Cardiovascular Risk Factors Predictive for Survival and Morbidity-Free Survival in the Oldest-Old Framingham Heart Study Participants

Article *in* Journal of the American Geriatrics Society · December 2005

DOI: 10.1111/j.1532-5415.2005.00465.x · Source: PubMed

Michael J Pencina
Boston University

Daniel Levy
National Heart, Lung, and Blood Institute, National Institutes of Health

Ralph B D'Agostino
Boston University

Cardiovascular Risk Factors Predictive for Survival and Morbidity-Free Survival in the Oldest-Old Framingham Heart Study Participants

Dellara F. Terry, MD, MPH, Michael J. Pencina, PhD,† Ramachandran S. Vasan, MD,‡§ Joanne M. Murabito, MD, ScM,§‖ Philip A. Wolf, MD,¶ Margaret Kelly Hayes, EdD, RN,§¶ Daniel Levy, MD,‡§# Ralph B. D'Agostino, PhD,†§ and Emelia J. Benjamin, MD, ScM‡§*

OBJECTIVES: To examine whether midlife cardiovascular risk factors predict survival and survival free of major comorbidities to the age of 85.

DESIGN: Prospective community-based cohort study.

SETTING: Framingham Heart Study, Massachusetts.

PARTICIPANTS: Two thousand five hundred thirty-one individuals (1,422 women) who attended at least two examinations between the ages of 40 and 50.

MEASUREMENTS: Risk factors were classified at routine examinations performed between the ages of 40 and 50. Stepwise sex-adjusted logistic regression models predicting the outcomes of survival and survival free of morbidity to age 85 were selected from the following risk factors: systolic and diastolic blood pressure, total serum cholesterol, glucose intolerance, cigarette smoking, education, body mass index, physical activity index, pulse pressure, antihypertensive medication, and electrocardiographic left ventricular hypertrophy.

RESULTS: More than one-third of the study sample survived to age 85, and 22% of the original study sample survived free of morbidity. Lower midlife blood pressure and total cholesterol levels, absence of glucose intolerance, nonsmoking status, higher educational attainment, and female sex predicted overall and morbidity-free survival. The predicted probability of survival to age 85 fell in the presence of accumulating risk factors: 37% for men with no risk factors to 2% with all five risk factors and 65% for women with no risk factors to 14% with all five risk factors.

CONCLUSION: Lower levels of key cardiovascular risk factors in middle age predicted overall survival and major morbidity-free survival to age 85. Recognizing and modifying these factors may delay, if not prevent, age-related morbidity and mortality. **J Am Geriatr Soc 53:1944–1950, 2005.**

Key words: aged; cohort studies; mortality; risk assessment; comorbidity

From the Departments of *Geriatrics, ‡Cardiology, §Preventive Medicine, ‖General Internal Medicine, and ¶Neurology, Boston Medical Center, School of Medicine, and †Department of Mathematics and Statistics, Boston University, Boston, Massachusetts; and #National Heart, Lung, and Blood Institute, Bethesda, Maryland.

The work was supported by Grants NO1-HC-25195 and 5R01-NS-17950 from the National Heart, Lung, and Blood Institute and Grants 1 K08 AG022785 (Dr. Terry) and K24-HL-04334 (Dr. Vasan) from the National Institute on Aging.

Address correspondence to Dellara F. Terry, MD, MPH, Geriatrics Section, Boston Medical Center, 88 East Newton St, Robinson 2, Boston, MA 02118. E-mail: laterry@bu.edu

DOI: 10.1111/j.1532-5415.2005.00465.x

Prior research has established that health-related behaviors and genetic influences play important roles in survival to exceptional old age.[1-3] Studies of centenarians and their offspring have demonstrated that the delay and avoidance of cardiovascular disease and its risk factors may play an important role in longevity,[4,5] although by virtue of the fact that it is not possible to predict who survives to very old age, these studies largely are cross-sectional in nature and focus only on the current health of long-lived individuals and their family members. Ideally, it would be desirable to know which, if any, modifiable cardiovascular risk factors during middle age are important in predicting survival to very old age. The Framingham Heart Study (FHS), a longitudinal community-based cohort study with extensive cardiovascular phenotypic characterization of participants from young to mid-adulthood through older age groups, is useful for addressing such a question.

A prior study from the FHS reported on risk factors measured in middle age that were associated with survival to the age of 75.[6] Although it is helpful to understand the relationships between these risk factors and average longevity, the prior work did not answer the question about which antecedent risk factors predict survival in the oldest old, commonly defined as age 85 and older.[7] Nor did it evaluate factors influencing morbidity-free survival to age 85. Other prospective examinations of risk factors for survival, such as those done by the Cardiovascular Health Study[8] and the Honolulu Heart Study,[9] have focused on importance of risk factors at an older age rather than at

0002-8614/05/$15.00

middle age. In contrast to the aforementioned studies, the current study examined the effect of favorable middle-age risk factors on survival to very old age. Furthermore, it was sought to understand factors associated with living in good health, as well as factors associated with survival per se. With individuals aged 85 and older constituting the fastest-growing segment of the U.S. population,[10] it is important to better understand which risk factors health-related behaviors can modify to prevent age-related morbidity and frailty.

METHODS

The FHS is a longitudinal study of risk factors for cardiovascular and other chronic diseases in a sample of residents initially from Framingham, Massachusetts. The original cohort included 5,209 persons aged 28 to 62 who have been followed with biennial examinations since 1948. The Boston Medical Center institutional review board reviewed the FHS examination protocols, and all participants signed informed consent.

The present study examined midlife cardiovascular risk factors that may be associated with survival to age 85 in the original FHS cohort. Eligible participants had to attend two or more examinations between the ages of 40 and 50, with at least one examination at age 47 or older (n = 3,054), to assure that measurements took place over the entire course of the fifth decade of life. Participants born after January 1, 1919, were excluded because they could not have achieved age 85 before the end of follow-up on January 1, 2004 (n = 161). Additional exclusions were death before age 50 (n = 26), known cardiovascular disease, valvular heart disease, cancer in the fifth decade (n = 261), and individuals with missing data on covariates (n = 75, of whom 67 were missing education data). The final study sample included 2,531 eligible participants. For the analysis of survival to age 85 free of comorbidities, five participants with comorbidity at baseline and 56 participants who were lost to follow-up were excluded. Data on survival were available for the 56 participants who were lost to follow-up; as such they were included in the analysis of survival to age 85.

Risk factors eligible for analyses were classified at the routine examinations performed at or after age 40 until age 50. Data for the midlife risk profile were taken from Examinations 1 through 11, which occurred between 1948 and 1971. At each FHS research examination, participants completed a physician-administered medical history and physical examination, a 12-lead electrocardiogram, standardized questionnaires, a panel of blood tests, and anthropometric measurements. Cigarette smoking was defined as present if the subject had smoked within the year before any baseline examination. Educational attainment was categorized as not having graduated from high school, having graduated from high school, and having education beyond high school. Body mass index was measured as weight in kilograms/height in meters squared. Electrocardiographic left ventricular hypertrophy was diagnosed using voltage criteria and repolarization abnormalities. Glucose intolerance was defined as a previous diagnosis of diabetes mellitus or an abnormal random blood sugar ($\geq$140 mg/dL)[11] at any examination between the ages of 40 and 50. The FHS physical activity index estimated the amount of metabolic work performed in a typical 24-hour period using a structured questionnaire that asked participants to report the number of hours asleep; at rest; and in slight, moderate, and heavy activity in a typical day. The index had a scale of 24 to 120, with 24 indicating resting state for 24 hours and 120 indicating heavy physical activity for 24 hours.[12,13] In the study sample, the physical activity index scores ranged from 26 to 76. Alcohol consumption was not used as a risk factor in the logistic regression model, because data on alcohol intake were not collected at all baseline examinations.

Because classifications of death in older people tend to be less accurate because of unwitnessed events and a tendency to perform less-thorough evaluations and diagnostic testing, all-cause mortality was examined as an endpoint. In the morbidity-free survival analysis, morbidities were selected based on their contribution to the leading causes of hospitalization and mortality in individuals aged 65 and older, including heart disease, cancer, and cerebrovascular disease.[14] The major morbidities were defined as myocardial infarction, coronary insufficiency, congestive heart failure, stroke, cancer (excluding nonmelanoma skin cancer), and moderate or severe dementia. A panel of three investigators reviewed suspected cardiovascular events using all available data, including hospital records and personal physician records, in addition to FHS clinic records. Similarly, a separate independent panel of study neurologists determined stroke events. A neurologist and a neuropsychologist (PAW) reviewed the evidence for dementia diagnosis. Two independent reviewers examined records for all cancer cases.

Statistical Analysis

To evaluate the influence of various risk factors on survival to age 85, stepwise logistic regression[15] was employed ($P < .05$ for retention). Risk factors considered were systolic, diastolic, and pulse pressures; total serum cholesterol; glucose intolerance; cigarette smoking; educational attainment; body mass index; physical activity; antihypertensive medication; and electrocardiographic left ventricular hypertrophy. For continuous variables, the mean was calculated across all available examinations occurring between the ages of 40 and 50. Categorical variables were coded as present if they occurred at one or more examinations. Sex-by–risk factor interaction was examined to verify whether the odds ratios for each of the risk factors was roughly comparable between men and women, because it was desired to improve statistical power by presenting sex-pooled analyses.

An analogous approach was adopted to examine the risk factors related to survival to or past age 85 free of major comorbidity. To compare the relative importance of risk factors contributing to survival to very old age identified in the stepwise regression procedure, odds ratios were calculated corresponding to a change by approximately one standard deviation of the risk factor for continuous variables (20 mmHg systolic blood pressure, 10 mmHg diastolic blood pressure, and 40 mg/dL total cholesterol) or presence versus absence for dichotomous variables (smokers vs nonsmokers, participants with and without glucose intolerance) and one category increase for education (less than high school graduate to high school graduate or high school graduate to beyond high school). The overall model performance was assessed through its discrimination ability quantified by the C-statistic.[16]

Variables significant in the final logistic regression model were used to estimate probabilities of survival corresponding to low versus high levels of each risk factor, adjusting for all other retained risk factors, and to calculate probabilities of survival associated with accumulating numbers of risk factors. The higher and lower levels were defined using a cutoff of 140 mmHg for systolic blood pressure (based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seven criteria),[17] and 240 mg/dL for total serum cholesterol (based on National Cholesterol Education Program Adult Treatment Panel III criteria).[18,19] Absence/presence categories were used to define low and high risk for smoking and glucose intolerance. In the case of education, those who did not complete high school represented lower levels, and those who had completed high school education and beyond represented higher levels.

Because the participants were aged 30 to 60 when initially recruited and hence were eligible for the baseline examinations (aged 40–50) during different calendar decades, a secondary analysis was performed to examine the significance of calendar decade (individuals were born in 1900–1909 or 1910–1919) in the stepwise model.

All analyses were performed using SAS, version 8 (SAS Institute Inc., Cary, NC). All tests were two-sided, and $P < .05$ was considered to be statistically significant.

RESULTS

Table 1 includes baseline characteristics of the participants between the ages of 40 and 50, classified by whether they survived to age 85. More than one-third (35.7%) of the study sample survived to age 85, as shown in Figure 1, with more women (44.7%) surviving than men (24.1%).

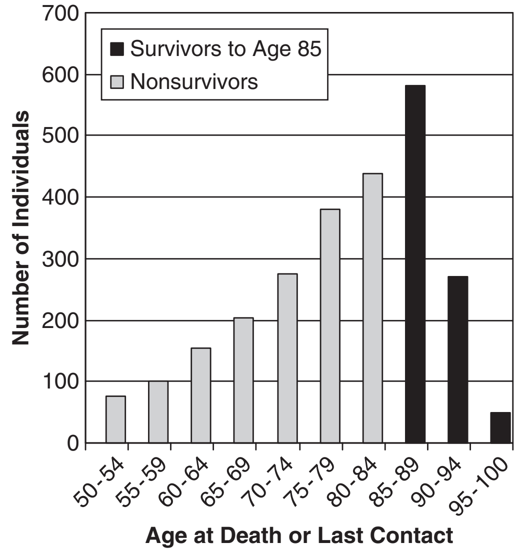

Figure 1. Distribution of age at death or age at last contact for survivors and nonsurvivors to age 85.

Of all eligible participants at baseline, 22% (542/2,475; the denominator did not include the 56 individuals who were lost to follow-up) survived to age 85 free of the morbidities examined. Of those who survived to age 85, 60% (542/903) survived without any of the morbidities examined. Stepwise logistic regression was used to determine risk predictors for survival to age 85 and survival free of major morbidity (Table 2). Individuals were considered to have achieved healthy aging if they did not die or develop myocardial infarction, coronary insufficiency, congestive

Table 1. Baseline Characteristics of Those Who Did and Did Not Survive to Age 85

Characteristic	Nonsurvivors n = 1,628	Survivors n = 903
Female, n (%)*	786 (48)	636 (70)
Systolic blood pressure, mmHg, mean ± SD*	132 ± 17	125 ± 14
Diastolic blood pressure, mmHg, mean ± SD*	84 ± 10	80 ± 8
Total serum cholesterol, mg/dL, mean ± SD*	236 ± 39	229 ± 36
Glucose intolerant, n (%)*	60 (4)	8(1)
Cigarette smoker, n (%)*	1,149 (71)	458 (51)
Education, n (%)*		
<High school graduate	645 (40)	268(30)
High school graduate	519 (32)	312 (34)
>High school	464 (28)	323 (36)
Body mass index, kg/m^2, mean ± SD	25.8 ± 4.1	25.0 ± 3.5
Alcohol, ounces/wk, mean ± SD†	20 ± 31	13 ± 22
Physical Activity Index, mean ± SD‡	33 ± 6	32 ± 5
Pulse pressure, mmHg, mean ± SD	47 ± 10	45 ± 8
Antihypertensive usage, n (%)	117 (7)	33 (4)
Left ventricular hypertrophy, n (%)	17 (1)	0 (0)

* These seven covariates were retained in the most parsimonious models. Subsequent covariates were not retained in the model.
† Information on alcohol intake was available on 1,623 nonsurvivors and 903 survivors. It was not included in the logistic regression model, because it was not collected at all baseline examinations.
‡ Physical activity index (description in methods section) was available on 1,465 nonsurvivors and 822 survivors.
SD = standard deviation.

Table 2. Multivariate-Adjusted Odds Ratios (OR) and Confidence Intervals (CIs) for Risk Factors Related to Survival and Survival Free of Major Morbidity to Age 85 and Older

Risk Factor	Survival to Age 85 (n = 903)			Survival to Age 85 Free of Major Comorbidity* (n = 542)		
	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Female	2.00	(1.66–2.41)	<.001	2.08	(1.66–2.61)	<.001
Systolic blood pressure (per 20 mmHg)	0.57	(0.50–0.64)	<.001	—	—	—
Diastolic blood pressure (per 10 mmHg)	—	—	—	0.64	(0.57–0.72)	<.001
Serum cholesterol (per 40 mg/dL)	0.89	(0.79–0.96)	.005	0.82	(0.76–0.92)	.001
Glucose intolerance (present vs absent)	0.30	(0.14–0.64)	.002	0.13	(0.03–0.54)	.005
Smoking history (present vs absent)	0.47	(0.39–0.57)	<.001	0.51	(0.41–0.63)	<.001
Education (one category increase)	1.25	(1.12–1.39)	<.001	1.20	(1.06–1.35)	.004

Note: Risk factors considered in stepwise models were sex, systolic blood pressure, diastolic blood pressure, pulse pressure, antihypertensive medication usage, total serum cholesterol, body mass index, glucose intolerance, electrocardiographic left ventricular hypertrophy, smoking, education, and physical activity index. For covariate definitions, see Methods.

* Comorbidities were myocardial infarction, coronary insufficiency, congestive heart failure, stroke, cancer, and dementia.

heart failure, stroke, cancer (excluding nonmelanoma skin cancer), or moderate or severe dementia before age 85. The most parsimonious model retained sex and five risk factors: blood pressure, total serum cholesterol, glucose intolerance, history of smoking, and education (Table 2). For the models predicting survival, systolic blood pressure was selected; for the models predicting survival free of major morbidity, diastolic blood pressure was selected. Tests for effect modification by sex for the factors retained in the most parsimonious model were not statistically significant. In secondary analysis, birth cohort did not enter the most parsimonious model.

None of the individuals with a diagnosis of definite diabetes mellitus or electrocardiographic left ventricular hypertrophy between the ages of 40 and 50 survived to age 85. Because of the small number affected, there was a lack of power to demonstrate a significant relationship between diabetes mellitus or left ventricular hypertrophy and mortality by age 85. Hence, glucose intolerance, which was a significant predictor of mortality, was examined. The presence of glucose intolerance significantly decreased the odds of survival to age 85 to 0.30 and the odds of survival to age 85 without major comorbidity to 0.13.

In addition to glucose intolerance, other factors were significantly related to survival and major comorbidity–free survival. Being female doubled the odds of surviving to age 85 and surviving free of major comorbidity. Having high systolic blood pressure decreased the odds of survival to age 85 to 0.57, and having high diastolic blood pressure decreased the odds of survival to age 85 free of major comorbidity to 0.64. Having elevated serum cholesterol decreased the odds of survival to age 85 to 0.89 and of major comorbidity–free survival to 0.82. Similarly, the presence of smoking history decreased the odds of survival to age 85 to 0.47 and major comorbidity–free survival to 0.51. One category increase in education increased the odds of survival to age 85 to 1.25 and of major comorbidity–free survival to 1.20. A C-statistic of 0.71 characterized the model's discrimination ability.

Estimated probabilities of survival to age 85 were examined by evaluating individual risk factors (Figure 2) that were retained in the most parsimonious model. Each risk factor was examined separately at lower and higher levels; all of the other risk factor values were modeled at their mean level. Lower levels of each risk factor were associated with a higher probability of survival to age 85. For example, nonsmokers had a 45% probability of surviving to age 85, whereas the survival probability for smokers was 28%.

Sex-specific accumulated risks from multiple risk factors are demonstrated in Figure 3. The first bar of the figure demonstrates the probability of survival to age 85 for individuals with no risk factors, whereas each successive bar demonstrates the probability of survival to age 85 in the presence of an increasing number of risk factors. The predicted probability of survival to age 85 fell in the presence of accumulating risk factors: 37% for men with no risk factors

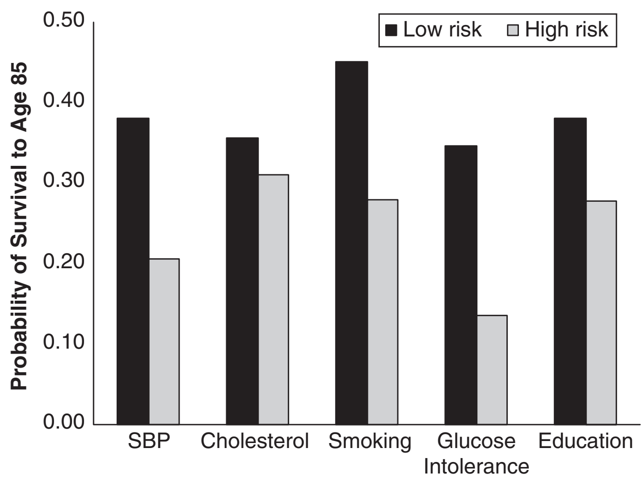

Figure 2. Model predicted probability of survival to age 85 for lower- versus higher-risk-factor levels. The lower and higher risk levels were defined using presence or absence for smoking and glucose intolerance and a threshold of 140 mmHg for systolic blood pressure (SBP), and 40 mg/dL for total serum cholesterol (cholesterol). In the case of education, those who did not complete high school represented lower levels, and those who had completed high school represented higher levels.

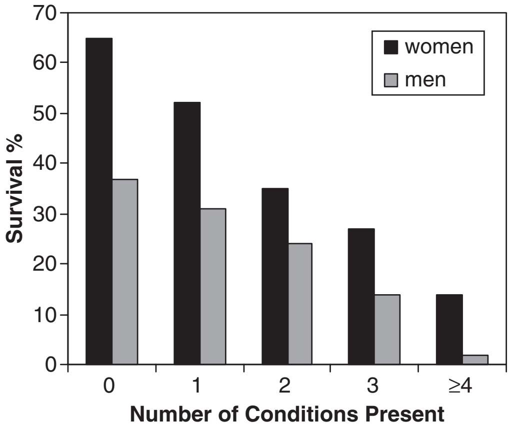

Figure 3. Sex-specific probability of survival to age 85 based on the number of risk factors present. The first bar represents the probability of survival to age 85 for an individual with no risk factors. Because the number of individuals with four and five risk factors present was small, these numbers were merged in the final bar.

to 2% with four or more risk factors and 65% for women with no risk factors to 14% with four or more risk factors.

DISCUSSION

In the FHS original cohort, lower levels of cardiovascular risk factors in middle age, including blood pressure (systolic for survival to age 85 and diastolic for survival free of major morbidity), serum cholesterol, lack of glucose intolerance, and the absence of cigarette smoking, predicted survival, as well as major morbidity-free survival, to age 85. In addition, female sex and higher educational attainment predicted survival to age 85 and survival free of major morbidity. Furthermore, the predicted probability of survival to age 85 fell dramatically in the presence of an increasing number of these risk factors measured during middle age: 37% for men with no risk factors to 2% with four or more risk factors and 65% for women with no risk factors to 14% with four or more risk factors.

Other large long-term cohort studies have demonstrated the importance of individual risk factors in young adulthood and midlife in relation to long-term mortality.[20-22] For example, one examined cardiovascular and noncardiovascular mortality 16 to 22 years after an initial assessment of risk factors in five large low-risk cohorts of young adult and middle-age men and women from the Multiple Risk Factor Intervention Trial and the Chicago Heart Association Detection Project in Industry and reported that those with low risk-factor profiles (total cholesterol <200 mg/dL; blood pressure <120/80; and absence of smoking, diabetes mellitus, and myocardial infarction) had significantly lower coronary heart disease and cardiovascular disease death rates than those at higher risk.[23] The current study extended this knowledge by examining survival to very old age and by including education, an indicator of socioeconomic status, as a candidate risk factor. Moreover, the current study differed by examining not only survival but also morbidity-free survival.

Of those who survived to age 85, 60% (542/903) survived without major morbidity from the age-related diseases that were examined. The results are consistent with other studies that indicate that individuals who survive to older ages often do so in good health, avoiding frailty and morbidity.[24,25]

The factors predicting survival to age 85 and older identified in this study are congruent with the factors cited by the 2002 World Health Organization (WHO) report as major contributors to the global burden of disease in the developed world.[26] In addition to the cardiovascular risk factors noted above, the WHO report noted that elevated body mass index, low intake of fruits and vegetables, and lack of physical activity increased burden of disease.[26] According to the WHO's Comparative Risk Assessment Collaborating Group, hypertension, hypercholesterolemia, elevated body mass index, low intake of fruits and vegetables, lack of physical activity, and smoking contribute to 13.5%, 12.9%, 10%, 6%, 5.6%, and 23.6%, respectively, of deaths in developed nations. The WHO also noted that these factors contribute significantly to loss of healthy life as measured using disability-adjusted life years.[27]

Other studies have demonstrated that socioeconomic status is an independent risk factor for all-cause[28] and cardiovascular-disease mortality.[29,30] To assess this risk, education was included in the model as a proxy for socioeconomic status, and it was demonstrated that it was an independent predictor of longevity and morbidity-free longevity. In models not including educational attainment, lower body mass index was predictive of survival and major morbidity–free survival to age 85 (data not shown). Other factors that it was not possible to assess, such as health behaviors and access to healthcare, may also affect survival and the development of age-related disease.

Fortunately, all of the middle-age cardiovascular risk factors in this model predicting survival and major morbidity–free survival to age 85 are modifiable. For example, antihypertensive medications have been demonstrated not only to reduce elevated blood pressure but also to improve cardiovascular prognosis.[31] Lifestyle interventions in high-risk subjects have been shown to prevent type 2 diabetes mellitus.[32] The benefits of lifestyle changes and treatments for smoking cessation,[33,34] weight loss,[35] and cholesterol reduction[36,37] have been demonstrated as well. Modest improvements in these factors could lead to substantial gains in disease-free survival.[26,38-40]

One of the most notable findings was that all of the FHS participants included in the study sample that had definite diabetes mellitus between the ages of 40 and 50 died before age 85. The uniform lethality of diabetes mellitus in this study may be in part due to temporal factors such as a lack of therapeutic options and a lack of understanding of the importance of tight glucose control, which have subsequently become the standard of medical care. Nevertheless, in view of the increasing prevalence of obesity[41] and its contribution to diabetes mellitus, hypertension, and hypercholesterolemia, these results are troubling. Without a concerted effort to reduce obesity and diabetes mellitus on a population-wide basis, currently lengthening life expectancies may begin to be reversed.

None of the individuals with a diagnosis of electrocardiographic left ventricular hypertrophy between ages 40 and 50 survived to age 85. Analogous to diabetes mellitus, the uniform lethality of left ventricular hypertrophy in this series may be in part due to the less-aggressive approach to the treatment of blood pressure during the earlier part of follow-up. Recent data indicate that the return to normal of left ventricular hypertrophy,[42,43] according to electrocardiogram or echocardiogram, is associated with decreased cardiovascular events. Unfortunately, many individuals with hypertension are still not treated adequately.[44]

Strengths and Limitations

One of the major strengths of this study is the use of data from the FHS cohort, which has been well characterized over 5 decades. Furthermore, because the data were collected and recorded longitudinally, they were not subject to recall or survivor bias. This study is distinct from prior studies in several ways. The measurements of risk factors in this study included an average of assessments over a period of 10 years, as opposed to examination of risk factors at a single point. By using an average of multiple examinations over a 10-year period, it was possible to reduce regression dilution bias. In addition, survival to very old age, commonly defined in the geriatric literature as age 85 and older, was examined. This cutpoint is substantially later than the ages used in the above studies. Finally, and most importantly, the study examined not only survival but also morbidity-free survival.

Several limitations must be acknowledged. Reflecting the earlier period of baseline data collection (late 1940s until early 1970s), diabetes mellitus was defined as having random blood glucose of 200 or higher or receiving diabetes mellitus treatment. Because these criteria are less stringent than the current criteria, the category was expanded to glucose intolerance, which included individuals meeting the above criteria as well as those with random whole blood glucose of 140 or higher.[11]

Measurements of alcohol use were not included as a factor in the analyses, because the data were not obtained at each assessment. This made it impossible to obtain an accurate alcohol classification during the time of interest.

Lack of physical activity has been shown to increase disability and mortality risk.[45,46] Nevertheless, in this study, the physical activity index was not predictive of survival to age 85 and therefore was not included in the model. It is possible that lack of physical activity is the first step in a causal pathway leading to increased disability and mortality risk and that adjustment for other downstream risk factors may mask its role.

In addition, because the focus of the FHS has been on cardiovascular disease, it should be noted that the risk factors that were examined pertained to vascular diseases. Hence, clinically important risk factors for noncardiovascular disease morbidity and mortality may have been missed. Measurements of lung function were considered, but they were not included in the model because lung function may represent an intermediate mechanism of smoking rather than a direct causal factor. In addition, unlike the other factors assessed, little can be done to modify or reverse declines in pulmonary function once the damage has occurred.

This study examined a limited number of major morbidities, and other morbidities, such as chronic lung disease and chronic renal failure, may significantly affect the quality of life of older individuals. Nevertheless, the morbidities selected are the largest contributors to hospitalization and mortality in the geriatric population.[14] Furthermore, one of this study's strengths was the use of validated medical outcomes rather than self-report.

Because the risk factor data were collected from participants several decades ago, they do not reflect the influence of current treatment patterns and change in awareness of the effect of health behaviors. As such, the contemporary presence of these risk factors may have different prognostic implications. For instance, diabetes mellitus, systolic blood pressure, and hypercholesterolemia are now treated much more aggressively, and such treatment has been demonstrated to improve prognosis. Furthermore, this study did not capture the effect of risk factor modification; participants may have reversed their risk factors by smoking cessation and blood pressure treatment, among other things. What the results indicate is the importance of recognizing and treating the risk factors during middle age to delay, if not prevent, major age-related morbidity and mortality.

The study may have been underpowered to detect modest interactions between sex and the five risk factors, but the effect modification by sex was not significant in the model. In addition, because the study cohort was white, the generalizability of the findings to other races/ethnicities remains to be determined.

Implications

Lower midlife levels of blood pressure, body mass index, serum cholesterol; absence of glucose intolerance; nonsmoking history; female sex; and higher educational attainment predicted survival to age 85 and major morbidity-free survival in the FHS cohort. Prior studies have demonstrated that modifying these risk factors in middle age is cost-effective and beneficial for the disease-free survival of individuals to very old age. These data emphasize the importance of health promotion in young and mid-adulthood to promote healthy aging. Further research is needed to determine the relative contribution of temporal trends in cardiovascular disease risk factors and treatments to compression of morbidity and improved survival.

ACKNOWLEDGMENTS

Financial Disclosures: None of the authors have any financial conflicts of interest to disclose.

Author Contributions: Drs. Terry, Pencina, Vasan, D'Agostino, and Benjamin were involved in study conceptualization and design, data analyses and interpretation, and manuscript preparation. Drs. Murabito, Wolf, Kelly Hayes, and Levy were involved in data and subject acquisition and manuscript preparation.

Sponsor's Role: There was no sponsor for this study.

REFERENCES

1. Barzilai N, Atzmon G, Schechter C et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. JAMA 2003;290:2030–2040.
2. Perls T, Terry D. Understanding the determinants of exceptional longevity. Ann Intern Med 2003;139:445–449.
3. Puca AA, Daly MJ, Brewster SJ et al. A genome-wide scan for linkage to human exceptional longevity identifies a locus on chromosome 4. Proc Natl Acad Sci U S A 2001;98:10505–10508.

4. Evert J, Lawler E, Bogan H et al. Morbidity profiles of centenarians: Survivors, delayers and escapers. J Gerontol A Biol Sci Med Sci 2003;58A:232–237.
5. Terry DF, Wilcox M, McCormick MA et al. Cardiovascular advantages among the offspring of centenarians. J Gerontol A Biol Sci Med Sci 2003;58A:M425–M431.
6. Goldberg RJ, Larson M, Levy D. Factors associated with survival to 75 years of age in middle-aged men and women. The Framingham Study. Arch Intern Med 1996;156:505–509.
7. Suzman R, Willis DP, eds. Introducing the Oldest Old. New York: Oxford University Press, 1992.
8. Fried LP, Kronmal RA, Newman AB et al. Risk factors for 5-year mortality in older adults. The Cardiovascular Health Study. JAMA 1998;279:585–592.
9. Reed DM, Foley DJ, White LR et al. Predictors of healthy aging in men with high life expectancies. Am J Public Health 1998;88:1463–1468.
10. The 65 Years and Over Population. Washington, DC: U.S. Department of the Census, 2000.
11. World Health Organization. Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: World Health Organization, 1999.
12. Sherman SE, D'Agostino RB, Cobb JL. Does exercise reduce mortality rates in the elderly? Experience from the Framingham Heart Study. Am Heart J 1994;128:965–972.
13. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham Study. Arch Intern Med 1979;139:857–861.
14. Desai MM, Zhang P, Hennessy CH. Surveillance for morbidity and mortality among older adults—United States, 1995–1996. MMWR CDC Surveill Summ 1999;48:7–13.
15. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley and Sons Inc, 1989.
16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.
17. Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure The JNC 7 Report. JAMA 2003;289:2560–2572.
18. 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.
19. Clinical Guidelines on the Identification Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, 1998.
20. Daviglus ML, Stamler J, Pirzada A et al. Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. JAMA 2004;292:1588–1592.
21. Miura K, Daviglus ML, Dyer AR et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men. The Chicago Heart Association Detection Project in Industry. Arch Intern Med 2001;161:1501–1508.
22. Stamler J, Daviglus ML, Garside DB et al. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA 2000;284: 311–318.
23. Stamler J, Stamler R, Neaton JD et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: Findings for 5 large cohorts of young adult and middle-aged men and women. JAMA 1999;282:2012–2018.
24. Strandberg A, Strandberg TE, Salomaa VV et al. A follow-up study found that cardiovascular risk in middle age predicted mortality and quality of life in old age. J Clin Epidemiol 2004;57:415–421.
25. Hitt R, Young-Xu Y, Silver M et al. Centenarians: The older you get, the healthier you have been. Lancet 1999;354:652.
26. Quantifying selected major risks to health. In: World Health Report: Reducing Risks Promoting Healthy Life. Geneva: World Health Organization, 2002, pp 57–61.
27. Ezzati M, Lopez AD, Rodgers A et al. Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347–1360.
28. Feldman JJ, Makuc DM, Kleinman JC et al. National trends in educational differentials in mortality. Am J Epidemiol 1989;129:919–933.
29. Mackenbach JP, Cavelaars AE, Kunst AE et al. Socioeconomic inequalities in cardiovascular disease mortality: An international study. Eur Heart J 2000;21:1141–1151.
30. Capewell S, MacIntyre K, Stewart S et al. Age, sex, and social trends in out-of-hospital cardiac deaths in Scotland 1986–95: A retrospective cohort study. Lancet 2001;358:1213–1217.
31. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: A meta-analysis. Lancet 2001;358:1305–1315.
32. Tuomilehto J, Lindstrom J, Eriksson JG et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350.
33. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: A statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. Circulation 1997;96:3243–3247.
34. Gordon T, Kannel WB, McGee D et al. Death and coronary attacks in men after giving up cigarette smoking. A report from the Framingham Study. Lancet 1974;2:1345–1348.
35. Eckel RH. Obesity and heart disease: A statement for healthcare professionals from the Nutrition Committee, American Heart Association. Circulation 1997;96:3248–3250.
36. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. The Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344: 1383–1389.
37. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Executive Summary of the 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). JAMA 2001;285:2486–2497.
38. Shepherd J, Cobbe SM, Ford I et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–1307.
39. Ferrucci L, Izmirlian G, Leveille S et al. Smoking, physical activity, and active life expectancy. Am J Epidemiol 1999;149:645–653.
40. Stamler J, Dyer AR, Shekelle RB et al. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: Findings from long-term follow-up of Chicago cohorts. Cardiology 1993;82:191–222.
41. Flegal KM, Carroll MD, Ogden CL et al. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288:1723–1727.
42. Devereux RB, Wachtell K, Gerdts E et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 2004;292: 2350–2356.
43. Okin PM, Devereux RB, Jern S et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA 2004;292:2343–2349.
44. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA 2003;290: 199–206.
45. de Groot LC, Verheijden MW, de Henauw S et al. Lifestyle, nutritional status, health, and mortality in elderly people across Europe: A review of the longitudinal results of the SENECA study. J Gerontol A Biol Sci Med Sci 2004;59A:1277–1284.
46. Vita AJ, Terry RB, Hubert HB et al. Aging, health risks, and cumulative disability. N Engl J Med 1998;338:1035–1041.