37–1.71] for EF ≥50%).[66]
- Patients with rapid development of significant tricuspid regurgitation have worse survival than patients in whom severe tricuspid regurgitation develops more slowly (log rank *P*=0.001). Fast development of severe tricuspid regurgitation is the most powerful predictor of all-cause mortality (HR per preceding year of development, 0.92 [95% CI, 0.90–0.94]; *P*<0.001).[67]
- An analysis of the NIS demonstrated an increase in the number of isolated tricuspid valve surgeries performed over a 10-year period, from 290 in 2004 to 780 in 2013. In-hospital mortality was consistent over this time period at 8.8%.[68]
- In a cohort of 64 consecutive patients (mean age 76.6±10 years) at excessive surgical risk who underwent compassionate MitraClip treatment of chronic, severe tricuspid regurgitation, tricuspid regurgitation was reduced by at least 1 grade in 91% of the patients at a mean of 14±18 days. There were no intraprocedural deaths, cardiac tamponade, emergency surgeries, strokes, MIs, or major vascular complications. There was a significant improvement of NYHA class (*P*<0.001) and 6-minute walking distance (177.4±103.0 m versus 193.5±115.9 m; *P*=0.007).[69]

Rheumatic Fever/Rheumatic HD (See Table 21-1 and Charts 21-4 through 21-6)
ICD-9 390 to 398; *ICD-10* I00 to I09.

2017: Mortality—3320. Any-mention mortality—6668.
2016: Hospital discharges—26 000.

Prevalence

- Rheumatic HD is uncommon in high-income countries such as the United States but remains endemic in some low- and middle-income countries.[70]

Subclinical Disease

- The prevalence of subclinical or latent rheumatic HD among children is estimated by echocardiography and can be classified as definite or borderline.[71] The prevalence of combined definite and borderline disease ranges between 10 and 45 per 1000 in recent studies from endemic countries (eg,

Nepal, Brazil, and Uganda) compared with <8 per 1000 in low-risk populations.[72–75]

- The natural history of latent rheumatic HD detected by echocardiography is not clear. Emerging data suggest that up to 20% to 30% of children with definite rheumatic HD may have progression of disease, but 30% to 50% of those with borderline rheumatic HD may return to normal over 2 to 8 years of follow-up.[76–79]
- Few echocardiographic screening studies for rheumatic HD have been conducted in adults, for whom the criteria are not well validated. In a study from Uganda, the prevalence of rheumatic HD in adults >20 years of age was 2.34% (95% CI, 1.49%–3.49%).[80]
- Latent rheumatic HD appears to be half as common among HIV-infected youth compared with the general Uganda population (1.5% [95% CI, 0.88%–2.54%] versus 3% [95% CI, 2.7%–3.24%]), possibly related to improved access to preventive care or nearly universal trimethoprim-sulfamethoxazole prophylaxis among HIV-infected youth.[81]

Awareness, Treatment, and Control

- The REMEDY study highlighted consistently poor access to recommended therapies among people living with rheumatic HD: only 55% were taking penicillin prophylaxis, and only 3.6% of females of childbearing age were using contraception. Although 70% of those with indications (mechanical valve, AF, or severe mitral stenosis) were appropriately prescribed anticoagulant drugs, only a quarter of these had therapeutic international normalized ratios.[82]
- In Uganda, retention in care over time is poor (56.9% [95% CI, 54.1%–59.7%] seen in clinic in the past 12 months), but among those retained in care, optimal adherence to benzathine penicillin G is high (91.4% [95% CI, 88.7%–93.5%]).[83]

Mortality

- In the United States in 2017, mortality attributable to rheumatic fever/rheumatic HD was 3320 for all ages (2217 females and 1103 males; Table 21-1).
- Mortality attributable to rheumatic HD varies widely across the United States, with the highest rates clustered in Alaska, Mississippi, Alabama, Kentucky, and Utah, where age-standardized mortality rates were estimated to be 5 to 10 per 100 000 population in 2014.[84]
- In 1950, ≈15 000 Americans (adjusted for changes in *ICD* codes) died of rheumatic fever/rheumatic HD compared with ≈3300 annually in the present era (Table 21-1). Recent declines in mortality have been slowest in the South compared with other regions.[84]

Complications

- People living with rheumatic HD experience high rates of morbid complications. In the international REMEDY cohort study, 33% had HF, 22% had AF, 7% had prior stroke, and 4% had prior endocarditis at baseline.[82] After 2 years of follow-up, the incidence of new events was 38 per 1000 patient-years for HF, 8.5 per 1000 patient-years for stroke or TIA, and 3.7 per 1000 patient-years for endocarditis.[85]
- Prognosis after development of complications is also worse for people living with rheumatic HD. In Thailand, patients with rheumatic mitral valve disease who had ischemic stroke had a higher risk of cardiac arrest (OR, 2.1), shock (OR, 2.1), arrhythmias (OR, 1.7), respiratory failure (OR, 2.1), pneumonia (OR, 2.0), and sepsis (OR, 1.4) after controlling for age, sex, and other comorbid chronic diseases.[86]
- The PAR of rheumatic HD for maternal mortality may approach 10% in sub-Saharan Africa.[87]

Global Burden of Rheumatic HD (See Charts 21-4 through 21-6)

- In 2015, 33.4 million people were estimated to be living with rheumatic HD around the world, with sub-Saharan Africa and Oceania having the highest concentration of DALYs attributable to rheumatic HD.[70]
- Globally, age-standardized mortality from rheumatic HD was estimated to have declined 47.8% from 1990 to 2015; however, the prevalence of HF attributable to rheumatic HD increased by 88% in the same time period.[70]
- The REMEDY study is a prospective registry of 3343 patients with rheumatic HD from 25 hospitals in 12 African countries, India, and Yemen. The age and sex distribution of the subjects are shown in Chart 21-4. Rheumatic HD was twice as common among females, a finding consistent with prior studies across a variety of populations.[82]
- Mortality attributable to rheumatic HD remains exceptionally high in endemic settings. In a study from Fiji of 2619 people followed up during 2008 to 2012, the age-standardized death rate was 9.9 (95% CI, 9.8–10.0) per 100 000, or more than twice the GBD estimates.[88] Prognosis is exceptionally poor in sub-Saharan Africa, as highlighted by a follow-up study of REMEDY, which had a mortality rate of 116 per 1000 patient-years in the first year and 65 per 1000 patient-years in the second year.[85]
- The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.[89]

— Age-standardized mortality attributable to rheumatic HD is highest in South Asia, sub-Saharan Africa, and Oceania (Chart 21-5).
— Rheumatic HD prevalence is generally highest in sub-Saharan Africa and Oceania (Chart 21-6).

Infective Endocarditis (See Table 21-2) *ICD-9* 421.0; *ICD-10* I33.0.

2017: Mortality—1464. Any-mention mortality—3303.
2016: Hospital discharges—12 000.

Prevalence and Incidence

- In 2011, there were 47 134 cases of IE and valve replacement in the United States (Table 21-2).
- Data from the NIS (2000–2011)[90] suggested no change in temporal trends in the incidence of IE before and after publication of the 2007 AHA guideline for antibiotic prophylaxis before dental procedures.[91] These findings from referral centers were corroborated by a community-based review of adults in Olmsted County, MN.[92] In the Olmsted County study, age- and sex-adjusted incidence of IE was 7.4 (95% CI, 5.3–9.4) cases per 100 000 person-years. In addition, these guideline changes do not appear to have altered rates of pediatric endocarditis. Using 2003 to 2010 data from 37 centers in the Pediatric Health Information Systems Database, Pasquali and colleagues[93] did not demonstrate a significant difference in the number of IE hospitalizations after the guidelines were implemented in 2007 (1.6% difference after versus before guideline implementation [95% CI, –6.4% to 10.3%]; *P*=0.7).
- A systematic review that included 160 studies and 27 083 patients from 1960 to 2011 demonstrated that in hospital-based studies (142 studies; 23 606 patients), staphylococcal endocarditis has increased over time (coagulase-negative *Staphylococcus* 2% to 10%, *P*<0.001), with recent increases in *S aureus* IE (21% to 30%; *P*<0.05) and enterococcal IE (6.8% to 10.5%; *P*<0.001) over the past decade and a corresponding decrease in streptococcal endocarditis (32% to 17%) over the same time period.[94]

Risk Factors

- The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 to 1998) among Olmsted County, MN, residents was 1.1±0.4% (incidence, 86.6 cases per 100 000 person-years [95% CI, 43.3–173.2 cases per 100 000 person-years]); there was a higher age- and sex-adjusted risk of IE in patients with mitral valve prolapse (RR, 8.1 [95% CI, 3.6–18.0]) compared with the general population of Olmsted County (*P*<0.001). No IE cases were identified among patients without previously diagnosed MR. Conversely, there was a higher incidence of IE in patients with mitral valve prolapse and moderate, moderate-severe, or severe MR (289.5 cases per 100 000 person-years [95% CI, 108.7–771.2 cases per 100 000 person-years]; *P*=0.02 compared with trivial, mild, or mild-moderate MR) and in patients with a flail mitral leaflet (715.5 cases per 100 000 person-years [95% CI, 178.9–2861.0 cases per 100 000 person-years]; *P*=0.02 compared with no flail mitral leaflet).[95]
- Admissions for endocarditis related to injection drug use have risen in recent years in parallel with the opioid drug crisis. The prevalence of documented intravenous drug use among patients admitted for endocarditis in the NIS rose from 4.3% in 2008 to 10% in 2014. This trend was accentuated among the young (<30 years of age) and among whites (compared with blacks and other races).[96]
- Cardiac device IE appears to be present in 6.4% (95% CI, 5.5%–7.4%) of patients with definite IE, according to data from ICE-PCS (2000–2006). Nearly half (45.8% [95% CI, 38.3%–53.4%]) of such cases were related to healthcare-associated infection. In-hospital and 1-year mortality rates for these patients were 14.7% (26 of 177 [95% CI, 9.8%–20.8%]) and 23.2% (41 of 177 [95% CI, 17.2%–30.1%]), respectively. Although not based on randomized data, compared with individuals without initial hospitalization device removal, there appeared to be a 1-year survival benefit in individuals undergoing device explantation during the index hospitalization (HR, 0.42 [95% CI, 0.22–0.82]).[97]
- Prosthetic valve IE continues to be associated with high in-hospital and 1-year mortality, although early surgery is associated with improved outcomes compared with medical therapy alone (1-year mortality 22% versus 27%; HR, 0.68 [95% CI, 0.53–0.87]), even in propensity-adjusted analyses (HR, 0.57 [95% CI, 0.49–0.67]).[98]
- Antibiotic prophylaxis is currently not recommended for bicuspid aortic valve and mitral valve prolapse.[91] However, in a Spanish registry of 3208 consecutive patients with IE, subjects with these conditions had a higher incidence of viridans group streptococci IE than did a high-risk group with an antibiotic prophylaxis indication and patients in a low- to moderate-risk group without an antibiotic prophylaxis indication (35.2% and 39.3% versus 12.1% and 15.0%, respectively; all *P*<0.01). Subjects with bicuspid aortic valve and mitral valve prolapse had more intracardiac complications than

did those at low or moderate risk (50% and 47.2% versus 30.6%; both $P<0.01$) and were similar to patients in the high-risk group.[99]

Awareness, Treatment, and Control

- Surgery was performed in 47% of cases of definite left-sided, non–cardiac device–related IE in the ICE-PLUS registry of 1296 patients from 16 countries.[100]
- In a randomized, noninferiority multicenter trial of 400 stable cases with left-sided native IE, the combined outcome of all-cause mortality, unplanned surgery, embolic events, or relapse of bacteremia was similar in those treated with continuous intravenous antibiotic drugs compared with those switched from intravenous to oral antibiotic drugs after 10 days (24 cases or 12.1% versus 18 cases or 9%; between-group difference, 3.1 percentage points [95% CI, −3.4 to 9.6]; $P=0.40$).[101]

Mortality

- According to the 2015 GBD study, the age-standardized death rate attributable to IE in 2015 was 1.3 per 100 000.[102]
- Data collected between 2004 and 2010 from the Pediatric Health Information System database from 37 centers that included 1033 cases of IE demonstrated a mortality rate of 6.7% (n=45) and 3.5% (n=13) among children (0–19 years of age) with and without congenital HD, respectively.[103]

Complications

- Among 162 cases of left-sided native-valve *S aureus* IE retrospectively identified in 1254 patients hospitalized between 1990 and 2010 for IE, *Staphylococcus* represented 18% of all IE cases and 23% of native-valve IE cases. HF occurred in 45% of IE cases, acute renal failure in 23%, sepsis in 29%, neurological events in 36%, systemic embolic events in 55%, and in-hospital mortality in 25%. The risk of in-hospital mortality was higher in patients with HF (OR, 2.5; $P=0.04$) and sepsis (OR, 5.3; $P=0.001$). Long-term 5-year survival was 49.6±4.9%. There was higher long-term risk of death among individuals with HF (OR, 1.7; $P=0.03$), sepsis (OR, 3.0; $P=0.0001$), and delayed surgery (OR, 0.43; $P=0.003$). When the authors compared 2 study periods, 1990 to 2000 and 2001 to 2010, there was a significant increase in bivalvular involvement, valvular insufficiency, and acute renal failure from 2001 to 2010. In-hospital mortality rates and long-term 5-year survival were not significantly different between the 2 study periods (28.1% versus 23.5%; $P=0.58$).[104]

Heart Valve Procedure Costs

- In 2013, for heart valve procedures[105]:
  - The mean inflation-adjusted cost per hospitalization in 2013 dollars was $51 415, compared with $53 711 in 2005 and $43 829 in 2000.
  - The number of discharges for which heart valve surgery was the principal operating room procedure was 102 425, which was an increase from 93 802 in 2005 and 79 719 in 2000.
- Total inflation-adjusted national cost in 2013 dollars (in millions) was $5264, which was an increase from the mean cost (in millions) of $5058 in 2005 and $3488 in 2000.[105]

Table 21-1. Rheumatic Fever/Rheumatic HD in the United States

Population Group	Mortality, 2017: All Ages*	Hospital Discharges, 2016: All Ages
Both sexes	3320	26 000
Males	1103 (33.2%)†	11 000
Females	2217 (66.8%)†	15 000
NH white males	887	…
NH white females	1791	…
NH black males	95	…
NH black females	176	…
Hispanic males	72	…
Hispanic females	155	…
NH Asian or Pacific Islander males	38‡	…
NH Asian or Pacific Islander females	75‡	…
NH American Indian or Alaska Native	25	…

Ellipses (…) indicate data not available; HD, heart disease; and NH, non-Hispanic.

*Mortality for American Indian or Alaska Native and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Mortality: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017[1]; data represent underlying cause of death only. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016[3]; data include those inpatients discharged alive, dead, or of unknown status.

Table 21-2. Incidence of IE and Valve Replacement, United States, 2000 to 2011

Year	Total IE Cases	IE Incidence per 100 000	Valve Replacement per 1000 IE Cases
2000	29 820	11	14
2001	31 526	11	16
2002	32 229	11	19
2003	35 190	12	18
2004	36 660	13	19
2005	37 508	13	23
2006	40 573	14	23
2007	38 207	12	30
2008	41 143	14	19
2009	43 502	14	27
2010	43 560	14	27
2011	47 134	15	26

IE indicates infective endocarditis.

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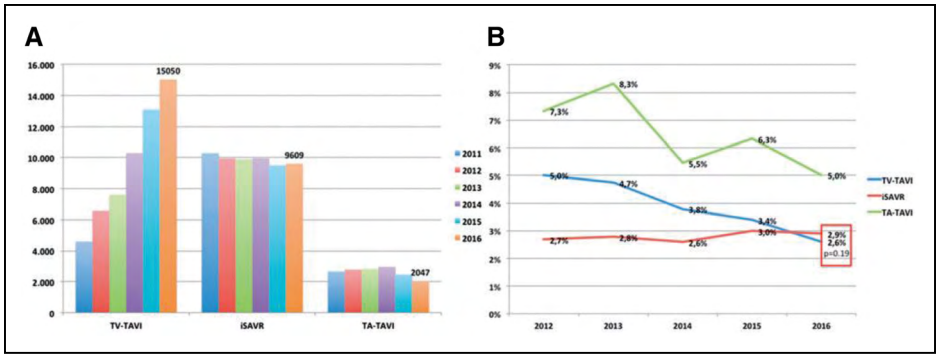

Chart 21-1. Number of TAVI and surgical aortic valve replacement (SAVR) procedures performed and in-hospital mortality according to type of procedure, Germany, 2011 to 2016.

A, Number of TAVI and SAVR procedures. **B**, In-hospital mortality.

iSAVR indicates isolated SAVR; TA, transapical; TAVI, transcatheter aortic valve implantation; and TV, transvascular.

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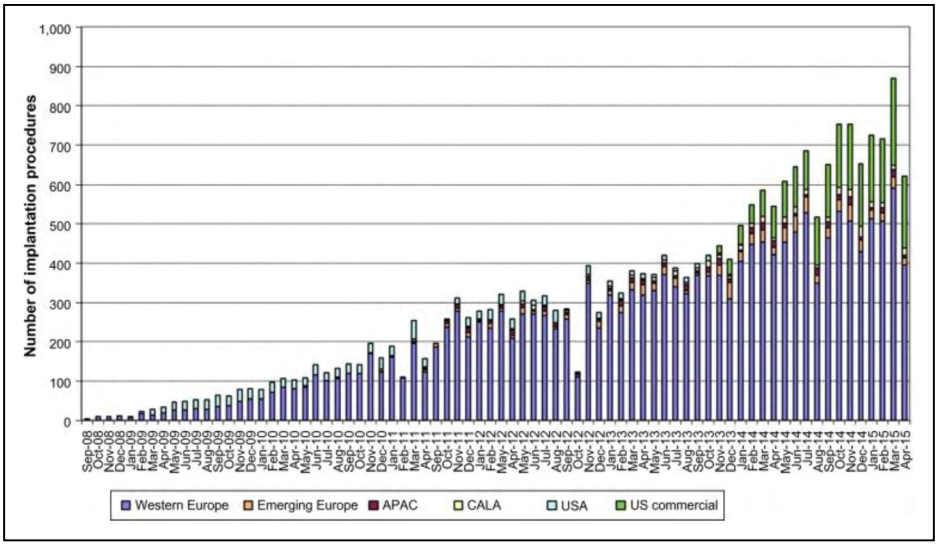

Chart 21-2. Worldwide experience with the MitraClip procedure from September 2008 until April 2015.
APAC indicates Asia-Pacific; and CALA, Caribbean and Latin America.
Source: Figure courtesy of Abbott Laboratories.

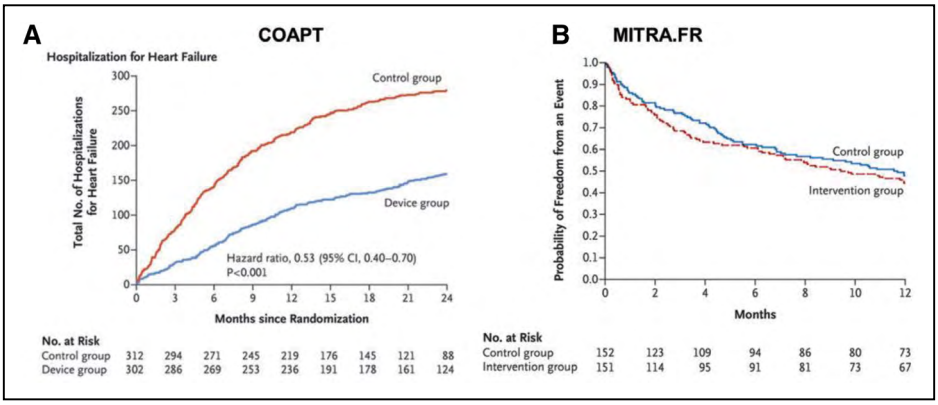

Chart 21-3. Comparison of primary outcomes after MitraClip implantation for secondary mitral regurgitation in COAPT and MITRA-FR trials.
A, COAPT trial; (**B**) MITRA-FR trial.
COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; and MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation.
Source: **A**, Reprinted from Stone et al[49] with permission from the Massachusetts Medical Society. Copyright © 2018, Massachusetts Medical Society. **B**, Reprinted from Obadia et al[50] with permission from the Massachusetts Medical Society. Copyright © 2018, Massachusetts Medical Society.

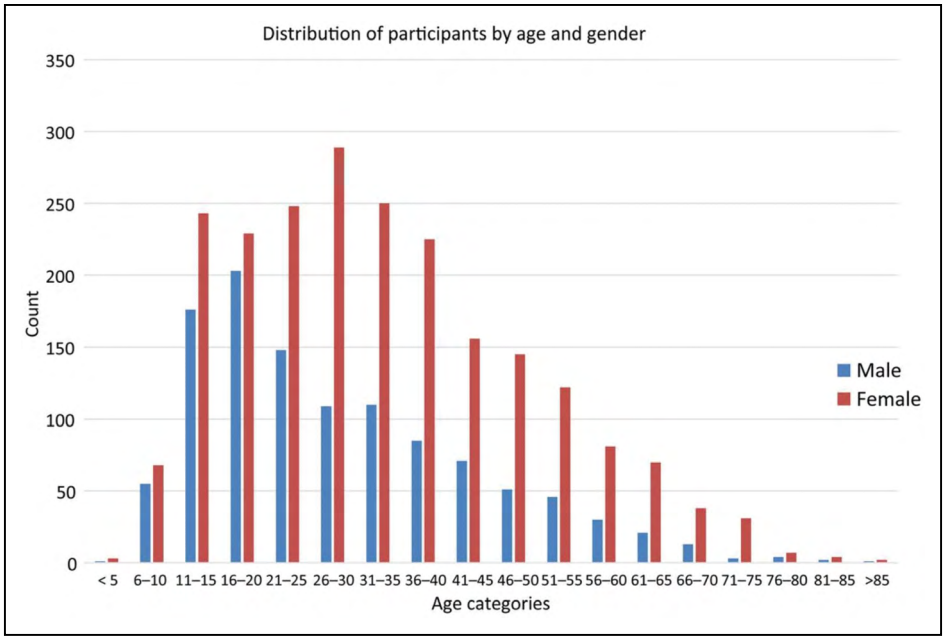

Chart 21-4. Age and sex distribution of 3343 subjects with rheumatic heart disease participating in the REMEDY (Global Rheumatic Heart Disease Registry) study, 2010 to 2012.
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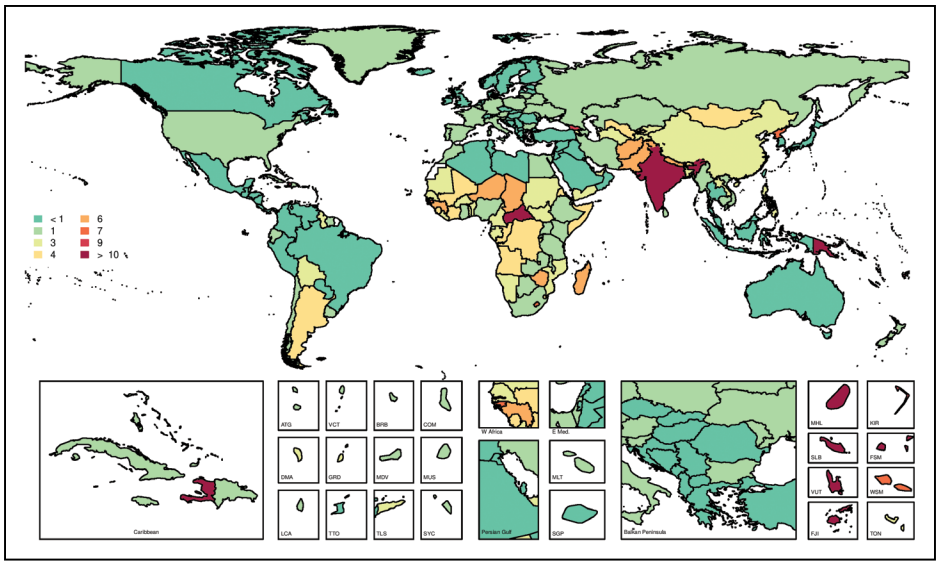

Chart 21-5. Age-standardized global mortality rates of rheumatic heart disease (HD) per 100 000, both sexes, 2017.
Age-standardized mortality attributable to rheumatic HD is highest in South Asia, sub-Saharan Africa, and Oceania.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[89] Printed with permission. Copyright © 2018, University of Washington.

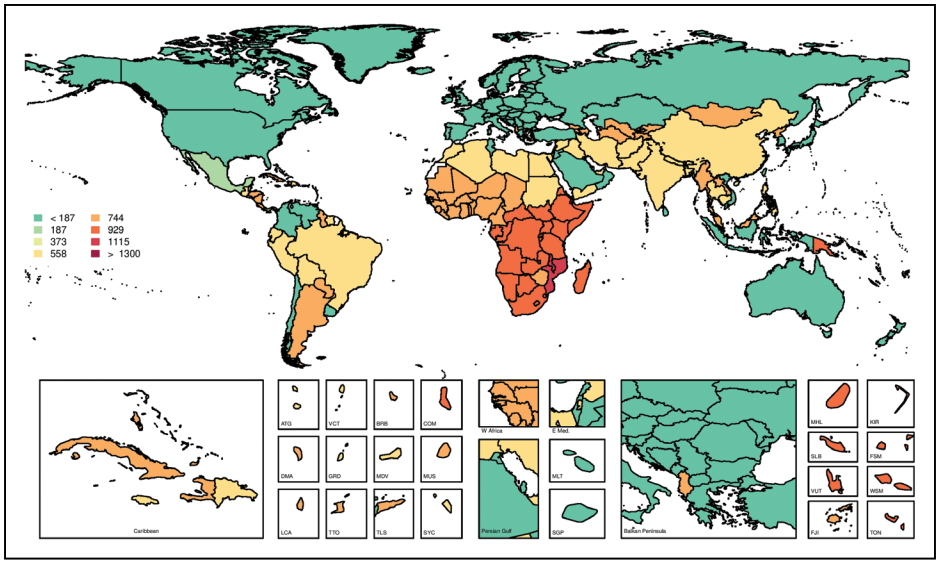

Chart 21-6. Age-standardized global prevalence rates of rheumatic heart disease (HD) per 100 000, both sexes, 2016.
Rheumatic HD prevalence is generally highest in sub-Saharan Africa and Oceania.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[89] Printed with permission.

REFERENCES

1. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death microdata files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
2. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019
3. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
4. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, Frangou E, Farmer AJ, Mant D, Wilson J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J.* 2016;37:3515–3522. doi: 10.1093/eurheartj/ehw229
5. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B, Sundquist K, Smith JG. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart.* 2017;103:1696–1703. doi: 10.1136/heartjnl-2016-310894
6. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: the AGES-Reykjavík study. *Int J Cardiol.* 2014;176:916–922. doi: 10.1016/j.ijcard.2014.08.053
7. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicego D, Thiene G, De Dominicis E. An echocardiographic survey of primary school children for bicuspid aortic valve. *Am J Cardiol.* 2004;93:661–663. doi: 10.1016/j.amjcard.2003.11.031
8. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. *Circulation.* 2015;131:988–994. doi: 10.1161/CIRCULATIONAHA.114.012906
9. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis: the Tromsø study. *Heart.* 2013;99:396–400. doi: 10.1136/heartjnl-2012-302265
10. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, Tu JV, Wijeysundera HC, Ko DT. Association between cardiovascular risk factors and aortic stenosis: the CANHEART Aortic Stenosis Study. *J Am Coll Cardiol.* 2017;69:1523–1532. doi: 10.1016/j.jacc.2017.01.025
11. Rodrigues I, Agapito AF, de Sousa L, Oliveira JA, Branco LM, Galrinho A, Abreu J, Timóteo AT, Rosa SA, Ferreira RC. Bicuspid aortic valve outcomes. *Cardiol Young.* 2017;27:518–529. doi: 10.1017/S1047951116002560
12. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechlivanis S, Budoff MJ, Harris TB, et al; CHARGE Extracoronary Calcium Working Group. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med.* 2013;368:503–512. doi: 10.1056/NEJMoa1109034
13. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, Rukh G, Dufresne L, Almgren P, Owens DS, et al; Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) Extracoronary Calcium Working Group. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA.* 2014;312:1764–1771. doi: 10.1001/jama.2014.13959
14. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *J Am Coll Cardiol.* 2004;44:138–143. doi: 10.1016/j.jacc.2004.03.050
15. Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, Grossfeld PD, Srivastava D. Mutations in NOTCH1 cause aortic valve disease. *Nature.* 2005;437:270–274. doi: 10.1038/nature03940
16. Padang R, Bagnall RD, Richmond DR, Bannon PG, Semsarian C. Rare non-synonymous variations in the transcriptional activation domains of GATA5 in bicuspid aortic valve disease. *J Mol Cell Cardiol.* 2012;53:277–281. doi: 10.1016/j.yjmcc.2012.05.009
17. Yang B, Zhou W, Jiao J, Nielsen JB, Mathis MR, Heydarpour M, Lettre G, Folkersen L, Prakash S, Schurmann C, et al. Protein-altering and regulatory genetic variants near GATA4 implicated in bicuspid aortic valve. *Nat Commun.* 2017;8:15481. doi: 10.1038/ncomms15481
18. Helgadottir A, Thorleifsson G, Gretarsdottir S, Stefansson OA, Tragante V, Thorolfsdottir RB, Jonsdottir I, Bjornsson T, Steinthorsdottir V, Verweij N, et al. Genome-wide analysis yields new loci associating with aortic valve stenosis. *Nat Commun.* 2018;9:987. doi: 10.1038/s41467-018-03252-6
19. Thériault S, Gaudreault N, Lamontagne M, Rosa M, Boulanger MC, Messika-Zeitoun D, Clavel MA, Capoulade R, Dagenais F, Pibarot P, et al. A transcriptome-wide association study identifies PALMD as a susceptibility gene for calcific aortic valve stenosis. *Nat Commun.* 2018;9:988. doi: 10.1038/s41467-018-03260-6
20. Martinsson A, Li X, Zoller B, Andell P, Andersson C, Sundquist K, Smith JG. Familial aggregation of aortic valvular stenosis: a nationwide

study of sibling risk. *Circ Cardiovasc Genet*. 2017;10:e001742. doi: 10.1161/CIRCGENETICS.117.001742
21. Holmes DR Jr, Nishimura RA, Grover FL, Brindis RG, Carroll JD, Edwards FH, Peterson ED, Rumsfeld JS, Shahian DM, Thourani VH, et al. Annual outcomes with transcatheter valve therapy: from the STS/ACC TVT Registry. *J Am Coll Cardiol*. 2015;66:2813–2823. doi: 10.1016/j.jacc.2015.10.021
22. Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, Brindis RG, Shahian DM, Ruiz CE, Jacobs JP, et al. 2016 annual report of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *J Am Coll Cardiol*. 2017;69:1215–1230. doi: 10.1016/j.jacc.2016.11.033
23. Bob-Manuel T, Sharma A, Nanda A, Ardeshna D, Skelton WP, Khouzam RN. A review of racial disparities in transcatheter aortic valve replacement (TAVR): accessibility, referrals and implantation. *Ann Transl Med*. 2018;6:10. doi: 10.21037/atm.2017.10.17
24. Doshi R, Shlofmitz E, Meraj P. Comparison of outcomes and complications of transcatheter aortic valve implantation in women versus men (from the National Inpatient Sample). *Am J Cardiol*. 2018;121:73–77. doi: 10.1016/j.amjcard.2017.09.015
25. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, et al; PARTNER 1 Trial Investigators. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/S0140-6736(15)60308-7
26. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, et al; U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798. doi: 10.1056/NEJMoa1400590
27. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331. doi: 10.1056/NEJMoa1700456
28. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514616
29. Mack MJ, Leon MB. Transcatheter aortic-valve replacement in low-risk patients: reply. *N Engl J Med*. 2019;381:684–685. doi: 10.1056/NEJMc1908500
30. Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement in low-risk patients: reply. *N Engl J Med*. 2019;381:685. doi: 10.1056/NEJMc1908500
31. Coffey S, Cox B, Williams MJ. Lack of progress in valvular heart disease in the pre-transcatheter aortic valve replacement era: increasing deaths and minimal change in mortality rate over the past three decades. *Am Heart J*. 2014;167:562–567.e2. doi: 10.1016/j.ahj.2013.12.030
32. Michelena HI, Suri RM, Katan O, Eleid MF, Clavel MA, Maurer MJ, Pellikka PA, Mahoney D, Enriquez-Sarano M. Sex differences and survival in adults with bicuspid aortic valves: verification in 3 contemporary echocardiographic cohorts. *J Am Heart Assoc*. 2016;5:e004211. doi: 10.1161/JAHA.116.004211
33. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, Eidem B, Edwards WD, Sundt TM 3rd, Enriquez-Sarano M. Incidence of aortic complications in patients with bicuspid aortic valves. *JAMA*. 2011;306:1104–1112. doi: 10.1001/jama.2011.1286
34. Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA, Galper BZ, Meduri CU, Arnold SV, Baron SJ, et al; CoreValve US High Risk Pivotal Trial Investigators. Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. *J Am Coll Cardiol*. 2016;67:29–38. doi: 10.1016/j.jacc.2015.10.046
35. Goodall G, Lamotte M, Ramos M, Maunoury F, Pejchalova B, de Pouvourville G. Cost-effectiveness analysis of the SAPIEN 3 TAVI valve compared with surgery in intermediate-risk patients. *J Med Econ*. 2019;22:289–296. doi: 10.1080/13696998.2018.1559600
36. de Marchena E, Badiye A, Robalino G, Junttila J, Atapattu S, Nakamura M, De Canniere D, Salerno T. Respective prevalence of the different Carpentier classes of mitral regurgitation: a stepping stone for future therapeutic research and development. *J Card Surg*. 2011;26:385–392. doi: 10.1111/j.1540-8191.2011.01274.x
37. Delling FN, Gona P, Larson MG, Lehman B, Manning WJ, Levine RA, Benjamin EJ, Vasan RS. Mild expression of mitral valve prolapse in the Framingham offspring: expanding the phenotypic spectrum. *J Am Soc Echocardiogr*. 2014;27:17–23. doi: 10.1016/j.echo.2013.09.015
38. Delling FN, Rong J, Larson MG, Lehman B, Fuller D, Osypiuk E, Stantchev P, Hackman B, Manning WJ, Benjamin EJ, et al. Evolution of mitral valve prolapse: insights from the Framingham Heart Study. *Circulation*. 2016;133:1688–1695. doi: 10.1161/CIRCULATIONAHA.115.020621
39. Nesta F, Leyne M, Yosefy C, Simpson C, Dai D, Marshall JE, Hung J, Slaugenhaupt SA, Levine RA. New locus for autosomal dominant mitral valve prolapse on chromosome 13: clinical insights from genetic studies. *Circulation*. 2005;112:2022–2030. doi: 10.1161/CIRCULATIONAHA.104.516930
40. Delling FN, Rong J, Larson MG, Lehman B, Osypiuk E, Stantchev P, Slaugenhaupt SA, Benjamin EJ, Levine RA, Vasan RS. Familial clustering of mitral valve prolapse in the community. *Circulation*. 2015;131:263–268. doi: 10.1161/CIRCULATIONAHA.114.012594
41. Kyndt F, Gueffet JP, Probst V, Jaafar P, Legendre A, Le Bouffant F, Toquet C, Roy E, McGregor L, Lynch SA, et al. Mutations in the gene encoding filamin A as a cause for familial cardiac valvular dystrophy. *Circulation*. 2007;115:40–49. doi: 10.1161/CIRCULATIONAHA.106.622621
42. Dina C, Bouatia-Naji N, Tucker N, Delling FN, Toomer K, Durst R, Perrocheau M, Fernandez-Friera L, Solis J, Le Tourneau T, et al; PROMESA Investigators; MVP-France; Leducq Transatlantic MITRAL Network. Genetic association analyses highlight biological pathways underlying mitral valve prolapse. *Nat Genet*. 2015;47:1206–1211. doi: 10.1038/ng.3383
43. Durst R, Sauls K, Peal DS, deVlaming A, Toomer K, Leyne M, Salani M, Talkowski ME, Brand H, Perrocheau M, et al. Mutations in DCHS1 cause mitral valve prolapse. *Nature*. 2015;525:109–113. doi: 10.1038/nature14670
44. Toomer KA, Yu M, Fulmer D, Guo L, Moore KS, Moore R, Drayton KD, Glover J, Peterson N, Ramos-Ortiz S, et al. Primary cilia defects causing mitral valve prolapse. *Sci Transl Med*. 2019;11:eaax0290. doi: 10.1126/scitranslmed.aax0290
45. Delling FN, Li X, Li S, Yang Q, Xanthakis V, Martinsson A, Andell P, Lehman BT, Osypiuk EW, Stantchev P, et al. Heritability of mitral regurgitation: observations from the Framingham Heart Study and Swedish population. *Circ Cardiovasc Genet*. 2017;10:e001736. doi: 10.1161/CIRCGENETICS.117.001736
46. Sorajja P, Mack M, Vemulapalli S, Holmes DR Jr, Stebbins A, Kar S, Lim DS, Thourani V, McCarthy P, Kapadia S, et al. Initial experience with commercial transcatheter mitral valve repair in the United States. *J Am Coll Cardiol*. 2016;67:1129–1140. doi: 10.1016/j.jacc.2015.12.054
47. Feldman T, Foster E, Glower DD, Glower DG, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, et al; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation [published correction appears in *N Engl J Med*. 2011;365:189]. *N Engl J Med*. 2011;364:1395–1406. doi: 10.1056/NEJMoa1009355
48. Wojakowski W, Baumgartner H. The year in cardiology 2018: valvular heart disease. *Eur Heart J*. 2019;40:414–421. doi: 10.1093/eurheartj/ehy893
49. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318. doi: 10.1056/NEJMoa1806640
50. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–2306. doi: 10.1056/NEJMoa1805374
51. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, Blackstone EH, Lytle BW. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol*. 2007;49:2191–2201. doi: 10.1016/j.jacc.2007.02.043
52. Smith PK, Puskas JD, Ascheim DD, Voisine P, Gelijns AC, Moskowitz AJ, Hung JW, Parides MK, Ailawadi G, Perrault LP, et al; Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178–2188. doi: 10.1056/NEJMoa1410490
53. Dziadzko V, Clavel MA, Dziadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet*. 2018;391:960–969. doi: 10.1016/S0140-6736(18)30473-2
54. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G, Hülsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J*. 2018;39:39–46. doi: 10.1093/eurheartj/ehx402
55. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes

of mitral valve prolapse. *Ann Intern Med.* 2008;149:787–795. doi: 10.7326/0003-4819-149-11-200812020-00003
56. Avierinos JF, Gersh BJ, Melton LJ 3rd, Bailey KR, Shub C, Nishimura RA, Tajik AJ, Enriquez-Sarano M. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation.* 2002;106:1355–1361. doi: 10.1161/01.cir.0000028933.34260.09
57. Cameron HL, Bernard LM, Garmo VS, Hernandez JB, Asgar AW. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip system in high surgical risk patients with significant mitral regurgitation. *J Med Econ.* 2014;17:599–615. doi: 10.3111/13696998.2014.923892
58. Allen H, Shaddy R, Penny D, Feltes T, Cetta F. *Heart Disease in Infants, Children, and Adolescents*. 9th ed; Baltimore, MD: Wolters Kluwer; 2016.
59. Aggarwal V, Mulukutla V, Maskatia S, Justino H, Mullins CE, Qureshi AM. Outcomes after balloon pulmonary valvuloplasty for critical pulmonary stenosis and incidence of coronary artery fistulas. *Am J Cardiol.* 2018;121:1617–1623. doi: 10.1016/j.amjcard.2018.02.049
60. Chatterjee A, Bajaj NS, McMahon WS, Cribbs MG, White JS, Mukherjee A, Law MA. Transcatheter pulmonary valve implantation: a comprehensive systematic review and meta-analyses of observational studies. *J Am Heart Assoc.* 2017;6:e006432. doi: 10.1161/JAHA.117.006432
61. Gillespie MJ, Rome JJ, Levi DS, Williams RJ, Rhodes JF, Cheatham JP, Hellenbrand WE, Jones TK, Vincent JA, Zahn EM, et al. Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. *Circ Cardiovasc Interv.* 2012;5:862–870. doi: 10.1161/CIRCINTERVENTIONS.112.972216
62. Haas NA, Carere RG, Kretschmar O, Horlick E, Rodés-Cabau J, de Wolf D, Gewillig M, Mullen M, Lehner A, Deutsch C, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN XT transcatheter heart valve system. *Int J Cardiol.* 2018;250:86–91. doi: 10.1016/j.ijcard.2017.10.015
63. Patel A, Patel A, Bhatt P, Savani C, Thakkar B, Sonani R, Patel NJ, Arora S, Panaich S, Singh V, et al. Transcatheter pulmonary valve implantation: a cross-sectional US experience. *Int J Cardiol.* 2015;199:186–188. doi: 10.1016/j.ijcard.2015.07.021
64. Lee C, Kim YM, Lee CH, Kwak JG, Park CS, Song JY, Shim WS, Choi EY, Lee SY, Baek JS. Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement. *J Am Coll Cardiol.* 2012;60:1005–1014. doi: 10.1016/j.jacc.2012.03.077
65. Bokma JP, Geva T, Sleeper LA, Babu Narayan SV, Wald R, Hickey K, Jansen K, Wassall R, Lu M, Gatzoulis MA, et al. A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Heart.* 2018;104:738–744. doi: 10.1136/heartjnl-2017-312048
66. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol.* 2004;43:405–409. doi: 10.1016/j.jacc.2003.09.036
67. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, Stone GW, Leon MB, Ajmone Marsan N, Delgado V, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. *Eur Heart J.* 2018;39:3574–3581. doi: 10.1093/eurheartj/ehy352
68. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol.* 2017;70:2953–2960. doi: 10.1016/j.jacc.2017.10.039
69. Nickenig G, Kowalski M, Hausleiter J, Braun D, Schofer J, Yzeiraj E, Rudolph V, Friedrichs K, Maisano F, Taramasso M, et al. Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique. *Circulation.* 2017;135:1802–1814. doi: 10.1161/CIRCULATIONAHA.116.024848
70. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med.* 2017;377:713–722. doi: 10.1056/NEJMoa1603693
71. Nunes MCP, Sable C, Nascimento BR, Lima EM, da Silva JLP, Diamantino AC, Oliveira KKB, Okello E, Aliku T, Lwabi P, et al. Simplified echocardiography screening criteria for diagnosing and predicting progression of latent rheumatic heart disease. *Circ Cardiovasc Imaging.* 2019;12:e007928. doi: 10.1161/CIRCIMAGING.118.007928
72. Nascimento BR, Beaton AZ, Nunes MC, Diamantino AC, Carmo GA, Oliveira KK, Oliveira CM, Meira ZM, Castilho SR, Lopes EL, et al; PROVAR (Programa de RastreamentO da VAlvopatia Reumática) Investigators. Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: data from the PROVAR study. *Int J Cardiol.* 2016;219:439–445. doi: 10.1016/j.ijcard.2016.06.088
73. Ploutz M, Lu JC, Scheel J, Webb C, Ensing GJ, Aliku T, Lwabi P, Sable C, Beaton A. Handheld echocardiographic screening for rheumatic heart disease by non-experts. *Heart.* 2016;102:35–39. doi: 10.1136/heartjnl-2015-308236
74. Shrestha NR, Karki P, Mahto R, Gurung K, Pandey N, Agrawal K, Rothenbühler M, Urban P, Jüni P, Pilgrim T. Prevalence of subclinical rheumatic heart disease in eastern Nepal: a school-based cross-sectional study. *JAMA Cardiol.* 2016;1:89–96. doi: 10.1001/jamacardio.2015.0292
75. Clark BC, Krishnan A, McCarter R, Scheel J, Sable C, Beaton A. Using a low-risk population to estimate the specificity of the World Heart Federation criteria for the diagnosis of rheumatic heart disease. *J Am Soc Echocardiogr.* 2016;29:253–258. doi: 10.1016/j.echo.2015.11.013
76. Engelman D, Wheaton GR, Mataika RL, Kado JH, Colquhoun SM, Remenyi B, Steer AC. Screening-detected rheumatic heart disease can progress to severe disease. *Heart Asia.* 2016;8:67–73. doi: 10.1136/heartasia-2016-010847
77. Bertaina G, Rouchon B, Huon B, Guillot N, Robillard C, Noël B, Nadra M, Tribouilloy C, Marijon E, Jouven X, et al. Outcomes of borderline rheumatic heart disease: a prospective cohort study. *Int J Cardiol.* 2017;228:661–665. doi: 10.1016/j.ijcard.2016.11.234
78. Zühlke L, Engel ME, Lemmer CE, van de Wall M, Nkepu S, Meiring A, Bestawros M, Mayosi BM. The natural history of latent rheumatic heart disease in a 5 year follow-up study: a prospective observational study. *BMC Cardiovasc Disord.* 2016;16:46. doi: 10.1186/s12872-016-0225-3
79. Beaton A, Aliku T, Dewyer A, Jacobs M, Jiang J, Longenecker CT, Lubega S, McCarter R, Mirabel M, Mirembe G, et al. Latent rheumatic heart disease: identifying the children at highest risk of unfavorable outcome. *Circulation.* 2017;136:2233–2244. doi: 10.1161/CIRCULATIONAHA.117.029936
80. Scheel A, Ssinabulya I, Aliku T, Bradley-Hewitt T, Clauss A, Clauss S, Crawford L, DeWyer A, Donofrio MT, Jacobs M, et al. Community study to uncover the full spectrum of rheumatic heart disease in Uganda. *Heart.* 2019;105:60–66. doi: 10.1136/heartjnl-2018-313171
81. Hovis IW, Namuyonga J, Kisitu GP, Ndagire E, Okello E, Longenecker CT, Sanyahumbi A, Sable CA, Penny DJ, Lwabi P, et al. Decreased prevalence of rheumatic heart disease confirmed among HIV-positive youth. *Pediatr Infect Dis J.* 2019;38:406–409. doi: 10.1097/INF.0000000000002161
82. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J.* 2015;36:1115–1122a. doi: 10.1093/eurheartj/ehu449
83. Longenecker CT, Morris SR, Aliku TO, Beaton A, Costa MA, Kamya MR, Kityo C, Lwabi P, Mirembe G, Nampijja D, et al. Rheumatic heart disease treatment cascade in Uganda. *Circ Cardiovasc Qual Outcomes.* 2017;10:e004037. doi: 10.1161/CIRCOUTCOMES.117.004037
84. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Naghavi M, Mokdad AH, Murray CJL. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. *JAMA.* 2017;317:1976–1992. doi: 10.1001/jama.2017.4150
85. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, Islam S, Daniels R, Francis V, Ogendo S, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the global Rheumatic Heart Disease Registry (the REMEDY Study). *Circulation.* 2016;134:1456–1466. doi: 10.1161/CIRCULATIONAHA.116.024769
86. Wood AD, Mannu GS, Clark AB, Tiamkao S, Kongbunkiat K, Bettencourt-Silva JH, Sawanyawisuth K, Kasemsap N, Barlas RS, Mamas M, et al. Rheumatic mitral valve disease is associated with worse outcomes in stroke: a Thailand national database study. *Stroke.* 2016;47:2695–2701. doi: 10.1161/STROKEAHA.116.014512
87. Beaton A, Okello E, Scheel A, DeWyer A, Ssembatya R, Baaka O, Namisanvu H, Njeri A, Matovu A, Namagembe I, et al. Impact of heart disease on maternal, fetal and neonatal outcomes in a low-resource setting. *Heart.* 2019;105:755–760. doi: 10.1136/heartjnl-2018-313810
88. Parks T, Kado J, Miller AE, Ward B, Heenan R, Colquhoun SM, Bärnighausen TW, Mirabel M, Bloom DE, Bailey RL, et al. Rheumatic heart disease-attributable mortality at ages 5-69 years in Fiji: a five-year, national, population-based record-linkage cohort study. *PLoS Negl Trop Dis.* 2015;9:e0004033. doi: 10.1371/journal.pntd.0004033
89. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.

90. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, Hirsch GA, Mehta JL. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol.* 2015;65:2070–2076. doi: 10.1016/j.jacc.2015.03.518
91. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, et al; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Surgery and Anesthesia; Quality of Care and Outcomes Research Interdisciplinary Working Group. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in *Circulation*. 2007;116:e376–e377]. *Circulation.* 2007;116:1736–1754. doi: 10.1161/CIRCULATIONAHA.106.183095
92. DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, Steckelberg JM, Wilson WR, Baddour LM. Temporal trends in infective endocarditis epidemiology from 2007 to 2013 in Olmsted County, MN. *Am Heart J.* 2015;170:830–836. doi: 10.1016/j.ahj.2015.07.007
93. Pasquali SK, He X, Mohamad Z, McCrindle BW, Newburger JW, Li JS, Shah SS. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Am Heart J.* 2012;163:894–899. doi: 10.1016/j.ahj.2012.03.002
94. Slipczuk L, Codolosa N, Carlos D, Romero-Corral A, Pressman G, Figueredo V. Systematic review & meta-analysis of infective endocarditis microbiology over 5 decades. *Circulation*. 2012;126:A15138.
95. Katan O, Michelena HI, Avierinos JF, Mahoney DW, DeSimone DC, Baddour LM, Suri RM, Enriquez-Sarano M. Incidence and predictors of infective endocarditis in mitral valve prolapse: a population-based study. *Mayo Clin Proc.* 2016;91:336–342. doi: 10.1016/j.mayocp.2015.12.006
96. Deo SV, Raza S, Kalra A, Deo VS, Altarabsheh SE, Zia A, Khan MS, Markowitz AH, Sabik JF 3rd, Park SJ. Admissions for infective endocarditis in intravenous drug users. *J Am Coll Cardiol.* 2018;71:1596–1597. doi: 10.1016/j.jacc.2018.02.011
97. Athan E, Chu VH, Tattevin P, Selton-Suty C, Jones P, Naber C, Miró JM, Ninot S, Fernández-Hidalgo N, Durante-Mangoni E, et al; ICE-PCS Investigators. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA.* 2012;307:1727–1735. doi: 10.1001/jama.2012.497
98. Lalani T, Chu VH, Park LP, Cecchi E, Corey GR, Durante-Mangoni E, Fowler VG Jr, Gordon D, Grossi P, Hannan M, et al; International Collaboration on Endocarditis–Prospective Cohort Study Investigators. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis [published correction appears in *JAMA Intern Med*. 2013;173:1846]. *JAMA Intern Med.* 2013;173:1495–1504. doi: 10.1001/jamainternmed.2013.8203
99. Zegri-Reiriz I, de Alarcón A, Muñoz P, Martínez Sellés M, González-Ramallo V, Miro JM, Falces C, Gonzalez Rico C, Kortajarena Urkola X, Lepe JA, et al; Spanish Collaboration on Endocarditis—Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES). Infective endocarditis in patients with bicuspid aortic valve or mitral valve prolapse. *J Am Coll Cardiol.* 2018;71:2731–2740. doi: 10.1016/j.jacc.2018.03.534
100. Chu VH, Park LP, Athan E, Delahaye F, Freiberger T, Lamas C, Miro JM, Mudrick DW, Strahilevitz J, Tribouilloy C, et al; for the International Collaboration on Endocarditis (ICE) Investigators. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. *Circulation.* 2015;131:131–140. doi: 10.1161/CIRCULATIONAHA.114.012461
101. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, Bruun NE, Høfsten DE, Fursted K, Christensen JJ, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med.* 2019;380:415–424. doi: 10.1056/NEJMoa1808312
102. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;389:e1]. *Lancet*. 2016;388:1459–1544. doi: 10.1016/S0140-6736(16)31012-1
103. Ware AL, Tani LY, Weng HY, Wilkes J, Menon SC. Resource utilization and outcomes of infective endocarditis in children. *J Pediatr.* 2014;165:807–812.e1. doi: 10.1016/j.jpeds.2014.06.026
104. Abdallah L, Remadi JP, Habib G, Salaun E, Casalta JP, Tribouilloy C. Long-term prognosis of left-sided native-valve *Staphylococcus aureus* endocarditis. *Arch Cardiovasc Dis.* 2016;109:260–267. doi: 10.1016/j.acvd.2015.11.012
105. National Center for Health Statistics. *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities.* Hyattsville, MD: National Center for Health Statistics; 2016.
106. Gaede L, Blumenstein J, Liebetrau C, Dörr O, Kim WK, Nef H, Husser O, Elsässer A, Hamm CW, Möllmann H. Outcome after transvascular transcatheter aortic valve implantation in 2016. *Eur Heart J.* 2018;39:667–675. doi: 10.1093/eurheartj/ehx688

22. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

See Charts 22-1 and 22-2

Click here to return to the Table of Contents

In this chapter, 2017 mortality data come from unpublished NHLBI tabulations using the NVSS[1] and CDC WONDER.[2] Hospital discharge data come from unpublished NHLBI tabulations using the HCUP.[3]

Abbreviations Used in Chapter 22

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
BNP	B-type natriuretic peptide
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CI	confidence interval
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVI	chronic venous insufficiency
DM	diabetes mellitus
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ED	emergency department
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FHS	Framingham Heart Study
FVL	factor V Leiden
GRS	genetic risk score(s)
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
NYHA	New York Heart Association
OR	odds ratio
PAH	pulmonary arterial hypertension
PE	pulmonary embolism
PH	pulmonary hypertension
PTS	postthrombotic syndrome
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RCT	randomized controlled trial
RR	relative risk
RV	right ventricular
VTE	venous thromboembolism
WHO	World Health Organization

Pulmonary Embolism
ICD-9 415.1; *ICD-10* I26.

Mortality—8704. Any-mention mortality—35 605. Hospital discharges—185 000 (principal diagnosis), 367 000 (all-listed diagnoses).

Deep Vein Thrombosis
ICD-9 451.1, 451.2, 451.81, 451.9, 453.0, 453.1, 453.2, 453.3, 453.4, 453.5, 453.9; *ICD-10* I80.1, I80.2, I80.3, I80.9, I82.0, I82.1, I82.2, I82.3, I82.4, I82.5, I82.9.

Mortality—3172. Any-mention mortality—17 006. Hospital discharges—102 000 (principal diagnosis), 602 000 (all-listed diagnoses).

Venous Thromboembolism

Incidence (Charts 22-1 and 22-2)

- VTE includes both DVT and PE. The HCUP NIS (Charts 22-1 and 22-2) shows increasing numbers of hospitalized cases for PE from 1996 to 2016. Focusing on all-listed diagnoses, the number of hospitalized DVT cases also increased from 2005 to 2016. Extrapolating from these data and using all-listed diagnoses, if we assume 30% of DVTs were treated in the outpatient setting, we estimate that in 2016 there were ≈857 000 DVTs, ≈370 000 PEs, and ≈1 220 000 total VTE events in the United States (US population was 323 million in 2016).
- In 2016, there were 1 001 000 physician office visits and 211 000 ED visits with a principal diagnosis of DVT (unpublished NHLBI tabulation using NAMCS[4] and NHAMCS[5]).
- Interpretation of the HCUP NIS, as well as most other sources of VTE incidence data, should be viewed in light of secular trends and data characteristics that could have resulted in an increase in VTE diagnosis that might overstate changes in VTE incidence (eg, advances in PE imaging, which enable the detection of smaller PEs,[6] increased the use of full leg ultrasound, which detects distal DVT; the co-occurrence of codes for DVT and PE in the same patient) and other factors that could lead to underestimation of VTE incidence (eg, outpatient management of ≈35% of DVT cases[7] and a smaller portion of PE cases,[8,9] misdiagnosis of VTE events, and failure to ascertain fatal PEs because of low autopsy rates).
- Using administrative data in the United States, the estimated admissions for PE increased from 23 per 100 000 in 1993 to 65 per 100 000 in 2012.[10] Trends in DVT incidence were not reported.

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- Incidence rates for PE and DVT increase exponentially with advancing age for both males and females.[11–13]
- VTE incidence varies by race/ethnicity.[14–17] Blacks appear to be at greatest risk, followed by whites, Hispanics, and Asians, respectively.
- Educational attainment has been inversely associated with VTE risk.[18]

Lifetime Risk

- The remaining lifetime risk of VTE at 45 years of age was 8.1% (95% CI, 7.1%–8.7%) overall, 11.5% in blacks, 10.9% in those with obesity, 17.1% in individuals with the FVL genetic mutation, and 18.2% in people with sickle cell trait or disease, using data derived from nearly 20 000 participants of 2 US cohorts who were 45 to 99 years of age.[19]

Risk Factors

- Approximately 50% of VTEs are provoked because of immobilization, trauma, surgery, or hospitalization in the antecedent 3 months; 20% are associated with cancer; and 30% are unprovoked.[20–22]
- Independent VTE risk factors include increasing age, obesity, family history or personal history of thrombosis, recent surgery, trauma/fracture, hospitalization, prolonged immobility, nursing home residence, active cancer, indwelling central venous catheter or transvenous pacemaker, prior superficial vein thrombosis, infection, inherited or acquired thrombophilia, kidney disease, neurological disease with leg paresis, sickle cell anemia and sickle cell trait, and long-distance travel.[23–25] Autoimmune diseases, such as lupus and Sjögren syndrome, and acute infection have also been associated with elevated VTE risk.[26–31]
- Among females, VTE risk is elevated among those using estrogen-based contraceptives, hormone therapy, or infertility treatment.[32] Risk is also elevated in pregnancy and the postpartum period. Pregnancy-associated VTE has an incidence of 1 to 2 per 1000 person-years; compared with nonpregnant females of childbearing age, the RR for VTE is increased 4-fold.[33–35] VTE risk is higher for pregnancies after in vitro fertilization than for natural pregnancies,[36] and with multiple gestation, cesarean delivery, or other pregnancy complications.[37,38] Risk factors associated with VTE in the general population (eg, obesity) are also associated with pregnancy-associated VTE.
- Traditional atherosclerotic risk factors, including hypertension, hyperlipidemia, and DM, were not associated with VTE risk in a 2017 individual-level meta-analysis of >240 000 participants from 9 cohorts.[39] Cigarette smoking was associated with provoked but not with unprovoked VTE events. Similar findings were reported in a 2019 publication combining data from the Emerging Risk Factors Collaboration and UK Biobank whereby there was no association with hypertension and dyslipidemia, although for DM, the association was inconsistent. Age and obesity were associated with greater risk in this analysis.[40]

Family History and Genetics

- VTE is highly heritable.[41,42]
- FVL is the most common inherited thrombophilia in populations of European descent but is rare in African and Asian populations.[43] In ARIC, ≈5% of Caucasians and <1% of African Americans are heterozygous carriers of FVL, and lifetime risk of VTE was 17.1% in individuals with the FVL genetic mutation.[19] Pooling data from 36 epidemiological studies, Simone et al[44] found that risk of VTE was increased 4-fold in heterozygous FVL (OR, 4.2 [95% CI, 3.4–5.3]) and 11-fold in homozygous FVL (OR, 11.4 [95% CI, 6.8–19.3]) compared with noncarriers.
- Antithrombin deficiency is a rare mutation that is associated with greatly increased risk of incident VTE (OR ≈14).[45] A bayesian meta-analysis found that for childbearing females with this mutation, VTE risk was 7% in the antepartum period and 11% postpartum.[46] The authors suggested that thrombosis prophylaxis should be considered for childbearing females with this mutation.
- More common genetic variants associated with VTE have a lesser risk of VTE than rare mutations and include non-O blood group, prothrombin 20210A, and sickle cell disease and trait.[47] GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.[48] These common variants individually increase the risk of VTE to a small extent, but a GRS composed of a combination of these variants yielded an OR for VTE risk of 7.5.[49] Exome-wide analysis of rare variants in >24 000 individuals of European ancestry and 1858 individuals of African ancestry confirmed previously implicated loci but did not uncover novel rare variants associated with VTE.[50] Similarly, targeted sequencing efforts did not uncover novel rare variants for DVT.[51]

Treatment

- In the latter half of the past decade, substantial progress has been made in the management of patients with suspected VTE. This includes patient-tailored diagnostic and therapeutic strategies because of the confluence of refined use of biomarkers (eg age-adjusted D-dimer threshold), risk prediction algorithms (PE Rule-Out Criteria), and the introduction of DOACs.[52]

- VTE is generally treated for 3 to 6 months with anticoagulation (primary treatment), at which point the risks and benefits of continued anticoagulation should be assessed (secondary prevention).[53] When oral anticoagulation is contraindicated or ineffective, inferior vena cava filters can be used. However, in general they should be avoided.[52] Thrombolysis is generally reserved for patients with massive PE or those with DVT that is threatening to result in limb loss.[52]
- Current treatment guidelines consider anticoagulation with either warfarin or DOAC drugs (ie, apixaban, rivaroxaban, dabigatran, edoxaban) as the standard of care.[53] In phase III RCTs of VTE primary treatment,[54–57] the DOAC drugs were each shown to be as effective as warfarin in the prevention of recurrent VTE and VTE-related death. A meta-analysis[58] of these trials suggested that DOAC drugs have a lower risk of bleeding complications than warfarin.
- Observational studies have also indicated that statins reduce the risk of recurrent VTE. An RCT published in 2018 demonstrated that among VTE patients, randomization to rosuvastatin was associated with improved coagulation profiles relative to those not randomized to a statin.[59]

Mortality

- Among Medicare beneficiaries with DVT, the 30-day mortality rate was 5.1% and the 1-year mortality rate was 19.6% in 2010.[60] These rates were similar to those in 1999 (5.0% and 21.5%, respectively).
- Among Medicare beneficiaries with PE, the 30-day mortality rate was 9.1% and the 6-month mortality rate was 19.6% in 2010.[61] These rates only showed slight improvements from rates in 1999 (12.3% and 23.0%, respectively).
- An analysis using administrative data for first-time VTE in Quebec, Canada, reported that the 1-year survival rate for VTE was 77% overall, but when stratified by VTE-provoking status, it was 47% for cancer-associated VTE, 84% for provoked VTE, and 93% for unprovoked VTE.[62]
- Asymptomatic DVTs diagnosed with compression ultrasound were associated with a 3-fold increased risk of short-term all-cause mortality in patients with acute medical illness relative to those with no evidence of DVT.[63]

Complications

- VTE is a chronic disease with episodic recurrence; in the absence of long-term anticoagulation, ≈30% of patients develop recurrence within the next 10 years.[18,23,64]
- Independent predictors of recurrence within 180 days include active cancer and inadequate anticoagulation. Two-week case-fatality rates are 2% for recurrent DVT alone and 11% for recurrent PE with or without DVT.[65]
- Because of the use of anticoagulant therapy to treat VTE, bleeding is a major potential complication. Data from phase III RCTs suggest that use of DOACs, instead of warfarin, for VTE primary treatment could further reduce bleeding risk.[58]
- PTS/venous stasis syndrome and venous stasis ulcers are important complications of proximal lower-extremity DVT, which are discussed in greater depth in the Chronic Venous Insufficiency section of this chapter. After proximal lower-extremity DVT, the 20-year cumulative incidences of PTS/venous stasis syndrome and venous stasis ulcers are 30% and 3.7%, respectively.[66]
- CTEPH affects ≈4% of patients with PE within 2 years of their initial PE event.[67]

Costs

- A literature review estimated incremental direct medical costs (2014 US dollars) per case among 1-year survivors of acute VTE at $12 000 to $15 000 and the cost of complications, including recurrent VTE, PTS, CTEPH, and anticoagulation-related adverse events, at $18 000 to $23 000 per case. This review assumed 375 000 to 425 000 new cases in the United States annually and estimated the annual overall cost at $7 billion to $10 billion.[68]

Chronic Venous Insufficiency *ICD-10* I87.2.

Mortality—57. Any-mention mortality—543.

Prevalence

- Varicose veins are a common manifestation of CVI. In the San Diego Population Study (mean age, 59 years), visible disease was common; 6.2% had trophic changes (eg, hyperpigmentation, edema, ulcers), 23.3% had varicose veins, and 51.9% had spider veins.[69]
- PTS is a common complication of DVT that develops in 20% to 50% of cases after proximal DVT and is severe in 5% to 10% of cases.[70] Approximately 4% of patients with DVT experience venous stasis ulcers.[67]

Incidence

- The FHS reported an annual incidence of varicose veins of 2.6% in females and 1.9% in males.[71]

Risk Factors

- The prevalence of moderate CVI increases with advancing age, family history, hernia surgery, obesity, number of births, and presence of flat feet in females and is less likely in those with hypertension;

risk factors for more severe CVI include smoking in males and leg injury in females.[72] Inflammation, endothelial dysfunction, and blood coagulation disorders are all thought to predispose to CVI.[73,74]

- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT, obesity, more extensive DVT, poor quality of initial anticoagulation, ongoing symptoms or signs of DVT 1 month after diagnosis, and elevated D-dimer at 1 month.[70,75,76]
- Using data from 762 DVT patients, Rabinovich et al[77] developed a clinical prediction model for PTS. High-risk predictors were index DVT in the iliac vein; BMI of ≥35 kg/m^2; and moderate to severe Villalta (PTS severity) score at DVT diagnosis.
- In a meta-analysis of DVT patients who underwent ultrasonography at least 6 weeks after their DVT, 2 ultrasound parameters were predictive of PTS: residual vein thrombosis (pooled OR, 2.17 [95% CI,1.79–2.63]) and venous reflux at the popliteal level (pooled OR, 1.34 [95% CI, 1.03–1.75]).[78]
- Data from 2018 demonstrated that among DVT patients, initial compression with either compression hosiery or multilayer bandaging was associated with fewer irreversible skin signs, edema, and pain on calf compression versus no compression.[79] Multilayer bandaging was slightly more effective than hosiery but has substantially higher costs, without a gain in health-related quality of life.
- For patients with DVT, use of compression stockings for 24 months is standard therapy for the prevention of PTS. In a 2018 RCT, a total of 865 patients were randomized to either standard duration or individualized therapy length.[80] Individualized therapy was noninferior to standard duration of therapy of 24 months. Individualization of therapy duration may potentially enhance patients' well-being.
- Rabinovich and Kahn described the best means to prevent PTS as prevention of future DVT and appropriate anticoagulation of existing DVT.[81]

Family History and Genetics

- Varicose veins are more likely to occur in the setting of a positive family history, consistent with a heritable component. Although a number of genes have been implicated,[82] the genetic factors predisposing to varicose veins have not been definitively identified.[83]

Complications

- More severe venous disease often includes manifestations such as hyperpigmentation, venous eczema, lipodermatosclerosis, atrophie blanche, and healed or active venous ulcers.[84]
- Analysis of NIS data for black and white Americans demonstrated declines in ulcer debridement, vein stripping, and sclerotherapy procedures from 1998 to 2011. Blacks presented at younger ages and more often had ulcer debridement and history of DVT than whites.[85]
- A 2017 publication that used a database of 300 patients treated for advanced CVI with radiofrequency ablation procedures showed that blacks presented with higher-severity CVI and had less improvement with ablation.[86]

Cost

- The estimated cost in the United States to treat venous ulcers is $1 billion annually.[84]

Pulmonary Hypertension
ICD-10 I27.0, I27.2.

Mortality—7618. Any-mention mortality—24 584.

Incidence

- In the United States, between 2001 and 2010, hospitalization rates for PH increased significantly, and among those ≥85 years of age, hospitalization rates nearly doubled.[87] In 2010, the age-adjusted rate of hospitalization associated with PH was 131 per 100 000 discharges overall and 1527 per 100 000 for those ≥85 years of age.[87]
- The WHO classifies PH into 5 groups (described below) according to underlying pathogenesis. Limited information is available on prevalence of PH subtypes in nonreferral settings. In one study conducted in Armadale, Australia, the most commonly identified PH subtypes were left-sided HD (WHO group 2: 68%); lung disease (WHO group 3: 9%); WHO group 1, underlying causes combined (3%); and CTEPH (WHO group 4: 2%). Fifteen percent were unclassifiable.[88]
- The prevalence of WHO group 1 PH (idiopathic, heritable, drug/toxin induced, or associated with other factors including connective tissue disease, infections [HIV, schistosomiasis], portal hypertension, and congenital HD) is estimated at 6.6 to 26.0 per million adults and the incidence at 1.1 to 7.6 per million adults annually.[89]
- WHO group 2 PH is attributable to left-sided HD. Estimates of the incidence and prevalence are difficult to ascertain but most likely would track with HF prevalence rates.[89]
- The prevalence and incidence of WHO group 3 PH (attributable to lung disease or hypoxia) is difficult to estimate but likely would track with lung disease prevalence.[89]
- The prevalence of WHO group 4 PH (CTEPH and other pulmonary obstructions) ranges from 1.0% to 8.8% among those with PE.[89] CTEPH incidence, however, may be underestimated based on general population data; in a 2017 modeling study, only 7% to 29% of CTEPH cases were diagnosed.[90]

- WHO group 5 PH has multifactorial mechanisms. When it accompanies sickle cell disease, the prevalence is 6% to 10% and increases with advancing age. When it accompanies thalassemia, the prevalence is 2.1%.[89,91]

Risk Factors

- Risk factors are implicit in the WHO disease classification of the 5 mechanistic subtypes of PH described above. The most common risk factors are left-sided HD and lung disease.
- In a cohort of 23 329 patients with first VTE (mean follow-up, 3.5 years) 283 patients were diagnosed with CTEPH. Cumulative incidence was 1.3% and 3.3% at 2 and 10 years after PE and 0.3% and 1.3% after DVT, respectively. Risk factors for CTEPH included age >70 years, being female, chronic obstructive pulmonary disease, HF, and AF.[92]
- In a study of 772 consecutive PE patients without major comorbidities such as cancer, the risk factors for CTEPH were unprovoked PE, hypothyroidism, symptom onset >2 weeks before PE diagnosis, RV dysfunction on CT or echocardiography, DM, and thrombolytic therapy or embolectomy; a risk prediction score that included these factors was able to predict a group with a CTEPH incidence of 10% (95% CI, 6.5%–15%).[93] It is not clear to what extent these factors may be affected by the possibility that the index presentation was caused by worsening RV failure in the setting of CTEPH rather than acute PE. Higher BMI also has been associated with CTEPH risk after PE.[94]
- A 2018 analysis of 2368 REVEAL registry patients with PH reported that patients with a ≥10% decline in eGFR from baseline over ≥1 year had a significantly increased risk of death (HR, 1.66; $P<0.0001$) and the composite of all-cause hospitalization and death (HR, 1.33; $P=0.002$).[95] This decline predicted survival independently of changes in 6-minute walk distance and functional class. Likewise, using PH patients from the same registry, both baseline and change in concentrations of plasma BNP were associated with increased risk of death. Comparing those with high (>340 pg/mL) versus low (≤340 pg/mL) baseline BNP, the HR was 3.6 (95% CI, 3.0–4.2).[96]
- Among patients with ESRD, PH is associated with a 2-fold increased risk of all-cause mortality for both patients receiving maintenance dialysis and those with a functioning kidney transplant.[97]

Family History and Genetics

- A 2018 study reported clustering of CTEPH in families, providing novel evidence that heritable genetic factors influence an individual's risk of developing CTEPH.[98]
- A Japanese family study also identified the bone morphogenetic protein type 2 receptor gene (*BMPR2*) as a risk factor for PAH.[99]

Treatment

- Galiè and colleagues[100] performed a double-blind RCT of 500 treatment-naïve patients with WHO group 2 or 3 PH, randomizing them to ambrisentan, tadalafil, or both in combination. The combination group (versus the pooled monotherapy groups) was at lower risk for the composite primary end point of death, PAH hospitalization, or clinical disease progression (HR, 0.50 [95% CI, 0.35–0.72]).
- In a large, placebo-controlled, double-blind RCT of 1156 patients with PAH randomized to selexipag, an oral selective IP prostacyclin receptor agonist, versus placebo, Sitbon and colleagues[101] found a significant reduction in the primary composite end point of death attributable to any cause or PAH-related complication (HR, 0.60 [99% CI, 0.46–0.78]). This observed benefit was driven by differences in disease progression and hospitalization; no significant difference in mortality was seen between selexipag and placebo.
- Pulido and colleagues[102] performed a 250-patient RCT of 3 mg or 10 mg of macitentan, a dual endothelin receptor antagonist, versus placebo, with a primary end point composite of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH. Macitentan was shown to have statistically and clinically significant benefit at either tested dose; the HR for 3 mg of macitentan versus placebo was 0.70 (97.5% CI, 0.52–0.96), and for 10 mg of macitentan versus placebo, the HR was 0.55 (97.5% CI, 0.39–0.76).[102]

Mortality

Mortality of PH depends on the cause and treatment. On the basis of 2010 NHDS data, the death rate for PH as a contributing cause of death was 6.5 per 100 000.[87]

- Five-year survival was 61.2% to 65.4% in the US-based REVEAL registry of patients with group 1 PH. Lower 5-year survival was strongly and directly associated with worse functional class at presentation.[103] In an earlier study from this registry, 6-minute walk distance was also shown to be a strong predictor, with 97%, 90%, and 68% 1-year survival for patients with >440, 165 to 440, and <165 meter walk distances, respectively. A decline of >15% over time also predicted a significantly worse outcome compared with a stable or improving 6-minute walk distance.[104]
- A German single-center registry study reported 5-year survival rates of 65.3% for patients with idiopathic PH, 50.9% for those with PH associated with connective tissue disease, 74.5% for those with PH

caused by congenital HD, and 18.7% for those with pulmonary venous occlusive disease, respectively.[105]

- In a French registry study of 981 patients with idiopathic, heritable, or drug-induced PAH enrolled between 2006 and 2016, survival at 1 and 3 years was 90% and 73%, respectively.[106]
- In sickle cell disease–related PH, the 5-year survival rate in one study was 63% with and 83% without PH.[107]
- An international prospective registry that included 679 patients with CTEPH estimated that the 3-year survival was 89% with and 70% without pulmonary thromboendarterectomy.[108] Among the patients with CTEPH, treatments for PH did not affect survival. High NYHA functional class, increased right atrial pressure, and history of cancer were associated with mortality regardless of surgery.

Costs

- Healthcare costs associated with PH are substantial. In an analysis of administrative data, the per-patient per-month total all-cause healthcare costs for patients with PH who were commercially insured was $9503 for those on monotherapy and $16 240 for those on combination therapy. Among PH patients with Medicare Advantage and Part D, the monthly costs for patients on monotherapy and combination therapy were $6271 and $14 340, respectively.[109]

Global Burden

- 80% of patients with PH live in developing countries, and the cause of their PH is primarily HD and lung disease, but schistosomiasis, rheumatic HD, HIV, and sickle cell disease remain prominent compared with developed countries. In these countries, younger people are more often affected (average age of onset <40 years).[89]
- In high-income countries, rates of CTEPH are believed to be lower in Japan than in the United States and Europe.[90]

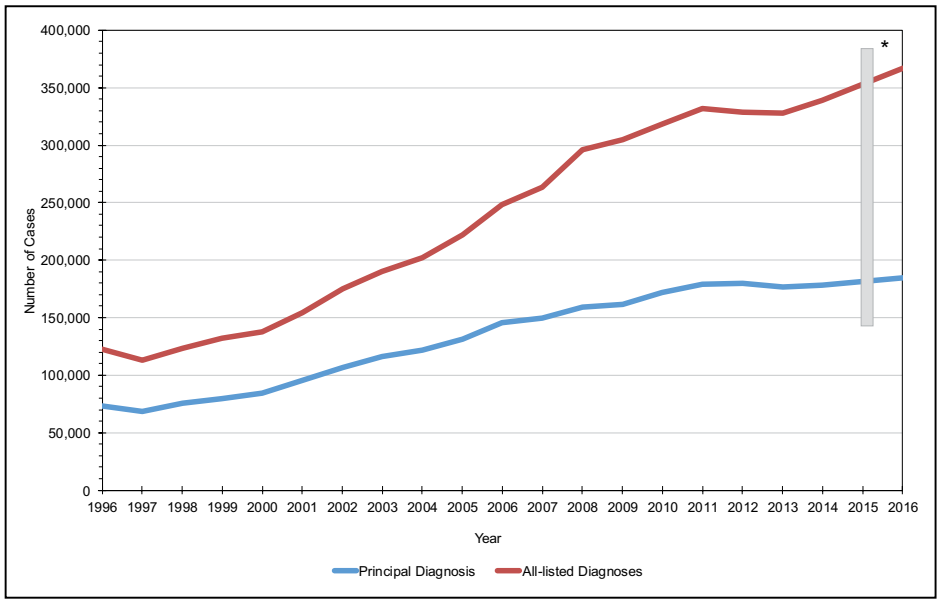

Chart 22-1. Trends in hospitalized pulmonary embolism, United States, 1996 to 2016.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[3]

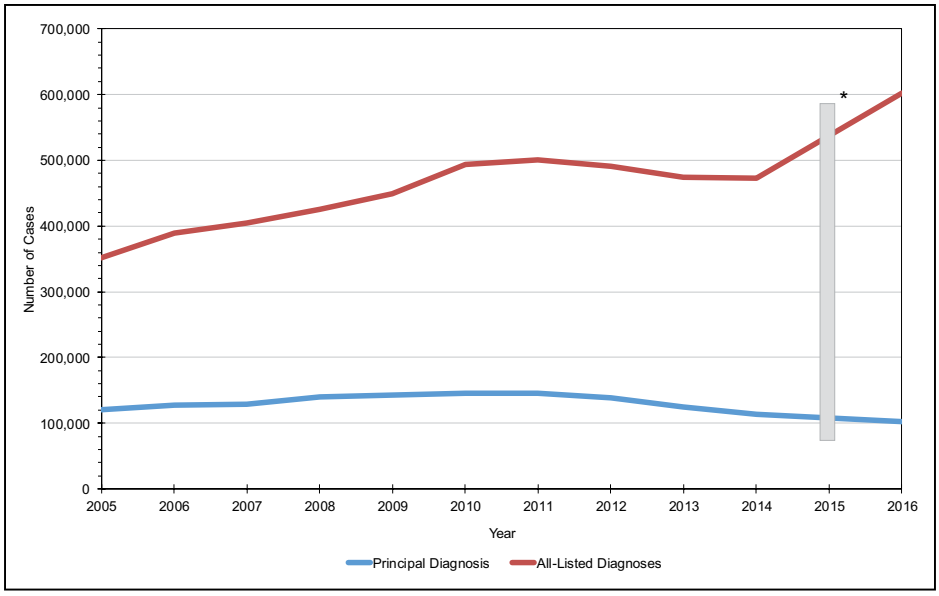

Chart 22-2. Trends in hospitalized deep vein thrombosis, United States, 2005 to 2016.
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.[3]

REFERENCES

1. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death microdata files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
2. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
3. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
4. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
5. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
6. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med.* 2011;171:831–837. doi: 10.1001/archinternmed.2011.178
7. Stein PD, Matta F, Hughes MJ. Home treatment of deep venous thrombosis according to comorbid conditions. *Am J Med.* 2016;129:392–397. doi: 10.1016/j.amjmed.2015.10.022
8. Stein PD, Matta F, Hughes PG, Hourmouzis ZN, Hourmouzis NP, White RM, Ghiardi MM, Schwartz MA, Moore HL, Bach JA, et al. Home treatment of pulmonary embolism in the era of novel oral anticoagulants. *Am J Med.* 2016;129:974–977. doi: 10.1016/j.amjmed.2016.03.035
9. Klil-Drori AJ, Coulombe J, Suissa S, Hirsch A, Tagalakis V. Temporal trends in outpatient management of incident pulmonary embolism and associated mortality. *Thromb Res.* 2018;161:111–116. doi: 10.1016/j.thromres.2017.10.026
10. Smith SB, Geske JB, Kathuria P, Cuttica M, Schimmel DR, Courtney DM, Waterer GW, Wunderink RG. Analysis of national trends in admissions for pulmonary embolism. *Chest.* 2016;150:35–45. doi: 10.1016/j.chest.2016.02.638
11. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med.* 2004;117:19–25. doi: 10.1016/j.amjmed.2004.01.018
12. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158:585–593. doi: 10.1001/archinte.158.6.585
13. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost.* 2007;5:692–699. doi: 10.1111/j.1538-7836.2007.02450.x
14. Folsom AR, Basu S, Hong CP, Heckbert SR, Lutsey PL, Rosamond WD, Cushman M; Atherosclerosis Risk in Communities (ARIC) study. Reasons for differences in the incidence of venous thromboembolism in black versus white Americans. *Am J Med.* 2019;132:970–976. doi: 10.1016/j.amjmed.2019.03.021
15. White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. *Thromb Haemost.* 2005;93:298–305. doi: 10.1160/TH04-08-0506
16. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. *Am J Cardiol.* 2000;85:1334–1337. doi: 10.1016/s0002-9149(00)00766-9
17. Stein PD, Kayali F, Olson RE, Milford CE. Pulmonary thromboembolism in Asians/Pacific Islanders in the United States: analysis of data from the National Hospital Discharge Survey and the United States Bureau of the Census. *Am J Med.* 2004;116:435–442. doi: 10.1016/j.amjmed.2003.11.020
18. Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR Jr, Folsom AR. Correlates and consequences of venous thromboembolism: the Iowa Women's Health Study. *Am J Public Health.* 2010;100:1506–1513. doi: 10.2105/AJPH.2008.157776
19. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med.* 2016;129:339.e19–e26. doi: 10.1016/j.amjmed.2015.10.014
20. Connolly GC, Francis CW. Cancer-associated thrombosis. *Hematology Am Soc Hematol Educ Program.* 2013;2013:684–691. doi: 10.1182/asheducation-2013.1.684
21. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood.* 2013;122:1712–1723. doi: 10.1182/blood-2013-04-460121
22. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost.* 2017;117:219–230. doi: 10.1160/TH16-08-0615

23. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol.* 2008;28:370–372. doi: 10.1161/ATVBAHA.108.162545
24. Folsom AR, Tang W, Roetker NS, Kshirsagar AV, Derebail VK, Lutsey PL, Naik R, Pankow JS, Grove ML, Basu S, et al. Prospective study of sickle cell trait and venous thromboembolism incidence. *J Thromb Haemost.* 2015;13:2–9. doi: 10.1111/jth.12787
25. Mahmoodi BK, Gansevoort RT, Næss IA, Lutsey PL, Brækkan SK, Veeger NJ, Brodin EE, Meijer K, Sang Y, Matsushita K, et al. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation.* 2012;126:1964–1971. doi: 10.1161/CIRCULATIONAHA.112.113944
26. Ahlehoff O, Wu JJ, Raunsø J, Kristensen SL, Khalid U, Kofoed K, Gislason G. Cutaneous lupus erythematosus and the risk of deep venous thrombosis and pulmonary embolism: a Danish nationwide cohort study. *Lupus.* 2017;26:1435–1439. doi: 10.1177/0961203317716306
27. Annangi S, Dammalapati TR, Nutalapati S, Henriques King MN. Prevalence of pulmonary embolism among systemic lupus erythematosus discharges: a decade of analysis of the National Hospital Discharge Survey. *J Clin Rheumatol.* 2017;23:200–206. doi: 10.1097/RHU.0000000000000521
28. Aviña-Zubieta JA, Jansz M, Sayre EC, Choi HK. The risk of deep venous thrombosis and pulmonary embolism in primary Sjögren syndrome: a general population-based study. *J Rheumatol.* 2017;44:1184–1189. doi: 10.3899/jrheum.160185
29. Cohoon KP, Ashrani AA, Crusan DJ, Petterson TM, Bailey KR, Heit JA. Is infection an independent risk factor for venous thromboembolism? A population-based, case-control study. *Am J Med.* 2018;131:307–316.e2. doi: 10.1016/j.amjmed.2017.09.015
30. Budnik I, Brill A. Immune factors in deep vein thrombosis initiation. *Trends Immunol.* 2018;39:610–623. doi: 10.1016/j.it.2018.04.010
31. Grimnes G, Isaksen T, Tichelaar YIGV, Brækkan SK, Hansen JB. Acute infection as a trigger for incident venous thromboembolism: results from a population-based case-crossover study. *Res Pract Thromb Haemost.* 2018;2:85–92. doi: 10.1002/rth2.12065
32. Ge SQ, Tao X, Cai LS, Deng XY, Hwang MF, Wang CL. Associations of hormonal contraceptives and infertility medications on the risk of venous thromboembolism, ischemic stroke, and cardiovascular disease in women. *J Investig Med.* 2019;67:729–735. doi: 10.1136/jim-2018-000750
33. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol.* 2006;194:1311–1315. doi: 10.1016/j.ajog.2005.11.008
34. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis.* 2016;41:92–128. doi: 10.1007/s11239-015-1309-0
35. Greer IA. Thrombosis in pregnancy: updates in diagnosis and management. *Hematology Am Soc Hematol Educ Program.* 2012;2012:203–207. doi: 10.1182/asheducation-2012.1.203
36. Henriksson P, Westerlund E, Wallén H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after *in vitro* fertilisation: cross sectional study. *BMJ.* 2013;346:e8632. doi: 10.1136/bmj.e8632
37. McLean K, Cushman M. Venous thromboembolism and stroke in pregnancy. *Hematology Am Soc Hematol Educ Program.* 2016;2016:243–250. doi: 10.1182/asheducation-2016.1.243
38. Tepper NK, Boulet SL, Whiteman MK, Monsour M, Marchbanks PA, Hooper WC, Curtis KM. Postpartum venous thromboembolism: incidence and risk factors. *Obstet Gynecol.* 2014;123:987–996. doi: 10.1097/AOG.0000000000000230
39. Mahmoodi BK, Cushman M, Anne Næss I, Allison MA, Bos WJ, Brækkan SK, Cannegieter SC, Gansevoort RT, Gona PN, Hammerstrøm J, et al. Association of traditional cardiovascular risk factors with venous thromboembolism: an individual participant data meta-analysis of prospective studies [published correction appears in *Circulation*. 2017;135:e788]. *Circulation.* 2017;135:7–16. doi: 10.1161/CIRCULATIONAHA.116.024507
40. Gregson J, Kaptoge S, Bolton T, Pennells L, Willeit P, Burgess S, Bell S, Sweeting M, Rimm EB, Kabrhel C, et al; Emerging Risk Factors Collaboration. Cardiovascular risk factors associated with venous thromboembolism. *JAMA Cardiol.* 2019;4:163–173. doi: 10.1001/jamacardio.2018.4537
41. Zöller B, Li X, Sundquist J, Sundquist K. A nationwide family study of pulmonary embolism: identification of high risk families with increased risk of hospitalized and fatal pulmonary embolism. *Thromb Res.* 2012;130:178–182. doi: 10.1016/j.thromres.2012.02.002
42. Zöller B, Ohlsson H, Sundquist J, Sundquist K. Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden [published correction appears in *Thromb Haemost*. 2013;110:204]. *Thromb Haemost.* 2013;109:458–463. doi: 10.1160/TH12-10-0743
43. Kujovich JL. Factor V Leiden thrombophilia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. GeneReviews [Internet]. Seattle, WA: University of Washington; 1993.
44. Simone B, De Stefano V, Leoncini E, Zacho J, Martinelli I, Emmerich J, Rossi E, Folsom AR, Almawi WY, Scarabin PY, et al. Risk of venous thromboembolism associated with single and combined effects of factor V Leiden, prothrombin 20210A and methylenetethraydrofolate [sic] reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. *Eur J Epidemiol.* 2013;28:621–647. doi: 10.1007/s10654-013-9825-8
45. Croles FN, Borjas-Howard J, Nasserinejad K, Leebeek FWG, Meijer K. Risk of venous thrombosis in antithrombin deficiency: a systematic review and bayesian meta-analysis. *Semin Thromb Hemost.* 2018;44:315–326. doi: 10.1055/s-0038-1625983
46. Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *BMJ.* 2017;359:j4452. doi: 10.1136/bmj.j4452
47. Morange PE, Suchon P, Trégouët DA. Genetics of venous thrombosis: update in 2015. *Thromb Haemost.* 2015;114:910–919. doi: 10.1160/TH15-05-0410
48. Klarin D, Emdin CA, Natarajan P, Conrad MF, Kathiresan S; INVENT Consortium. Genetic analysis of venous thromboembolism in UK Biobank identifies the ZFPM2 locus and implicates obesity as a causal risk factor. *Circ Cardiovasc Genet*. 2017;10:e001643. doi: 10.1161/CIRCGENETICS.116.001643
49. de Haan HG, Bezemer ID, Doggen CJ, Le Cessie S, Reitsma PH, Arellano AR, Tong CH, Devlin JJ, Bare LA, Rosendaal FR, et al. Multiple SNP testing improves risk prediction of first venous thrombosis. *Blood.* 2012;120:656–663. doi: 10.1182/blood-2011-12-397752
50. Lindstrom S, Brody JA, Turman C, Germain M, Bartz TM, Smith EN, Chen MH, Puurunen M, Chasman D, Hassler J, et al; INVENT Consortium. A large-scale exome array analysis of venous thromboembolism. *Genet Epidemiol*. 2019;43:449-457. doi: 10.1002/gepi.22187
51. de Haan HG, van Hylckama Vlieg A, Lotta LA, Gorski MM, Bucciarelli P, Martinelli I, Baglin TP, Peyvandi F, Rosendaal FR; INVENT Consortium. Targeted sequencing to identify novel genetic risk factors for deep vein thrombosis: a study of 734 genes. *J Thromb Haemost.* 2018;16:2432–2441. doi: 10.1111/jth.14279
52. Tritschler T, Kraaijpoel N, Le Gal G, Wells PS. Venous thromboembolism: advances in diagnosis and treatment [published correction appears in *JAMA*. 2018;320:2486]. *JAMA*. 2018;320:1583–1594. doi: 10.1001/jama.2018.14346
53. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in *Chest*. 2016;150:988]. *Chest.* 2016;149:315–352. doi: 10.1016/j.chest.2015.11.026
54. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361:2342–2352. doi: 10.1056/NEJMoa0906598
55. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510. doi: 10.1056/NEJMoa1007903
56. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism [published correction appears in *N Engl J Med*. 2014;370:390]. *N Engl J Med*. 2013;369:1406–1415. doi: 10.1056/NEJMoa1306638
57. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369:799–808. doi: 10.1056/NEJMoa1302507
58. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost.* 2014;12:320–328. doi: 10.1111/jth.12485
59. Biedermann JS, Kruip MJHA, van der Meer FJ, Rosendaal FR, Leebeek FWG, Cannegieter SC, Lijfering WM. Rosuvastatin use improves

measures of coagulation in patients with venous thrombosis. *Eur Heart J.* 2018;39:1740–1747. doi: 10.1093/eurheartj/ehy014
60. Minges KE, Bikdeli B, Wang Y, Attaran RR, Krumholz HM. National and regional trends in deep vein thrombosis hospitalization rates, discharge disposition, and outcomes for Medicare beneficiaries. *Am J Med.* 2018;131:1200–1208. doi: 10.1016/j.amjmed.2018.04.033
61. Minges KE, Bikdeli B, Wang Y, Kim N, Curtis JP, Desai MM, Krumholz HM. National trends in pulmonary embolism hospitalization rates and outcomes for adults aged ≥65 years in the United States (1999 to 2010). *Am J Cardiol.* 2015;116:1436–1442. doi: 10.1016/j.amjcard.2015.07.068
62. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med.* 2013;126:832.e13–e21. doi: 10.1016/j.amjmed.2013.02.024
63. Kalayci A, Gibson CM, Chi G, Yee MK, Korjian S, Datta S, Nafee T, Gurin M, Haroian N, Qamar I, et al. Asymptomatic deep vein thrombosis is associated with an increased risk of death: insights from the APEX Trial. *Thromb Haemost.* 2018;118:2046–2052. doi: 10.1055/s-0038-1675606
64. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism: a prospective cohort study in 1,626 patients. *Haematologica.* 2007;92:199–205. doi: 10.3324/haematol.10516
65. Heit JA, Lahr BD, Petterson TM, Bailey KR, Ashrani AA, Melton LJ 3rd. Heparin and warfarin anticoagulation intensity as predictors of recurrence after deep vein thrombosis or pulmonary embolism: a population-basedcohortstudy.*Blood.*2011;118:4992–4999.doi:10.1182/blood-2011-05-357343
66. Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. *Mayo Clin Proc.* 2000;75:1249–1256. doi: 10.4065/75.12.1249
67. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, et al; Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;350:2257–2264. doi: 10.1056/NEJMoa032274
68. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res.* 2016;137:3–10. doi: 10.1016/j.thromres.2015.11.033
69. Criqui MH, Jamosmos M, Fronek A, Denenberg JO, Langer RD, Bergan J, Golomb BA. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol.* 2003;158:448–456. doi: 10.1093/aje/kwg166
70. Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res.* 2018;164:100–109. doi: 10.1016/j.thromres.2017.07.026
71. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. *Am J Prev Med.* 1988;4:96–101.
72. Criqui MH, Denenberg JO, Bergan J, Langer RD, Fronek A. Risk factors for chronic venous disease: the San Diego Population Study. *J Vasc Surg.* 2007;46:331–337. doi: 10.1016/j.jvs.2007.03.052
73. Cushman M, Callas PW, Denenberg JO, Bovill EG, Criqui MH. Risk factors for peripheral venous disease resemble those for venous thrombosis: the San Diego Population Study. *J Thromb Haemost.* 2010;8:1730–1735. doi: 10.1111/j.1538-7836.2010.03924.x
74. Castro-Ferreira R, Cardoso R, Leite-Moreira A, Mansilha A. The role of endothelial dysfunction and inflammation in chronic venous disease. *Ann Vasc Surg.* 2018;46:380–393. doi: 10.1016/j.avsg.2017.06.131
75. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, Gupta DK, Prandoni P, Vedantham S, Walsh ME, et al; on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2015;131:e359]. *Circulation.* 2014;130:1636–1661. doi: 10.1161/CIR.0000000000000130
76. Busuttil A, Lim CS, Davies AH. Post thrombotic syndrome. *Adv Exp Med Biol.* 2017;906:363–375. doi: 10.1007/5584_2016_126
77. Rabinovich A, Ducruet T, Kahn SR; SOX Trial investigators. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. *J Thromb Haemost.* 2018;16:262–270. doi: 10.1111/jth.13909
78. Dronkers CEA, Mol GC, Maraziti G, van de Ree MA, Huisman MV, Becattini C, Klok FA. Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis. *Thromb Haemost.* 2018;118:1428–1438. doi: 10.1055/s-0038-1666859
79. Amin EE, Joore MA, ten Cate H, Meijer K, Tick LW, Middeldorp S, Mostard GJM, ten Wolde M, van den Heiligenberg SM, van Wissen S, et al. Clinical and economic impact of compression in the acute phase of deep vein thrombosis. *J Thromb Haemost.* 2018;16:1555–1563. doi: 10.1111/jth.14163
80. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, Mostard GJM, Ten Wolde M, van den Heiligenberg SM, van Wissen S, et al; IDEAL DVT Investigators. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol.* 2018;5:e25–e33. doi: 10.1016/S2352-3026(17)30227-2
81. Rabinovich A, Kahn SR. The postthrombotic syndrome: current evidence and future challenges. *J Thromb Haemost.* 2017;15:230–241. doi: 10.1111/jth.13569
82. Slonková V, Slonková V Jr, Vašků A, Vašků V. Genetic predisposition for chronic venous insufficiency in several genes for matrix metalloproteinases (MMP-2, MMP-9, MMP-12) and their inhibitor TIMP-2. *J Eur Acad Dermatol Venereol.* 2017;31:1746–1752. doi: 10.1111/jdv.14447
83. Anwar MA, Georgiadis KA, Shalhoub J, Lim CS, Gohel MS, Davies AH. A review of familial, genetic, and congenital aspects of primary varicose vein disease. *Circ Cardiovasc Genet.* 2012;5:460–466. doi: 10.1161/CIRCGENETICS.112.963439
84. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation.* 2014;130:333–346. doi: 10.1161/CIRCULATIONAHA.113.006898
85. Dua A, Desai SS, Heller JA. The impact of race on advanced chronic venous insufficiency. *Ann Vasc Surg.* 2016;34:152–156. doi: 10.1016/j.avsg.2016.01.020
86. Dua A, Heller JA. Advanced chronic venous insufficiency. *Vasc Endovascular Surg.* 2017;51:12–16. doi: 10.1177/1538574416682175
87. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. *Chest.* 2014;146:476–495. doi: 10.1378/chest.14-0527
88. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, Gabbay E. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart.* 2012;98:1805–1811. doi: 10.1136/heartjnl-2012-301992
89. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, Jing ZC, Gibbs JS. A global view of pulmonary hypertension. *Lancet Respir Med.* 2016;4:306–322. doi: 10.1016/S2213-2600(15)00543-3
90. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev.* 2017;26:160121. doi: 10.1183/16000617.0121-2016
91. Derchi G, Galanello R, Bina P, Cappellini MD, Piga A, Lai ME, Quarta A, Casu G, Perrotta S, Pinto V, et al; on behalf of the Webthal Pulmonary Arterial Hypertension Group. Prevalence and risk factors for pulmonary arterial hypertension in a large group of β-thalassemia patients using right heart catheterization: a Webthal study. *Circulation.* 2014;129:338–345. doi: 10.1161/CIRCULATIONAHA.113.002124
92. Martinez C, Wallenhorst C, Teal S, Cohen AT, Peacock AJ. Incidence and risk factors of chronic thromboembolic pulmonary hypertension following venous thromboembolism, a population-based cohort study in England. *Pulm Circ.* 2018;8:2045894018791358. doi: 10.1177/2045894018791358
93. Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuß G, Huisman MV, Konstantinides S, Lankeit M. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost.* 2016;14:121–128. doi: 10.1111/jth.13175
94. Barros A, Baptista R, Nogueira A, Jorge E, Teixeira R, Castro G, Monteiro P, Providência LA. Predictors of pulmonary hypertension after intermediate-to-high risk pulmonary embolism. *Rev Port Cardiol.* 2013;32:857–864. doi: 10.1016/j.repc.2013.02.008
95. Chakinala MM, Coyne DW, Benza RL, Frost AE, McGoon MD, Hartline BK, Frantz RP, Selej M, Zhao C, Mink DR, et al. Impact of declining renal function on outcomes in pulmonary arterial hypertension: a REVEAL registry analysis. *J Heart Lung Transplant.* 2018;37:696–705. doi: 10.1016/j.healun.2017.10.028

96. Frantz RP, Farber HW, Badesch DB, Elliott CG, Frost AE, McGoon MD, Zhao C, Mink DR, Selej M, Benza RL. Baseline and serial brain natriuretic peptide level predicts 5-year overall survival in patients with pulmonary arterial hypertension: data from the REVEAL Registry. *Chest.* 2018;154:126–135. doi: 10.1016/j.chest.2018.01.009
97. Tang M, Batty JA, Lin C, Fan X, Chan KE, Kalim S. Pulmonary hypertension, mortality, and cardiovascular disease in CKD and ESRD patients: a systematic review and meta-analysis. *Am J Kidney Dis.* 2018;72:75–83. doi: 10.1053/j.ajkd.2017.11.018
98. Dodson MW, Allen-Brady K, Brown LM, Elliott CG, Cannon-Albright LA. Chronic thromboembolic pulmonary hypertension cases cluster in families. *Chest.* 2019;155:384–390. doi: 10.1016/j.chest.2018.10.004
99. Gamou S, Kataoka M, Aimi Y, Chiba T, Momose Y, Isobe S, Hirayama T, Yoshino H, Fukuda K, Satoh T. Genetics in pulmonary arterial hypertension in a large homogeneous Japanese population. *Clin Genet.* 2018;94:70–80. doi: 10.1111/cge.13154
100. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, et al; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med.* 2015;373:834–844. doi: 10.1056/NEJMoa1413687
101. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, et al; GRIPHON Investigators. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med.* 2015;373:2522–2533. doi: 10.1056/NEJMoa1503184
102. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med.* 2013;369:809–818. doi: 10.1056/NEJMoa1213917
103. Farber HW, Miller DP, Poms AD, Badesch DB, Frost AE, Muros-Le Rouzic E, Romero AJ, Benton WW, Elliott CG, McGoon MD, et al. Five-year outcomes of patients enrolled in the REVEAL Registry. *Chest.* 2015;148:1043–1054. doi: 10.1378/chest.15-0300
104. Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant.* 2015;34:362–368. doi: 10.1016/j.healun.2014.08.020
105. Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, Franco OH, Hofman A, Schermuly RT, Weissmann N, et al. The Giessen Pulmonary Hypertension Registry: survival in pulmonary hypertension subgroups. *J Heart Lung Transplant.* 2017;36:957–967. doi: 10.1016/j.healun.2017.02.016
106. Weatherald J, Boucly A, Chemla D, Savale L, Peng M, Jevnikar M, Jaïs X, Taniguchi Y, O'Connell C, Parent F, et al. Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. *Circulation.* 2018;137:693–704. doi: 10.1161/CIRCULATIONAHA.117.029254
107. Mehari A, Alam S, Tian X, Cuttica MJ, Barnett CF, Miles G, Xu D, Seamon C, Adams-Graves P, Castro OL, et al. Hemodynamic predictors of mortality in adults with sickle cell disease. *Am J Respir Crit Care Med.* 2013;187:840–847. doi: 10.1164/rccm.201207-1222OC
108. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation.* 2016;133:859–871. doi: 10.1161/CIRCULATIONAHA.115.016522
109. Studer S, Hull M, Pruett J, Koep E, Tsang Y, Drake W 3rd. Treatment patterns, healthcare resource utilization, and healthcare costs among patients with pulmonary arterial hypertension in a real-world US database. *Pulm Circ.* 2019;9:2045894018816294. doi: 10.1177/2045894018816294

23. PERIPHERAL ARTERY DISEASE AND AORTIC DISEASES

ICD-9 440.20 to 440.24, 440.30 to 440.32, 440.4, 440.9, 443.9, 445.02; ICD-10 I70.2, I70.9, I73.9, I74.3, I74.4. See Tables 23-1 through 23-3 and Charts 23-1 through 23-9

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Abbreviations Used in Chapter 23

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACC	American College of Cardiology
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
FH	familial hypercholesterolemia
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
GBD	Global Burden of Disease
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HF	heart failure
HR	hazard ratio
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
IRAD	International Registry of Acute Aortic Dissection
KD	Kawasaki disease
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	Nationwide Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
OVER	Open Versus Endovascular Repair
PA	physical activity
PAD	peripheral artery disease
PCSK9	proprotein convertase subtilisin/kexin type 9
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
SNP	single-nucleotide polymorphism
TGF	transforming growth factor
UI	uncertainty interval

Peripheral Artery Disease

Prevalence and Incidence (Charts 23-1 and 23-2)

- On the basis of data from several US cohorts during the 1970s to 2000s and the 2000 US Census, 6.5 million Americans ≥40 years of age (5.8%) are estimated to have low ABI (<0.9).[1]
- Further accounting for PAD cases with ABI >0.9 (after revascularization or false-negative results with ABI), in 2000, PAD was estimated to affect ≈8.5 million Americans ≥40 years of age (7.2%).[1]
- Estimates of PAD prevalence in males and females by age and ethnicity are shown in Charts 23-1 and 23-2.
- The highest prevalence of low ABI (<0.9) has been observed among older adults (22.7% among individuals ≥80 years of age versus 1.6% among those 40–49 years of age) and NH blacks (≈11.6% in NH blacks versus ≈5.5% in whites).[1] The prevalence of low ABI (<0.9) is similar between females (5.9%) and males (5.0%).
- Only ≈10% of people with PAD have the classic symptom of intermittent claudication. Approximately 40% do not complain of leg pain, whereas the remaining 50% have a variety of leg symptoms different from classic claudication (ie, exertional pain that either did not stop the individual from walking or did stop the individual from walking but did not involve the calves or did not resolve within 10 minutes of rest).[2,3]
- On the basis of *ICD* codes in nationwide claims data from large employers' health plans and from Medicare and Medicaid programs between 2003 and 2008, among adults >40 years of age, the annual incidence and prevalence of PAD were 2.69% and 12.02%, respectively.[4] The corresponding estimates for critical limb ischemia, the most severe form of PAD, were 0.35% and 1.33%, respectively.
- Data from the NIS demonstrate that admission rates because of critical limb ischemia remained constant from 2003 to 2011.[5]

Risk Factors

- The risk factors for PAD are similar but not identical to those for CHD. Cigarette smoking is a stronger risk factor for PAD than for CHD.[6] The age- and sex-adjusted OR for heavy smoking was 3.94 for symptomatic PAD and 1.66 for CHD.[6]
- Among males in the Health Professionals Follow-up Study, smoking, type 2 DM, hypertension, and hypercholesterolemia accounted for 75% (95% CI, 64%–87%) of risk associated with development of clinical PAD.[7]
- In a meta-analysis of 34 studies from high-income countries and low- to middle-income

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countries, respectively, important risk factors for PAD included cigarette smoking (OR, 2.72 versus 1.42), DM (OR, 1.88 versus 1.47), hypertension (OR, 1.55 versus 1.36), and hypercholesterolemia (OR, 1.19 versus 1.14).[8]

- A study of 3.3 million people 40 to 99 years of age primarily self-referring for vascular screening tests in the United States showed that risk factor burden was associated with increased prevalence of PAD, and there was a graded relationship between the number of traditional risk factors and the prevalence of PAD.[9]
- Other risk factors for PAD include sedentary lifestyle, elevated inflammation markers, hypertension in pregnancy, and CKD.[9–12]
- Blacks have a 37% higher amputation risk than whites (HR, 1.37 [95% CI, 1.30–1.45]). Lower SES is an independent predictor for amputation (HR, 1.12 [95% CI, 1.06–1.17]).[13]
- A secondary analysis of a randomized feeding trial showed reduced risk of incident PAD with the Mediterranean diet compared with a control diet.[14]
- In the ARIC study, the incidence of PAD was higher among participants with lower household income and educational attainment.[15]

Genetics

- Atherosclerotic PAD is heritable, even independent of risk factors for PAD which themselves are heritable.
- In the ethnically diverse San Diego Population Study, a family history of PAD was independently associated with a 1.83-fold higher odds of PAD.[16] In the Swedish Twin Registry, the OR of PAD in a monozygotic twin was 17.7, and 5.7 in dizygotic twins; estimated genetic effects accounted for 58% and nonshared environmental effects for 42% of the phenotypic variance between twins.[17] The NHLBI Twin Study found that 48% of the variability in ABI with similar environmental risk factors could be attributed to additive genetic effects.[18]
- There are monogenic (mendelian) diseases that result in PAD, including familial lipoprotein disorders such as chylomicronemia and FH, hyperhomocysteinemia, and pseudoxanthoma elasticum.[19]
- GWASs have identified genetic loci associated with atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus, which has been shown to be associated with PAD, AAA, and intracranial aneurysm.[20] Other PAD-associated genetic loci found through GWASs include SNPs in chromosome 9 near *CDKN2B*, DAB2 interaction protein (*DAB21P*), and cytochrome B-245 α-chain (*CYBA*) genes.[21]
- GWASs have also identified genetic variants associated with inflammatory forms of PAD such as KD.[22]

Awareness, Treatment, and Control

- A US survey of >2500 adults ≥50 years of age found that 25% expressed familiarity with PAD in contrast to >65% for CHD, stroke, and HF. Only 50% of the population were aware that DM and smoking are risk factors of PAD. One in 4 knew that PAD is associated with increased risk of MI and stroke, and only 14% were aware that PAD could result in amputation. Lower income and education levels were related to lower levels of all knowledge domains.[23]
- In data concerning people ≥70 years of age or those 50 to 69 years of age with a history of DM or smoking, as well as their physicians, 83% of patients with a previous diagnosis of PAD recognized the diagnosis, but only half of their physicians were aware of the diagnosis.[2]
- A 2011 systematic review evaluated lower-extremity aerobic exercise against usual care and demonstrated a range of benefits, including the following[24]:
  - Increased time to claudication by 71 seconds (79%), to 918 seconds (422%)
  - Increased distance before claudication by 15 m (5.6%), to 232 m (200%)
  - Increased walking distance/time by 67% to 101% after 40 minutes of walking 2 to 3 times per week
- Observational studies have found that the risks of death,[25] MI,[26] and amputation[25] are substantially greater in individuals with PAD who continue to smoke than in those who have stopped smoking.
- The "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease" noted that several randomized and observational studies demonstrated that statins reduced the risk of MACE and amputation among people with PAD.[27]
- A few studies have reported that statin therapy may reduce the risk of adverse leg outcomes among patients with PAD.[28,29]
- The FOURIER trial demonstrated that a PCSK9 inhibitor, evolocumab, reduced the risk of major adverse limb events, including acute limb ischemia, major amputation, and urgent revascularization (HR 0.58 [95% CI, 0.38–0.88]), among patients with a history of MI, stroke, or PAD.[30]
- A few novel antithrombotic medications (rivaroxaban and vorapaxar) have been shown to reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.[31,32]

- A recent Danish trial in males 65 to 74 years of age reported that screening of PAD (with ABI), AAA (with abdominal ultrasound), and hypertension followed by optimal care resulted in 7% lower risk of 5-year mortality compared with no screening.[33]
- Data from the US Department of Veterans Affairs during 2013 to 2014 demonstrate that patients with PAD alone receive optimal medical therapy less frequently than patients with CHD (including those with concomitant PAD; statin use 59% versus 72% and antiplatelet use 66% versus 84%, respectively).[34]
- In a study that randomized patients with PAD to 3 groups (optimal medical care, supervised exercise training, and iliac artery stent placement), supervised exercise resulted in superior treadmill walking distance compared with stenting. Results in the exercise group and stent group were superior to optimal medical care alone.[35]
- In 2017, the Centers for Medicare & Medicaid Services decided to cover supervised exercise therapy (up to 36 sessions over 12 weeks) for eligible symptomatic PAD patients with intermittent claudication.[36]
- Endovascular therapies for critical limb ischemia are being used with greater frequency in the United States. From 2003 to 2011, there was a significant increase in endovascular treatment of critical limb ischemia (from 5.1% to 11.0%), which was accompanied by lower rates of in-hospital mortality and major amputation, as well as shorter length of stay.[5]

Mortality (See Chart 23-3)

- In 2017, the overall any-mention age-adjusted death rate for PAD was 14.4 per 100 000. Any-mention death rates in males were 17.8 for NH whites, 22.1 for NH blacks, 7.3 for NH Asians or Pacific Islanders, 17.1 for NH American Indians or Alaska Natives, and 13.4 for Hispanic males. In females, rates were 12.4 for NH whites, 14.8 for NH blacks, 5.3 for NH Asians or Pacific Islanders, 13.1 for NH American Indians or Alaska Natives, and 9.1 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER[37]).
- In 2017, PAD was the underlying cause in 12 805 deaths. The number of any-mention deaths attributable to PAD was 56 938 in 2017 (unpublished NHLBI tabulation using NVSS[38] and CDC WONDER[37]).
- A 2008 meta-analysis of 24 955 males and 23 339 females from 16 cohorts demonstrated a reverse-J-shaped association between ABI and mortality in which participants with an ABI of 1.11 to 1.40 were at lowest risk for mortality. In males, low ABI (≤0.9) carried a 3-fold (RR, 3.33 [95% CI, 2.74–4.06]) risk of all-cause death compared with a normal ABI (1.11–1.40), and a similar risk was observed in females (RR, 2.71 [95% CI, 2.03–3.62]).[38] A similar reverse-J-shaped association between ABI and cardiovascular mortality was observed (Chart 23-3).
- In-hospital mortality was higher in females than males, regardless of disease severity or types of procedure, even after adjustment for age and comorbidities: 0.5% versus 0.2% after percutaneous revascularization for intermittent claudication; 1.0% versus 0.7% after surgical revascularization for intermittent claudication; 2.3% versus 1.6% after percutaneous revascularization for critical limb ischemia; and 2.7% versus 2.2% after surgical revascularization for critical limb ischemia (P<0.01 for all comparisons).[39]

Complications

- PAD is a marker for systemic atherosclerotic disease, and thus, people with PAD are more likely to have atherosclerosis in other vascular beds (eg, coronary, carotid, and renal arteries and abdominal aorta).[40–43]
- Pooled data from 11 studies in 6 countries found that the pooled age-, sex-, risk factor–, and CVD-adjusted RRs in people with PAD (defined by ABI <0.9) versus those without were 1.45 (95% CI, 1.08–1.93) for CHD and 1.35 (95% CI, 1.10–1.65) for stroke.[44]
- A recent study with ≈28 000 patients with a history of CVD demonstrated that patients with symptomatic PAD but no prior MI or stroke had ≈2 times higher risk of CVD events than those with prior MI or stroke but no symptomatic PAD.[30]
- From 2000 to 2008, the overall rate of lower-extremity amputation decreased significantly, from 7258 to 5790 per 100 000 Medicare beneficiaries with PAD. Patients with PAD who underwent major lower-extremity amputation were more likely to have DM (60.3% versus 35.7% with PAD without amputation; P<0.001).[45]
- However, a recent report from the NIS demonstrated that after declining trends, the rate of nontraumatic lower-extremity amputation increased by 50% between 2009 and 2015 in adults with DM.[46]
- Significant geographic variation in the rate of lower-extremity amputation within the United States was reported, from 5500 amputations per 100 000 PAD patients in the Mountain region to 8400 amputations per 100 000 PAD patients in the East South Central region. Lower-extremity amputation was performed more frequently in the East South Central region (adjusted OR, 1.152 [95% CI, 1.131–1.174]; P<0.001) and West South Central

region (adjusted OR, 1.115 [95% CI, 1.097–1.133]; *P*<0.001) and less in the Middle Atlantic region (OR, 0.833 [95% CI, 0.820–0.847]; *P*<0.001) versus the South Atlantic reference region.[45]

- Among 186 338 older Medicare PAD patients undergoing major lower-extremity amputation, mortality was found to be 48.3% at 1 year.[47]
- A study of Medicare beneficiaries reported that between 2006 and 2011, 39 339 required revascularization for PAD, and the annual rate of peripheral vascular intervention increased slightly from 401.4 to 419.6 per 100 000 people.[48]
- Among 6391 patients with PAD in the COMPASS trial, 128 (2.0%) experienced leg revascularization or amputation during a median follow-up of 21 months. PAD patients who experienced leg revascularization or amputation had higher risk of adverse outcomes such as all-cause mortality (HR, 3.23 [95% CI, 1.87–5.56]) and any subsequent hospitalization (HR, 7.21 [95% CI, 5.51–9.43]).[31]
- People with PAD have impaired function and quality of life, regardless of whether or not they report leg symptoms. Furthermore, patients with PAD, including those who are asymptomatic, experience a significant decline in lower-extremity function over time.[49–51] A few recent studies have demonstrated that even individuals with low-normal ABI (0.91–0.99) have reduced physical function compared with those with normal ABI.[52]
- Among patients with established PAD, higher PA levels during daily life are associated with better overall survival rate, a lower risk of death because of CVD, and slower rates of functional decline.[53,54] In addition, better 6-minute walk performance and faster walking speed are associated with lower rates of all-cause mortality, cardiovascular mortality, and mobility loss.[55,56]

Healthcare Utilization: Hospital Discharges and Ambulatory Care Visits (See Table 23-1)

- Principal diagnosis discharges for PAD decreased from 2006 to 2016, with first-listed discharges of 156 000 and 111 000, respectively (HCUP,[57] unpublished NHLBI tabulation; Table 23-1).
- In 2016, there were 1 600 000 physician office visits and 11 000 ED visits with a primary diagnosis of PAD (NAMCS[58]/NHAMCS,[59] unpublished NHLBI tabulation).

Global Burden (See Table 23-2 and Charts 23-4 through 23-6)

- A systematic review of 34 studies reported that globally, 202 million people have PAD, and during 2000 to 2010, the number of people with PAD increased by 28.7% in low- to middle-income countries and by 13.1% in high-income countries.[8] The prevalence of PAD increased with age in both men and women and in both low/middle- and high-income countries (Chart 23-4).
- Global mortality attributable to PAD and global prevalence of PAD by sex from the GBD 2017 study are shown in Table 23-2.[60] The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.
  - PAD mortality is highest in Eastern Europe (Chart 23-5).
  - PAD prevalence is highest in North America, Southeast Asia, and Oceania (Chart 23-6).

Aortic Diseases
ICD-9 440, 441, 444, and 447; *ICD-10* I70, I71, I74, I77, and I79.

Aortic Aneurysm and Acute Aortic Dissection (See Charts 23-7 and 23-8)
ICD-9 441; ICD-10 I71.

Prevalence and Incidence

- The prevalence of AAAs that are 2.9 to 4.9 cm in diameter ranges from 1.3% in males 45 to 54 years of age to 12.5% in males 75 to 84 years of age. For females, the prevalence ranges from 0% in the youngest to 5.2% in the oldest age groups.[61]
- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated that mean aneurysm growth rate was 2.21 mm per year and did not vary significantly by age and sex. Growth rates were higher in smokers versus former or never smokers (by 0.35 mm/y) and lower in people with DM than in those without DM (by 0.51 mm/y).[62]
- A study from Olmsted County, MN,[63] demonstrated annual age- and sex-adjusted incidences per 100 000 people of 3.5 (95% CI, 2.2–4.9) for thoracic aortic aneurysm rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection.

Risk Factors

- Many risk factors for atherosclerosis are also associated with increased risk for AAAs.[64] Of these, smoking is the most important modifiable risk factor for AAAs.[65]
- A 2014 systematic review of 17 community-based observational studies demonstrated a consistent, inverse association between DM and prevalent AAAs (OR, 0.80 [95% CI, 0.70–0.90]).[66]
- On the basis of nationally representative data from the United Kingdom, giant cell arteritis has been demonstrated to be associated with a 2-fold

higher risk (sub-HR, 1.92 [95% CI, 1.52–2.41]) after adjustment for competing risks for developing an AAA.[67]

Genetics

- Monogenic diseases that cause thoracic aortic disease include Marfan syndrome (caused by fibrillin gene mutations), Loeys-Dietz syndrome (*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3* gene mutations, all within the TGF-β pathway), vascular Ehlers-Danlos syndrome (*COL3A1* mutations), arterial tortuosity syndrome (*SLC2A10* mutations), and familial thoracic aortic aneurysm syndrome (*ACTA2, TGBR2*, and mutations in several other genes).
  - Mutations in the genes causing these disorders significantly increase the risk of developing vascular aneurysms. If these disorders are suspected (eg, because of strong family history or co-occurrence of nonaortic features typical of the disease), referral to a specialty clinic for genetic testing can be useful for diagnosis, treatment, and cascade screening in family members. The identification of a genetic cause of thoracic aortic disease can influence treatment decisions, including need for screening for aneurysms in other vascular beds and a lower threshold for aneurysm diameter for consideration of surgical repair.
- GWASs have identified genetic variants associated with nonfamilial forms of thoracic aortic aneurysm/dissection, including common variants in the fibrillin gene (*FBN1*; rare mutations in this gene cause Marfan syndrome) and variants in the LDL receptor protein–related 1 (*LRP1*) and unc-51–like kinase 4 (*ULK4*) genes.[68,69]
- AAA is heritable; a family history of AAA is a risk factor for AAA, particularly in male siblings of male patients, for whom the RR for AAA is as high as 18.[70,71]
- GWASs and other studies have identified genetic variants associated with AAA, including a locus on chromosome 3p12.3 and SNPs in *DAB2IP*, *LDLR*, *LRP1*, *MMP3*, *TGFBR2*, and *SORT1*.[72,73]
- A GWAS has also identified common genetic variants for intracranial aneurysms.[74] In addition, rare variants in *ANGPTL6* are associated with increased risk of intracranial aneurysms.[75]
- Despite the co-occurrence of different types of aneurysms, a meta-analysis has found no shared genetic variants for intracranial, thoracic, and aortic aneurysms.[70]
- Nonatherosclerotic forms of arterial disease such as fibromuscular dysplasia and spontaneous coronary artery dissection are more difficult to evaluate for genetic components given their lesser prevalence and heterogeneous nature, but studies of these diseases are ongoing. A recent study has identified a noncoding SNP in the phosphatase and actin regulator 1 gene (*PHACTR1*) as being associated with fibromuscular dysplasia.[76]

Awareness, Treatment, and Control

- Results from 4 trials (N=3314 participants) evaluating the effect of open or endovascular repair of small AAAs (4.0–5.5 cm) did not demonstrate an advantage to earlier intervention compared with routine ultrasound surveillance.[77]
- Data from 23838 patients with ruptured AAAs collected through the NIS (2005–2010) demonstrated in-hospital mortality of 53.1% (95% CI, 51.3%–54.9%), with 80.4% of patients (95% CI, 79.0%–81.9%) undergoing intervention for repair. Of individuals who underwent repair, 20.9% (95% CI, 18.6%–23.2%) underwent endovascular repair, with a 26.8% (95% CI, 23.7%–30.0%) postintervention mortality rate, and 79.1% (95% CI, 76.8%–81.4%) underwent open repair, with a 45.6% (95% CI, 43.6%–47.5%) postintervention mortality rate.[78]
- Data from the NIS suggest that the use of endovascular repair of AAAs rose substantially between 2000 and 2010 (5% versus 74% of all AAA repairs, respectively), whereas the overall number of AAAs (≈45000 per year) remained stable. In-hospital mortality and length of stay declined during this period, but costs rose.[79]
- At least for the first 3 years after elective repair of an AAA, individuals who have endovascular repair may have better outcomes than those who undergo open repair. After multivariable adjustment, Medicare patients who underwent open AAA repair had a higher risk of all-cause mortality (HR, 1.24 [95% CI, 1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year than patients who underwent endovascular repair.[80] However, after 8 years of follow-up, survival in the open repair group was similar to that in the endovascular repair group. Of note, individuals in the endovascular repair group had a higher rate of eventual aneurysm rupture (5.4%) than patients who underwent open repair (1.4%).[81] Similar findings were observed in the OVER Veterans Affairs Cooperative trial, which compared open AAA repair to endovascular repair in 881 patients and demonstrated reductions in mortality from endovascular repair at 2 years (HR, 0.63 [95% CI, 0.40–0.98]) and 3 years (HR, 0.72 [95% CI, 0.51–1.00]).[82] However, there was no survival difference between open and endovascular repair in individuals followed up for up to 9 years (mean, 5 years; HR, 0.97 [95% CI, 0.77–1.22]).[82]
- In comparisons of the United States and the United Kingdom, the United States demonstrated

a higher rate of AAA repair, smaller AAA diameter at the time of repair, and lower rates of AAA rupture and AAA-related death.[83]
- In ruptured AAAs, implementation of an endovascular-first protocol was associated with decreased perioperative adverse outcomes and improved long-term prognosis in a retrospective analysis of 88 consecutive patients seen at an academic medical center.[84]
- Perioperative mortality of endovascular aneurysm repair was not related to surgeon case volume but was lower in hospitals with higher volume (eg, 1.9% in hospitals with <10 cases a year versus 1.4% in those with 49–198 cases; *P*<0.01). Perioperative mortality after open repair was inversely related to both surgeon case volume (6.4% in ≤3 cases versus 3.8% in 14–62 cases; *P*<0.01) and hospital case volume (6.3% in ≤5 cases versus 3.8% in 14–62 cases; *P*<0.01).[85]
- The data for surgery in thoracic aortic aneurysms are more mixed between open and endovascular repair. A sample of 12 573 and 2732 Medicare patients who underwent open thoracic aortic aneurysm and endovascular repair from 1998 to 2007 demonstrated higher perioperative mortality for open repair in both intact (7.1% versus 6.1%; *P*=0.56) and ruptured (45% versus 28%; *P*<0.001) thoracic aortic aneurysms but higher 5-year survival rates (70% versus 56%; *P*<0.001).[86] Perioperative mortality rates for open repair of thoracic aortic aneurysms were higher for NH black Medicare patients than for white Medicare patients (14% versus 7%; *P*<0.001), but rates were similar for endovascular repair (7% versus 6%; *P*=0.54).[87] On the basis of data from the NIS (N=1400), weekend repair for thoracic aortic aneurysm rupture (n=322) was associated with higher mortality than weekday repair (n=1078; OR, 2.55 [95% CI, 1.77–3.68]), likely because of delays in surgical intervention.[88]
- Seventeen-year trends in the IRAD database (1996–2013) demonstrate an increase in surgical repair of type A thoracic dissections (from 79% to 90%) and a significant decrease in in-hospital and surgical mortality for type A dissections (from 31% to 22% [*P*<0.001] and from 25% to 18% [*P*=0.003], respectively). Type B dissections were more likely to be treated with endovascular therapies, but no significant changes in mortality were observed.[89]

Mortality

2017: Mortality—9928. Any-mention mortality—16 954.

Complications

(See Charts 23-7 and 23-8)

- Rates of rupture of small AAAs (3.0–5.4 cm in diameter) range from 0.71 to 11.03 per 1000 person-years, with higher rupture rates in smokers (pooled HR, 2.02 [95% CI, 1.33–3.06]) and females (pooled HR, 3.76 [95% CI, 2.58–5.47]; *P*<0.001).[62]
- There is a dose-response association between the diameter and the minimum and maximum risk of AAA rupture per year (Chart 23-7).[90]
- A 2015 systematic review that included 4 randomized trials of ultrasound screening demonstrated lower AAA-associated mortality, emergency operations, and rupture with screening, but with higher AAA-associated elective repair rates; however, there was no effect on all-cause mortality (Chart 23-8).[91] Similar results were reported in a systematic review report prepared for the US Preventive Services Task Force[87] and in a 2016 Swedish study evaluating a nationwide screening program targeting 65-year-old males.[92]
- Data from IRAD demonstrated that the rate of mesenteric malperfusion in 1809 patients with type A acute dissections was 3.7%, with a higher mortality rate than for patients without malperfusion (63.2% versus 23.8%; *P*<0.001).[93]
- Data from IRAD demonstrated that patients with acute type B aortic dissection have heterogeneous in-hospital outcomes. In-hospital mortality in patients with and without complications (such as mesenteric ischemia, renal failure, limb ischemia, or refractory pain) was 20.0% and 6.1%, respectively. In patients with complications, in-hospital mortality associated with surgical and endovascular repair was 28.6% and 10.1% (*P*=0.006), respectively.[94]

Healthcare Utilization: Hospital Discharges

- In 2016, there were 68 000 hospital discharges with aortic aneurysm as principal diagnoses, of which 49 000 were males and 19 000 were females (HCUP,[57] unpublished NHLBI tabulation).

Global Burden

(See Table 23-3 and Chart 23-9)

- Global mortality attributable to and prevalence of aortic aneurysm by sex are shown in Table 23-3. The highest age-standardized mortality rates attributable to aortic aneurysm are reported in Northern Europe, southern Latin America, New Zealand, and Fiji (Chart 23-9).

Atherosclerotic Renal Artery Stenosis *ICD-9* 440.1; *ICD-10* I70.1.

Prevalence and Incidence

- A US community-based cohort of older adults (≥65 years of age) reported the prevalence of renal artery disease as 6.8%.[95] Among those with renal

artery stenoses, 88% were unilateral and 12% were bilateral.

- A US study using Medicare data reported that the incidence rate of renal artery stenosis was 3.1 per 1000 patient-years.[96] The incidence of renal artery stenosis increased by ≈5-fold from 1992 to 2004.

Risk Factors

- Traditional atherosclerotic risk factors such as advanced age, DM, smoking, and hypertension are associated with higher prevalence of atherosclerotic renal artery stenosis.[97]

Awareness, Treatment, and Control

- The CORAL study compared medical therapy alone versus medical therapy plus renal artery stenting in patients with atherosclerotic renal artery stenosis and hypertension. Although there was a significant difference in SBP favoring the stent group (–2.3 mm Hg [95% CI, –4.4 to –0.2 mm Hg]), there was no difference in the primary end point of major cardiovascular or kidney event.[98]

Complications

- Atherosclerotic renal artery stenosis is often a cause of drug-resistant hypertension.[97]
- An Irish study reported that among a total of 3987 patients undergoing coronary angiography, the presence of renal artery stenosis conferred 2 times higher mortality risk.[99]

Table 23-1. PAD in the United States

Population Group	Prevalence, 2000, Age ≥40 y	Mortality, 2017, All Ages*	Hospital Discharges, 2016, All Ages
Both sexes	≥6.5 Million	12 805	111 000
Males	2.8 Million	5764 (45.0%)†	66 000
Females	3.7 Million	7041 (55.0%)†	45 000
NH white males	2.1 Million	4594	…
NH white females	3.0 Million	5658	…
NH black males	0.5 Million	696	…
NH black females	0.1 Million	811	…
Hispanic males	0.1 Million	333	…
Hispanic females	0.1 Million	364	…
NH Asian or Pacific Islander males	…	99‡	…
NH Asian or Pacific Islander females	…	140‡	…
NH American Indian/Alaska Native	…	61	…

Ellipses (…) indicate data not available; NH, non-Hispanic; and PAD, peripheral artery disease.

*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality attributable to PAD that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: Data derived from Allison et al.[1] Prevalence of PAD is based on an ankle-brachial index <0.9 or a previous revascularization for PAD. Mortality: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017.[100] Hospital Discharges: Unpublished NHLBI tabulation using Hospital Cost and Utilization Project, 2017.[57]

Table 23-2. Global Mortality From and Prevalence of PAD by Sex, 2017

	Both Sexes Combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	0.1 (0.0 to 0.1)	118.1 (102.7 to 134.4)	0.0 (0.0 to 0.1)	53.1 (46.1 to 60.7)	0.0 (0.0 to 0.1)	65.0 (56.7 to 73.8)
Percent change total number, 2007 to 2017	55.7 (31.0 to 74.2)	30.0 (29.1 to 30.8)	55.6 (27.1 to 72.6)	29.9 (28.8 to 30.9)	55.8 (25.6 to 79.9)	30.1 (29.2 to 30.9)
Percent change total number, 1990 to 2017	251.2 (118.8 to 411.1)	91.5 (90.1 to 93.0)	236.8 (89.7 to 361.1)	94.3 (92.2 to 96.6)	265.7 (100.5 to 483.2)	89.2 (87.6 to 90.8)
Rate per 100 000	1.0 (0.6 to 1.7)	1,480.4 (1290.2 to 1681.9)	1.1 (0.6 to 2.0)	1,438.5 (1251.7 to 1637.9)	0.8 (0.4 to 1.9)	1,520.0 (1326.0 to 1727.2)
Percent change rate, 2007 to 2017	10.5 (–6.8 to 24.1)	–1.7 (–2.2 to –1.2)	11.1 (–8.7 to 23.8)	–2.3 (–3.0 to –1.7)	10.2 (–11.1 to 27.4)	–1.1 (–1.7 to –0.6)
Percent change rate, 1990 to 2017	50.3 (–6.3 to 117.8)	–5.5 (–6.1 to –4.9)	45.6 (–19.0 to 99.8)	–6.4 (–7.2 to –5.6)	53.1 (–16.2 to 143.6)	-4.9 (–5.5 to –4.2)

PAD indicates peripheral artery disease; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[60] Printed with permission. Copyright © 2018, University of Washington.

Table 23-3. Global Mortality From and Prevalence of Aortic Aneurysm by Sex, 2017

	Both Sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions)	0.2 (0.2 to 0.2)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)
Percent change total number, 1990 to 2017	59.6 (52.2 to 66.1)	53.3 (45.5 to 61.8)	71.8 (60.1 to 81.7)
Percent change total number, 2007 to 2017	23.7 (19.9 to 27.6)	22.0 (17.5 to 27.0)	26.8 (22.2 to 30.7)
Rate per 100 000	2.2 (2.1 to 2.3)	3.1 (3.0 to 3.4)	1.4 (1.4 to 1.5)
Percent change rate, 2007 to 2017	–8.5 (–11.2 to –5.8)	–10.5 (–13.6 to –7.0)	–6.6 (–10.0 to –3.8)
Percent change rate, 1990 to 2017	–24.1 (–27.4 to –21.4)	–28.9 (–32.3 to –25.4)	–19.4 (–24.7 to –15.0)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[60] Printed with permission. Copyright © 2018, University of Washington.

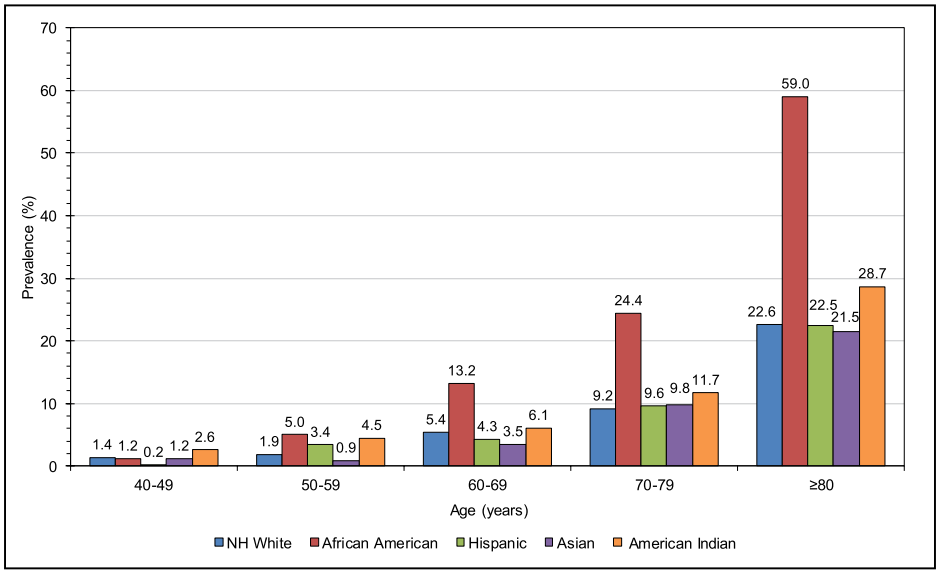

Chart 23-1. Estimates of prevalence of peripheral artery disease in males by age and ethnicity, United States, 2000.

NH indicates non-Hispanic.

Source: Data derived from Allison et al.[1]

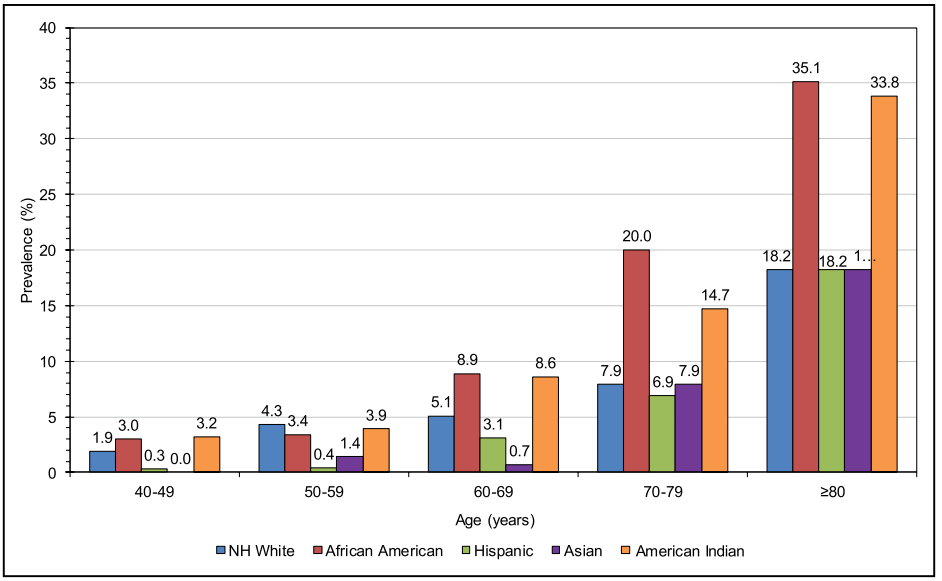

Chart 23-2. Estimates of prevalence of peripheral artery disease in females by age and ethnicity, United States, 2000.
NH indicates non-Hispanic.
Source: Data derived from Allison et al.[1]

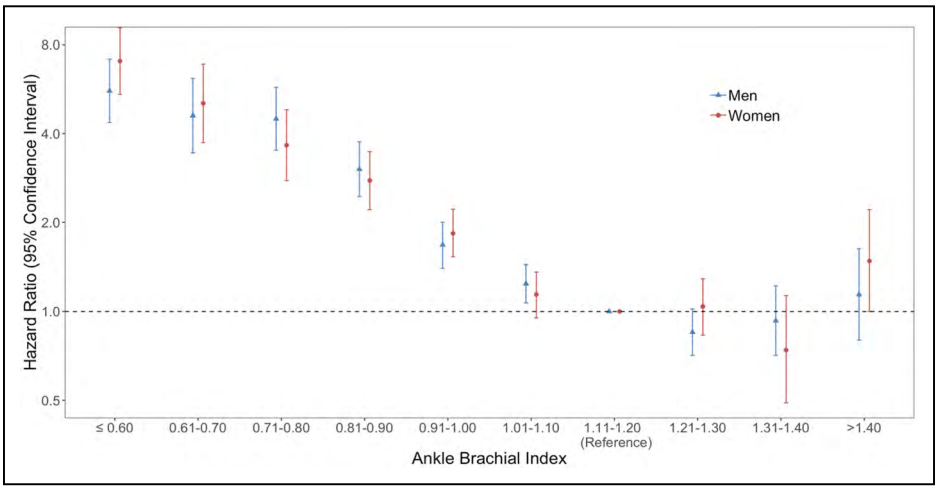

Chart 23-3. Hazard ratios of global cardiovascular mortality with 95% CI by ankle-brachial index categories, 1976 to 2000 (baseline years).
Source: Data derived from Fowkes et al.[38]

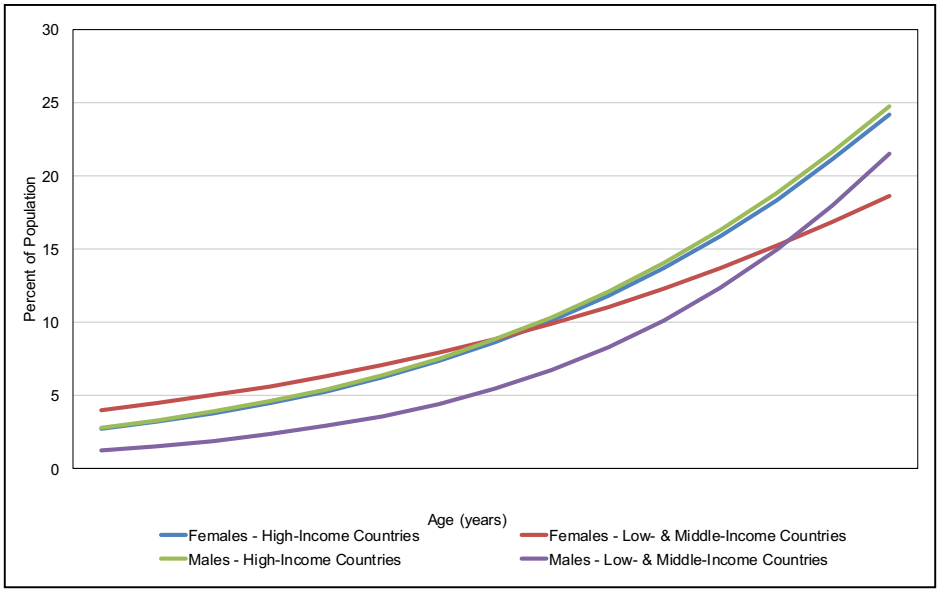

Chart 23-4. Global prevalence of peripheral artery disease by age in males and females in high-income countries and low-income or middle-income countries, 1995 to 2009.
Source: Adapted from *The Lancet* (Fowkes et al[8]) with permission from Elsevier. Copyright © 2013, Elsevier Ltd.

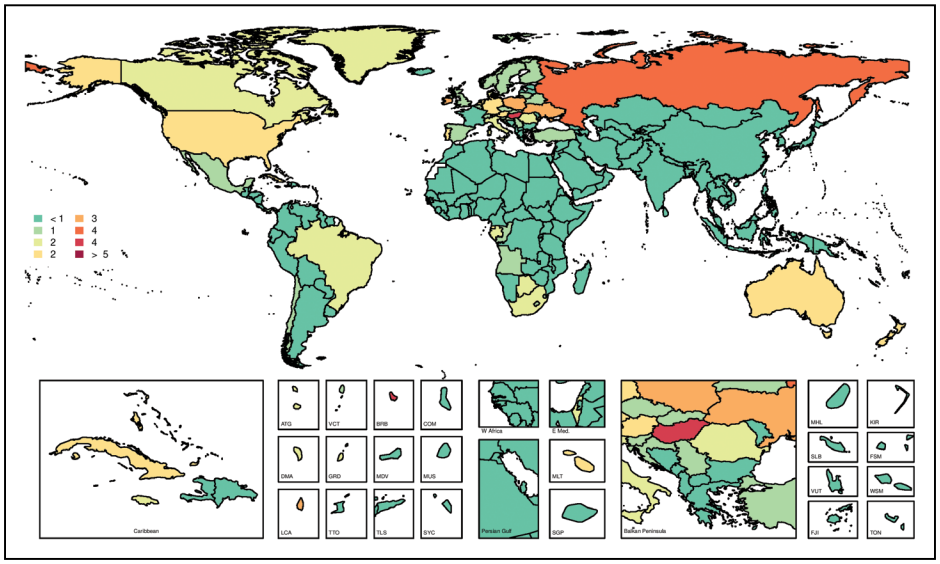

Chart 23-5. Age-standardized mortality rates of peripheral artery disease per 100 000, both sexes, 2017.
Peripheral artery disease mortality is highest in Eastern Europe.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[60] Printed with permission. Copyright © 2018, University of Washington

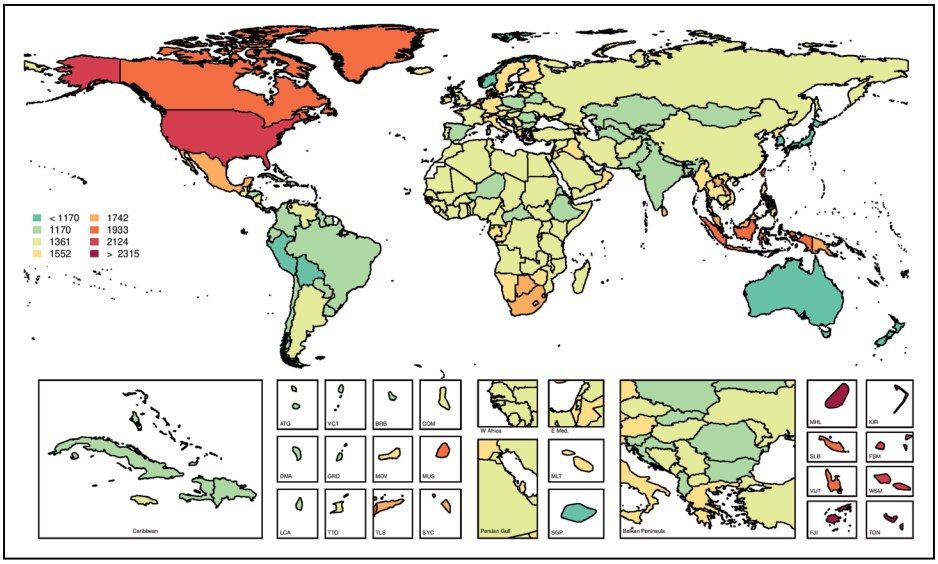

Chart 23-6. Age-standardized prevalence of peripheral artery disease per 100 000, both sexes, 2017.
Peripheral artery disease prevalence is highest in North America, Southeast Asia, and Oceania.
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[60] Printed with permission.

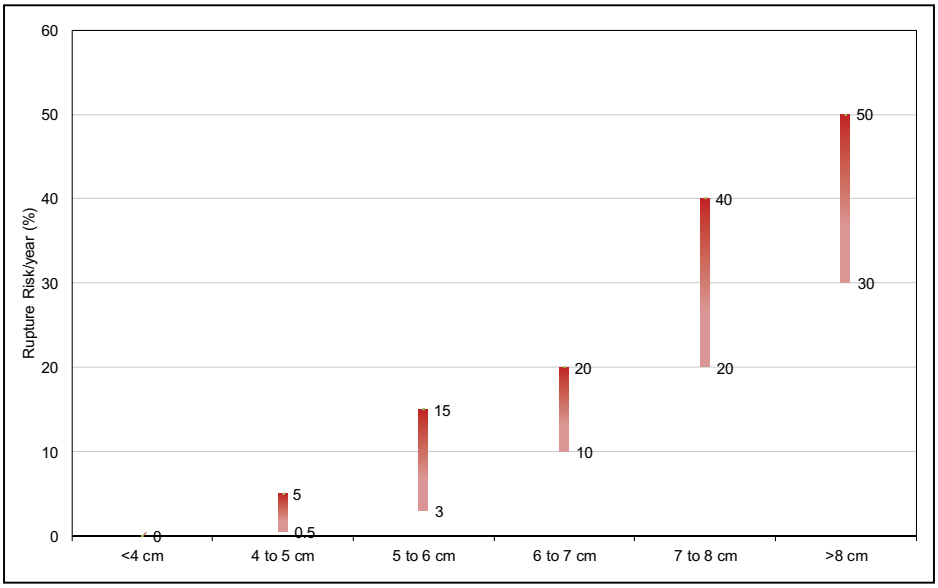

Chart 23-7. Association between diameter and minimum and maximum risk of abdominal aortic aneurysm rupture per year.
Source: Data derived from Brewster et al.[90]

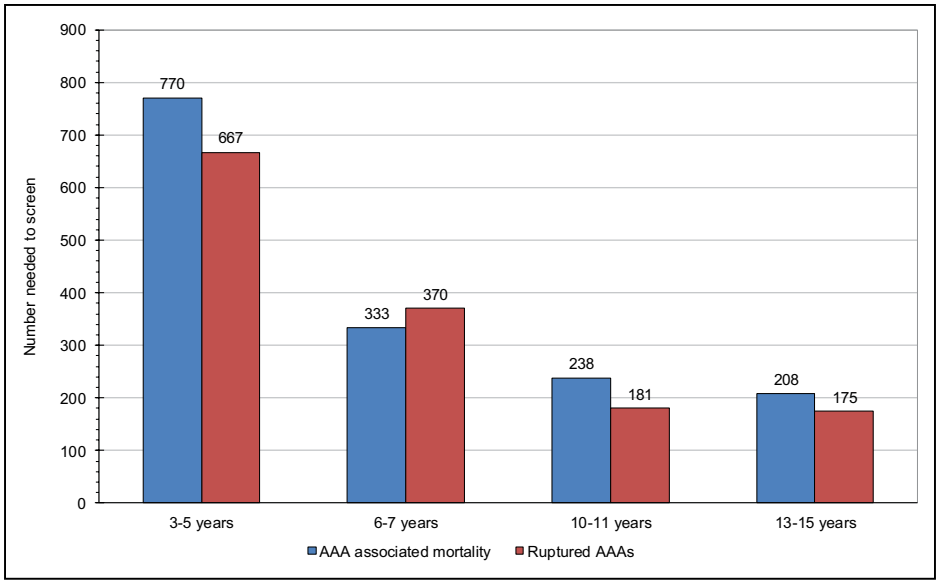

Chart 23-8. Numbers needed to screen to avoid an AAA-associated death and a ruptured AAA, 1988 to 1999 (baseline years) with average follow-up of 4 to 15 years.
Global data.
AAA indicates abdominal aortic aneurysm.
Source: Data derived from Eckstein et al.[91]

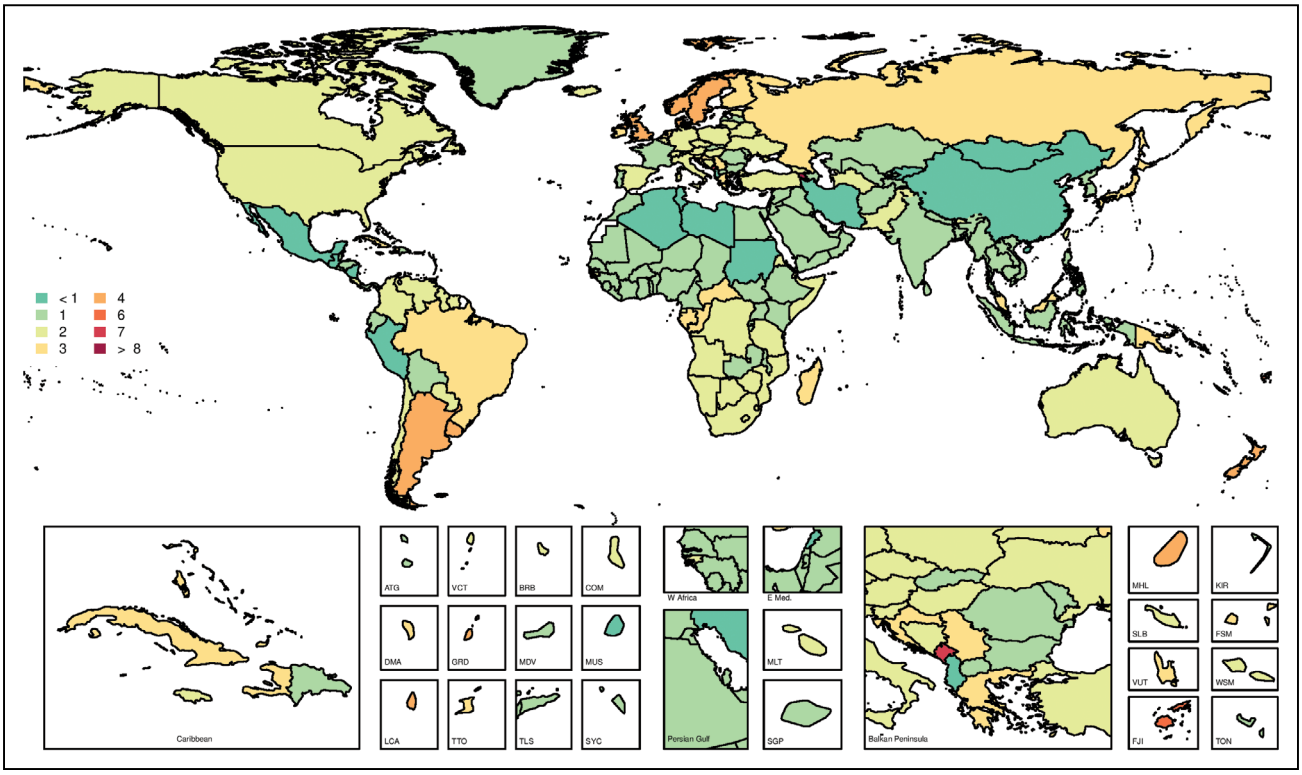

Chart 23-9. Age-standardized mortality rates of aortic aneurysm per 100 000, both sexes, 2017.
The highest age-standardized mortality rates attributable to aortic aneurysm are reported in Northern Europe, Southern Latin America, New Zealand, and Fiji. Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.[60] Printed with permission. Copyright © 2018, University of Washington.

REFERENCES

1. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States [published correction appears in *Am J Prev Med*. 2014;47:103]. *Am J Prev Med*. 2007;32:328–333. doi: 10.1016/j.amepre.2006.12.010
2. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324. doi: 10.1001/jama.286.11.1317
3. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599–1606. doi: 10.1001/jama.286.13.1599
4. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60:686–695.e2. doi: 10.1016/j.jvs.2014.03.290
5. Agarwal S, Sud K, Shishehbor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: from 2003-2011. *J Am Coll Cardiol*. 2016;67:1901–1913. doi: 10.1016/j.jacc.2016.02.040
6. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J*. 1999;20:344–353. doi: 10.1053/euhj.1998.1194
7. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA*. 2012;308:1660–1667. doi: 10.1001/jama.2012.13415
8. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340. doi: 10.1016/S0140-6736(13)61249-0
9. Berger JS, Hochman J, Lobach I, Adelman MA, Riles TS, Rockman CB. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673–681.e1. doi: 10.1016/j.jvs.2013.01.053
10. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, Djoussé L, Sutton-Tyrrell K, Newman AB, Cushman M, et al. Metabolic syndrome and risk of incident peripheral artery disease: the Cardiovascular Health Study. *Hypertension*. 2014;63:413–419. doi: 10.1161/HYPERTENSIONAHA.113.01925
11. Matsushita K, Ballew SH, Coresh J, Arima H, Ärnlöv J, Cirillo M, Ebert N, Hiramoto JS, Kimm H, Shlipak MG, et al; Chronic Kidney Disease Prognosis Consortium. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2017;5:718–728. doi: 10.1016/S2213-8587(17)30183-3
12. Weissgerber TL, Turner ST, Bailey KR, Mosley TH Jr, Kardia SL, Wiste HJ, Miller VM, Kullo IJ, Garovic VD. Hypertension in pregnancy is a risk factor for peripheral arterial disease decades after pregnancy. *Atherosclerosis*. 2013;229:212–216. doi: 10.1016/j.atherosclerosis.2013.04.012
13. Arya S, Binney Z, Khakharia A, Brewster LP, Goodney P, Patzer R, Hockenberry J, Wilson PWF. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. *J Am Heart Assoc*. 2018;7:e007425. doi: 10.1161/JAHA.117.007425
14. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvadó J, Martínez-González MA. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial [published correction appears in *JAMA*. 2018;320:2272]. *JAMA*. 2014;311:415–417. doi: 10.1001/jama.2013.280618
15. Vart P, Coresh J, Kwak L, Ballew SH, Heiss G, Matsushita K. Socioeconomic status and incidence of hospitalization with lower-extremity peripheral artery disease: Atherosclerosis Risk in Communities Study. *J Am Heart Assoc*. 2017;6:e004995. doi: 10.1161/JAHA.116.004995
16. Wassel CL, Loomba R, Ix JH, Allison MA, Denenberg JO, Criqui MH. Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego population study. *J Am Coll Cardiol*. 2011;58:1386–1392. doi: 10.1016/j.jacc.2011.06.023
17. Wahlgren CM, Magnusson PK. Genetic influences on peripheral arterial disease in a twin population. *Arterioscler Thromb Vasc Biol*. 2011;31:678–682. doi: 10.1161/ATVBAHA.110.210385
18. Carmelli D, Fabsitz RR, Swan GE, Reed T, Miller B, Wolf PA. Contribution of genetic and environmental influences to ankle-brachial blood pressure index in the NHLBI Twin Study. *Am J Epidemiol*. 2000;151:452–458. doi: 10.1093/oxfordjournals.aje.a010230
19. Kullo IJ, Leeper NJ. The genetic basis of peripheral arterial disease: current knowledge, challenges, and future directions. *Circ Res*. 2015;116:1551–1560. doi: 10.1161/CIRCRESAHA.116.303518
20. Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJ, Blankensteijn JD, Ronkainen A, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet*. 2008;40:217–224. doi: 10.1038/ng.72
21. Murabito JM, White CC, Kavousi M, Sun YV, Feitosa MF, Nambi V, Lamina C, Schillert A, Coassin S, Bis JC, et al. Association between chromosome 9p21 variants and the ankle-brachial index identified by a meta-analysis of 21 genome-wide association studies. *Circ Cardiovasc Genet*. 2012;5:100–112. doi: 10.1161/CIRCGENETICS.111.961292
22. Khor CC, Davila S, Breunis WB, Lee YC, Shimizu C, Wright VJ, Yeung RS, Tan DE, Sim KS, Wang JJ, et al; Hong Kong–Shanghai Kawasaki Disease Genetics Consortium; Korean Kawasaki Disease Genetics Consortium; Taiwan Kawasaki Disease Genetics Consortium; International Kawasaki Disease Genetics Consortium; US Kawasaki Disease Genetics Consortium; Blue Mountains Eye Study. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. *Nat Genet*. 2011;43:1241–1246. doi: 10.1038/ng.981
23. Hirsch AT, Murphy TP, Lovell MB, Twillman G, Treat-Jacobson D, Harwood EM, Mohler ER 3rd, Creager MA, Hobson RW 2nd, Robertson RM, et al; for the Peripheral Arterial Disease Coalition. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation*. 2007;116:2086–2094. doi: 10.1161/CIRCULATIONAHA.107.725101
24. Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis*. 2011;218:1–12. doi: 10.1016/j.atherosclerosis.2011.04.024
25. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2014;60:1565–1571. doi: 10.1016/j.jvs.2014.08.064
26. Jonason T, Bergström R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta Med Scand*. 1987;221:253–260.
27. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2017;135:e791–e792]. *Circulation*. 2017;135:e726–e779. doi: 10.1161/CIR.0000000000000471
28. Ramos R, García-Gil M, Comas-Cufí M, Quesada M, Marrugat J, Elosua R, Sala J, Grau M, Martí R, Ponjoan A, et al. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. *J Am Coll Cardiol*. 2016;67:630–640. doi: 10.1016/j.jacc.2015.11.052
29. Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol*. 2014;63:682–690. doi: 10.1016/j.jacc.2013.09.073
30. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.117.032235
31. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol*. 2018;71:2306–2315. doi: 10.1016/j.jacc.2018.03.008
32. Bonaca MP, Creager MA, Olin J, Scirica BM, Gilchrist IC Jr, Murphy SA, Goodrich EL, Braunwald E, Morrow DA. Peripheral revascularization in patients with peripheral artery disease with vorapaxar: insights from the TRA 2°P-TIMI 50 trial. *JACC Cardiovasc Interv*. 2016;9:2157–2164. doi: 10.1016/j.jcin.2016.07.034

33. Lindholt JS, Søgaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet*. 2017;390:2256–2265. doi: 10.1016/S0140-6736(17)32250-X
34. Hira RS, Cowart JB, Akeroyd JM, Ramsey DJ, Pokharel Y, Nambi V, Jneid H, Deswal A, Denktas A, Taylor A, et al. Risk factor optimization and guideline-directed medical therapy in US veterans with peripheral arterial and ischemic cerebrovascular disease compared to veterans with coronary heart disease. *Am J Cardiol*. 2016;118:1144–1149. doi: 10.1016/j.amjcard.2016.07.027
35. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, Massaro JM, Lewis BA, Cerezo J, Oldenburg NC, et al; on behalf of the CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation*. 2012;125:130–139. doi: 10.1161/CIRCULATIONAHA.111.075770
36. Decision memo for supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD) (CAG-00449N). May 25, 2017. Centers for Medicare & Medicaid Services website. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=287. Accessed April 1, 2019.
37. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death, 1999 - 2017. CDC WONDER Online Database [database online]. Released December 2018. Atlanta, GA: Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed April 1, 2019.
38. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208. doi: 10.1001/jama.300.2.197
39. Lo RC, Bensley RP, Dahlberg SE, Matyal R, Hamdan AD, Wyers M, Chaikof EL, Schermerhorn ML. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. *J Vasc Surg*. 2014;59:409–418.e3. doi: 10.1016/j.jvs.2013.07.114
40. Barba A, Estallo L, Rodríguez L, Baquer M, Vega de Céniga M. Detection of abdominal aortic aneurysm in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg*. 2005;30:504–508. doi: 10.1016/j.ejvs.2005.05.011
41. Kurvers HA, van der Graaf Y, Blankensteijn JD, Visseren FL, Eikelboom B; SMART Study Group. Screening for asymptomatic internal carotid artery stenosis and aneurysm of the abdominal aorta: comparing the yield between patients with manifest atherosclerosis and patients with risk factors for atherosclerosis only. *J Vasc Surg*. 2003;37:1226–1233. doi: 10.1016/s0741-5214(02)75140-9
42. Lee JY, Lee SW, Lee WS, Han S, Park YK, Kwon CH, Jang JY, Cho YR, Park GM, Ahn JM, et al. Prevalence and clinical implications of newly revealed, asymptomatic abnormal ankle-brachial index in patients with significant coronary artery disease. *JACC Cardiovasc Interv*. 2013;6:1303–1313. doi: 10.1016/j.jcin.2013.08.008
43. Leertouwer TC, Pattynama PM, van den Berg-Huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? *Kidney Int*. 2001;59:1480–1483. doi: 10.1046/j.1523-1755.2001.0590041480.x
44. Heald CL, Fowkes FG, Murray GD, Price JF; Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis*. 2006;189:61–69. doi: 10.1016/j.atherosclerosis.2006.03.011
45. Jones WS, Patel MR, Dai D, Subherwal S, Stafford J, Calhoun S, Peterson ED. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000-2008. *J Am Coll Cardiol*. 2012;60:2230–2236. doi: 10.1016/j.jacc.2012.08.983
46. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. *Diabetes Care*. 2019;42:50–54. doi: 10.2337/dc18-1380
47. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, Peterson ED. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;165:809–815.e1. doi: 10.1016/j.ahj.2012.12.002
48. Jones WS, Mi X, Qualls LG, Vemulapalli S, Peterson ED, Patel MR, Curtis LH. Trends in settings for peripheral vascular intervention and the effect of changes in the outpatient prospective payment system. *J Am Coll Cardiol*. 2015;65:920–927. doi: 10.1016/j.jacc.2014.12.048
49. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study [published correction appears in *Ann Intern Med*. 2003;139:306]. *Ann Intern Med*. 2002;136:873–883. doi: 10.7326/0003-4819-136-12-200206180-00008
50. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292:453–461. doi: 10.1001/jama.292.4.453
51. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, Sharma L, Criqui MH. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). *J Am Coll Cardiol*. 2009;53:1056–1062. doi: 10.1016/j.jacc.2008.09.063
52. Matsushita K, Ballew SH, Sang Y, Kalbaugh C, Loehr LR, Hirsch AT, Tanaka H, Heiss G, Windham BG, Selvin E, et al. Ankle-brachial index and physical function in older individuals: the Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis*. 2017;257:208–215. doi: 10.1016/j.atherosclerosis.2016.11.023
53. Garg PK, Liu K, Tian L, Guralnik JM, Ferrucci L, Criqui MH, Tan J, McDermott MM. Physical activity during daily life and functional decline in peripheral arterial disease. *Circulation*. 2009;119:251–260. doi: 10.1161/CIRCULATIONAHA.108.791491
54. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, Tan J, McDermott MM. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114:242–248. doi: 10.1161/CIRCULATIONAHA.105.605246
55. McDermott MM, Guralnik JM, Tian L, Ferrucci L, Liu K, Liao Y, Criqui MH. Baseline functional performance predicts the rate of mobility loss in persons with peripheral arterial disease. *J Am Coll Cardiol*. 2007;50:974–982. doi: 10.1016/j.jacc.2007.05.030
56. McDermott MM, Tian L, Liu K, Guralnik JM, Ferrucci L, Tan J, Pearce WH, Schneider JR, Criqui MH. Prognostic value of functional performance for mortality in patients with peripheral artery disease. *J Am Coll Cardiol*. 2008;51:1482–1489. doi: 10.1016/j.jacc.2007.12.034
57. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
58. National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
59. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use data files. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm#data. Accessed April 1, 2019.
60. Global Burden of Disease Study 2017 (GBD 2017). Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed April 1, 2019.
61. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation*. 2006;113:e463–e654. doi: 10.1161/CIRCULATIONAHA.106.174526
62. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br J Surg*. 2012;99:655–665. doi: 10.1002/bjs.8707
63. Clouse WD, Hallett JW Jr, Schaff HV, Spittell PC, Rowland CM, Ilstrup DM, Melton LJ 3rd. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc*. 2004;79:176–180. doi: 10.4065/79.2.176
64. Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromsø Study. *Am J Epidemiol*. 2001;154:236–244. doi: 10.1093/aje/154.3.236

65. Lederle FA. In the clinic: abdominal aortic aneurysm. *Ann Intern Med.* 2009;150:ITC5-1. doi: 10.7326/0003-4819-150-9-200905050-01005
66. De Rango P, Farchioni L, Fiorucci B, Lenti M. Diabetes and abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg.* 2014;47:243–261. doi: 10.1016/j.ejvs.2013.12.007
67. Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, Hamilton W, Emin A, Culliford D, Luqmani RA. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. *Ann Rheum Dis.* 2015;74:129–135. doi: 10.1136/annrheumdis-2013-204113
68. Guo DC, Grove ML, Prakash SK, Eriksson P, Hostetler EM, LeMaire SA, Body SC, Shalhub S, Estrera AL, Safi HJ, et al; GenTAC Investigators; BAVCon Investigators. Genetic variants in LRP1 and ULK4 are associated with acute aortic dissections. *Am J Hum Genet.* 2016;99:762–769. doi: 10.1016/j.ajhg.2016.06.034
69. LeMaire SA, McDonald ML, Guo DC, Russell L, Miller CC 3rd, Johnson RJ, Bekheirnia MR, Franco LM, Nguyen M, Pyeritz RE, et al. Genome-wide association study identifies a susceptibility locus for thoracic aortic aneurysms and aortic dissections spanning FBN1 at 15q21.1. *Nat Genet.* 2011;43:996–1000. doi: 10.1038/ng.934
70. van 't Hof FN, Ruigrok YM, Lee CH, Ripke S, Anderson G, de Andrade M, Baas AF, Blankensteijn JD, Bottinger EP, Bown MJ, et al. Shared genetic risk factors of intracranial, abdominal, and thoracic aneurysms [published correction appears in *J Am Heart Assoc.* 2018;7:e004150]. *J Am Heart Assoc.* 2016;5:e002603. doi: 10.1161/JAHA.115.002603
71. Verloes A, Sakalihasan N, Koulischer L, Limet R. Aneurysms of the abdominal aorta: familial and genetic aspects in three hundred thirteen pedigrees. *J Vasc Surg.* 1995;21:646–655. doi: 10.1016/s0741-5214(95)70196-6
72. Davis FM, Rateri DL, Daugherty A. Abdominal aortic aneurysm: novel mechanisms and therapies. *Curr Opin Cardiol.* 2015;30:566–573. doi: 10.1097/HCO.0000000000000216
73. Gretarsdottir S, Baas AF, Thorleifsson G, Holm H, den Heijer M, de Vries JP, Kranendonk SE, Zeebregts CJ, van Sterkenburg SM, Geelkerken RH, et al. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. *Nat Genet.* 2010;42:692–697. doi: 10.1038/ng.622
74. Yasuno K, Bilguvar K, Bijlenga P, Low SK, Krischek B, Auburger G, Simon M, Krex D, Arlier Z, Nayak N, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet.* 2010;42:420–425. doi: 10.1038/ng.563
75. Bourcier R, Le Scouarnec S, Bonnaud S, Karakachoff M, Bourcereau E, Heurtebise-Chrétien S, Menguy C, Dina C, Simonet F, Moles A, et al; ICAN Study Group. Rare coding variants in ANGPTL6 are associated with familial forms of intracranial aneurysm. *Am J Hum Genet.* 2018;102:133–141. doi: 10.1016/j.ajhg.2017.12.006
76. Kiando SR, Tucker NR, Castro-Vega LJ, Katz A, D'Escamard V, Tréard C, Fraher D, Albuisson J, Kadian-Dodov D, Ye Z, et al. PHACTR1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLoS Genet.* 2016;12:e1006367. doi: 10.1371/journal.pgen.1006367
77. Filardo G, Powell JT, Martinez MAM, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. *Cochrane Database Syst Rev.* 2015;(2):CD001835. doi: 10.1002/14651858.CD001835.pub4
78. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, Thompson MM. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet.* 2014;383:963–969. doi: 10.1016/S0140-6736(14)60109-4
79. Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg.* 2014;59:1512–1517. doi: 10.1016/j.jvs.2014.01.007
80. Jackson RS, Chang DC, Freischlag JA. Comparison of long-term survival after open vs endovascular repair of intact abdominal aortic aneurysm among Medicare beneficiaries. *JAMA.* 2012;307:1621–1628. doi: 10.1001/jama.2012.453
81. Schermerhorn ML, Buck DB, O'Malley AJ, Curran T, McCallum JC, Darling J, Landon BE. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. *N Engl J Med.* 2015;373:328–338. doi: 10.1056/NEJMoa1405778
82. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT Jr, Kohler TR, Kougias P, Jean-Claude JM, Cikrit DF, Swanson KM; OVER Veterans Affairs Cooperative Study Group. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. *N Engl J Med.* 2012;367:1988–1997. doi: 10.1056/NEJMoa1207481
83. Karthikesalingam A, Vidal-Diez A, Holt PJ, Loftus IM, Schermerhorn ML, Soden PA, Landon BE, Thompson MM. Thresholds for abdominal aortic aneurysm repair in England and the United States. *N Engl J Med.* 2016;375:2051–2059. doi: 10.1056/NEJMoa1600931
84. Ullery BW, Tran K, Chandra V, Mell MW, Harris EJ, Dalman RL, Lee JT. Association of an endovascular-first protocol for ruptured abdominal aortic aneurysms with survival and discharge disposition. *JAMA Surg.* 2015;150:1058–1065. doi: 10.1001/jamasurg.2015.1861
85. Zettervall SL, Schermerhorn ML, Soden PA, McCallum JC, Shean KE, Deery SE, O'Malley AJ, Landon B. The effect of surgeon and hospital volume on mortality after open and endovascular repair of abdominal aortic aneurysms. *J Vasc Surg.* 2017;65:626–634. doi: 10.1016/j.jvs.2016.09.036
86. Goodney PP, Brooke BS, Wallaert J, Travis L, Lucas FL, Goodman DC, Cronenwett JL, Stone DH. Thoracic endovascular aneurysm repair, race, and volume in thoracic aneurysm repair. *J Vasc Surg.* 2013;57:56–63.e1. doi: 10.1016/j.jvs.2012.07.036
87. Guirguis-Blake J, Beil T, Sun XX, Senger C, Whitlock E. Primary Care Screening for Abdominal Aortic Aneurysm: An Evidence Update for the U.S. Preventive Services Task Force. Evidence Syntheses, No. 109. AHRQ publication No. 14-05202-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
88. Groves EM, Khoshchehreh M, Le C, Malik S. Effects of weekend admission on the outcomes and management of ruptured aortic aneurysms. *J Vasc Surg.* 2014;60:318–324. doi: 10.1016/j.jvs.2014.02.052
89. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmel T, Larsen M, Harris KM, Greason K, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol.* 2015;66:350–358. doi: 10.1016/j.jacc.2015.05.029
90. Brewster DC, Cronenwett JL, Hallett JW Jr, Johnston KW, Krupski WC, Matsumura JS; Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. Guidelines for the treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg.* 2003;37:1106–1117. doi: 10.1067/mva.2003.363
91. Eckstein H-H, Reeps C, Zimmermann A, Söllner H. Ultrasound screening for abdominal aortic aneurysms. *Gefässchirurgie.* 2015;20(suppl 1):1–12.
92. Wanhainen A, Hultgren R, Linné A, Holst J, Gottsäter A, Langenskiöld M, Smidfelt K, Björck M, Svensjö S; on behalf of the Swedish Aneurysm Screening Study Group (SASS). Outcome of the Swedish Nationwide Abdominal Aortic Aneurysm Screening Program. *Circulation.* 2016;134:1141–1148. doi: 10.1161/CIRCULATIONAHA.116.022305
93. Di Eusanio M, Trimarchi S, Patel HJ, Hutchison S, Suzuki T, Peterson MD, Di Bartolomeo R, Folesani G, Pyeritz RE, Braverman AC, et al. Clinical presentation, management, and short-term outcome of patients with type A acute dissection complicated by mesenteric malperfusion: observations from the International Registry of Acute Aortic Dissection. *J Thorac Cardiovasc Surg.* 2013;145:385–390.e1. doi: 10.1016/j.jtcvs.2012.01.042
94. Trimarchi S, Tolenaar JL, Tsai TT, Froehlich J, Pegorer M, Upchurch GR, Fattori R, Sundt TM 3rd, Isselbacher EM, Nienaber CA, et al. Influence of clinical presentation on the outcome of acute B aortic dissection: evidences from IRAD. *J Cardiovasc Surg (Torino).* 2012;53:161–168.
95. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg.* 2002;36:443–451. doi: 10.1067/mva.2002.127351
96. Kalra PA, Guo H, Gilbertson DT, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in the United States. *Kidney Int.* 2010;77:37–43. doi: 10.1038/ki.2009.406
97. Shafique S, Peixoto AJ. Renal artery stenosis and cardiovascular risk. *J Clin Hypertens (Greenwich).* 2007;9:201–208.
98. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, Cohen DJ, Matsumoto AH, Steffes M, Jaff MR, et al; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med.* 2014;370:13–22. doi: 10.1056/NEJMoa1310753
99. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int.* 2001;60:1490–1497. doi: 10.1046/j.1523-1755.2001.00953.x
100. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.

24. QUALITY OF CARE

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The Institute of Medicine defines quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge,"[1] identifying 6 specific domains for improving health care: safety, effectiveness, patient or people-centeredness, timeliness, efficiency, and equity.

Abbreviations Used in Chapter 24

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHA_2DS_2-VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes mellitus, and sex (1 point each); age ≥75 y and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65–74 y, and (female) sex category
CHD	coronary heart disease
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CPR	cardiopulmonary resuscitation
CVD	cardiovascular disease
DM	diabetes mellitus
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical services
ERR	excess readmission ratio
GLORIA-AF	Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GWTG	Get With The Guidelines
HbA_{1c}	hemoglobin A_{1c} (glycosylated hemoglobin)
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HMO	health maintenance organization
HR	hazard ratio
HRRP	Hospital Readmissions Reduction Program
ICD-10	*International Classification of Diseases, 10th Revision*
IHCA	in-hospital cardiac arrest
IQR	interquartile range
IV	intravenous
LDL-C	low-density lipoprotein cholesterol

(*Continued*)

Abbreviations Used in Chapter 24 Continued

LV	left ventricular
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
N/A	not available or not applicable
NCDR	National Cardiovascular Data Registry
NIHSS	National Institutes of Health Stroke Scale
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non–ST-segment–elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PA	physical activity
PCI	percutaneous coronary intervention
PINNACLE	Practice Innovation and Clinical Excellence
PPO	preferred provider organization
RR	relative risk
RSMR	risk-standardized mortality rate
SES	socioeconomic status
STEMI	ST-segment–elevation myocardial infarction
TIA	transient ischemic stroke
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
tPA	tissue-type plasminogen activator
UA	unstable angina
UFH	unfractionated heparin

Assessing care quality requires the development and implementation of performance measures, explicit standards or metrics of care against which care delivery can be judged.[2] This differs from guidelines, which provide clinical recommendations to inform usual clinical scenarios but ultimately leave decisions to reasonable clinician discretion. Measuring performance requires a robust process for data collection across care facilities and clinicians, data transfer, analysis, and dissemination.

Over the past decades, clinical registries in the United States and worldwide have helped to better understand and improve quality, performance, and outcomes. Early registries focused on the inpatient setting (MI, HF, stroke) or discrete procedures (PCI, defibrillator implantation, peripheral vascular interventions, cardiothoracic surgery). In the United States, these have been principally run by the ACC's NCDR[3] and the AHA's GWTG Program.[4] Elective procedural registries were also developed by the AHA and ACC, such as those for AF ablation and left atrial appendage occlusion. Additionally, outpatient registries such as the ACC's PINNACLE Registry use electronic health record data transfer rather than case report form data entry to examine performance measures across a wide range of cardiovascular conditions. Increasingly, outpatient postmarketing registries have been sponsored by pharmaceutical or device companies and managed by contract research organizations, such as for anticoagulation in AF. Finally, medical claims data from payers (Medicare,

commercial claims) or integrated healthcare systems (Veterans Affairs) have also examined quality.

In the following sections, data on quality of care will be presented across these 6 domains, grouped by disease or therapeutic area. Where possible, data are reported from recently published literature or as standardized quality indicators drawn from quality-improvement registries whose methods are consistent with performance measures endorsed by the ACC and the AHA.[2,5,6]

Additional data on adherence to ACC/AHA clinical practice guidelines are also included to supplement performance measures data. The select data presented are meant to provide illustrative examples of quality of care and are not meant to be comprehensive given the sheer volume of quality data published each year.

Acute Myocardial Infarction (See Tables 24-1 through 24-4)

- The ACC's Chest Pain – MI Registry (formerly the ACTION Registry)[7] is currently the largest US-based hospital registry of inpatient AMI care (Tables 24-1 through 24-4).
- Wadhera and colleagues[5] examined a large cohort of Medicare beneficiaries with 642 105 index hospitalizations for AMI and showed that higher 30-day payments were associated with lower 30-day mortality after adjustment for patient characteristics and comorbidities (adjusted OR for additional $1000 payments, 0.986 [95% CI, 0.979–0.992]; $P<0.001$). This could have implications for payment programs incentivizing reduction in payments without considering value.
- The association of state Medicaid expansion with quality of AMI care and outcomes was investigated in 55 737 low-income patients <65 years of age across 765 sites using NCDR data from January 1, 2012, to December 31, 2016.[8] During this study period, Medicaid coverage increased from 7.5% to 14.4% in expansion states, compared with 6.2% to 6.6% in nonexpansion states ($P<0.001$). In expansion compared with nonexpansion states, there was no change in use of procedures such as PCI for NSTEMI, and delivery of defect-free care increased to a lesser extent in expansion states. In-hospital mortality improved to a similar extent in expansion and nonexpansion states: 3.2% to 2.8% (adjusted OR, 0.93 [95% CI, 0.77–1.12]) versus 3.3% to 3.0% (adjusted OR, 0.85 [95% CI, 0.73–0.99]; $P_{interaction}=0.48$).
- Chatterjee and Joynt Maddox[6] examined patterns in 30-day mortality from AMI in relation to public outcome reporting from 2009 to 2015 across 2751 hospitals. They showed that 30-day mortality was highest among baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) but improved more over time compared with other hospitals (from 18.6% in 2009 to 14.6% in 2015 [–0.74% per year; $P<0.001$] versus from 15.7% in 2009 to 14.0% in 2015 [–0.26% per year; $P<0.001$]; $P_{interaction}<0.001$).
- Examining hospitals with higher-than-expected risk-adjusted 30-day readmission rates (ERR >1) after AMI, Pandey and colleagues[9] showed that risk-adjusted 30-day readmission rates were not associated with in-hospital quality of AMI care (adjusted OR, 0.94 [95% CI, 0.81–1.08] per 0.1-unit increase in AMI ERR for overall defect-free care). Among 51 453 patients with 1-year outcomes data, higher AMI ERR was associated with higher all-cause readmission within 1 year of discharge; however, this association was largely driven by readmissions early after discharge and was not significant in landmark analyses beginning 30 days after discharge. The AMI ERR was not associated with risk for mortality within 1 year of discharge.
- In 119 735 patients with AMI who were admitted to 1824 hospitals, Bucholz and colleagues[10] showed that patients admitted to high-performing hospitals after AMI had longer life expectancies than patients treated at low-performing hospitals. This signal appeared in the first 30 days and persisted over 17 years of follow-up. Patients treated at high-performing hospitals lived on average 0.74 to 1.14 years longer than patients treated at low-performing hospitals.
- Makam and Nguyen[11] showed cardiac biomarker testing in the ED is common even among those without symptoms suggestive of ACS. Biomarker testing occurred in 8.2% of visits in the absence of symptoms related to ACS, representing 8.5 million visits. Among individuals who were subsequently hospitalized, cardiac biomarkers were tested in 47% of all visits. Biomarkers were tested in 35.4% of visits in this group despite the absence of ACS-related symptoms.
- If patients who have cardiac biomarker testing without ACS symptoms are misclassified as having AMI, this could have negative implications for value-based programs focused on AMI care. A single-center study by McCarthy et al[12] of 633 patients spanning 2017 to 2018 examined whether patients with nonischemic myocardial injury may be miscoded as having type 2 MI (demand ischemia) using the new *ICD-10* system. After adjudication using the fourth universal definition of MI, 56.7% had type 2 MI, 41.9% had myocardial injury, 0.9% had type 1 MI, and 0.5% had UA. Patients with type 2 MI and patients with

myocardial injury each had high 30-day readmission and mortality rates.

- The CMS and Hospital Quality Alliance started to publicly report 30-day mortality measures for AMI and HF in 2007, subsequently expanding to include 30-day readmission rates. According to national Medicare data from July 2015 through June 2016, the median (IQR) hospital RSMR for MI was 13.1% (12.6%, 13.5%), and the median (IQR) risk-standardized 30-day readmission rate was 15.8% (15.5%, 16.2%).[13]
- Mathews and colleagues[14] examined post-MI medication adherence as a hospital-level variable using data from 347 US hospitals participating in the ACTION Registry–GWTG. They observed that postdischarge use of secondary prevention medications varied significantly across US hospitals and was inversely associated with 2-year outcomes at the hospital level.
- Two recent studies examined the association of the HRRP with mortality among Medicare fee-for-service beneficiaries ≥65 years of age and hospitalized with AMI.
  - The study by Khera et al[15] spanned 2006 to 2014 and included 1.7 million hospitalizations for AMI. Before the HRRP announcement, monthly postdischarge mortality was stable for AMI (slope for monthly change, 0.002% [95% CI, –0.001% to 0.006% per month]), with no change inflection in slope around HRRP announcement or implementation (P>0.05). In-hospital mortality decreased for AMI from 10.4% to 9.7%, and 30-day postdischarge mortality decreased from 7.4% to 7.0% (P for trend<0.001).
  - The study by Wadhera et al[16] spanned 2005 to 2015 and included 1.8 million hospitalizations for AMI. Evaluating outcomes in relation to announcement and implementation of the HRRP, the study evaluated 4 time periods. Periods 1 and 2 were before the HRRP: April 2005 to September 2007 and October 2007 to March 2010. Periods 3 and 4 were after HRRP announcement (April 2010 to September 2012) and HRRP implementation (October 2012 to March 2015). The HRRP announcement was associated with a reduction in 30-day postdischarge mortality in patients with AMI (0.18% pre-HRRP increase versus 0.08% post-HRRP announcement decrease; difference in change, –0.26%; P=0.01) and did not significantly change after HRRP implementation.
- A 20-year evaluation from January 1, 1995, to December 31, 2014, evaluated AMI outcomes in older adults.[17] The sample included 4 367 485 Medicare fee-for-service beneficiaries ≥65 years of age cared for at 5680 US hospitals. The rate of AMI hospitalization decreased from 914 to 566 per 100 000 beneficiary-years, with improvements in 30-day mortality from 20.0% to 12.4%, 30-day all-cause readmissions from 21.0% to 15.3%, and 1-year recurrent AMI from 7.1% to 5.1%.

Heart Failure (See Tables 24-5 and 24-6)

- Current US HF quality data are best captured by the widespread but voluntary GWTG–HF program (Tables 24-5 and 24-6).
- In a study based on the GWTG–HF program linked with Medicare data, the association between 30-day readmission rates and 3-year mortality and median survival was not significant at the hospital level. The HR for 3-year mortality comparing the top and bottom quartiles for readmission was 0.9 (95% CI, 0.90–1.01), whereas median survival time was highest for the bottom quartile.[18]
- In an evaluation of the validity of use of hospital volume as a structural metric for quality of HF care, Kumbhani and colleagues[19] examined the relationship between admission volume, process-of-care metrics, and short- and long-term outcomes in patients admitted with acute HF in the GWTG–HF registry with linked Medicare inpatient data. In their cohort of 125 595 patients at 342 hospitals, they found that hospital volume correlated with process measures but not with 30-day outcomes and only marginally with outcomes up to 6 months of follow-up. Lower-volume hospitals were significantly less likely to be adherent to HF process measures than higher-volume hospitals. On multivariable modeling, higher hospital volume was not associated with a difference in the in-hospital mortality (OR, 0.99 [95% CI, 0.94–1.05]; P=0.78), 30-day mortality (HR, 0.99 [95% CI, 0.97–1.01]; P=0.26), or 30-day readmissions (HR, 0.99 [95% CI, 0.97–1.00]; P=0.10).
- In a national cohort study including 241 533 patients admitted with HF at all 591 acute care institutions in Canada, authors found inverse associations between in-patient mortality and hospital volume, with 11.3% mortality in low-volume centers versus 17.3% in high-volume centers, with an adjusted OR of 0.90 (95% CI, 0.80–1.00) and with a similar trend for 30-day readmissions (OR, 0.91 [95% CI, 0.85–0.97]).[20]
- Gupta and colleagues[21] examined the association of the HRRP with readmission and mortality outcomes among patients hospitalized with HF. Among a cohort of 115 245 fee-for-service Medicare beneficiaries discharged after HF

hospitalizations, the 1-year risk-adjusted readmission rate declined from 57.2% to 56.3% (HR, 0.92 [95% CI, 0.89–0.96]), and the 1-year risk-adjusted mortality rate increased from 31.3% to 36.3% (HR, 1.10 [95% CI, 1.06–1.14]) after the HRRP implementation.

- However, in an interrupted time-series analysis of the HRRP evaluating the changes in slope for HF-related mortality from 2006 to 2014, no significant increase in in-hospital mortality was noted, despite a reduction in readmissions after HRRP implementation.[15]
- In a longitudinal cohort study of 48 million hospitalizations among 20 million Medicare fee-for-service patients across 3497 hospitals, Desai and colleagues[22] showed that patients at hospitals subject to penalties under the HRRP had greater reductions in readmission rates than those at nonpenalized hospitals. Reductions in readmission rates were greater for target versus nontarget conditions for patients at the penalized hospitals but not at nonpenalized hospitals.
- Chatterjee and Joynt-Maddox[6] examined patterns in 30-day mortality from HF as they relate to public reporting of these outcomes. In data from 2009 to 2015 from 3796 hospitals with publicly reported mortality data for HF, they showed baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) improved over time (from 13.5% to 13.0%; –0.12% per year; $P<0.001$), but mean mortality among all other HF hospitals increased during the study period (from 10.9% to 12.0%; 0.17% per year; $P<0.001$, $P_{interaction}<0.001$).
- Yet another evaluation of the HRRP among Medicare beneficiaries suggested an increase in 30-day mortality after hospitalization after HF but no association between HRRP and mortality within 45 days of admission. The authors concluded that further research is needed to better understand whether the increase in 30-day mortality is related to the implementation of the HRRP.[16]
- In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, Pokharel and colleagues[23] observed that the most recent of a series of Kansas City Cardiomyopathy Questionnaire scores was most strongly associated with subsequent death and cardiovascular hospitalization.
- Among 106 304 patients hospitalized with HF at 317 centers in the GWTG–HF registry, there was a graded inverse association between 30-day RSMR and long-term mortality (quartile 1 versus quartile 4: 5-year mortality, 73.7% versus 76.8%). Lower hospital-level 30-day RSMR was associated with greater 1-, 3-, and 5-year survival for patients with HF. These differences in 30-day survival continued to accrue beyond 30 days and persisted long term, which suggests that 30-day RSMR could be a useful HF performance metric.[24]
- Pandey et al[9] reported results from the GWTG–HF registry evaluating the association between HF ERR and performance measures, as well as in-hospital and 1-year clinical outcomes. They stratified participating centers into groups with low (HF ERR ≤1) versus high (HF ERR >1) risk-adjusted readmission rates. There were no differences between the low and high risk-adjusted 30-day readmission groups in median adherence rate to all performance measures (95.7% versus 96.5%, $P=0.37$) or median percentage of defect-free care (90.0% versus 91.1%, $P=0.47$). The composite 1-year outcome of death or all-cause readmission rates was also not different between the 2 groups (median 62.9% versus 65.3%; $P=0.10$). The high HF ERR group had higher 1-year all-cause readmission rates (median 59.1% versus 54.7%; $P=0.01$); however, 1-year mortality rates were lower among the high versus low group, with a trend toward statistical significance (median 28.2% versus 31.7%; $P=0.07$). The authors concluded that the quality of care and clinical outcomes were comparable among hospitals with high versus low risk-adjusted 30-day HF readmission rates.
- According to national Medicare data from July 2015 through June 2016, the median (IQR) hospital RSMR for HF was 11.6% (10.8%, 12.4%), and the median (IQR) risk-standardized 30-day readmission rate was 21.4% (20.8%, 22.1%).[13]
- Krumholz and colleagues[25] examined readmission outcomes among patients who had multiple admissions at >1 hospital within a given year to attempt to separate hospital from patient effects. They found the observed readmission rate to be consistently higher among patients admitted to hospitals in a worse-performing quartile than among those admitted to hospitals in a better-performing quartile, but the only statistically significant difference was observed when one was in the best-performing quartile and the other was in the worst (absolute difference in readmission rate 2.0 percentage points [95% CI, 0.4–3.5]).
- In a Medicare cohort comprising almost 3 million admissions for HF and 1.2 million for MI, Dharmarajan and colleagues[26] studied the association between changes in hospital readmission rates and changes in mortality rates. They observed that among Medicare fee-for-service beneficiaries hospitalized for HF and AMI, reductions in hospital 30-day readmission rates were weakly but significantly correlated with reductions in hospital 30-day mortality rates after discharge.

- Home time after admission for HF may be calculated as the time spent alive outside a hospital, skilled nursing facility, or rehabilitation facility after discharge. In a study using GWTG–HF data between 2011 and 2014, home time 30 days and 1-year after discharge was highly correlated with survival and survival free from HF readmissions.[27]
- In the GWTG–HF registry, discharge to hospice after HF admissions increased from 2.0% in 2005 to 4.9% in 2014. For individuals discharged to hospice, the median postdischarge survival was 11 days, with 34.1% mortality within 3 days and a 15.0% survival after 6 months. Among those discharged to hospice, the readmission rate (4.1%) was significantly lower than for other patients with advanced HF (27.2%) or other HF in the registry (22.2%).[28]

Prevention and Risk Factor Modification (See Table 24-7)

- The National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set consists of established measures of quality of care related to CVD prevention in the United States (Table 24-7).[29]
- Pokharel and colleagues[30] examined practice-level variation in statin therapy among patients 40 to 75 years of age with DM and no CVD between May 2008 and October 2013 from the ACC's PINNACLE Registry. Among 215 193 patients (582 048 encounters) from 204 cardiology practices, statins were prescribed in 61.6% of patients with DM. Among 182 practices with ≥30 patients with DM, the median practice statin prescription rate was 62.3%, with no noticeable change over time. There was a 57% practice-level variation in statin use for 2 similar patients that was not affected by adjustment for patient-related variables, which suggests that practice- or clinician-related factors primarily determined variation in statin use.
- Using data from the PINNACLE Registry, Hira and colleagues[31] showed that among 27 533 patients receiving prasugrel, 13.9% (n=3824) had a contraindication to prasugrel use (ie, history of TIA or stroke). This was considered inappropriate prasugrel use. A further 4.4% of patients (n=1210) were receiving it for a nonrecommended indication (>75 years of age without history of DM or MI or weight <60 kg). Both inappropriate and nonrecommended prasugrel use showed wide practice-level variation (median rate ratio of 2.89 [95% CI, 2.75–3.03] and 2.29 [95% CI, 2.05–2.51], respectively).
- In an analysis from the PINNACLE Registry, Hira and colleagues[32] showed that among 68 808 patients receiving aspirin therapy for primary prevention, roughly 11.6% (7972 of 68 808) were receiving inappropriate therapy (10-year risk of CVD <6%). There was significant practice-level variation in inappropriate aspirin use (range, 0%–71.8%; median, 10.1%; IQR, 6.4%) for practices with an adjusted median rate ratio of 1.63 (95% CI, 1.47–1.77).
- Using aspirin dosing data from 221 199 patients with MI enrolled in the ACTION Registry–GWTG, Hall and colleagues[33] showed a 25-fold variation in the use of high-dose aspirin (325 mg/d) across participating centers. Overall, 60.9% of patients were discharged on high-dose aspirin. High-dose aspirin was prescribed to 73% of patients treated with PCI and 44.6% of patients managed medically; 56.7% of patients with an in-hospital bleeding event were also discharged on high-dose aspirin. Among 9075 patients discharged on aspirin, thienopyridine, and warfarin, 44.0% were prescribed high-dose aspirin therapy. Given the increased risk of bleeding with high-dose aspirin and its unclear benefit, these findings may have implications for future quality improvement efforts.
- Data from the PINNACLE Registry showed that among 156 145 patients with CAD in 58 practices, just over two-thirds (n=103 830, or 66.5%) of patients were prescribed the optimal combination of medications (β-blockers, ACE inhibitors or angiotensin receptor blockers, statins) for which they were eligible. After adjustment for patient factors, the practice median rate ratio for prescription was 1.25 (95% CI, 1.20–1.32), which indicates a 25% likelihood that any 2 practices would differ in treating identical CAD patients.[34]
- Using data from MEPS, Salami and colleagues[35] described trends in statin use and related out-of-pocket expense from 2002 to 2013. Although statin use increased overall and among those with established ASCVD, use in higher-risk groups was suboptimal. Statin use was significantly lower in females (OR, 0.81 [95% CI, 0.79–0.85]) and racial/ethnic minorities (OR, 0.65 [95% CI, 0.61–0.70]). Gross domestic product–adjusted total cost for statins decreased from $17.2 billion (out-of-pocket cost, $7.6 billion) in 2002 to 2003 to $16.9 billion (out-of-pocket cost, $3.9 billion) in 2012 to 2013, and the mean annual out-of-pocket costs for patients decreased from $348 to $94.

Atrial Fibrillation

- Of all CVD, AF may have the largest quantity of registries, with at least 10 non–industry-funded and 6 industry-funded registries.[36] These largely emerged after the introduction of DOACs, and performance measures and use of anticoagulation have been a major focus.
- In 2016, the ACC and AHA revised the clinical performance and quality measures for AF and atrial

flutter.[37] The 3 pairs of inpatient and outpatient performance measures include documentation of CHA_2DS_2-VASc score, oral anticoagulant prescription, and planned or monthly international normalized ratio testing for warfarin. The 18 quality measures reflect metrics for appropriate medications for comorbidities (HF), inappropriate prescription of specific anticoagulant drugs and antiarrhythmic drugs in specific clinical scenarios, and documentation of shared decision making.

- Over the past decade, the proportion of patients with AF receiving oral anticoagulants has increased from ≈67% to >80%.[36] The highest uptake is reported in US and European registries (90%) and the lowest in Asia (58%). However, methodological factors are likely a major source of difference in estimates, including selection bias of both numerator and denominator (patient, clinician, site, and in some registries, requirement of informed consent), patient characteristics, and oral anticoagulant ascertainment methodology. For example, in the outpatient, electronic health record–based PINNACLE-AF US registry, oral anticoagulant prescription for those with CHA_2DS_2-VASc score ≥2 in 2014 was 48%. In the industry-funded, informed-consent, postmarketing GLORIA-AF international registry, oral anticoagulant prescription between 2011 and 2014 was 80%.[38] The AHA GWTG–AF program has been designed to track the 2016 performance measures.[39] An analysis of data from the AHA GWTG–AF program examined prescription of oral anticoagulation therapy at discharge in 33 235 patients with a CHA_2DS_2-VASc score ≥2 hospitalized for AF at one of 115 sites from 2013 to 2017. Oral anticoagulation use increased consistently over time, and there was a high level of adherence, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.[40]
- Potential overuse in low-risk patients remains a concern, with oral anticoagulants administered to AF patients with no stroke risk factors.[36] Methodological limitations of comorbidity ascertainment could lead to overestimation of overuse.
- Inappropriate use of aspirin for patients at moderate to high risk of stroke remains a concern. In PINNACLE-AF, which examined the use of aspirin rather than guideline-recommended oral anticoagulants for patients with CHA_2DS_2-VASc score ≥2, 40% of patients were treated with aspirin alone, and this was influenced by CHD comorbidities.[41]
- Treating specialty can influence likelihood of therapy and resultant outcomes. In the Veterans Health Administration, the largest integrated healthcare system in the United States, provision of cardiology outpatient care within 90 days of newly diagnosed AF was associated with a reduced adjusted risk of stroke (HR, 0.91 [95% CI, 0.86–0.96]) and death (HR, 0.89 [95% CI, 0.88–0.91]), although with an increased risk of arrhythmia-related hospitalization (HR, 1.38 [95% CI, 1.35–1.42]).[42] This finding was statistically mediated by an increase in 90-day oral anticoagulant prescription.

Other Treatments

Data from AHA GWTG–AF on use of rate versus rhythm control, appropriate and inappropriate use of antiarrhythmic drugs, and procedural factors related to catheter ablation are expected to be forthcoming. The NCDR AF ablation and left atrial appendage occlusion registries have also not yet published data.

Stroke (See Tables 24-4 and 24-8)

- The AHA GWTG–Stroke program (Tables 24-4 and 24-8) remains the largest stroke quality improvement program. The US-based program is an ongoing, voluntary hospital registry and performance improvement initiative for acute stroke and supplies most of the quality data for acute stroke care.
- Care processes that would lead to best functional outcomes after acute stroke are poorly understood. A study of 2083 patients with ischemic stroke from 82 hospitals with data in both the AVAIL registry and GWTG–Stroke found that one-third of patients with acute stroke were functionally dependent or dead at 3 months after stroke. Functional rates varied considerably across hospitals, which indicates the need to understand which process measures could be targeted to minimize hospital variation and improve poststroke functional outcomes.[43]
- Door-to-needle time for tPA administration decreased on average by 10 minutes, from 77 minutes (IQR, 60–98 minutes) to 67 minutes (IQR, 51–87 minutes), after implementation of Target: Stroke Phase I, the first stage of the AHA's GWTG–Stroke quality improvement program. During this period, in-hospital all-cause mortality declined (from 9.93% to 8.25%; adjusted OR, 0.89 [95% CI, 0.83–0.94]), and discharge to home became more frequent (37.6% versus 42.7%; adjusted OR, 1.14 [95% CI, 1.09–1.19]; $P<.001$).[44]
- Target: Stroke Phase II was launched in April 2014 to promote further reduction in door-to-needle time. There was significant site variation in door-to-needle time, and 16 strategies were identified that were significantly associated with reduced door-to-needle time. It was estimated that door-to-needle time could be reduced on average by an additional 20 minutes if all strategies were implemented.[45]

- A study of 204 591 patients with ischemic and hemorrhagic strokes admitted to 1563 GWTG–Stroke participating hospitals between April 1, 2003, and June 30, 2010, showed that 63.7% of the patients arrived at the hospital by EMS. Older patients, those with Medicaid and Medicare, and those with severe strokes were more likely to activate EMS. Conversely, minority race/ethnicity (black, Hispanic, Asian) and living in rural communities were associated with a lower likelihood of EMS use. EMS transport was independently associated with an onset-to-door time ≤3 hours, a higher proportion of patients meeting door-to-imaging time of ≤25 minutes, more patients meeting a door-to-needle time of ≤60 minutes, and more eligible patients being treated with tPA if onset of symptoms was ≤2 hours. The authors concluded that although EMS use was associated with rapid evaluation and treatment of stroke, more than one-third of stroke patients fail to use EMS.[46]
- Because of the poor survival after stroke, interventions related to improvement in end-of-life care are desirable to improve quality of care for those patients. In a study using GWTG–Stroke data, it was demonstrated that discharge from a Medicare Shared Savings Program hospital or alignment with a related organization was associated with a 16% increase in the odds of hospice enrollment (OR, 1.16 [95% CI, 1.06–1.26]) for patients with high mortality risk, with absolute rates of 20% versus 22%. However, a reduction in patient conform measures or hospice enrollment in individuals at lower mortality risk was noted in the same organizations, from 9% to 8% (OR, 0.82 [95% CI, 0.74–0.91]).[47]
- In an analysis comparing individuals presenting with stroke at institutions participating in the GWTG–Stroke program versus institutions not enrolled in the program, those in the GWTG–Stroke program were more likely to receive intravenous tPA (RR, 3.74 [95% CI, 1.65–8.50]), to receive education on risk factors (RR, 1.54 [95% CI, 1.16–2.05]), to be evaluated for swallowing (RR, 1.25 [95% CI, 1.04–1.50]), to receive a lipid evaluation (RR, 1.18 [95% CI, 1.05–1.32]), and to be evaluated by a neurologist (RR, 1.12 [95% CI, 1.05–1.20]).[48]

Implantable Defibrillators

- In a comparative effectiveness study of single- versus dual-chamber implantable cardioverter-defibrillators using data from the ACC's Implantable Cardioverter Defibrillator Registry, Peterson and colleagues[49] found that among patients receiving an implantable cardioverter-defibrillator for primary prevention without indications for pacing, the use of a dual-chamber device compared with a single-chamber device was associated with a higher risk of device-related complications and similar 1-year mortality and hospitalization outcomes. In a propensity-matched cohort, rates of complications were lower for single-chamber devices (3.51% versus 4.72%; $P<0.001$; risk difference, −1.20 [95% CI, −1.72 to −0.69]), but device type was not significantly associated with 1-year mortality (unadjusted rate, 9.85% versus 9.77%; HR, 0.99 [95% CI, 0.91–1.07]; $P=0.79$), 1-year all-cause hospitalization (unadjusted rate, 43.86% versus 44.83%; HR, 1.00 [95% CI, 0.97–1.04]; $P=0.82$), or hospitalization for HF (unadjusted rate, 14.73% versus 15.38%; HR, 1.05 [95% CI, 0.99–1.12]; $P=0.19$).

Resuscitation (See Table 24-9)

- Quality measures in resuscitation have targeted inpatient care settings. Started in 1999, the AHA GWTG–Resuscitation Registry remains the dominant source of US quality improvement data (Table 24-9). GWTG–Resuscitation is a voluntary hospital registry and performance improvement initiative for IHCA.
- Process measures for in-hospital resuscitation are generally based on time to correct administration of specific resuscitation and postresuscitation procedures, drugs, or therapies. Recent findings are discussed here.
- Among Medicare beneficiaries participating in GWTG–Resuscitation, 1-year survival after IHCA has increased modestly over the past decade[50] However, despite an overall improvement in survival, there remains lower survival in IHCA during off-hours (nights and weekends) compared with on-hours events.[51]
- Of 103 932 IHCAs between 2000 and 2014, 12.7% had delays to epinephrine administration, with marked variation across hospitals. The delay was inversely correlated to risk-standardized survival. Whether reduction in this process measure could improve outcomes has not yet been demonstrated.[52]
- A composite performance score for in-hospital arrest varied significantly across hospitals (89.7% [IQR, 85.4%–93.1%]). Hospital process composite quality performance was associated with risk-standardized discharge rates and favorable neurological status at discharge.[53]
- Stub et al[54] reported a post hoc secondary analysis of a large, partial factorial trial of interventions for patients with OHCA. The quality of hospital-based postresuscitation care given to each patient was assigned an evidence-based quality score that considered (1) initiation of temperature management; (2) achievement of target temperature 32°C to

34°C; (3) continuation of temperature management for >12 hours; (4) performance of coronary angiography within 24 hours; and (5) no withdrawal of life-sustaining treatment before day 3. These were aggregated as hospital-level composite performance scores, which varied widely (median [IQR] scores from lowest to highest hospital quartiles, 21% [20%–25%] versus 59% [55%–64%]). Adjusted survival to discharge increased with each quartile of composite performance score (from lowest to highest: 16.2%, 20.8%, 28.5%, and 34.8%; $P<0.01$). Adjusted rates of favorable neurological outcome also increased (from lowest quartile to highest: 8.3%, 13.8%, 22.2%, and 25.9%; $P<0.01$). Hospital score was significantly associated with outcome after risk adjustment for established baseline factors (highest versus lowest adherence quartile: adjusted OR of survival, 1.64 [95% CI, 1.13–2.38]).[54]

Social Determinants

- In NCDR data collected at 586 hospitals from July 2008 to December 2013, Udell et al[55] examined AMI care in 390 692 patients stratified by neighborhood SES. They reported longer median arrival-to-angiography time in lower SES neighborhoods (lowest, 8.0 hours; low, 5.5 hours; medium, 4.8 hours; high, 4.5 hours; and highest, 3.4 hours; $P<0.0001$), and a higher proportion of patients with STEMI treated with fibrinolysis (lowest, 23.1%; low, 20.2%; medium, 18.0%; high, 14.2%; and highest, 5.9%; $P<0.0001$). Although overall defect-free acute care appeared similar after controlling for covariates, patients from lower SES neighborhoods had greater independent risk of in-hospital mortality, major bleeding, and a lower quality of discharge care. These results indicate further opportunities to improve the quality of AMI care in patients from the most disadvantaged neighborhoods.
- Graham et al[56] assessed the degree to which non-race characteristics explain survival differences between white and black patients with AMI in a prospective registry study across 31 US hospitals from 2003 to 2008. Propensity scores associated with black race were calculated using 8 domains of patient characteristics. Among 6402 patients with AMI, 5-year mortality occurred in 28.9% of black patients (476 of 1648) and 18.0% of white patients (856 of 4754; HR, 1.72 [95% CI, 1.54–1.92]; $P<0.001$). Controlling for propensity associated with being a black patient, no difference in mortality by race was observed (adjusted HR, 1.09 [95% CI, 0.93–1.26]; $P=.37$). These findings suggest that most of the mortality rate difference between black and white patients is mediated by patient characteristics.
- Healthcare insurance coverage may influence oral anticoagulant and novel oral anticoagulant use. An analysis of 363 309 patients with prevalent AF from the PINNACLE-AF outpatient registry found considerable variation in oral anticoagulant use across insurance plans.[57] Relative to Medicare, Medicaid insurance was associated with a lower odds of oral anticoagulant prescription and of novel oral anticoagulant use.
- Before HRRP implementation, there was a continuous trend in the reduction of racial disparities for MI and HF, particularly in safety-net hospitals. For example, although blacks had 13% higher odds of readmission if treated in safety-net hospitals in 2007, this difference decreased to 5% in 2010. Data suggest those improvements persisted after HRRP implementation.[58]
- Using NIS data, Ziaeian and colleagues[59] showed HF hospitalization rates decreased 30.8% between 2002 and 2013. The ratio of males to females increased from 20% greater to 39% greater ($P_{trend}=0.002$) over that time. Black males and black females had hospitalization rates that were 229% ($P_{trend}=0.141$) and 240% ($P_{trend}=0.725$) those of whites in 2013. Hispanic males had rates that were 32% greater in 2002, and the difference narrowed to 4% greater ($P_{trend}=0.047$) in 2013 relative to whites. For Hispanic females, the rate was 55% greater in 2002 and narrowed to 8% greater ($P_{trend}=0.004$) in 2013 relative to whites. Asian/Pacific Islander males had a 27% lower hospitalization rate in 2002, which improved to 43% lower ($P_{trend}=0.040$) in 2013 relative to whites. For Asian/Pacific Islander females, the hospitalization rate was 24% lower in 2002 and improved to 43% lower ($P_{trend}=0.021$) in 2013 relative to whites.
- In an analysis from GWTG–Stroke, Asian American individuals presented with more severe strokes, with an OR of 1.35 (95% CI, 1.30–1.40; $P<0.001$) for an NIHSS score >16, and were less likely to receive intravenous tPA (OR, 0.95 [95% CI, 0.91–0.91]; $P=0.003$). They also had higher in-hospital mortality (OR, 1.14 [95% CI, 1.09–1.19]; $P<0.001$) and more symptomatic hemorrhage after tPA (OR, 1.36 [95% CI, 1.20–1.55]; $P<0.001$) than white patients, although the mortality was in fact lower after adjustment for stroke severity (OR, 0.95 [95% CI, 0.91–0.99]; $P=0.008$). Additionally, Asian American patients had better adherence to rehabilitation (OR, 1.27 [95% CI, 1.18–1.36]; $P<0.001$) and intensive statin therapy (OR, 1.14 [95% CI, 1.10–1.18]; $P<0.001$).[60]
- In a temporal trend evaluation of survival to discharge after IHCA across races, there was a significant increase in survival in blacks (11.3% in 2000 versus 21.4% in 2014) and in whites (15.8% versus 23.2%), although a reduction in the difference between races was noted ($P_{interaction}<0.001$).[61]

Table 24-1. AMI Quality-of-Care Measures, 2018

Quality-of-Care Measure	Chest Pain – MI Registry*	
	STEMI	NSTEMI
Aspirin within 24 h of arrival†	98.5	98.0
Aspirin at discharge‡	99.3	98.7
β-Blockers at discharge	98.1	97.0
Lipid-lowering medication at discharge§	99.7	99.3
ARB/ACE inhibitor at discharge for patients with LVEF <40%	92.4	89.6
ACE inhibitor at discharge for AMI patients	58.6	46.5
ARB at discharge for AMI patients	16.6	20.0
Adult smoking cessation advice/counseling	98.2	98.1
Cardiac rehabilitation referral for AMI patients	87.8	80.5

Values are percentages. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*Chest Pain – MI Registry: STEMI and NSTEMI patients are reported separately. Patients must be admitted with acute ischemic symptoms within the previous 24 hours, typically reflected by a primary diagnosis of STEMI or NSTEMI. Patients who are admitted for any other clinical condition are not eligible. Data reported include data from the first quarter of 2018 to the fourth quarter of 2018.

†Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

‡Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

§Denotes statin use at discharge. Use of nonstatin lipid-lowering agent was 3.4% for STEMI patients and 5.9% for NSTEMI patients in the Chest Pain – MI Registry.

Source: Data from the American College of Cardiology's Chest Pain - MI Registry.[7]

Table 24-2. Time Trends in the Chest Pain – MI Registry's CAD Quality-of-Care Measures, 2010 to 2018

Quality-of-Care Measure	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aspirin within 24 h of arrival*	97	97.6	97.8	95.4	98.1	98.6	98.5	98.5	98.7
Aspirin at discharge†	98	98.3	98.4	98.4	98.7	98.7	98.7	98.7	98.9
β-Blockers at discharge	96	96.7	97.1	97.1	97.6	97.5	97.5	97.4	97.4
Statin use at discharge	92	98.4	98.8	98.8	99.1	99.2	99.4	99.4	99.5
ARB/ACE inhibitor at discharge for patients with LVEF <40%	86	87.8	89.7	90.0	91.2	90.2	91.0	90.3	90.9
Adult smoking cessation advice/counseling	98	98.4	98.4	98.4	98.6	98.0	98.1	98.0	98.2
Cardiac rehabilitation referral for AMI patients	75	76.5	77.3	77.2	79.4	77.8	78.6	80.4	83.3

Values are percentages. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

*Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

†Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

Source: Data from the American College of Cardiology's Chest Pain – MI Registry.[7]

Table 24-3. Additional Chest Pain – MI Registry Quality-of-Care Metrics for AMI Care, 2018

Quality Metrics	Overall	STEMI	NSTEMI
ECG within 10 min of arrival	68.6	77.3	65.1
Aspirin within 24 h of arrival	98.7	98.5	98.0
Any anticoagulant use*	96.1	97.3	95.3
Dosing errors			
UFH dose	43.2	41.2	43.3
Enoxaparin dose	9.8	7.3	10.0
Glycoprotein IIb/IIIa inhibitor dose	4.3	4.5	3.8
Discharge			
Aspirin at discharge	98.9	99.3	98.7
Prescribed statins on discharge	99.5	99.7	99.3
Adult smoking cessation advice/counseling	98.2	98.2	98.1
Cardiac rehabilitation referral	83.3	87.8	80.5
In-hospital mortality† (95% CI)	4.12 (3.96–4.39	6.30 (5.96–6.97)	2.65 (2.51–2.88)

Values are percentages. Data reported include data from the first quarter of 2018 to the fourth quarter of 2018. AMI indicates acute myocardial infarction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and UFH, unfractionated heparin.

*Includes UFH, low-molecular-weight heparin, or direct thrombin inhibitor use.

†Includes all patients.

Source: Data from the American College of Cardiology's Chest Pain – MI Registry.[7]

Table 24-4. Timely Reperfusion for AMI and Stroke

Quality-of-Care Measure	GWTG–Stroke (for Stroke) 7/1/2017–6/30/2018	Chest Pain – MI Registry: STEMI, 2018
STEMI		
Thrombolytic agents within 30 min	N/A	56.1
PCI within 90 min*	N/A	96.0
Stroke		
IV tPA in patients who arrived <2 h after symptom onset, treated ≤3 h	89.8†	N/A
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h	83.7†‡	N/A
IV tPA door-to-needle time ≤60 min	82.4†	N/A

Values are percentages. AMI indicates acute myocardial infarction; IV, intravenous; MI, myocardial infarction; N/A, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and tPA, tissue plasminogen activator.

*Excludes transfers.

†Reflects analysis performed for the Heart Disease and Stroke Statistics—2020 Update.

‡The "IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h" measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Chest pain data from the American College of Cardiology's Chest Pain – MI Registry.[7] Stroke data from unpublished data, Get With The Guidelines–Stroke, July 1, 2017, to June 30, 2018.

Table 24-5. HF Quality-of-Care Measures, July 1, 2017, to June 30, 2018

Quality-of-Care Measure	AHA GWTG–HF
LVEF assessment	98.6
ARB/ACE inhibitor at discharge for patients with LVSD	92.4
Complete discharge instructions	93.4
β-Blockers at discharge for patients with LVSD, no contraindications	98.0
Anticoagulation for AF or atrial flutter, no contraindications	87.6

Values are percentages. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; GWTG–HF, Get With The Guidelines–Heart Failure; HF, heart failure; LVEF, left ventricular ejection fraction; and LVSD, left ventricular systolic dysfunction.

Source: Unpublished American Heart Association tabulation, GWTG–HF, July 1, 2017, to June 30, 2018.

Table 24-6. Quality of Care by Race/Ethnicity and Sex in the GWTG–HF Program, July 1, 2017, to June 30, 2018

Quality-of-Care Measure	Race/Ethnicity			Sex	
	White	Black	Hispanic	Males	Females
Postdischarge appointment*	82.42	79.96	78.82	80.95	81.21
Complete set of discharge instructions	92.07	93.75	94.07	93.41	91.67
Measure of LV function*	99.14	98.98	98.62	98.96	98.80
ACE inhibitor or ARB at discharge for patients with LVSD, no contraindications*	92.21	92.97	92.23	92.58	92.06
Smoking cessation counseling, current smokers	91.36	92.96	91.01	91.83	91.79
Evidence-based specific β-blockers*	93.01	95.20	93.40	94.01	93.11
β-Blockers at discharge for patients with LVSD, no contraindications	98.03	97.96	97.47	98.04	97.74
Hydralazine/nitrates at discharge for patients with LVSD, no contraindications†	0.00	32.49	0.00	34.07	29.42
Anticoagulation for AF or atrial flutter, no contraindications	87.96	85.78	85.23	87.65	87.19
Composite quality-of-care measure (using discharge instructions and β-blocker at discharge)	96.09	96.15	96.07	96.08	95.76

Values are percentages. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; GWTG–HF, Get With The Guidelines–Heart Failure; LV, left ventricular; and LVSD, left ventricular systolic dysfunction.

*Indicates the 4 key achievement measures targeted in GWTG–HF.

†For black patients only.

Source: Unpublished American Heart Association tabulation, GWTG–HF, July 1, 2017, to June 30, 2018.

Table 24-7. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, DM, Tobacco, Nutrition, and Lifestyle, 2017

	Commercial		Medicare		Medicaid
	HMO	PPO	HMO	PPO	HMO
CVD					
β-Blocker persistence after MI*	85.4	84.0	90.0	90.7	78.5
BP control†	62.2	54.4	70.9	72.0	56.9
Statin therapy for patients with CVD	80.4	80.9	79.0	79.1	76.1
DM					
HbA_{1c} testing	91.2	89.8	93.7	93.5	87.6
HbA_{1c} >9.0%	31.7	41.2	25.4	22.3	40.5
Eye examination performed	55.0	49.0	71.9	71.1	57.2
Monitoring nephropathy	90.4	88.2	95.7	95.1	90.1
BP <140/90 mm Hg	62.2	50.3	67.4	63.6	62.7
Statin therapy for patients with DM	61.5	60.1	72.3	69.6	61.4
Tobacco, nutrition, and lifestyle					
Advising smokers and tobacco users to quit	75.9	72.5	86.2	84.5	77.0
BMI percentile assessment in children and adolescents (3–17 y of age)	70.3	56.6	N/A	N/A	72.5
Nutrition counseling (children and adolescents [3–17 y of age])	64.3	52.9	N/A	N/A	67.1
Counseling for PA (children and adolescents [3–17 y of age])	59.5	47.8	N/A	N/A	60.6
BMI assessment for adults 18–74 y of age	80.3	67.1	95.0	94.6	84.5
PA discussion in older adults (≥65 y of age) (2016 data)	N/A		55.1	58.4	N/A
PA advice in older adults (≥65 y of age) (2016 data)	N/A		52.0	51.2	N/A

Values are percentages. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HMO, health maintenance organization; MI, myocardial infarction; N/A, not available or not applicable; PA, physical activity; and PPO, preferred provider organization.

*β-Blocker persistence: received persistent β-blocker treatment for 6 months after hospital discharge for acute myocardial infarction.

†Adults 18 to 59 years of age with BP <140/90 mm Hg, adults 60 to 85 years of age with a diagnosis of DM and BP <140/90 mm Hg, and adults 60 to 85 years of age without a diagnosis of DM and BP <150/90 mm Hg.

Source: Healthcare Effectiveness Data and Information Set, 2017.[29]

Table 24-8. Quality of Care by Race/Ethnicity and Sex in the GWTG–Stroke Program, July 1, 2017, to June 30, 2018

Quality-of-Care Measure	Race/Ethnicity			Sex	
	White	Black	Hispanic	Males	Females
IV tPA in patients who arrived ≤2 h after symptom onset, treated ≤3 h*	87.17	86.57	87.55	87.85	86.62
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h†	81.28	81.30	83.23	82.14	81.04
IV tPA door-to-needle time ≤60 min	83.91	83.50	83.24	84.64	83.14
Thrombolytic complications: IV tPA and life-threatening, serious systemic hemorrhage	9.17	10.78	7.18	9.81	8.35
Antithrombotic agents <48 h after admission*	97.21	96.76	96.48	97.25	96.80
DVT prophylaxis by second hospital day*	99.25	99.27	98.99	99.24	99.21
Antithrombotic agents at discharge*	98.90	98.72	98.26	98.89	98.64
Anticoagulation for AF at discharge*	96.43	95.55	96.92	96.58	96.20
Therapy at discharge if LDL-C >100 mg/dL or LDL-C not measured or on therapy at admission*	98.44	98.78	98.26	98.75	98.24
Counseling for smoking cessation*	97.33	97.01	96.69	97.11	97.19
Lifestyle changes recommended for BMI >25 kg/m^2	50.81	53.79	55.11	52.00	51.88
Composite quality-of-care measure	97.95	97.91	97.50	98.04	97.72

Values are percentages. AF indicates atrial fibrillation; BMI, body mass index; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; and tPA, tissue-type plasminogen activator.

*Indicates the 7 key achievement measures targeted in GWTG–Stroke.

†This measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Unpublished American Heart Association tabulation, GWTG–Stroke, July 1, 2017, to June 30, 2018.

Table 24-9. Quality of Care of Patients With IHCA Among GWTG–Resuscitation Hospitals, 2018

	Adults	Children
Event outside critical care setting	45.8	13.0
All objective CPR data collected	99.0	99.6
End-tidal co_2 monitoring used during arrest	11.6	40.3
Induced hypothermia after resuscitation from shockable rhythm	7.8	8.8

Values are mean percentages. CPR indicates cardiopulmonary resuscitation; GWTG, Get With The Guidelines; and IHCA, in-hospital cardiac arrest.

Source: GWTG-Resuscitation Registry unpublished data, 2018.

REFERENCES

1. Committee on Quality of Health Care in America, Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press; 2001.
2. Quality of Care and Outcomes Research in CVD and Stroke Working Group. Measuring and improving quality of care: a report from the American Heart Association/American College of Cardiology First Scientific Forum on Assessment of Healthcare Quality in Cardiovascular Disease and Stroke. *Circulation*. 2000;101:1483–1493. doi: 10.1161/01.cir.101.12.1483
3. NCDR registries. American College of Cardiology Quality Improvement for Institutions website. https://cvquality.acc.org/NCDR-Home/Registries. Accessed March 24, 2019.
4. Focus on quality. American Heart Association website. https://www.heart.org/en/professional/quality-improvement. Accessed March 24, 2019.
5. Wadhera RK, Joynt Maddox KE, Wang Y, Shen C, Bhatt DL, Yeh RW. Association between 30-day episode payments and acute myocardial infarction outcomes among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004397. doi: 10.1161/CIRCOUTCOMES.117.004397
6. Chatterjee P, Joynt Maddox KE. US national trends in mortality from acute myocardial infarction and heart failure: policy success or failure? *JAMA Cardiol*. 2018;3:336–340. doi: 10.1001/jamacardio.2018.0218
7. Chest Pain – MI Registry. American College of Cardiology Quality Improvement for Institutions website. https://cvquality.acc.org/NCDR-Home/registries/hospital-registries/chest-pain-mi-registry. Accessed May 1, 2019.
8. Wadhera RK, Bhatt DL, Wang TY, Lu D, Lucas J, Figueroa JF, Garratt KN, Yeh RW, Joynt Maddox KE. Association of state Medicaid expansion with quality of care and outcomes for low-income patients hospitalized with acute myocardial infarction. *JAMA Cardiol*. 2019;4:120–127. doi: 10.1001/jamacardio.2018.4577
9. Pandey A, Golwala H, Xu H, DeVore AD, Matsouaka R, Pencina M, Kumbhani DJ, Hernandez AF, Bhatt DL, Heidenreich PA, et al. Association of 30-day readmission metric for heart failure under the Hospital Readmissions Reduction Program with quality of care and outcomes. *JACC Heart Fail*. 2016;4:935–946. doi: 10.1016/j.jchf.2016.07.003
10. Bucholz EM, Butala NM, Ma S, Normand ST, Krumholz HM. Life expectancy after myocardial infarction, according to hospital performance. *N Engl J Med*. 2016;375:1332–1342. doi: 10.1056/NEJMoa1513223
11. Makam AN, Nguyen OK. Use of cardiac biomarker testing in the emergency department. *JAMA Intern Med*. 2015;175:67–75. doi: 10.1001/jamainternmed.2014.5830
12. McCarthy C, Murphy S, Cohen JA, Rehman S, Jones-O'Connor M, Olshan DS, Singh A, Vaduganathan M, Januzzi JL Jr, Wasfy JH. Misclassification of myocardial injury as myocardial infarction: implications for assessing

outcomes in value-based programs. *JAMA Cardiol*. 2019;4:460–464. doi: 10.1001/jamacardio.2019.0716
13. Medicare Hospital Quality 2017 Chartbook: Performance Report on Outcome Measures. Centers for Medicare & Medicaid Services website. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html. Accessed April 20, 2019.
14. Mathews R, Wang W, Kaltenbach LA, Thomas L, Shah RU, Ali M, Peterson ED, Wang TY. Hospital variation in adherence rates to secondary prevention medications and the implications on quality. *Circulation*. 2018;137:2128–2138. doi: 10.1161/CIRCULATIONAHA.117.029160
15. Khera R, Dharmarajan K, Wang Y, Lin Z, Bernheim SM, Wang Y, Normand ST, Krumholz HM. Association of the Hospital Readmissions Reduction Program with mortality during and after hospitalization for acute myocardial infarction, heart failure, and pneumonia. *JAMA Netw Open*. 2018;1:e182777. doi: 10.1001/jamanetworkopen.2018.2777
16. Wadhera RK, Joynt Maddox KE, Wasfy JH, Haneuse S, Shen C, Yeh RW. Association of the Hospital Readmissions Reduction Program with mortality among Medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *JAMA*. 2018;320:2542–2552. doi: 10.1001/jama.2018.19232
17. Krumholz HM, Normand ST, Wang Y. Twenty-year trends in outcomes for older adults with acute myocardial infarction in the United States. *JAMA Netw Open*. 2019;2:e191938. doi: 10.1001/jamanetworkopen.2019.1938
18. Jalnapurkar S, Zhao X, Heidenreich PA, Bhatt DL, Smith EE, DeVore AD, Hernandez AF, Matsouaka R, Yancy CW, Fonarow GC. A hospital level analysis of 30-day readmission performance for heart failure patients and long-term survival: findings from Get With The Guidelines-Heart Failure. *Am Heart J*. 2018;200:127–133. doi: 10.1016/j.ahj.2017.11.018
19. Kumbhani DJ, Fonarow GC, Heidenreich PA, Schulte PJ, Lu D, Hernandez A, Yancy C, Bhatt DL. Association between hospital volume, processes of care, and outcomes in patients admitted with heart failure: insights from Get With The Guidelines–Heart Failure. *Circulation*. 2018;137:1661–1670. doi: 10.1161/CIRCULATIONAHA.117.028077
20. McAlister FA, Youngson E, van Diepen S, Ezekowitz JA, Kaul P. Influence of hospital volume on outcomes for patients with heart failure: evidence from a Canadian national cohort study. *Am Heart J*. 2018;202:148–150. doi: 10.1016/j.ahj.2018.05.014
21. Gupta A, Allen LA, Bhatt DL, Cox M, DeVore AD, Heidenreich PA, Hernandez AF, Peterson ED, Matsouaka RA, Yancy CW, et al. Association of the Hospital Readmissions Reduction Program implementation with readmission and mortality outcomes in heart failure. *JAMA Cardiol*. 2018;3:44–53. doi: 10.1001/jamacardio.2017.4265
22. Desai NR, Ross JS, Kwon JY, Herrin J, Dharmarajan K, Bernheim SM, Krumholz HM, Horwitz LI. Association between hospital penalty status under the Hospital Readmission Reduction Program and readmission rates for target and nontarget conditions. *JAMA*. 2016;316:2647–2656. doi: 10.1001/jama.2016.18533
23. Pokharel Y, Khariton Y, Tang Y, Nassif ME, Chan PS, Arnold SV, Jones PG, Spertus JA. Association of serial Kansas City Cardiomyopathy Questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials [published correction appears in *JAMA Cardiol*. 2018;3:181]. *JAMA Cardiol*. 2017;2:1315–1321. doi: 10.1001/jamacardio.2017.3983
24. Pandey A, Patel KV, Liang L, DeVore AD, Matsouaka R, Bhatt DL, Yancy CW, Hernandez AF, Heidenreich PA, de Lemos JA, et al. Association of hospital performance based on 30-day risk-standardized mortality rate with long-term survival after heart failure hospitalization: an analysis of the Get With The Guidelines-Heart Failure Registry. *JAMA Cardiol*. 2018;3:489–497. doi: 10.1001/jamacardio.2018.0579
25. Krumholz HM, Wang K, Lin Z, Dharmarajan K, Horwitz LI, Ross JS, Drye EE, Bernheim SM, Normand ST. Hospital-readmission risk: isolating hospital effects from patient effects. *N Engl J Med*. 2017;377:1055–1064. doi: 10.1056/NEJMsa1702321
26. Dharmarajan K, Wang Y, Lin Z, Normand ST, Ross JS, Horwitz LI, Desai NR, Suter LG, Drye EE, Bernheim SM, et al. Association of changing hospital readmission rates with mortality rates after hospital discharge. *JAMA*. 2017;318:270–278. doi: 10.1001/jama.2017.8444
27. Greene SJ, O'Brien EC, Mentz RJ, Luo N, Hardy NC, Laskey WK, Heidenreich PA, Chang CL, Turner SJ, Yancy CW, et al. Home-time after discharge among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2018;71:2643–2652. doi: 10.1016/j.jacc.2018.03.517
28. Warraich HJ, Xu H, DeVore AD, Matsouaka R, Heidenreich PA, Bhatt DL, Hernandez AF, Yancy CW, Fonarow GC, Allen LA. Trends in hospice discharge and relative outcomes among Medicare patients in the Get With The Guidelines-Heart Failure Registry. *JAMA Cardiol*. 2018;3:917–926. doi: 10.1001/jamacardio.2018.2678
29. Healthcare Effectiveness Data and Information Set (HEDIS) health plan employer data and information set measures of care on cardiovascular disease, diabetes mellitus, tobacco, nutrition, and lifestyle, 2017. National Committee for Quality Assurance website. https://www.ncqa.org/hedis-2018-measures/. Accessed March 24, 2019.
30. Pokharel Y, Gosch K, Nambi V, Chan PS, Kosiborod M, Oetgen WJ, Spertus JA, Ballantyne CM, Petersen LA, Virani SS. Practice-level variation in statin use among patients with diabetes: insights from the PINNACLE Registry. *J Am Coll Cardiol*. 2016;68:1368–1369. doi: 10.1016/j.jacc.2016.06.048
31. Hira RS, Kennedy K, Jneid H, Alam M, Basra SS, Petersen LA, Ballantyne CM, Nambi V, Chan PS, Virani SS. Frequency and practice-level variation in inappropriate and nonrecommended prasugrel prescribing: insights from the NCDR PINNACLE registry. *J Am Coll Cardiol*. 2014;63:2876–2877. doi: 10.1016/j.jacc.2014.04.011
32. Hira RS, Kennedy K, Nambi V, Jneid H, Alam M, Basra SS, Ho PM, Deswal A, Ballantyne CM, Petersen LA, et al. Frequency and practice-level variation in inappropriate aspirin use for the primary prevention of cardiovascular disease: insights from the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence registry. *J Am Coll Cardiol*. 2015;65:111–121. doi: 10.1016/j.jacc.2014.10.035
33. Hall HM, de Lemos JA, Enriquez JR, McGuire DK, Peng SA, Alexander KP, Roe MT, Desai N, Wiviott SD, Das SR. Contemporary patterns of discharge aspirin dosing after acute myocardial infarction in the United States: results from the National Cardiovascular Data Registry (NCDR). *Circ Cardiovasc Qual Outcomes*. 2014;7:701–707. doi: 10.1161/CIRCOUTCOMES.113.000822
34. Maddox TM, Chan PS, Spertus JA, Tang F, Jones P, Ho PM, Bradley SM, Tsai TT, Bhatt DL, Peterson PN. Variations in coronary artery disease secondary prevention prescriptions among outpatient cardiology practices: insights from the NCDR (National Cardiovascular Data Registry). *J Am Coll Cardiol*. 2014;63:539–546. doi: 10.1016/j.jacc.2013.09.053
35. Salami JA, Warraich H, Valero-Elizondo J, Spatz ES, Desai NR, Rana JS, Virani SS, Blankstein R, Khera A, Blaha MJ, et al. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *JAMA Cardiol*. 2017;2:56–65. doi: 10.1001/jamacardio.2016.4700
36. Mazurek M, Huisman MV, Lip GYH. Registries in atrial fibrillation: from trials to real-life clinical practice. *Am J Med*. 2017;130:135–145. doi: 10.1016/j.amjmed.2016.09.012
37. Heidenreich PA, Solis P, Mark Estes NA 3rd, Fonarow GC, Jurgens CY, Marine JE, McManus DD, McNamara RL. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures [published correction appears in *Circ Cardiovasc Qual Outcomes*. 2018;11:e000043]. *Circ Cardiovasc Qual Outcomes*. 2016;9:443–488. doi: 10.1161/HCQ.0000000000000018
38. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, et al; GLORIA-AF Investigators. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry phase 2. *J Am Coll Cardiol*. 2017;69:777–785. doi: 10.1016/j.jacc.2016.11.061
39. Lewis WR, Piccini JP, Turakhia MP, Curtis AB, Fang M, Suter RE, Page RL 2nd, Fonarow GC. Get With The Guidelines AFIB: novel quality improvement registry for hospitalized patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2014;7:770–777. doi: 10.1161/CIRCOUTCOMES.114.001263
40. Piccini JP, Xu H, Cox M, Matsouaka RA, Fonarow GC, Butler J, Curtis AB, Desai N, Fang M, McCabe PJ, et al; on behalf of the Get With The Guidelines-AFIB Clinical Working Group and Hospitals. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. *Circulation*. 2019;139:1497–1506. doi: 10.1161/CIRCULATIONAHA.118.035909
41. Hsu JC, Maddox TM, Kennedy K, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Aspirin instead of oral anticoagulant prescription in atrial fibrillation patients at risk for stroke. *J Am Coll Cardiol*. 2016;67:2913–2923. doi: 10.1016/j.jacc.2016.03.581
42. Perino AC, Fan J, Schmitt SK, Askari M, Kaiser DW, Deshmukh A, Heidenreich PA, Swan C, Narayan SM, Wang PJ, et al. Treating specialty

and outcomes in newly diagnosed atrial fibrillation: from the TREAT-AF study. *J Am Coll Cardiol*. 2017;70:78–86. doi: 10.1016/j.jacc.2017.04.054
43. Bettger JP, Thomas L, Liang L, Xian Y, Bushnell CD, Saver JL, Fonarow GC, Peterson ED. Hospital variation in functional recovery after stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e002391. doi: 10.1161/CIRCOUTCOMES.115.002391
44. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA*. 2014;311:1632-1640. doi: 10.1001/jama.2014.3203
45. Xian Y, Xu H, Lytle B, Blevins J, Peterson ED, Hernandez AF, Smith EE, Saver JL, Messe SR, Paulsen M, et al. Use of strategies to improve door-to-needle times with tissue-type plasminogen activator in acute ischemic stroke in clinical practice: findings from Target: Stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003227. doi: 10.1161/CIRCOUTCOMES.116.003227
46. Ekundayo OJ, Saver JL, Fonarow GC, Schwamm LH, Xian Y, Zhao X, Hernandez AF, Peterson ED, Cheng EM. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With The Guidelines–Stroke. *Circ Cardiovasc Qual Outcomes*. 2013;6:262–269. doi: 10.1161/CIRCOUTCOMES.113.000089
47. Kaufman BG, O'Brien EC, Stearns SC, Matsouaka RA, Holmes GM, Weinberger M, Schwamm LH, Smith EE, Fonarow GC, Xian Y, et al. Medicare shared savings ACOs and hospice care for ischemic stroke patients. *J Am Geriatr Soc*. 2019;67:1402–1409. doi: 10.1111/jgs.15852
48. Howard G, Schwamm LH, Donnelly JP, Howard VJ, Jasne A, Smith EE, Rhodes JD, Kissela BM, Fonarow GC, Kleindorfer DO, et al. Participation in Get With The Guidelines–Stroke and its association with quality of care for stroke. *JAMA Neurol.* 2018;75:1331–1337. doi: 10.1001/jamaneurol.2018.2101
49. Peterson PN, Varosy PD, Heidenreich PA, Wang Y, Dewland TA, Curtis JP, Go AS, Greenlee RT, Magid DJ, Normand SL, et al. Association of single- vs dual-chamber ICDs with mortality, readmissions, and complications among patients receiving an ICD for primary prevention. *JAMA*. 2013;309:2025–2034. doi: 10.1001/jama.2013.4982
50. Thompson LE, Chan PS, Tang F, Nallamothu BK, Girotra S, Perman SM, Bose S, Daugherty SL, Bradley SM; American Heart Association's Get With the Guidelines-Resuscitation Investigators. Long-term survival trends of Medicare patients after in-hospital cardiac arrest: insights from Get With The Guidelines-Resuscitation. *Resuscitation.* 2018;123:58–64. doi: 10.1016/j.resuscitation.2017.10.023
51. Ofoma UR, Basnet S, Berger A, Kirchner HL, Girotra S; American Heart Association Get With the Guidelines – Resuscitation Investigators. Trends in survival after in-hospital cardiac arrest during nights and weekends. *J Am Coll Cardiol*. 2018;71:402–411. doi: 10.1016/j.jacc.2017.11.043
52. Khera R, Chan PS, Donnino M, Girotra S; on behalf of the American Heart Association's Get With The Guidelines–Resuscitation Investigators. Hospital variation in time to epinephrine for nonshockable in-hospital cardiac arrest. *Circulation.* 2016;134:2105–2114. doi: 10.1161/CIRCULATIONAHA.116.025459
53. Anderson ML, Nichol G, Dai D, Chan PS, Thomas L, Al-Khatib SM, Berg RA, Bradley SM, Peterson ED. Association between hospital process composite performance and patient outcomes after in-hospital cardiac arrest care. *JAMA Cardiol*. 2016;1:37–45. doi: 10.1001/jamacardio.2015.0275
54. Stub D, Schmicker RH, Anderson ML, Callaway CW, Daya MR, Sayre MR, Elmer J, Grunau BE, Aufderheide TP, Lin S, et al; ROC Investigators. Association between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. *Resuscitation*. 2015;92:45–52. doi: 10.1016/j.resuscitation.2015.04.015
55. Udell JA, Desai NR, Li S, Thomas L, de Lemos JA, Wright-Slaughter P, Zhang W, Roe MT, Bhatt DL. Neighborhood socioeconomic disadvantage and care after myocardial infarction in the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004054. doi: 10.1161/CIRCOUTCOMES.117.004054
56. Graham GN, Jones PG, Chan PS, Arnold SV, Krumholz HM, Spertus JA. Racial disparities in patient characteristics and survival after acute myocardial infarction. *JAMA Netw Open.* 2018;1:e184240. doi: 10.1001/jamanetworkopen.2018.4240
57. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al; ACC PINNACLE Investigators. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: a report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J.* 2018;195:50–59. doi: 10.1016/j.ahj.2017.08.010
58. Kaplan CM, Thompson MP, Waters TM. How have 30-day readmission penalties affected racial disparities in readmissions? An analysis from 2007 to 2014 in five US states. *J Gen Intern Med*. 2019;34:878–883. doi: 10.1007/s11606-019-04841-x
59. Ziaeian B, Kominski GF, Ong MK, Mays VM, Brook RH, Fonarow GC. National differences in trends for heart failure hospitalizations by sex and race/ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003552. doi: 10.1161/CIRCOUTCOMES.116.003552
60. Song S, Liang L, Fonarow GC, Smith EE, Bhatt DL, Matsouaka RA, Xian Y, Schwamm LH, Saver JL. Comparison of clinical care and in-hospital outcomes of Asian American and white patients with acute ischemic stroke. *JAMA Neurol*. 2019;76:430–439. doi: 10.1001/jamaneurol.2018.4410
61. Joseph L, Chan PS, Bradley SM, Zhou Y, Graham G, Jones PG, Vaughan-Sarrazin M, Girotra S; American Heart Association Get With the Guidelines–Resuscitation Investigators. Temporal changes in the racial gap in survival after in-hospital cardiac arrest. *JAMA Cardiol.* 2017;2:976–984. doi: 10.1001/jamacardio.2017.2403

25. MEDICAL PROCEDURES

See Tables 25-1 and 25-2 and Charts 25-1 through 25-4

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Trends in Operations and Procedures (See Tables 25-1 and 25-2 and Charts 25-1 and 25-2)

- The mean hospital charges for cardiovascular procedures in 2014 ranged from $43 484 for CEA to $808 770 for heart transplantations (Table 25-1).
- The trends in the numbers of 5 common cardiovascular procedures in the United States from 1993 to 2014 are presented in Chart 25-1. Of the 5 procedures, cardiac catheterization was the most common procedure for all years presented (Chart 25-1).
- Of the 10 leading diagnostic groups in the United States, the greatest number of surgical procedures were cardiovascular and obstetric procedures (Chart 25-2).
- The total number of inpatient cardiovascular operations and procedures decreased 6%, from 8 461 000 in 2004 to 7 971 000 in 2014 (Table 25-2).
- Data from the HCUP were examined by the NHLBI for trends from 1997 to 2014 for use of PCI and CABG,[1] as discussed in this chapter.

Coronary Artery Bypass Grafting

- The number of inpatient discharges for CABG decreased from 683 000 in 1997 to 371 000 in 2014 (Chart 25-1).
- In 1997, the number of inpatient discharges for CABG was 484 000 for males and 199 000 for females; these numbers declined to 276 000 and 94 000, respectively, in 2014 (Table 25-2).[1]

Abbreviations Used in Chapter 25

ASD	atrial septal defect
AV	atrioventricular
CABG	coronary artery bypass graft
CEA	carotid endarterectomy
HCUP	Healthcare Cost and Utilization Project
HLHS	hypoplastic left heart syndrome
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
NHLBI	National Heart, Lung, and Blood Institute
PCI	percutaneous coronary intervention
STS	Society of Thoracic Surgeons
VSD	ventricular septal defect

Inpatient Cardiac Catheterization and PCI (See Tables 25-1 and 25-2 and Chart 25-1)

- Inpatient PCI discharges decreased from 359 000 for males and 190 000 for females in 1997 to 325 000 and 155 000, respectively, by 2014 (Table 25-2).
- Data on Medicare beneficiaries undergoing a coronary revascularization procedure between 2008 and 2012 indicate that the rapid growth in nonadmission PCIs (from 60 405 to 106 495) has been more than offset by the decrease in PCI admissions (from 363 384 to 295 434).[2]
- In 2014, the mean inpatient hospital charge for PCI was $84 813 (Table 25-1).
- From 2004 to 2014, the number of inpatient cardiac catheterizations decreased from 1 486 000 to 1 016 000 annually (Chart 25-1).
- In 2014, an estimated 480 000 inpatient PCIs (previously referred to as percutaneous transluminal coronary angioplasty) procedures were performed in the United States (Chart 25-1).
- In 2014, ≈68% of PCI procedures were performed on males, and ≈50% were performed on people ≥65 years of age (Table 25-2).
- Inpatient hospital deaths for PCI increased from 0.8% in 2004 to 2.1% in 2014 (Table 25-1). In 2014, ≈82% of stents implanted during PCI were drug-eluting stents compared with 18% that were bare-metal stents.
- The rate of any cardiac stent procedure per 10 000 population rose by 61% from 1999 to 2006, then declined by 27% between 2006 and 2009.[3]

Cardiac Open Heart Surgery

- Data from the STS Adult Cardiac Surgery Database, which voluntarily collects data from ≈80% of all hospitals that perform CABG in the United States, indicate that a total of 159 869 procedures involved isolated CABG in 2016.[4]
- Among other major procedures in 2016, there were 28 493 isolated aortic valve replacements and 7706 isolated mitral valve replacements; 17 507 procedures involved both aortic valve replacement and CABG, whereas 2935 procedures involved both mitral valve replacement and CABG.[4]

Congenital Heart Surgery, 2013 to 2016

According to data from the STS Congenital Heart Surgery Database[5]:

- There were 122 459 congenital heart surgeries performed from July 2014 to June 2018. The in-hospital mortality rate was 2.9% during that time period. The 5 most common diagnoses were

type 2 VSD (6.3%), open sternum with open skin (5.9%), HLHS (5.8%), patent ductus arteriosus (4.2%), and secundum ASD (4.0%).
- The 5 most common primary procedures were delayed sternal closure (8.3%), patch VSD repair (6.3%), mediastinal exploration (3.5%), patch ASD repair (3.2%), and complete AV canal (ASD) repair (2.8%).

Heart Transplantations (See Charts 25-3 and 25-4)

According to data from the Organ Procurement and Transplantation Network[6]:
- In 2018, 3408 heart transplantations were performed in the United States (Chart 25-3). There are 256 transplantation hospitals in the United States, 143 of which performed heart transplantations in 2018.
- Of the recipients in 2018, 69.8% were male, and 62.6% were white; 21.6% were black, 10.4% were Hispanic, and 3.9% were Asian. Heart transplantations by recipient age are shown in Chart 25-4.
- For transplantations that occurred between 2008 and 2015, the 1-year survival rate was 90.5% for males and 91.1% for females; the 5-year survival rates based on 2008 to 2015 transplantations were 78.4% for males and 77.7% for females. The 1- and 5-year survival rates for white cardiac transplantation patients were 90.7% and 79.1%, respectively. For black patients, they were 90.7% and 74.1%, respectively. For Hispanic patients, they were 90.1% and 80.0%, respectively. For Asian patients, they were 91.4% and 80.1%, respectively.
- As of July 22, 2019, 3779 patients were on the transplant waiting list for a heart transplant, and 46 patients were on the list for a heart/lung transplant.

Table 25-1. Mean Hospital Charges, In-Hospital Death Rates, and Mean Length of Stay for Various Cardiovascular Procedures, United States, 2014

Procedure	Mean Hospital Charges, $	In-Hospital Death Rate, %	Mean Length of Stay, d	*ICD-9-CM* Procedure Codes
Total vascular and cardiac surgery and procedures	90215	3.34	6.3	35–39, 00.50–00.51, 00.53–00.55, 00.61–00.66
CABG	168541	1.78	9.3	36.1–36.3
PCI	84813	2.07	3.5	00.66, 17.55, 36.01, 36.02, 36.05
Cardiac catheterization	57494	1.42	4.2	37.21–37.23
Pacemakers	83521	1.46	5.1	37.7–37.8, 00.50, 00.53
Implantable defibrillators	171476	0.69	6.3	37.94–37.99, 00.51, 00.54
CEA	43484	0.27	2.6	38.12
Heart valves	201557	3.36	9.7	35.00–35.14, 35.20–35.28, 35.96, 35.97, 35.99
Heart transplantations	808770	7.84	45.4	37.51

Principal procedure only. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; *ICD-9-CM*, *International Classification of Diseases, Clinical Modification, 9th Revision*; and PCI, percutaneous coronary intervention.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.[1]

Table 25-2. Estimated* Inpatient Cardiovascular Operations, Procedures, and Patient Data by Sex and Age (in Thousands), United States, 2014

Operation/Procedure/ Patients	*ICD-9-CM* Procedure Codes	All	Sex		Age, y			
			Male	Female	18–44	45–64	65–84	≥85
Heart valves	35.00–35.14, 35.20–35.28, 35.96, 35.97, 35.99	156	92	63	11	40	83	16
PCI	00.66, 17.55, 36.01, 36.02, 36.05	480	325	155	26	213	212	28
PCI with stents	36.06, 36.07	434	294	140	24	194	191	25
CABG	36.1–36.3	371	276	94	10	148	204	9
Cardiac catheterization	37.21–37.23	1016	625	391	68	432	455	54
Pacemakers	37.7, 37.8, 00.50, 00.53	351	185	166	9	57	197	85
Pacemaker devices	37.8, 00.53	141	72	69	3	19	80	38
Pacemaker leads	37.7, 00.50	210	114	97	7	38	117	47
Implantable defibrillators	37.94–37.99, 00.51, 00.54	60	43	17	4	21	30	3
CEA	38.12	86	51	35	0	20	60	6
Total vascular and cardiac surgery and procedures†‡	35–39, 00.50–00.51, 00.53– 00.55, 00.61–00.66	7971	4602	3368	777	2860	3402	558

These data do not reflect any procedures performed on an outpatient basis. Many more procedures are being performed on an outpatient basis. Some of the lower numbers in this table compared with 2006 probably reflect this trend. Data include procedures performed on newborn infants. Some of the *ICD-9-CM* procedure codes may have changed over the years. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; *ICD-9-CM*, *International Classification of Diseases, Clinical Modification, 9th Revision*; and PCI, percutaneous coronary intervention.

*Breakdowns are not available for some procedures, so entries for some categories do not add to totals. These data include codes for which the estimated number of procedures is <5000. Categories with such small numbers are considered unreliable by the National Center for Health Statistics and in some cases may have been omitted.

†Totals include procedures not shown here.

‡This estimate includes angioplasty and stent insertions for noncoronary arteries.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.[1]

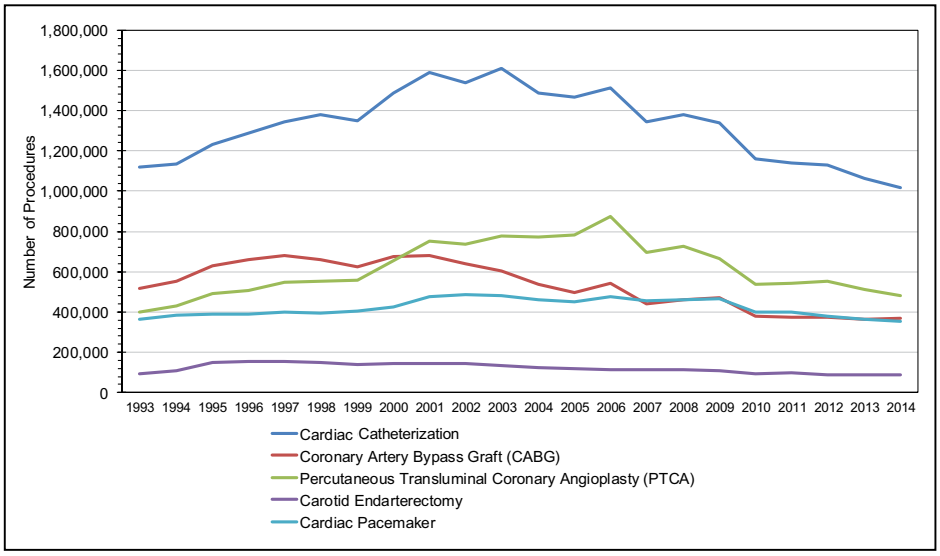

Chart 25-1. Trends in cardiovascular procedures, United States, 1993 to 2014; inpatient procedures only.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 1993 to 2014.[1]

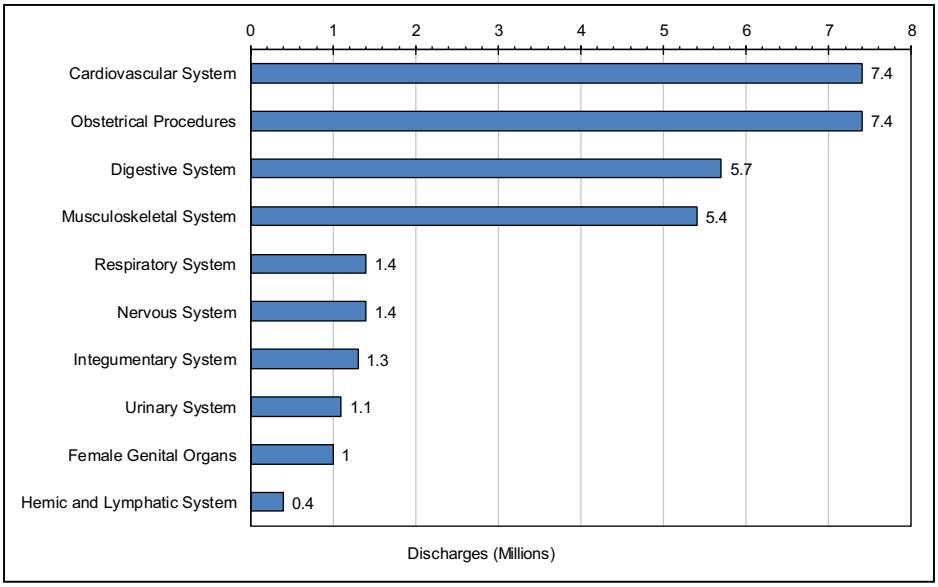

Chart 25-2. Number of surgical procedures in the 10 leading diagnostic groups, United States, 2014.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.[1]

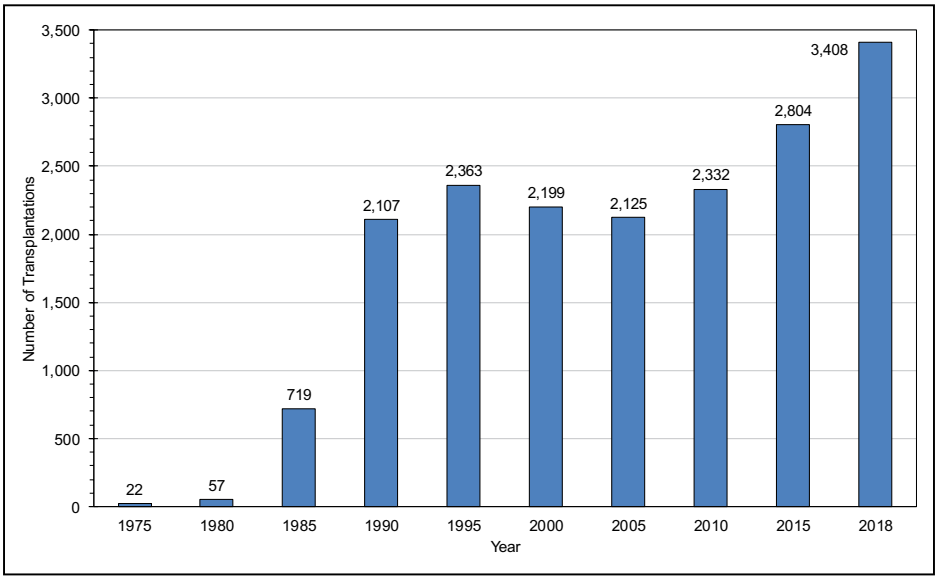

Chart 25-3. Trends in heart transplantations, United States, 1975 to 2018.
Source: Data derived from the Organ Procurement and Transplantation Network, 1975 to 2018.[6]

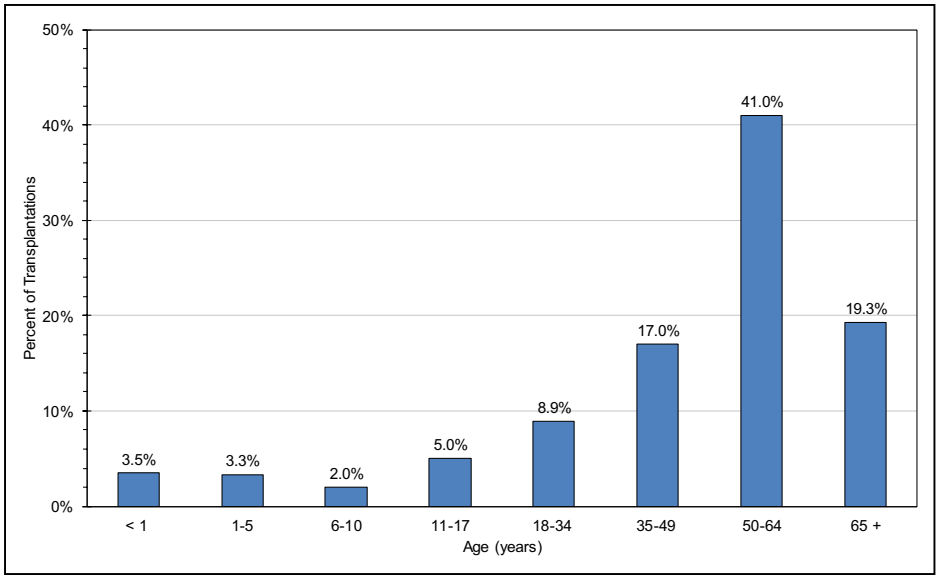

Chart 25-4. Heart transplantations by recipient age, United States, 2018.
Source: Data derived from the Organ Procurement and Transplantation Network, 2018.[6]

REFERENCES

1. Agency for Healthcare Research and Quality. HCUPnet, 1996–2016. Healthcare Cost and Utilization Project (HCUP) website. http://hcupnet.ahrq.gov/. Accessed April 1, 2019.
2. Culler SD, Kugelmass AD, Brown PP, Reynolds MR, Simon AW. Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012. *Circulation*. 2015;131:362–370. doi: 10.1161/CIRCULATIONAHA.114.012485
3. Auerbach DI, Maeda JL, Steiner C. Hospital Stays with Cardiac Stents, 2009. HCUP Statistical Brief #128. Rockville, MD: Agency for Health Care Research and Quality; April 2012. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb128.pdf. Accessed April 1, 2019.
4. Adult Cardiac Surgery Database: Executive Summary: 10 Years: STS Period Ending 06/30/2017. Society of Thoracic Surgeons website. https://www.sts.org/sites/default/files/documents/ACSD2017Harvest3_ExecutiveSummary.pdf. Accessed June 5, 2019.
5. STS Congenital Heart Surgery Data Summary: All Patients: STS Period Ending 06/30/2018. Society of Thoracic Surgeons website. https://www.sts.org/sites/default/files/documents/Fall2018CongenitalSTSExecSummary_AllPatients.pdf. Accessed March 18, 2019.
6. Organ Procurement and Transplantation Network website. https://optn.transplant.hrsa.gov/data/. Accessed July 22, 2019.

26. ECONOMIC COST OF CARDIOVASCULAR DISEASE

See Tables 26-1 and 26-2 and Charts 26-1 through 26-6

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Using data from MEPS (2014–2015),[1] the annual direct and indirect cost of CVD in the United States is an estimated $351.3 billion (Table 26-1 and Chart 26-1). This figure includes $213.8 billion in expenditures (direct costs, which include the cost of physicians and other professionals, hospital services, prescribed medications, and home health care, but not the cost of nursing home care) and $137.5 billion in lost future productivity (indirect costs) attributed to premature CVD and stroke mortality in 2014 to 2015.

The direct costs for CVD and stroke for 2014 to 2015 (average annual) are available on the website of the nationally representative MEPS of the Agency for Healthcare Research and Quality.[1] Details on the advantages or disadvantages of using MEPS data are provided in the "Heart Disease and Stroke Statistics–2011 Update."[2] Indirect mortality costs are estimated for 2014 to 2015 (average annual) by multiplying the number of deaths for those years attributable to CVD and stroke, in age and sex groups, by estimates of the present value of lifetime earnings for those age and sex groups as of 2014 to 2015. Mortality data are from the NVSS of the NCHS.[3] The present values of lifetime earnings are unpublished estimates furnished by the Institute for Health and Aging, University of California, San Francisco, by Wendy Max, PhD, on April 4, 2018. Those estimates incorporate a 3% discount rate, which is the recommended percentage.[4] The discount rate removes the effect of inflation in income over the lifetime of earnings. The estimate is for 2014, inflated to 2015 to account for the 2014 to 2015 change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.[5]

Abbreviations Used in Chapter 26

AHA	American Heart Association
CHD	coronary heart disease
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
GI	gastrointestinal (tract)
HBP	high blood pressure
HD	heart disease
HF	heart failure
MEPS	Medical Expenditure Panel Survey
NCHS	National Center for Health Statistics
NVSS	National Vital Statistics System

The indirect costs exclude lost productivity costs attributable to chronic, prevalent nonfatal CVD and stroke illness during 2014 to 2015 among workers, people keeping house, people in institutions, and people unable to work. Those morbidity costs were substantial in very old studies, but because of the lack of contemporary data, an adequate update could not be made.

Most Costly Diseases (See Tables 26-1 and 26-2 and Charts 26-2 and 26-3)

CVD accounted for 14% of total US health expenditures in 2014 to 2015, more than any major diagnostic group.[1] By way of comparison, CVD total direct costs shown in Table 26-1 are higher than the 2014 to 2015 Agency for Healthcare Research and Quality estimates for cancer, which were $84.0 billion (55% for outpatient or doctor office visits, 32% for inpatient care, and 9% for prescription drugs).[1]

Table 26-2 shows direct and indirect costs for CVD by sex and by 2 broad age groups. Chart 26-2 shows total direct costs for the 21 leading chronic diseases on the MEPS list. HD is the most costly condition.[6]

The estimated direct costs of CVD in the United States increased from $103.5 billion in 1996 to 1997 to $213.8 billion in 2014 to 2015 (Chart 26-3).

Economic Value of CVD Risk Factor Control

Cutler et al[7] analyzed individual-level Medicare and non-Medicare healthcare spending captured by Medicare Current Beneficiary Survey data from 1999 to 2012. Overall, increased use of lipid-lowering, antihypertensive, and anti-DM medications over time accounted for a combined 51% of the reduction in individual spending on CVD.[7]

Projections (See Charts 26-4 through 26-6)

- The AHA developed methodology to project future costs of care for HBP, CHD, HF, stroke, and all other CVD.[8] The methods used for the projections are very different from those used to derive the other direct and indirect costs in this chapter. For example, the projections estimates include the direct costs of nursing home care and the indirect costs of CVD morbidity.
- By 2035, 45.1% of the US population is projected to have some form of CVD.[8]
- Between 2015 and 2035, total direct medical costs of CVD are projected to increase from $318 billion to $749 billion (2015 dollars in billions). Of this total in 2035, 55.5% will be attributable to hospital costs, 15.3% to medications, 15.0% to

Circulation. 2020;141:e139–e596. DOI: 10.1161/CIR.0000000000000757

physicians, 7.2% to nursing home care, 5.5% to home health care, and 1.5% to other costs.[8]

- Indirect costs (attributable to lost productivity) for all fatal and nonfatal CVDs are estimated to increase from $237 billion in 2015 to $368 billion in 2035 (2015 dollars in billions), an increase of 55%.[8]
- Between 2015 and 2035, the total costs are expected to increase for total CVD, HBP and HBP as a risk factor, CHD, CHF, stroke, and other CVDs (Chart 26-4).
- Between 2015 and 2035, the projected total (direct and indirect) costs of total CVD are estimated to remain relatively stable for 18- to 44-year-olds, increase slightly for 45- to 64-year-olds, and increase sharply for 65- to 79-year-olds and adults ≥80 years of age (Chart 26-5).
- Whereas the direct costs of CVD for home health care, nursing homes, healthcare professionals, and medications are estimated to rise steadily between 2015 and 2035, projected hospital costs are estimated to more than double in this same time frame (Chart 26-6).
- These data indicate that CVD prevalence and costs are projected to increase substantially unless CVD incidence is reduced or short-term and long-term CVD care costs are better controlled.

Table 26-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD and Stroke, United States, Average Annual, 2014 to 2015

	HD*	Stroke	Hypertensive Disease†	Other Circulatory Conditions‡	Total CVD
Direct costs§					
Hospital inpatient stays	59.4	17.4	7.9	12.8	97.5
Hospital ED visits	6.3	0.8	1.3	1.0	9.4
Hospital outpatient or office-based provider visits	22.6	2.4	13.7	7.9	46.6
Home health care	11.1	6.6	8.2	1.6	27.5
Prescribed medicines	10.0	0.8	20.2	1.8	32.8
Total expenditures	109.4	28.0	51.3	25.1	213.8
Indirect costs‖					
Lost productivity/mortality	109.3	17.5	4.6	6.1	137.5
Grand totals	218.7	45.5	55.9	31.2	351.3

Numbers do not add to total because of rounding. CVD indicates cardiovascular disease; ED, emergency department; and HD, heart disease.

*This category includes coronary HD, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic HD; cardiomyopathy, pulmonary HD, and other or ill-defined HDs.

†Costs attributable to hypertensive disease are limited to hypertension without HD.

‡Other circulatory conditions include arteries, veins, and lymphatics.

§Medical Expenditure Panel Survey (MEPS) healthcare expenditures are estimates of direct payments for care of a patient with the given disease provided during the year, including out-of-pocket payments and payments by private insurance, Medicaid, Medicare, and other sources. Payments for over-the-counter drugs are not included. These estimates of direct costs do not include payments attributed to comorbidities. Total CVD costs are the sum of costs for the 4 diseases but with some duplication.

‖The Statistics Committee agreed to suspend presenting estimates of lost productivity attributable to morbidity until a better estimating method can be developed. Lost future earnings of people who died in 2015 to 2016, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Household Component of the MEPS for direct costs (average annual 2014 to 2015).[6] Indirect mortality costs are based on 2014 to 2015 counts of deaths by the National Center for Health Statistics and an estimated present value of lifetime earnings furnished for 2014 by Wendy Max (Institute for Health and Aging, University of California, San Francisco, April 4, 2018) and inflated to 2015 from change in worker compensation reported by the US Bureau of Labor Statistics.[5]

Table 26-2. Costs of Total CVD and Stroke in Billions of Dollars by Age and Sex, United States, Average Annual, 2014 to 2015

	Total	Males	Females	Age <65 y	Age ≥65 y
All direct	213.8	122.4	91.4	85.5	128.3
Indirect: mortality only	137.5	102.3	35.2	115.6	21.9
Total	351.3	224.7	126.6	201.1	150.2

Numbers may not add to total because of rounding. CVD indicates cardiovascular disease.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2014 to 2015 (direct costs) and mortality data from the National Vital Statistics System and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).[3,6]

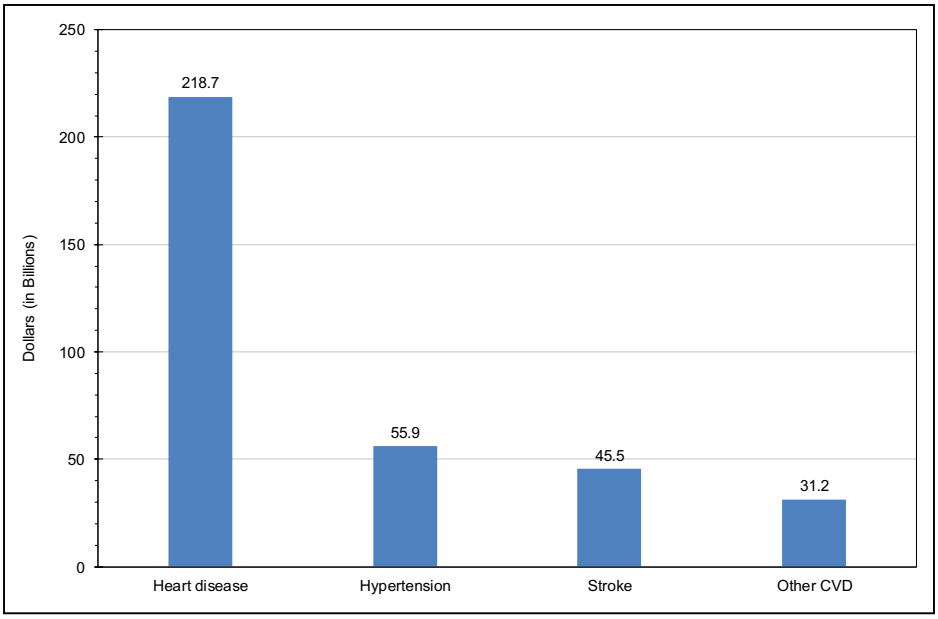

Chart 26-1. Direct and indirect costs of CVD (in billions of dollars), United States, average annual 2014 to 2015.
CVD indicates cardiovascular disease.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and mortality data from the National Vital Statistics System.[1,3]

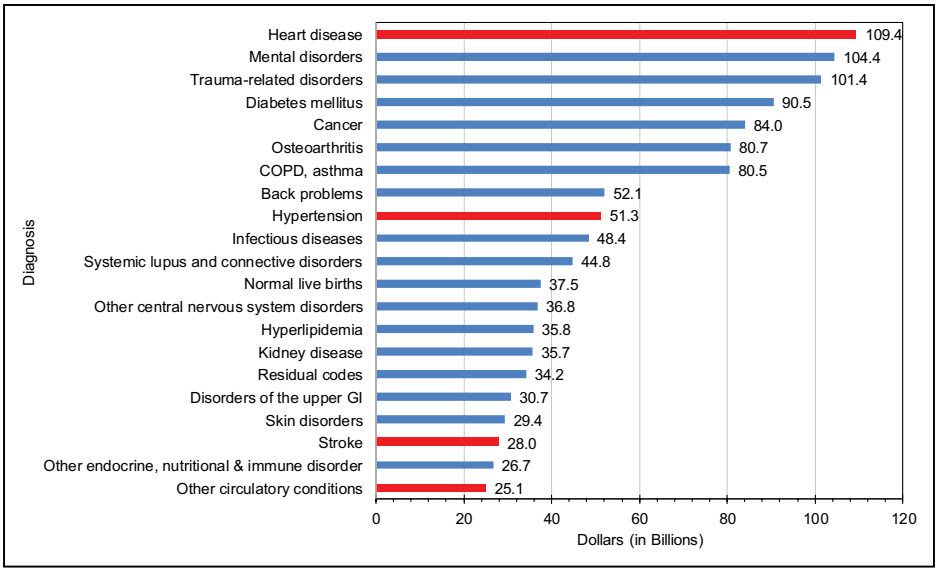

Chart 26-2. The 21 leading diagnoses for direct health expenditures, United States, average annual 2014 to 2015 (in billions of dollars).
COPD indicates chronic obstructive pulmonary disease; and GI, gastrointestinal (tract).
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and excluding nursing home costs.[1]

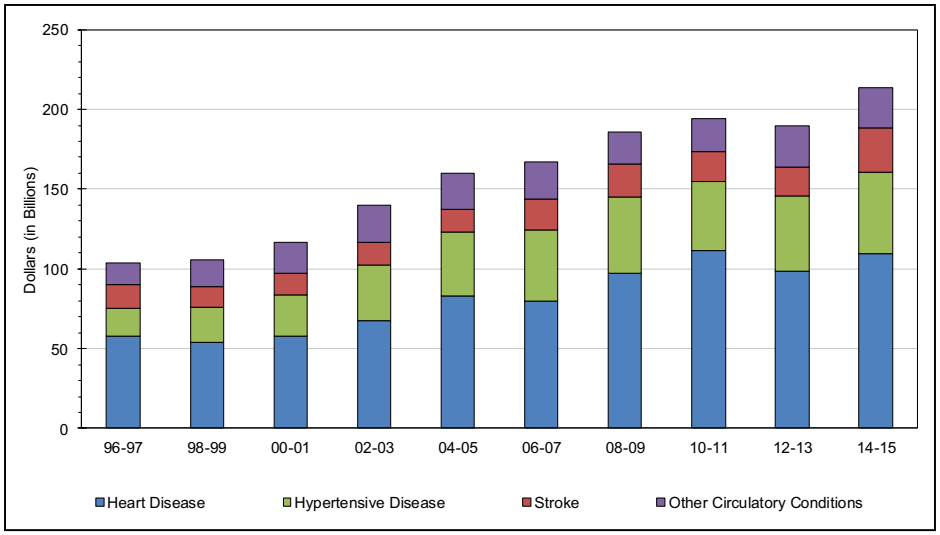

Chart 26-3. Estimated direct cost (in billions of dollars) of cardiovascular disease, United States, average annual (1996–1997 to 2014–2015).
Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 1996–1997 to 2014–2015).[1]

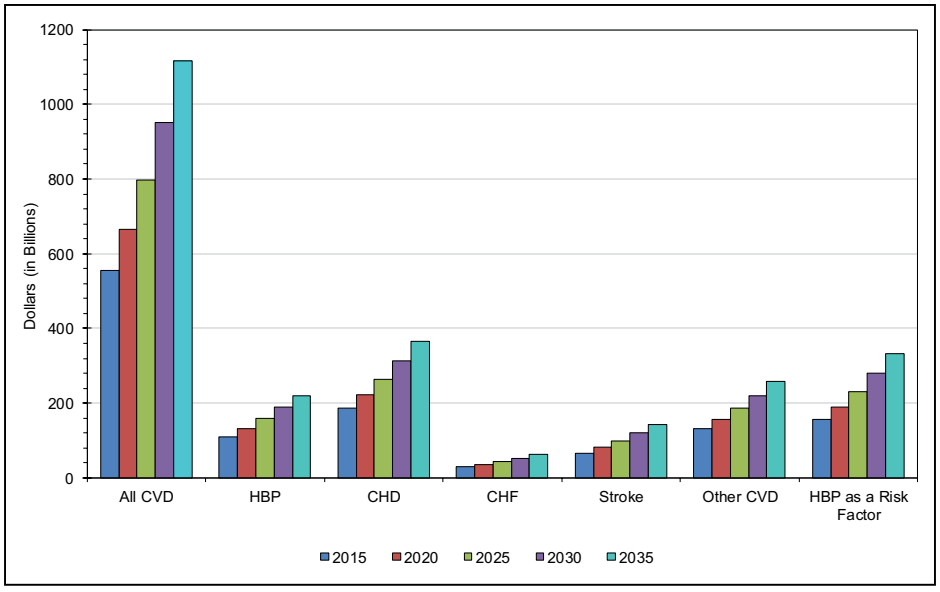

Chart 26-4. Projected total costs of CVD, United States, 2015 to 2035 (2015 dollars in billions).
CHD indicates coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; and HBP, high blood pressure.
Source: Data from RTI International.[8] Copyright © 2016, American Heart Association, Inc.

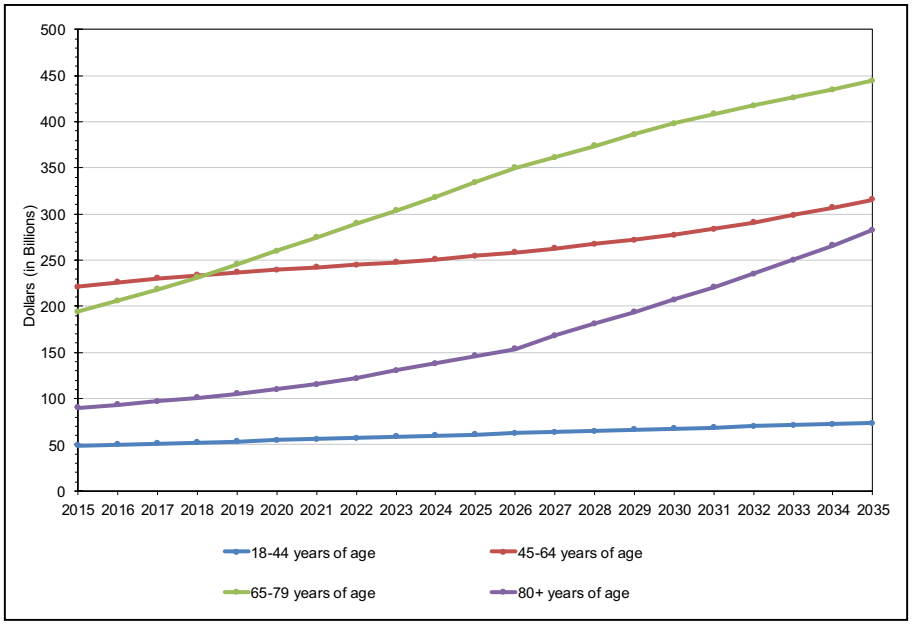

Chart 26-5. Projected total (direct and indirect) costs of total cardiovascular disease by age, United States, 2015 to 2035 (2015 dollars in billions).
Source: Data from RTI International.[8] Copyright © 2016, American Heart Association, Inc.

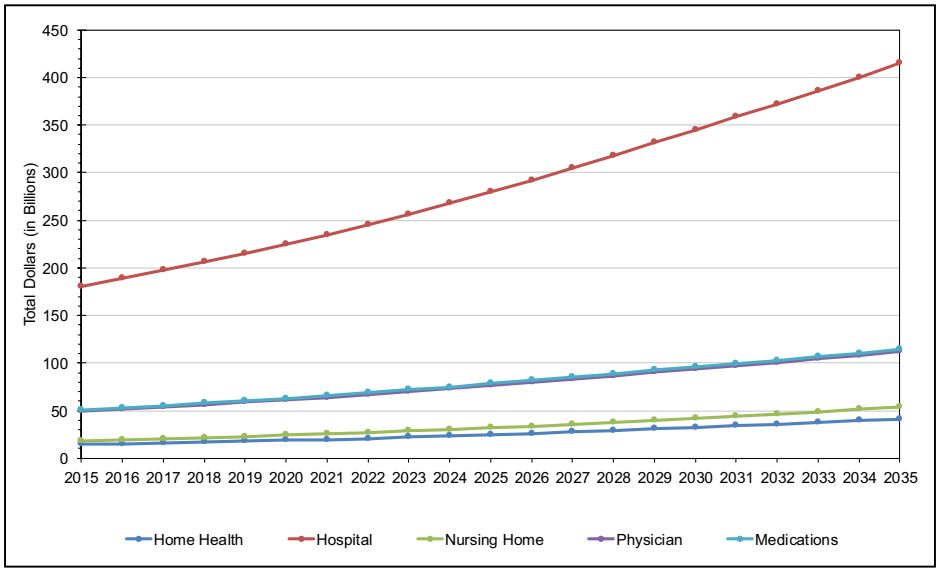

Chart 26-6. Projected direct costs of total cardiovascular disease by type of cost, United States, 2015 to 2035 (2015 dollars in billions).
Source: Data from RTI International.[8] Copyright © 2016, American Heart Association, Inc.

REFERENCES

1. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: medical conditions, United States, 1996–2015. Agency for Healthcare Research and Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed June 17, 2019.
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2011 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2011;123:e240 and *Circulation*. 2011;124:e426. *Circulation*. 2011;123:e18–e209. doi: 10.1161/CIR.0b013e3182009701
3. National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files, 2017. Centers for Disease Control and Prevention website. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed April 1, 2019.
4. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
5. US Bureau of Labor Statistics, Office of Compensation Levels and Trends. Employment Cost Index, Historical Listing – Volume V: Continuous Occupational and Industry Series: September 1975-December 2017. Table 4: employment cost index for total compensation, for civilian workers, by occupation and industry: continuous occupational and industry series. https://www.bls.gov/web/eci/ecicois.pdf. Accessed May 1, 2019.
6. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS): household component summary tables: total expenditures in millions by condition, United States, 2015–2016. Agency for Healthcare Research and Quality website. https://meps.ahrq.gov/mepstrends/hc_cond/. Accessed May 1, 2019.
7. Cutler DM, Ghosh K, Messer KL, Raghunathan TE, Stewart ST, Rosen AB. Explaining the slowdown in medical spending growth among the elderly, 1999-2012. *Health Aff (Millwood)*. 2019;38:222–229. doi: 10.1377/hlthaff.2018.05372
8. RTI International. Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]. Research Triangle Park, NC: RTI International; November 2016. RTI project number 021480.003.001.001.

27. AT-A-GLANCE SUMMARY TABLES

See Tables 27-1 through 27-3

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Sources: See the following summary tables for complete details:

- Prevalence of Overweight, Obesity, and Severe Obesity in Youth and Adults, United States, 2013 to 2016—Table 6-1
- High TC and LDL-C and Low HDL-C, United States, 2013 to 2016 (Age ≥20 Years)—Table 7-1
- HBP in the United States—Table 8-1
- DM in the United States—Table 9-1
- CVDs in the United States—Table 13-1
- Stroke in the United States—Table 14-1
- CCDs in the United States—Table 15-1
- CHD in the United States—Table 19-1; AP in the United States—Table 19-2
- HF in the United States —Table 20-2

Table 27-1. Males and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/Alaska Native*
Overweight and obesity							
Prevalence, 2013–2016							
Overweight and obesity, BMI ≥25.0 kg/m²†	168.1 M (71.1%)	85.3 M (74.3%)	75.6%	69.8%	81.3%	49.5%	…
Obesity, BMI ≥30.0 kg/m²†	73.8 M (31.2%)	35.7 M (31.1%)	31.3%	30.1%	35.3%	11.3%	…
Blood cholesterol							
Prevalence, 2013–2016							
Total cholesterol ≥200 mg/dL‡	92.8 M (38.2%)	41.2 M (35.4%)	35.4%	29.8%	39.9%	38.7%	…
Total cholesterol ≥240 mg/dL‡	28.5 M (11.7%)	12.4 M (10.7%)	10.5%	8.9%	13.0%	11.7%	…
LDL-C ≥130 mg/dL‡	69.6 M (28.9%)	34.8 M (30.1%)	29.4%	29.5%	33.5%	32.2%	…
HDL-C <40 mg/dL‡	45.6 M (19.2%)	33.7 M (29.0%)	29.7%	19.8%	32.6%	25.9%	…
HBP							
Prevalence, 2013–2016†	116.4 M (46.0%)	58.7 M (49.0%)	48.2%	58.6%	47.4%	46.4%	…
Mortality, 2017§‖	90098	43127 (47.9%)¶	29086	8690	3478	1269#	568
DM							
Prevalence, 2013–2016							
Diagnosed DM†	26.0 M (9.8%)	13.7 M (10.9%)	9.4%	14.7%	15.1%	12.8%	…
Undiagnosed DM†	9.4 M (3.7%)	5.5 M (4.6%)	4.7%	1.7%	6.3%	6.1%	…
Prediabetes†	91.8 M (37.6%)	51.7 M (44.0%)	43.7%	31.9%	48.1%	47.1%	…
Incidence, diagnosed DM, 2015**	1.5 M	…	…	…	…	…	…
Mortality, 2017§‖	83564	46302 (55.4%)¶	31343	7494	5054	1612#	1114
Total CVD							
Prevalence, 2013–2016†	121.5 M (48.0%)	61.5 M (51.2%)	50.6%	60.1%	49.0%	47.4%	…
Mortality, 2017§‖	859125	440460 (51.3%)¶	340026	54780	29366	11891#	4554
Stroke							
Prevalence, 2013–2016†	7.0 M (2.5%)	3.2 M (2.5%)	2.4%	3.1%	2.0%	1.1%	…
New and recurrent strokes§	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	…	…	…
Mortality, 2017§	146383	61645 (42.1%)¶	45078	8566	5073	2442#	737‡‡
CHD							
Prevalence, CHD, 2013–2016†	18.2 M (6.7%)	9.4 M (7.4%)	7.7%	7.2%	6.0%	4.8%	…
Prevalence, MI, 2013–2016†	8.4 M (3.0%)	5.1 M (4.0%)	4.0%	4.0%	3.4%	2.4%	…
Prevalence, AP, 2013–2016†	9.4 M (3.6%)	4.3 M (3.5%)	3.8%	3.6%	2.6%	2.0%	…
New and recurrent MI and fatal CHD§§	1.05 M	610.0 K	520.0 K††	90.0K††	…	…	…
New and recurrent MI§§	805.0 K	470.0 K	…	…	…	…	…

(*Continued*)

Table 27-1. Continued

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/Alaska Native*
Mortality, 2017, CHD§‖	365 914	213 295 (58.3%)¶	168 868	22 167	14 195	5721	2032
Mortality, 2017, MI§‖	110 346	64 436 (58.4%)¶	51 155	6595	4437	1693#	593
HF							
Prevalence, 2013–2016†	6.2 M (2.2%)	3.0 M (2.4%)	2.2%	3.5%	2.5%	1.7%	…
Incidence, 2014‖‖	1.0 M	495.0 K	430.0 K††	65.0 K††	…	…	…
Mortality, 2017§‖	80 480	36 824 (45.8%)¶	30 076	4068	1820	633#	339

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (…), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); and NH, non-Hispanic.

*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

§All ages.

‖Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

**Age ≥18 years.

††Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥55 years.

Table 27-2. Females and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native*
Overweight and obesity							
Prevalence, 2011–2014							
Overweight and obesity, BMI ≥25.0 kg/m²†	168.1 M (71.1%)	82.8 M (68.1%)	66.3%	80.5%	77.8%	36.5%	…
Obesity, BMI ≥30.0 kg/m²†	73.8 M (31.2%)	38.1 M (31.3%)	29.6%	40.6%	37.8%	13.3%	…
Blood cholesterol							
Prevalence, 2013–2016							
Total cholesterol ≥200 mg/dL‡	92.8 M (38.2%)	51.6 M (40.4%)	41.8%	33.1%	38.9%	39.6%	…
Total cholesterol ≥240 mg/dL‡	28.5 M (11.7%)	16.1 M (12.4%)	13.6%	9.0%	10.1%	10.8%	…
LDL-C ≥130 mg/dL, 2011–2014‡	69.6 M (28.9%)	34.8 M (27.6%)	29.7%	23.4%	23.8%	25.1%	…
HDL-C <40 mg/dL, 2013–2016‡	45.6 M (19.2%)	11.9 M (9.9%)	9.3%	8.1%	13.1%	7.9%	…
HBP							
Prevalence, 2013–2016†	116.4 M (46.0%)	57.7 M (42.8%)	41.3%	56.0%	40.8%	36.4%	…
Mortality, 2017§‖	90 098	46 971 (52.1 %)¶	33 396	8387	3282	1538#	568
DM							
Prevalence, 2013–2016							
Diagnosed DM†	26.0 M (9.8%)	12.3 M (8.9%)	7.3%	13.4%	14.1%	9.9%	…
Undiagnosed DM†	9.4 M (3.7%)	3.9 M (2.8%)	2.6%	3.3%	4.0%	2.1%	…
Prediabetes†	91.8 M (37.6%)	40.1 M (31.3%)	32.2%	24.0%	31.7%	29.4%	…
Incidence, diagnosed DM, 2015**	1.5 M	…	…	…	…	…	…
Mortality, 2017§‖	83 564	37 262 (44.6%) ¶	23 773	7304	4162	1435#	1114
Total CVD							
Prevalence, 2013–2016†	121.5 M (48.0%)	60.0 M (44.7%)	43.4%	57.1%	42.6%	37.2%	…
Mortality, 2017§‖	859 125	418 665 (48.7%)¶	326 447	52 528	25 309	11 242#	4554

(*Continued*)

Table 27-2. Continued

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native*
Stroke							
Prevalence, 2013–2016†	7.0 M (2.5%)	3.8 M (2.6%)	2.5%	3.8%	2.2%	1.6%	…
New and recurrent strokes§	795.0 K	425.0 K (53.5%)¶	365.0 K††	60.0 K††	…	…	…
Mortality, 2017§	146383	84738 (57.9%)¶	64960	10522	5702	2988#	737‡‡
CHD							
Prevalence, CHD, 2013–2016†	18.2 M (6.7%)	8.8 M (6.2%)	6.1%	6.5%	6.0%	3.2%	…
Prevalence, MI, 2013–2016†	8.4 M (3.0%)	3.3 M (2.3%)	2.2%	2.2%	2.0%	1.0%	…
Prevalence, AP, 2013–2016†	9.4 M (3.6%)	5.1 M (3.7%)	3.8%	3.8%	3.6%	1.6%	…
New and recurrent MI and fatal CHD§§	1.05 M	445.0 K	370.0 K††	75.0 K††	…	…	…
New and recurrent MI§§	805.0 K	335.0 K	…	…	…	…	…
Mortality, 2017, CHD§‖	365914	152619 (41.7%)¶	119151	18055	10041	4103	2032
Mortality, 2017, MI§‖	110346	45910 (41.6%)¶	35720	5458	3113	1271#	593
HF							
Prevalence, 2013–2016†	6.2 M (2.2%)	3.2 M (2.1%)	1.9%	3.9%	2.1%	0.7%	…
Incidence, 2014‖‖	1.0 M	505.0K	425.0 K‡‡	80.0 K‡‡	…	…	…
Mortality, 2017§‖	80480	43656 (54.2%)¶	36004	4683	1960	752#	339

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (…), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); and NH, non-Hispanic.

*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

§All ages.

‖Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

**Age ≥18 years.

††Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

‖‖Age ≥55 years.

Table 27-3. Children, Youth, and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Males	Total Females	NH Whites		NH Blacks		Hispanic		NH Asian	
				Males	Females	Males	Females	Males	Females	Males	Females
Overweight and obesity											
Prevalence, 2011–2014											
Overweight and obesity, ages 2–19 y*	25.4 M (34.2%)	13.0 M (34.2%)	12.5 M (34.3%)	30.9%	28.5%	32.4%	42.2%	43.8%	43.8%	24.2%	19.2%
Obesity, ages 2–19 y*	13.2 M (17.8%)	6.9 M (18.1%)	6.4 M (17.5%)	15.3%	14.1%	17.9%	23.0%	24.3%	22.9%	11.9%	7.4%
Blood cholesterol, 2013–2016											
Mean total cholesterol, mg/dL											
Ages 6–11 y	157.8	157.9	157.7	157.1	159.1	158.8	158.2	158.7	153.9	160.1	161.5
Ages 12–19 y	154.4	151.6	157.5	150.6	157.2	150.8	156.0	152.7	156.0	155.4	170.2
Mean HDL-C, mg/dL											
Ages 6–11 y	56.0	57.4	54.5	56.6	54.7	62.5	58.1	55.9	52.2	58.1	54.4
Ages 12–19 y	51.8	49.9	53.8	49.2	53.5	54.4	56.9	49.6	52.2	52.8	56.6
Mean LDL-C, mg/dL											
Ages 12–19 y	86.7	85.6	87.8	86.7	87.9	81.7	88.4	85.0	84.2	81.7	103.3
Congenital cardiovascular defects (all age groups: children and adults)											
Mortality, 2017†‡§‖	2906	1583 (54.5%)§	1323 (45.5%)§	923	779	273	225	301	239	62	59

CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; and NH, non-Hispanic.

*In children, overweight and obesity are based on body mass index (BMI)-for-age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.

†All ages.

‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

§These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

‖NH American Indian/Alaska Native, Mortality: 38.

28. GLOSSARY

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- *Age-adjusted rates*—Used mainly to compare the rates of ≥2 communities or population groups or the nation as a whole over time. The American Heart Association (AHA) uses a standard population (2000), so these rates are not affected by changes or differences in the age composition of the population. Unless otherwise noted, all death rates in this publication are age adjusted per 100 000 population and are based on underlying cause of death.
- *Agency for Healthcare Research and Quality (AHRQ)*—A part of the US Department of Health and Human Services, this is the lead agency charged with supporting research designed to improve the quality of health care, reduce the cost of health care, improve patient safety, decrease the number of medical errors, and broaden access to essential services. The AHRQ sponsors and conducts research that provides evidence-based information on healthcare outcomes, quality, cost, use, and access. The information helps healthcare decision makers (patients, clinicians, health system leaders, and policy makers) make more informed decisions and improve the quality of healthcare services. The AHRQ conducts the Medical Expenditure Panel Survey (MEPS; ongoing).
- *Body mass index (BMI)*—A mathematical formula to assess body weight relative to height. The measure correlates highly with body fat. It is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).
- *Centers for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS)*—The CDC is an agency within the US Department of Health and Human Services. The CDC conducts the Behavioral Risk Factor Surveillance System (BRFSS), an ongoing survey. The CDC/NCHS conducts or has conducted these surveys (among others):
  - National Health Examination Survey (NHES I, 1960–1962; NHES II, 1963–1965; NHES III, 1966–1970)
  - National Health and Nutrition Examination Survey I (NHANES I; 1971–1975)
  - National Health and Nutrition Examination Survey II (NHANES II; 1976–1980)
  - National Health and Nutrition Examination Survey III (NHANES III; 1988–1994)
  - National Health and Nutrition Examination Survey (NHANES; 1999 to …) (ongoing)
  - National Health Interview Survey (NHIS; ongoing)
  - National Hospital Discharge Survey (NHDS; 1965–2010)
  - National Ambulatory Medical Care Survey (NAMCS; ongoing)
  - National Hospital Ambulatory Medical Care Survey (NHAMCS; ongoing)
  - National Nursing Home Survey (periodic)
  - National Home and Hospice Care Survey (periodic)
  - National Vital Statistics System (ongoing)
- *Centers for Medicare & Medicaid Services*—The federal agency that administers the Medicare, Medicaid, and Child Health Insurance programs.
- *Comparability ratio*—Provided by the NCHS to allow time-trend analysis from one *International Classification of Diseases (ICD)* revision to another. It compensates for the "shifting" of deaths from one causal code number to another. Its application to mortality based on one *ICD* revision means that mortality is "comparability modified" to be more comparable to mortality coded to the other *ICD* revision.
- *Coronary heart disease (CHD) (ICD-10 codes I20–I25)*—This category includes acute myocardial infarction (I21–I22); certain current complications following acute myocardial infarction (I23); other acute ischemic (coronary) heart disease (I24); angina pectoris (I20); atherosclerotic cardiovascular disease (I25.0); and all other forms of chronic ischemic (coronary) heart disease (I25.1–I25.9).
- *Death rate*—The relative frequency with which death occurs within some specified interval of time in a population. National death rates are computed per 100 000 population. Dividing the total number of deaths by the total population gives a crude death rate for the total population. Rates calculated within specific subgroups, such as age-specific or sex-specific rates, are often more meaningful and informative. They allow well-defined subgroups of the total population to be examined. Unless otherwise stated, all death rates in this publication are age adjusted and are per 100 000 population.
- *Diseases of the circulatory system (ICD-10 codes I00–I99)*—Included as part of what the AHA calls "cardiovascular disease" ("Total cardiovascular disease" in this Glossary).
- *Diseases of the heart (ICD-10 codes I00–I09, 111, 113, 120-151)*—Classification the NCHS uses in compiling the leading causes of death. Includes acute rheumatic fever/chronic rheumatic heart diseases (I00–I09); hypertensive heart disease (I11); hypertensive heart and renal disease (I13); CHD (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); heart failure (I50); and other forms of heart disease

(I30–I49, I51). "Diseases of the heart" are not equivalent to "total cardiovascular disease," which the AHA prefers to use to describe the leading causes of death.

- *Hispanic origin*—In US government statistics, "Hispanic" includes people who trace their ancestry to Mexico, Puerto Rico, Cuba, Spain, the Spanish-speaking countries of Central or South America, the Dominican Republic, or other Spanish cultures, regardless of race. It does not include people from Brazil, Guyana, Suriname, Trinidad, Belize, or Portugal, because Spanish is not the first language in those countries. Most of the data in this update are for all Hispanics, as reported by government agencies or specific studies. In certain time-trend charts and tables, data for Mexican Americans are shown because data are not available for all Hispanics.
- *Hospital discharges*—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the principal diagnosis. Discharges include those discharged alive, dead, or "status unknown."
- *International Classification of Diseases (ICD) codes*—A classification system in standard use in the United States. The *ICD* is published by the World Health Organization. This system is reviewed and revised approximately every 10 to 20 years to ensure its continued flexibility and feasibility. The 10th revision (*ICD-10*) began with the release of 1999 final mortality data. The *ICD* revisions can cause considerable change in the number of deaths reported for a given disease. The NCHS provides "comparability ratios" to compensate for the "shifting" of deaths from one *ICD* code to another. To compare the number or rate of deaths with that of an earlier year, the "comparability-modified" number or rate is used.
- *Incidence*—An estimate of the number of new cases of a disease that develop in a population, usually in a 1-year period. For some statistics, new and recurrent attacks, or cases, are combined. The incidence of a specific disease is estimated by multiplying the incidence rates reported in community- or hospital-based studies by the US population. The rates in this report change only when new data are available; they are not computed annually.
- *Infective endocarditis*—An infection of the heart's inner lining (endocardium) or of the heart valves. The bacteria that most often cause endocarditis are streptococci, staphylococci, and enterococci.
- *Major cardiovascular diseases*—Disease classification commonly reported by the NCHS; represents *ICD-10* codes I00 to I78. The AHA does not use "major cardiovascular diseases" for any calculations. See "Total cardiovascular disease" in this Glossary.
- *Metabolic syndrome*—Metabolic syndrome is defined as the presence of any 3 of the following 5 diagnostic measures: Elevated waist circumference (>102 cm in males or >88 cm in females), elevated triglycerides (≥150 mg/dL [1.7 mmol/L] or drug treatment for elevated triglycerides), reduced high-density lipoprotein cholesterol (<40 mg/dL [0.9 mmol/L] in males, <50 mg/dL [1.1 mmol/L] in females, or drug treatment for reduced high-density lipoprotein cholesterol), elevated blood pressure (≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure, or drug treatment for hypertension), and elevated fasting glucose (≥100 mg/dL or drug treatment for elevated glucose).
- *Morbidity*—Incidence and prevalence rates are both measures of morbidity (ie, measures of various effects of disease on a population).
- *Mortality*—Mortality data for states can be obtained from the NCHS website (http://cdc.gov/nchs/), by direct communication with the CDC/NCHS, or from the AHA on request. The total number of deaths attributable to a given disease in a population during a specific interval of time, usually 1 year, are reported. These data are compiled from death certificates and sent by state health agencies to the NCHS. The process of verifying and tabulating the data takes ≈2 years.
- *National Heart, Lung, and Blood Institute (NHLBI)*—An institute in the National Institutes of Health in the US Department of Health and Human Services. The NHLBI conducts such studies as the following:
  - Framingham Heart Study (FHS; 1948 to …) (ongoing)
  - Honolulu Heart Program (HHP; 1965–2002)
  - Cardiovascular Health Study (CHS; 1989 to …) (ongoing)
  - Atherosclerosis Risk in Communities (ARIC) study (1987 to …) (ongoing)
  - Strong Heart Study (SHS; 1989 to …) (ongoing)
  - Multi-Ethnic Study of Atherosclerosis (MESA; 2000 to …) (ongoing)
- *National Institute of Neurological Disorders and Stroke (NINDS)*—An institute in the National Institutes of Health of the US Department of Health and Human Services. The NINDS sponsors and conducts research studies such as these:
  - Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)
  - Rochester (Minnesota) Stroke Epidemiology Project
  - Northern Manhattan Study (NOMAS)
  - Brain Attack Surveillance in Corpus Christi (BASIC) Project

- *Physical activity*—Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level.
- *Physical fitness*—The ability to perform daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and respond to emergencies. Physical fitness includes a number of components consisting of cardiorespiratory endurance (aerobic power), skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, balance, speed of movement, reaction time, and body composition.
- *Prevalence*—An estimate of the total number of cases of a disease existing in a population during a specified period. Prevalence is sometimes expressed as a percentage of population. Rates for specific diseases are calculated from periodic health examination surveys that government agencies conduct. Annual changes in prevalence as reported in this Statistical Update reflect changes in the population size. Changes in rates can be evaluated only by comparing prevalence rates estimated from surveys conducted in different years. Note: In the data tables, which are located in the different disease and risk factor chapters, if the percentages shown are age adjusted, they will not add to the total.
- *Race and Hispanic origin*—Race and Hispanic origin are reported separately on death certificates. In this publication, unless otherwise specified, deaths of people of Hispanic origin are included in the totals for whites, blacks, American Indians or Alaska Natives, and Asian or Pacific Islanders according to the race listed on the decedent's death certificate. Data for Hispanic people include all people of Hispanic origin of any race. See "Hispanic origin" in this Glossary.
- *Stroke (ICD-10 codes I60–I69)*—This category includes subarachnoid hemorrhage (I60); intracerebral hemorrhage (I61); other nontraumatic intracranial hemorrhage (I62); cerebral infarction (I63); stroke, not specified as hemorrhage or infarction (I64); occlusion and stenosis of precerebral arteries not resulting in cerebral infarction (I65); occlusion and stenosis of cerebral arteries not resulting in cerebral infarction (I66); other cerebrovascular diseases (I67); cerebrovascular disorders in diseases classified elsewhere (I68); and sequelae of cerebrovascular disease (I69).
- *Total cardiovascular disease (ICD-10 codes I00–I99)*—This category includes rheumatic fever/rheumatic heart disease (I00–I09); hypertensive diseases (I10–I15); ischemic (coronary) heart disease (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); other forms of heart disease (I30–I52); cerebrovascular disease (stroke) (I60–I69); atherosclerosis (I70); other diseases of arteries, arterioles, and capillaries (I71–I79); diseases of veins, lymphatics, and lymph nodes not classified elsewhere (I80–I89); and other and unspecified disorders of the circulatory system (I95–I99).
- *Underlying cause of death or any-mention cause of death*—These terms are used by the NCHS when defining mortality. Underlying cause of death is defined by the World Health Organization as "the disease or injury which initiated the chain of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Any-mention cause of death includes the underlying cause of death and up to 20 additional multiple causes listed on the death certificate.