# The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

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**Cardiovascular disease is the leading cause of death in women. Decades of grassroots campaigns have helped to raise awareness about the impact of cardiovascular disease in women, and positive changes affecting women and their health have gained momentum. Despite these efforts, there has been stagnation in the overall reduction of cardiovascular disease burden for women in the past decade. Cardiovascular disease in women remains understudied, under-recognised, underdiagnosed, and undertreated. This Commission summarises existing evidence and identifies knowledge gaps in research, prevention, treatment, and access to care for women. Recommendations from an international team of experts and leaders in the field have been generated with a clear focus to reduce the global burden of cardiovascular disease in women by 2030. This Commission represents the first effort of its kind to connect stakeholders, to ignite global awareness of sex-related and gender-related disparities in cardiovascular disease, and to provide a springboard for future research.**

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## Introduction

Cardiovascular disease is the leading cause of mortality for women and was responsible for 35% of total deaths in women in 2019.[1] Decades of grassroots campaigns have helped to raise awareness about the magnitude of cardiovascular disease in women. Relatedly, profound changes and movements that positively affect women and their agency concerning their health have gained momentum during this period. However, despite the influence of social and cultural progress and awareness, there has been confounding stagnation in the overall reduction of cardiovascular disease burden for women. Distinct strategies are urgently needed to tackle inequities in the diagnosis, treatment, and prevention of heart disease in women; to advance innovative solutions for early detection and targeted management; to unravel the underlying biological mechanisms that contribute to sex-specific differences in outcomes; and finally, to decrease the global cardiovascular disease burden in women.

Although age-standardised cardiovascular disease mortality in women has declined globally in the past 30 years, most of this decline was in countries with a high Socio-demographic Index (a measure of development defined as a composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates, as defined by the Global Burden of Disease [GBD] study).[2] By contrast, the GBD study reported that this mortality remained stagnant in most other regions of the world, with only a small change or no change. Indeed, in countries with a low Socio-demographic Index, the highest rates of cardiovascular disease mortality shift from men to women.[2] In high-income regions, the decline in cardiovascular disease mortality has slowed, and in 2017 it increased in women from some countries (eg, the USA and Canada).[3] Additional alarming trends, such as the rise in acute myocardial infarction in younger women, have been documented in the past decade.[4,5] In summary, cardiovascular disease in women remains understudied, under-recognised, underdiagnosed, and undertreated globally.

Many factors contribute to inequity between men and women in the detection and management of cardiovascular disease. Women have been under-represented in, or excluded from, cardiovascular clinical trials, which has reduced the ability to measure the safety and efficacy of therapies for women, the potential for identifying sex-specific differences in important outcomes, and the development of sex-specific strategies that could lead to improved guideline recommendations for the prevention and management of cardiovascular disease.[6] Although overall awareness about cardiovascular disease in women has increased during the past decade, most health-care providers and patients still tend to underestimate the cardiovascular risk in women.[7,8] Awareness campaigns have paid little attention to the role of physicians in assessing risk,[7] and risk-assessment models do not take into consideration risk factors that are specific to the female sex. The physicians who take direct care of women are underused in addressing cardiovascular risk and educating women about their individual risk. Although improvements have been made, current evidence suggests that women are still less likely than men to receive cardiovascular therapies recommended by guidelines, with the biggest shortfalls occurring in young women.[9–11] Sex-related differences in clinical presentation and comorbidities can contribute to this gap in guideline-recommended care, and sex-specific strategies are urgently needed to take these factors into account to provide optimal care for women.

Crucially, women are more likely than men to be subject to health disparities that arise from sociocultural factors and socioeconomic and political contexts. For instance, gender discrimination, socioeconomic burden, and constraints on physical mobility often limit women's access to optimal health care in general, and to cardiovascular disease care in particular.[12,13] Importantly, the biological differences in, and underlying sex-specific

### Key messages

**Accurate data on global prevalence and outcomes of cardiovascular disease in women are absent**
Recommendation: direct funding for real-time and accurate data collection on prevalence and outcomes of cardiovascular disease in women globally

**Women with cardiovascular disease remain understudied, under-recognised, underdiagnosed, and undertreated**
Recommendation: develop educational programmes on cardiovascular disease in women for physicians, scientists, allied health-care providers, and communities

**Sex-specific mechanisms in the pathophysiology and natural history of cardiovascular disease remain poorly understood**
Recommendation: prioritise sex-specific research focused on identifying the pathophysiology and natural history of cardiovascular disease

**Women are under-represented in the majority of cardiovascular clinical trials**
Recommendation: develop strategies to improve enrolment and retention of women in cardiovascular clinical trials

**Socioeconomic deprivation contributes substantially to the global burden of cardiovascular disease in women**
Recommendation: prioritise funding in global health organisations for cardiovascular disease health programmes in women from socioeconomically deprived regions

**Myocardial infarction and cardiovascular disease mortality are increasing in young women**
Recommendation: educate health-care providers and patients regarding early detection and prevention of cardiovascular disease in young women

**Hypertension, dyslipidaemia, and diabetes are the most crucial risk factors contributing to cardiovascular disease death in women**
Recommendation: establish policy-based initiatives and medical and community-outreach cardiovascular disease risk factor programmes in settings frequented by women

**Sex-specific and other under-recognised cardiovascular disease risk factors, such as psychosocial and socioeconomic factors, appear to contribute to the global burden of cardiovascular disease in women**
Recommendation: research is needed to identify the effect of sex-specific, psychosocial, and socioeconomic risk factors on cardiovascular disease in women, and evaluate intervention strategies

**Age-adjusted prevalence of cardiovascular disease in women is increasing in some of the most populous countries of the world**
Recommendation: scale up healthy heart programmes in highly populated and progressively industrialised regions

**There is no current established global policy to coordinate prevention and treatment of cardiovascular disease in women**
Recommendation: embrace public–private partnerships to develop broad-scale programmes to save lives in women with cardiovascular disease

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pathophysiology of, cardiovascular disease in women have not been well elucidated, and further research is urgently needed to inform strategies for the prevention and treatment of cardiovascular disease in women.

In 2015, the UN General Assembly identified cardiovascular disease as a specific target for achieving the goal of reducing premature mortality from non-communicable diseases by a third by 2030.[14] To achieve this important goal, bold and distinct strategies are needed, not only to modify contributors to cardiovascular disease, but also to identify sex-specific biological mechanisms of cardiovascular disease in women. Innovative solutions are needed for early detection and targeted management, alongside the development of evidence to support sex-specific therapies and interventions. Policy makers, clinicians, researchers, and the community need to work together to demand the availability of timely data from different global regions that is sex-specific and disease-specific, and to address deficiencies promptly as trends are seen. Reducing mortality from cardiovascular disease as the leading cause of death in women globally will require coordinated effort and productive partnerships among policy makers, clinicians, researchers, and the community.

## Aim of the *Lancet* Commission

The aim of this Commission article is to summarise the existing evidence and to identify the knowledge gaps in cardiovascular disease research, prevention, treatment, and access to care for women. Our aim is to reduce the global burden of cardiovascular disease by 2030. We believe that this reduction can be accomplished by promoting cardiovascular health in women globally via recommendations from an international team with expertise in biology, clinical care in specific disease states, clinical trial design and implementation, and health-care policy. We propose concrete strategies for addressing gaps, with priority given to targets that have the greatest potential effect for improving outcomes in women. Our Commission represents the first effort of its kind and is an ongoing mission to connect leaders, innovators, and advocates for women with cardiovascular disease, to ignite global awareness of sex-specific disparities in cardiovascular disease, and to provide a springboard for future research.

The second section of this Commission article reviews the global disease burden of, and risk factors for, cardiovascular disease in women, by drawing on data generated by the GBD Study.[1] These data describe the global distribution of cardiovascular disease morbidity and mortality, the specific risks in women, and illuminate important regional patterns and temporal trends. These observations provide some foundational considerations for generating actionable recommendations for reducing cardiovascular disease risk and for disease management strategies in women. The third section of this article discusses established behavioural and metabolic cardiovascular disease risk factors. Data also point to a range of psychological, social, economic, cultural, and sex-specific risk factors that need to be addressed in conjunction with well established modifiable risk factors in women. The fourth section reviews the major cardiovascular diseases, with an emphasis on clinical presentation, risk factors, and knowledge gaps pertaining

to women. The fifth section provides details about cardiovascular disease burden in women by region and describes the unique regional contexts in which cardiovascular disease needs to be addressed. The sixth section acknowledges and discusses important considerations and limitations of this Commission article. In the final section, we conclude with a synthesis of the evidence, to provide a platform for future work. The Commission, with the 2030 target date in view, will continue to observe trends, evaluate the effect of current recommendations, and suggest actionable key initiatives to combat cardiovascular disease in women during the next decade.

## Global burden of cardiovascular disease in women: insights from the GBD Study

### The value and limitations of big data

To provide an overview of the global burden of cardiovascular disease in women, including disease prevalence, mortality, and risk factors, the Commissioners used data from the GBD Study.[1] Although aggregated estimates like the GBD Study provide valuable global and regional information about the relative effect of diseases and risk factors for poor health and mortality, and can be used to track changes over time, there are some limitations associated with such measures.[15] GBD estimates are based on diverse and sometimes disparate data sources. For instance, in countries and regions in which consistent and complete censuses and crucial registration systems are missing, data sources such as verbal autopsy data are used.[16] Sex-specific risk factors for cardiovascular disease (eg, a history of early menopause, preterm delivery, or gestational hypertensive disorders can increase cardiovascular risk later in life and needs recognition to adjust preventive measures) are not necessarily captured by the GBD database. In the future, the GBD Study aims to increase the volume of high-quality data and the degree of estimated detail.[17] Methodological and analytical strategies to produce the best possible estimates to inform policy makers about how to determine priorities for health interventions are still evolving.[18] A priority for governments is to obtain and share high-quality data to contribute to a comprehensive global picture of cardiovascular disease burden and risk factors. Although from 2021 the frequency of GBD data release will increase to twice a year (compared with annual release since 2015, except for in 2018), other mechanisms are needed that can rapidly disseminate data to help crucial trends to be understood and acted on in a timely way. The Commission website allows easy access to, and navigation of, the GBD data on cardiovascular disease in women, and will be updated as new data are available.

To prevent, recognise, and treat cardiovascular disease in women, it is essential to collect increasingly precise and comprehensive data at both local and regional levels. Access to global data should be in real time and available to all. Efforts should be made to improve funding for increasingly streamlined data collection from different parts of the world.

### Cardiovascular disease prevalence in women

In 2019, there were an estimated 275·2 million (95% uncertainty interval [UI] 261·4 million to 289·8 million) cases of cardiovascular disease in women worldwide. A 95% UI depicts the range of values that in 95% of instances includes the correct estimate of health loss for a given cause; sparse amounts of data will create substantial uncertainty and result in a 95% UI with a wide range. The global age-standardised prevalence of cardiovascular disease in women was estimated at 6403 (95% UI 6079–6740) cases per 100 000). North Africa and the Middle East, high-income North America, eastern Europe, and central Asia had the highest age-standardised prevalence of cardiovascular disease (figure 1A). All parts of Latin America, western Europe, and Australasia belonged to the regions with the lowest age-standardised cardiovascular disease prevalence.

Since 1990, most regions have had a decline in the age-standardised prevalence, representing an overall decrease of 4·3% (95% UI –6·0% to –4·6%). The greatest decreases were in high-income Asia-Pacific (–19·2%; 95% UI –20·7% to –17·9%), western Europe (–18·2%, 95% UI –19·3% to –17·1%), and high-income North America (–14·6%, 95% UI –16·6% to –12·2%). However, in the same timeframe, several regions had an increase in cardiovascular disease prevalence: east Asia (7·2%, 95% UI 5·9% to 8·5%), western sub-Saharan Africa (4·5%, 95% UI 3·3% to 6·1%), and Oceania (3·6%, 95% UI 1·9% to 5·3%). The countries that showed an increase in cardiovascular disease prevalence include some of the world's most populous countries, such as China (7·5%, 95% UI 6·2% to 8·8%), Indonesia (4·8%, 95% UI 3·6 to 6·0%), and India (2·4%, 95% UI 1·6% to 3·2%). Although there was a decrease in the global age-standardised prevalence of cardiovascular disease in women between 1990 and 2010 (–5·8%, 95% UI –6·5% to –5·1%), there has been a slight although not statistically significant increase (1·0%, 95% UI 0·5% to 1·4%) since 2010 (figure 1B). In conclusion, the stagnation in the reduction of cardiovascular disease prevalence is an important observation and a call to action. Initiatives to expand prevention, diagnosis, and treatment of cardiovascular disease in women should be scaled up to target highly populated and industrialising regions.

### Cardiovascular disease mortality in women

There were an estimated 6·10 million (95% UI 5·62 million to 6·41 million) deaths from cardiovascular disease in women in 1990, rising to 8·94 million (95% UI 7·92 to 9·71 million) in 2019. The global age-standardised cardiovascular disease mortality in women in 2019 was estimated at 204 deaths per 100 000, representing a 35·1% (95% UI 30·1% to 40·3%) decrease since 1990. Regions

For more on the **data visualisation of the global burden of cardiovascular disease in women and the work of the Commission** see http://www.womencvdcommission.org/

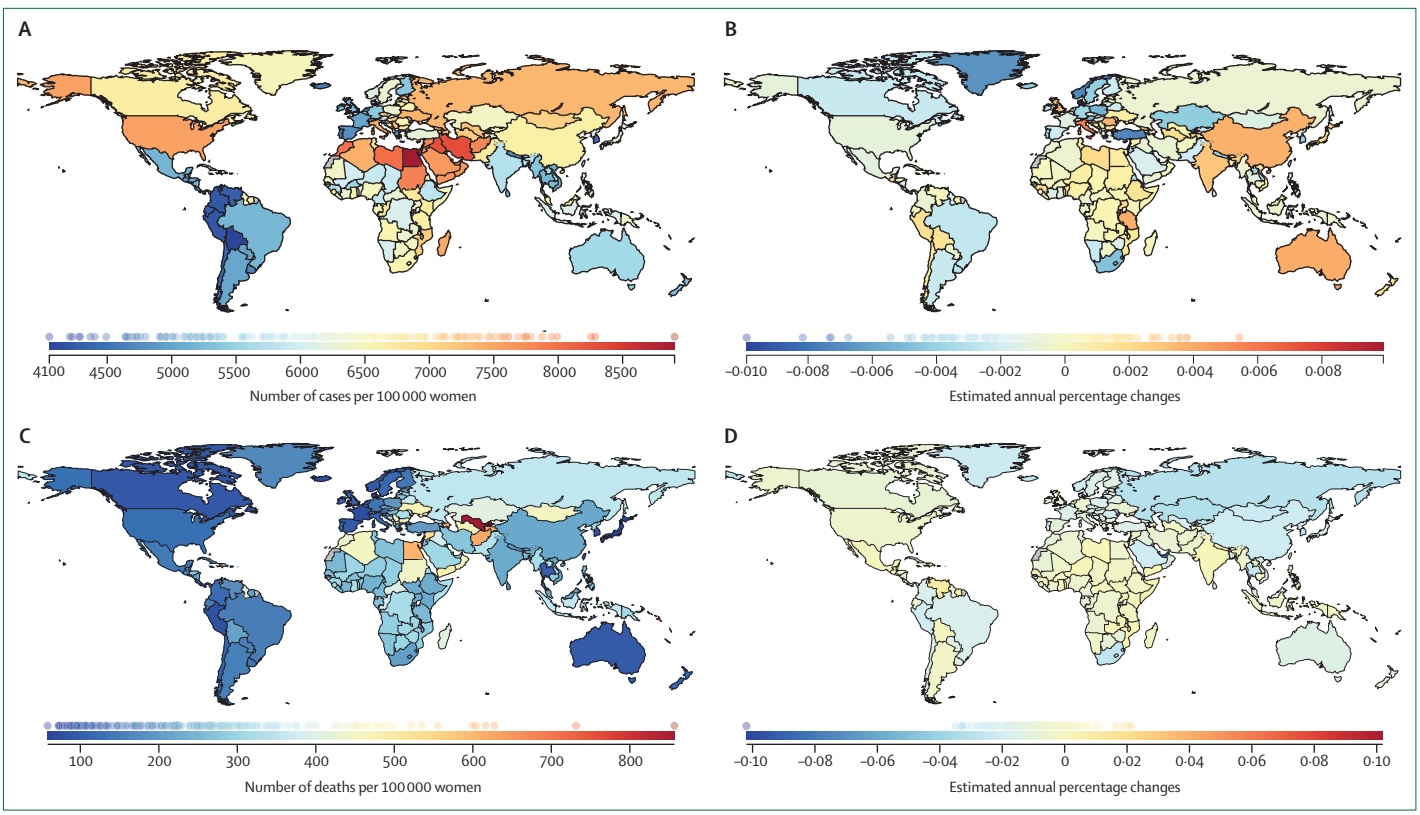


***Figure 1:*** **Global cardiovascular disease burden in women**
(A) Age-standardised cardiovascular disease prevalence per 100 000 women in 2019.[19] (B) Estimated annual percentage changes of age-standardised cardiovascular disease prevalence in women between 2010 and 2019.[20] (C) Age-standardised cardiovascular disease mortality per 100 000 women in 2019.[21] (D) Estimated annual percentage changes of age-standardised cardiovascular disease mortality in women between 2010 and 2019.[22]

with the greatest age-standardised cardiovascular disease mortality in 2019 were eastern Europe, north Africa and the Middle East, Oceania, central sub-Saharan Africa, and central Asia (which all had between 316–486 deaths per 100 000), whereas the lowest age-standardised cardiovascular disease mortality was found in high-income Asia-Pacific, Australasia, western Europe, Andean Latin America, and high-income North America (<130 deaths per 100 000; figure 1C). The estimated age-standardised cardiovascular disease mortality decreased from 1990 in all regions of the world, except for sub-Saharan Africa and Oceania in which there was no significant change, and central Asia, in which an increase (9.1%, 95% UI 1·7% to 17·0%) was noted. By country, the greatest decreases were in North Korea (–76·1%, 95% UI –79·4% to –73·2%), Singapore (–68·1%, 95% UI –71·3% to –65·7%), and Israel (–66·1%, 95% UI –68·8% to –64·1%). The decrease in global cardiovascular mortality slowed down markedly over the last decade compared with previous years (–11·2%, 95% UI –16·8% to –5·4% since 2010 versus –26·9%, 95% UI –30·0 to –23·7% between 1990 and 2010; figure 1D). In conclusion, the concerning slowdown in the decline in global cardiovascular disease mortality should prompt imminent action to understand and tackle the reasons.

## Cardiovascular disease subtypes and metabolic risk factors in women

Ischaemic heart disease was the primary cause of cardiovascular disease mortality in women worldwide in 2019, followed by stroke (figure 2). This applies to each GBD region except for southeast Asia, east Asia, high-income Asia-Pacific, and eastern and southern sub-Saharan Africa, in which the leading cause of cardiovascular disease mortality was stroke (ie, ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage combined). The regions with the highest age-standardised prevalence of ischaemic heart disease were central Asia, eastern Europe, the Middle East, and north Africa (with between 3196 and 4130 cases per 100 000), whereas regions with the lowest prevalence were southern Latin America, high-income Asia-Pacific, and Andean Latin America (all had <850 cases per 100 000). Globally, the relative ranking of the top ten subtype causes of mortality has not changed appreciably over the past 2 decades. Although age-standardised death from rheumatic heart disease has decreased noticeably, this condition remains highly prevalent in several regions of the world (eg, southern, central, and eastern sub-Saharan Africa have between 1160 and 1253 cases per 100 000), whereas the Caribbean, western sub-Saharan

Africa, and Andean and tropical Latin America have between 867 and 1045 cases per 100 000).

Among metabolic risk factors, high blood pressure is by far the most important contributor to age-standardised cardiovascular mortality in women globally, followed by high LDL cholesterol, high fasting plasma glucose, and high body-mass index (figure 3).

High blood pressure is the number one risk factor contributing to years of life lost from cardiovascular disease in each region, followed by high body-mass index in most regions, and high LDL cholesterol in east and south Asia, eastern Europe, western Europe, Australasia, and high-income Asia-Pacific.

In a previous publication, Roth and colleagues[25] used mortality, risk factor, and relative risk data from the GBD 2013 study to project cardiovascular disease mortality for 188 countries up to the year 2025. Modelling the effect of achieving the UN risk factor targets at the community scale showed different cardiovascular benefits between men and women.[25] In modelling interventions for hypertension, tobacco smoking, diabetes, and obesity to achieve reductions in cardiovascular disease in women globally, the greatest predicted decrease was from targeting hypertension, followed by targeting obesity. However, targeting tobacco smoking was predicted to reduce premature cardiovascular disease mortality in women in specific regions, such as high-income Asia-Pacific and western Europe.[25]

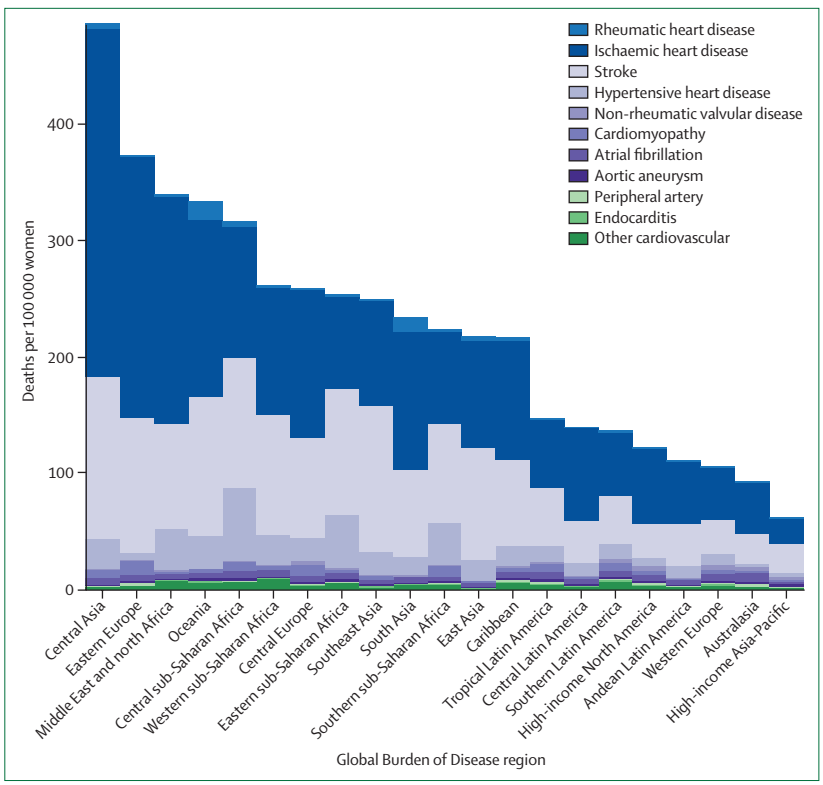


*Figure 2:* **Age-standardised deaths per 100 000 women that were attributable to specific causes of cardiovascular disease across Global Burden of Disease regions in 2019[23]**

## Cardiovascular risk factors in women

Early detection and management of cardiovascular risk factors remain paramount for improving women's cardiovascular health and reducing premature mortality. There is strong evidence that important established risk factors (eg, hypertension, dyslipidaemia, diabetes, obesity, unhealthy diet, sedentary lifestyle, and smoking) contribute to ischaemic heart disease. However, many other important under-recognised risks—including psychological, social, economic, and cultural factors that are often influenced by gender—appear to contribute to cardiovascular disease in women. Depression, intimate partner violence, socioeconomic status, and sociocultural roles disproportionately affect women compared with men and are emerging as important considerations in the development and manifestation of cardiovascular disease in women. Conditions specific to women can increase cardiovascular disease risk, such as obstetric and gynaecological history, including gestational hypertension, gestational diabetes, preterm delivery, premature menopause, and polycystic ovary syndrome (figure 4).

### Well established risk factors

#### *Hypertension*

Hypertension is the leading global risk factor for cardiovascular disease morbidity and mortality and is therefore the most substantial and neglected health burden in women. Women appear to have a higher risk of acute myocardial infarction associated with prevalence of hypertension than men have, as suggested by the results of the INTERHEART study.[26] In keeping with these findings, a study that included 1·25 million patients and 11 029 myocardial infarction events found a slightly higher relative risk (RR) in women than in men of myocardial infarction with increasing systolic but not diastolic blood pressure.[27] A study published in 2020 suggests sex-related differences in the presentation and course of hypertension, with a more rapid increase of progressive blood pressure elevation in women compared with men, beginning as young as 30–40 years.[28] Hypertension is also an important risk factor for stroke in women.[29] Studies also found that as a consequence of hypertension, women more often than men develop left ventricular hypertrophy (which appears to be less responsive to antihypertensive therapy in women than in men), diastolic dysfunction, heart failure with preserved ejection fraction, increased arterial stiffness, and chronic kidney disease.[30,31] Women also report more drug-related side-effects from antihypertensive therapy than men do.[30] The sex-specific mechanisms contributing to the multifactorial pathogenesis and varying consequences of hypertension in women are not well understood. Also, it is still unclear whether different blood pressure targets should be used in women than men because women

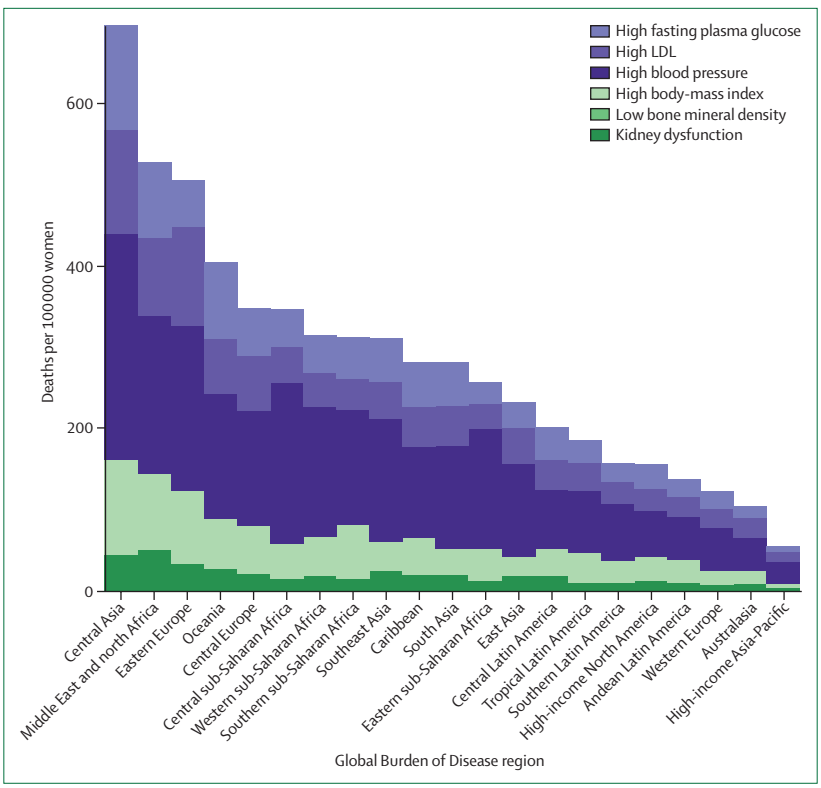


*Figure 3:* **Metabolic risk factors contributing to age-standardised deaths from cardiovascular disease per 100 000 women across Global Burden of Disease regions in 2019[24]**

have smaller arterial diameters and increased arterial stiffness compared with height-matched and weight-matched men.[32] Further research is warranted to address these knowledge gaps.

Management of high blood pressure is of utmost priority for reducing the burden of cardiovascular disease in women. This prevalent risk factor is a silent killer of women worldwide and therefore a global approach to education, screening, and treatment for hypertension is one of the most crucial priorities of this Commission.

### *Dyslipidaemia*

Elevated cholesterol is a major contributor to population attributable risk for myocardial infarction in women.[26] The Study of Women's Health Across the Nation investigated women during the menopause transition and documented a sharp increase in total cholesterol and LDL cholesterol concentrations within a 1-year period around the final menstrual period, which was associated with a higher risk of carotid plaque at later follow-up.[33,34] A previous study found similar cardiovascular risk associated with elevated cholesterol concentrations in women compared with men.[35] However, the INTERHEART study found that the ratios of APOB to APOA1, and of total cholesterol to HDL cholesterol, were more powerfully associated with acute myocardial infarction in women than in men, indicating that further research is needed to better understand whether dyslipidaemia confers a greater excess risk in women than in men.[36] Lipid-modifying treatment using statins reduces both cardiovascular events and mortality in women with established coronary artery disease; however, there are few data on primary prevention in women. Nevertheless, a large meta-analysis of individual patient data from 22 trials suggested that statins for the prevention of major vascular events had similar effectiveness in women and men.[37]

Importantly, physician adherence to the guidelines has been shown to be poor regarding therapy for lipid control in primary and secondary prevention of cardiovascular disease in women.[10] An analysis published in 2018 derived from commercial health insurance data, suggested that statin use after myocardial infarction is significantly lower in women than in men.[38] The underlying reasons are uncertain for disparities in the use of treatments recommended by guidelines. Although an analysis from the Women's Health Initiative study[39] found that statin use in women who were postmenopausal was associated with an increased risk of diabetes, there is no compelling evidence to suggest that statins are less safe in women than in men.

In the past 5 years, aggressive reduction of LDL cholesterol with PCSK9 inhibitors has shown a reduction in important ischaemic events in men and women with established coronary artery disease.[40,41] Sex differences in concentrations of circulating PCSK9 have been suggested by previous studies,[42] but clinical implications have yet to be investigated.

Research is needed to investigate the reasons for underuse of statins in women, and to identify statins that are especially effective and safe for women. Evaluation and treatment of dyslipidaemia, with a focus on reducing LDL cholesterol, is an important goal to reduce cardiovascular morbidity and mortality in women.

### *Diabetes*

The prevalence of diabetes is rising globally, linked to the almost ubiquitous increase in body-mass index caused by unhealthy diets, sedentary lifestyles, and expanding urbanisation, especially in populous regions. Based on data published in 2014 from 858 507 people in 64 prospective population-based cohort studies, the risk for incident coronary heart disease was 44% greater in women with diabetes than in men with the same condition.[43] Similarly, an analysis from the UK Biobank[44] found a 29% higher risk of myocardial infarction associated with diabetes in women than in men. Of note, independent of diabetes status, each 1% increase in glycated haemoglobin $A_{1c}$ was associated with an 18% greater risk of myocardial infarction in both women and men.[44] Another study found that in patients without known cardiovascular disease, the highest excess risk of cardiovascular events associated with type 2 diabetes was in young women (age ≤40 years) with early-onset diabetes.[45] Also, there is evidence that after ST-segment

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elevation myocardial infarction (STEMI), women with diabetes have significantly higher mortality and major adverse cardiac or cerebrovascular events defined as death, reinfarction, or stroke, than for men with diabetes.[46] However, it remains uncertain whether the increased risk of adverse outcomes in women compared with men is associated with diabetes itself or is attributable to sex-related differences in baseline confounding factors. Although women generally have more favourable cardiovascular risk profiles than men, this pattern can be reversed with the deterioration of glycaemic control.[43]

Studies suggest that a diabetes diagnosis tends to occur at a higher body-mass index, older age, and more advanced stage of disease progression in women than in men,[47] suggesting the need for increasingly vigorous screening and further research on additional biomarkers for earlier detection of diabetes in women. Also, it is crucial to address the early stages of diabetes to prevent disease progression and reduce cardiovascular risk. Special attention and follow-up are needed in women with high fasting glucose during pregnancy, owing to the increased risk of type 2 diabetes and cardiovascular disease risk later in life.[48]

For type 1 diabetes, age of onset determines survival and risk of cardiovascular disease, with women who were diagnosed with type 1 diabetes before age 10 years having the greatest risk compared with similarly aged man.[49] Compared with matched controls, women with type 1 diabetes onset before age 10 years had an almost 60 times increased risk of coronary heart disease (*vs* 17 times in men) and approximately 90 times increased risk of acute myocardial infarction (*vs* 15 times in men). The underlying reasons for such excess risks are uncertain; however, studies suggest that hyperglycaemia influences the concentration and activity of oestrogen receptors and inhibits any potential protective effects on the vascular wall, increasing oxidative stress and promoting vasoconstriction and platelet activation.[50]

Metabolic syndrome is a set of inter-related risk factors (eg, central obesity [visceral fat], elevated blood pressure, and dyslipidaemia), a proinflammatory and prothrombotic state, and also includes insulin resistance that can evolve into manifest diabetes and lead to cardiovascular morbidity and mortality.[51] The syndrome is evident in 20–30% of middle-aged women, with a marked increase in prevalence after menopause.[52]

### *Obesity*

Obesity is prevalent and increasing globally. Obesity and insufficient physical activity are closely associated with hypertension, and are more prevalent in women than in men. Analyses of US National Health and Nutrition Examination Survey data[53] have identified obesity (body-mass index ≥30 kg/m²) as the most important modifiable risk factor for hypertension and pre-hypertension in women of reproductive age. Data suggest that a similar increase in male or female body-mass index is associated with a greater increase in systolic blood pressure in women than in men.[54] In addition, data from the Framingham Heart Study[55] showed that the excess risk of cardiovascular disease attributed to obesity was 64% in women versus 46% in men. Obesity is also associated with adverse outcomes in pregnancy, such as hypertensive disorders of pregnancy and gestational diabetes.[56] Central obesity, which is a key feature of metabolic syndrome, is more common among women than men, and particularly affects women after menopause.[57] A study from Taiwan[58] found that in asymptomatic women, body-mass index and waist circumference cutoffs to detect subclinical cardiac pathology were lower than the current established WHO criteria.[59] Women, compared with men, showed steeper declines in global left ventricular circumferential strain and cardiac torsion obtained by echocardiography with increasing body-mass index and waist circumference, indicating sex-related differences in left ventricular remodelling as a response to obesity.

It is estimated that, together with diabetes, obesity contributes substantially to cardiovascular disease

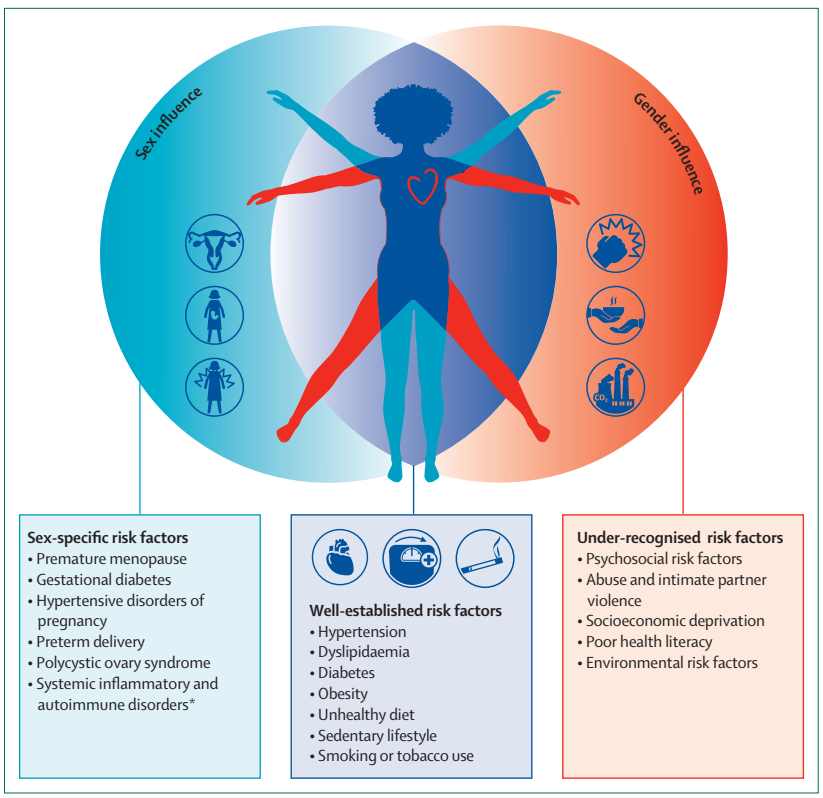


***Figure 4*: Risk factors for cardiovascular disease in women**
The figure categorises risk factors for cardiovascular disease in women into three categories: those that are well-established and affect both sexes but which might affect women differently to men (eg, hypertension, dyslipidaemia, and diabetes); those that are sex-specific (eg, premature menopause and pregnancy-related disorders); and those that are under-recognised (eg, intimate partner violence or poverty) and which can be related to gender and interaction with a woman's social and physical environment. Although research is beginning to recognise how these factors might interact or increase risk, acknowledging the effects of well established, sex-specific, and under-recognised risk factors is crucial to understanding cardiovascular disease in women. *Systemic inflammatory and autoimmune disorders are not sex-specific risk factors, but women are disproportionally affected by these conditions.

prevalence and mortality in women and should be a major target for health interventions.[60]

*Diet*

An analysis from the GBD Study[61] identified unhealthy diet as a substantial contributor to cardiovascular disease risk. Modelling was used to estimate that a balanced diet could prevent one in every five premature deaths and have a major effect on the rising amount of obesity that affects more women than men. The PURE study[62] showed only a minimal difference in the proportion of people adhering to healthy eating between women and men without cardiovascular disease; however, once a cardiovascular disease diagnosis had been established, women were more likely to follow a healthy diet than were men.

Although the majority (88·7%) of women included in the INTERHEART Latin American study[63] reported daily consumption of fruits and vegetables, there is a shift towards a higher intake of high-energy density food and sweetened beverages. Some Latin American countries (eg, Mexico, Brazil, and Chile) have implemented a tax policy for sweetened beverages to help to reduce obesity. Other future initiatives to prevent cardiovascular disease in women could promote plant-based dietary interventions, which are associated with an improvement in obesity-related inflammatory profiles, a reduction in atherogenic lipoproteins, and weight loss.[64,65] Continued and reinforced promotion of a healthy diet in women, starting at a young age, is crucial for reducing the global burden of cardiovascular disease. Socioeconomic inequities that affect quality of diet in women and children should be a major target for interventions and policies.

*Sedentary lifestyle*

It is well documented that sedentary behaviour is associated with increased cardiovascular disease risk and that girls and women are more sedentary than men are.[66] Conversely, an analysis involving 27 536 participants in the Women's Health Initiative study showed that physical activity was associated with decreased incidence of cardiovascular disease regardless of the individual cardiovascular risk.[67] Boys are more likely than girls to be encouraged to participate in physical activity from an early age, and this socialisation continues throughout later childhood and adolescence.[68,69] As women age, their participation in the amount of physical activity recommended by guidelines declines progressively.[70] The PURE study[62] showed that in participants without cardiovascular disease there was a lower rate of physical activity in women than in men; however, in participants with established cardiovascular disease, men had lower rates of physical activity than women had. Developing strategies to increase rates of physical activity in women, starting from early childhood onwards, is a crucial step in addressing the global obesity epidemic and cardiovascular disease burden. Sedentary lifestyle in women is especially prevalent in countries in which social norms, or religious norms, or both, restrict women from doing sports and physical activity. Therefore, initiatives for increasing physical activity in women need to be culturally sensitive and tailored to different regions and populations. The promotion of both physical activity and a healthy diet in women of all ages needs to remain a priority for health-care interventions to reduce the global burden of cardiovascular disease.

*Smoking, tobacco, and electronic cigarette use*

Globally, tobacco smoking and the use of electronic cigarettes (also known as e-cigarettes, vape pens, and vaping devices) are increasing in younger women (≤25 years). This epidemic could represent particular harm to women. A large meta-analysis found that the increased risk of cardiovascular disease associated with smoking was 25% higher in women than in men.[71] Conversely, the INTERHEART study[72] found that the risk of myocardial infarction associated with smoking was similar for both women and men. Further research is warranted to evaluate a potential interaction between sex and smoking with regards to cardiovascular disease outcomes.

Data from the GBD 2015 study[73] show that the worldwide age-standardised smoking prevalence in women in 2015 was 5·4% (95% UI 5·1–5·7), although in 34 (17%) of 195 countries analysed, the smoking prevalence in women exceeded 15·0%. Mostly, countries in western and central Europe greatly exceeded the global average in women's smoking prevalence, with an especially high prevalence among women aged 15–19 years. In the past decade, 53 (27%) of 195 countries and territories recorded significant decreases in age-standardised prevalence of male daily smoking, whereas only 32 (16%) recorded significant reductions for women. Although the lower overall global smoking prevalence in women compared with men should be acknowledged, it is notable that despite substantial tobacco-control initiatives, smoking prevalence in women has hardly changed and has even increased in many countries. Analyses from France found an increase in smoking prevalence among women aged 45–54 years, which probably contributed to the increase of myocardial infarction in this population.[74] Smoking cessation in young women should be a major target for health interventions worldwide.

The practice of smokeless tobacco, or of chewing betel quid or areca nut, is prevalent in many parts of Asia. Data from Taiwan showed an association between betel quid use and heart disease in women.[75] Unlike tobacco smoking, for which the WHO Framework Convention on Tobacco Control provides evidence-based policies for reducing use, there are no global policies for controlling use of betel quid and areca nut.[76]

E-cigarettes emit a range of toxicants and have been shown to negatively affect the cardiovascular system (eg, endothelial cell dysfunction, oxidative stress, and

platelet activation).[77] E-cigarettes are currently the most commonly used smoking product in the USA, including among younger women and teenagers. Many users perceive e-cigarettes to be a healthier choice than tobacco.[77] The marketing of flavoured (eg, fruit and mint) e-cigarette products to children is of great concern and there have been efforts to ban these items in the USA. The US Food and Drug Administration (FDA) has finalised an enforcement policy on sales of unauthorised flavoured cartridge-based e-cigarettes that appeal to children and teenagers. A policy statement by the American Heart Association (AHA) supports effective regulation to address e-cigarette marketing, labelling, quality control of manufacturing, and standards for contaminants.[78] The AHA also supports including e-cigarettes within smoke-free air laws and prohibiting sales of e-cigarettes to young people (aged ≤18 years).[78]

The use of tobacco and smoking products is increasing alarmingly in adolescents and young women. Smoking reduction among women will require tobacco-control policies (eg, stringent smoke-free air legislation, tobacco taxes, and plain packaging) and monitoring of smoking behaviours.[79]

## Sex-specific risk factors

It is increasingly recognised that a range of biological variations and genetic differences modify the risk for, and affect the pathogenesis of, cardiovascular disease in women. Sex-specific differences in cardiovascular physiology and pathophysiology might be partly related to endogenous and exogenous reproductive hormone differences, although contemporary data question the protective role of oestrogens.[80] Oestrogen mediates effects through both transcriptional and non-transcriptional mechanisms on endothelial cells, vascular smooth muscle cells, and cardiac myocytes and fibroblasts;[81] however, exogenous oestrogen therapy used for contraception and menopause does not lower cardiovascular disease risk.[82,83]

An analysis of the association between women's reproductive factors and incident cardiovascular disease, using UK Biobank data on more than 500 000 female participants aged 40–69 years, found that adjusted risks for cardiovascular disease were 1·10 (95% CI 1·01–1·30) for early menarche (age <12 years), 0·97 (0·96–0·98) for each year of age at time of first giving birth, 1·14 (1·02–1·28) for each stillbirth, and 1·33 (1·19–1·49) for early menopause (age <47 years).[84] Across the life course of a woman, reproductive factors might affect the risk of developing cardiovascular disease.

Research is urgently needed to investigate the mechanisms by which oestrogen affects the cardiovascular system in women.

### *Menopause*

Cardiovascular disease in women manifests later in life than in men, with the first acute myocardial infarction occurring about 9 years earlier in men than in women, as documented in the INTERHEART study.[26] Although cardiovascular disease risk is lower in women who are premenopausal than in age-matched men, it rises substantially after menopause. The US Study of Women's Health Across the Nation[52] found a sharp increase in LDL cholesterol during the 1-year period around the final menstrual period, but found no association between menopausal transition and changes in blood pressure, insulin, glucose, and body-mass index. Nevertheless, the odds of developing metabolic syndrome were significantly increased per each year in perimenopause (OR [odds ratio] 1·45, 95% CI 1·35–1·56),[52] and body composition changed with accelerated gains in fat mass and losses of lean mass during the menopause transition.[85] It has been hypothesised that endogenous hormone differences contribute to sex differences in cardiovascular disease risk and prevalence. For instance, evidence suggests that lower concentrations of oestrogen and higher concentrations of androgen after menopause might mediate the increased cardiovascular disease risk in women who are postmenopausal.[86] Also, premature menopause (age <40 years) was identified as a factor for increased cardiovascular disease risk before age 60 years in an analysis published in 2019.[87] Another study found that natural and surgical premature menopause were both associated with an increased incidence of a composite endpoint of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischaemic stroke, peripheral arterial disease, and venous thromboembolism.[88] By contrast, the study also analysed whether the use of extended systemic menopausal hormone therapy mitigated the cardiovascular disease risk associated with premature menopause, and did not find any significant interaction between premature menopause and menopausal hormone therapy.[88] Also, some experts suggest a reversed relationship, with increased premenopausal cardiovascular risk promoting premature menopause.[89] These data underline the need for additional research in women's health, including about endogenous and exogenous reproductive hormone sex differences.

### *Menopausal hormone replacement therapy*

Menopause is associated with the presentation of cardiovascular disease in women. The role of hormone replacement therapy has been of great interest in mitigating cardiovascular disease. Although observational studies on hormone replacement therapy after menopause showed promising results in lowering cardiovascular risk, larger randomised controlled trials have not confirmed any benefit in primary or secondary prevention. In fact, the Women's Health Initiative study[90] primary prevention trial included 27 347 women who were postmenopausal and showed that oestrogen use was associated with a small but statistically significant increased risk of cardiovascular events compared with placebo (hazard

ratio 1·11, 95% CI 1·01–1·22; p=0·03). Other secondary analyses of this study suggested that the effect of hormones on coronary heart disease might be modified by the number of years since menopause, with the highest risks in women who initiated therapy 20 or more years since menopause (or were aged ≥70 years).[91] Results from the Early versus Late Intervention Trial with Estradiol study[92] support the hypothesis that the effects of hormone replacement therapy vary by the timing of exposure. No robust data exist on clinical outcomes associated with the timing of exposure in relation to the onset of menopause. With regard to secondary prevention, the Heart and Estrogen–progestin Replacement Study[93] also did not show any benefit of conjugated equine oestrogen plus medroxyprogesterone acetate in the reduction of overall cardiac events in women with established coronary artery disease; instead, an increase in thromboembolic events was documented.

Currently, menopausal hormone replacement therapy is not indicated for primary or secondary prevention of cardiovascular disease. Whether the timing of therapy initiation in relation to the onset of menopause has an effect on the cardiovascular risk associated with menopausal hormone replacement therapy needs to be further investigated. However, hormone replacement therapy using low-dose oestrogen, or transdermal hormone therapy at the lowest feasible dose and shortest duration, for the management of menopausal symptoms in younger, low-risk women appears to be safe.[94] In women experiencing myocardial infarction, menopausal hormone replacement therapy should be discontinued.

*Pregnancy-related disorders*

Many pregnancy-related disorders are associated with increased cardiovascular risk. Complications such as gestational hypertensive disorder (eg, pre-eclampsia), gestational diabetes, or preterm delivery are risk factors for the development of cardiovascular disease later in life.[95–97] A clinical history of one of these complications warrants ongoing cardiovascular disease risk assessment, risk factor screening, and provision of coordinated cardiovascular disease prevention measures if indicated. Although it is well known that a history of pregnancy complications increases cardiovascular risk, further research is needed to better understand how these factors should be incorporated into risk prediction alongside well established risk factors.[98]

Not all physicians in high-income countries might be aware of the importance of pregnancy-related disorders such as pre-eclampsia for cardiovascular risk,[99] and women in low-income and middle-income countries (LMICs) might have little access to risk-assessment opportunities. A multidisciplinary team approach is mandated, and initiatives such as the Preeclampsia Foundation are crucial for patient support and education, raising public awareness, catalysing research, and improving health-care practices. Evaluation of pregnancy outcome offers a distinct opportunity to assess cardiovascular disease risk and prevent cardiovascular disease in women, and should be a joint effort across specialities.

For more on the **Preeclampsia Foundation** see https://www.preeclampsia.org/about-us

*Hormonal contraceptives*

Combined oestrogen–progesterone hormonal contraceptives include the pill, vaginal ring, and patch formulations. Available progesterone-only methods include medroxyprogesterone injections, etonogestrel implants, progesterone-only pills, and levonorgestrel-releasing intrauterine devices.[100] Hormonal contraceptives are generally considered safe and effective for the prevention of pregnancy, with reasonably few contraindications. However, women with specific risk factors associated with venous thromboembolism, or acute myocardial infarction, or both (eg, smokers aged 35 years or older, history of venous thromboembolism or pulmonary embolism, or hereditary thrombophilia) should be counselled for non-hormonal or progesterone-only contraceptives, and the risks of using hormonal contraceptives should be balanced against the potential risks of unintended pregnancy.[100-101]

Although overall risk is low, evidence suggests that combined hormonal contraceptives are associated with a 12 times increase in the risk of myocardial infarction in women with hypertension.[102] If multiple risk factors exist, combined hormonal contraception could increase a woman's cardiovascular disease risk to an unacceptable extent.[100] There is no robust evidence that past use of hormonal contraceptives has a significant effect on the risk of subsequent cardiovascular disease, regardless of duration of use, or time since last use.[103]

Women older than 40 years should be screened for additional cardiovascular disease risk factors, such as smoking, obesity, diabetes, hypertension, or migraine with aura. Progesterone-only oral contraceptives, subdermal implants, and levonorgestrel-releasing intrauterine devices are options to use in women with a history or at risk of myocardial infarction or stroke.[100]

*Polycystic ovary syndrome*

Polycystic ovary syndrome is defined as the presence of both androgen excess and oligo-anovulation, and globally affects 6–10% of women of reproductive age.[104] Women with polycystic ovary syndrome have a higher risk of hypertensive disorders in pregnancy and of gestational diabetes.[105] However, the Women's Ischemia Syndrome Evaluation study[106] reported that women who were postmenopausal, both with and without polycystic ovary syndrome, had similar cardiovascular event-free survival. Two subsequent meta-analyses found an association between polycystic ovary syndrome and stroke but not all-cause mortality,[107] and an association with cardiovascular disease but not myocardial infarction.[108] The clustering of insulin resistance, obesity, and metabolic syndrome in polycystic ovary syndrome helps to explain the predisposition for type 2 diabetes, dyslipidaemia, and

arterial hypertension in women with polycystic ovary syndrome,[109,110] but the effect of this condition (apart from risk factors and its association with cardiovascular events and mortality) remains uncertain. Further research on the risk and management of cardiovascular disease in women with polycystic ovary syndrome is warranted.

*Systemic inflammatory and autoimmune disorders*

Although systemic autoimmune disease is not a sex-specific risk factor, women are disproportionally affected by this condition compared with men;[111] among patients with this condition, 78% are women.[112] The chronic inflammation caused by autoimmune disease is associated with endothelial dysfunction and the acceleration of atherosclerotic disease.[111,113] Also, steroid therapy is commonly used in patients with autoimmune disease and can result in the worsening of both hyperglycaemia and dyslipidaemia. A cohort study (incident user design with time-stratified propensity score matching using a general population database in the UK) showed that statin use in women with rheumatoid arthritis reduced the risk of all-cause mortality by 29% (hazard ratio 0·71, 95% CI 0·59–0·86).[114] These results were independent of age, body-mass index, socioeconomic status, relevant comorbidities, cardiovascular medication use, total cholesterol concentrations, and health-care usage. Although the incident user design and the intention-to-treat analysis approach might have helped to mitigate selection bias arising from investigating prevalent statin users, a randomised controlled trial is needed to identify the effect of the anti-inflammatory and lipid-lowering effects of statins on cardiovascular disease risk and mortality in patients with systemic inflammatory and autoimmune disorders.

The presence of systemic inflammatory and autoimmune disorders should be considered in cardiovascular disease risk estimation, and aggressive screening and management of additional cardiovascular disease risk factors should be the goal of care for women with these conditions. Enhanced communication and coordination of services between rheumatologists and cardiologists can help to mitigate cardiovascular disease risk in women with systemic inflammatory and autoimmune disorders.

## Under-recognised risk factors in women

*Psychosocial risk factors*

Depression and anxiety are associated with increased risk of cardiovascular disease morbidity and mortality. Depression is an independent and long-term risk factor for both obstructive[115] and non-obstructive coronary artery disease in women.[116] In addition, depression has consistently been associated with worse outcomes after acute myocardial infarction, with a 2–4 times higher risk of adverse cardiac events, independent of other prognostic factors such as coronary artery disease severity, left ventricular dysfunction, and history of myocardial infarction.[117–119] A study found that younger and middle-aged women (aged 18–55 years) report higher amounts of perceived stress than men during the first 12 months of recovery after myocardial infarction.[120]

Psychosocial disadvantages (eg, unemployment, chronic stress, insufficient social support, and bereavement or widowhood) are more common in women than in men, which contributes to increased depression and anxiety.[117,121] Despite depression being a well documented risk factor for cardiovascular disease and health outcomes, it receives little attention in routine clinical practice. Only 3% of cardiologists were found to screen for depression[122] and, conversely, women who present with chest pain are often misdiagnosed with anxiety. It is crucial that health-care providers recognise depression as an important factor for risk and prognosis of cardiovascular disease, and screen patients to initiate appropriate treatment if indicated.[123] Addressing depression and anxiety with mental health care providers can have an important effect in improving health outcomes and preventing cardiovascular disease in women.

*Abuse and intimate partner violence*

Physical and psychological abuse of women and, in particular, intimate partner violence, affects 15–71% of women in their lifetime.[124] Analyses suggest that intimate partner violence is associated with an increased incidence of cardiovascular disease.[125–127] Direct physiological mechanisms and indirect effects of abuse might increase cardiovascular disease risk in women. The major direct effect of abuse is chronic stress, which persists even after the abuse stops, and which, along with depression, is a known risk factor for cardiovascular disease. Indirect effects of intimate partner violence include its effect on mental health, or modification of health behaviours, or both. Women who report intimate partner violence are increasingly likely to be current smokers, engage in heavy or binge drinking, and not to seek routine medical care.[128] A population-based cohort study reported that intimate partner violence was also associated with abdominal obesity, low HDL cholesterol, and elevated triglycerides.[129] Also, it was found that victimised women who were postmenopausal had higher ambulatory blood pressure.[130] Data are deficient on the cultural victimisation of women in different parts of the world, and its prevalence and effect on cardiovascular disease remain uncertain.

This Commission endorses organisations dedicated to ending violence against women.

*Health literacy*

Inadequate health literacy is associated with an increased risk of cardiovascular disease and contributes to poor health outcomes and low use of health-care services.[131,132] Health literacy refers to an individual's motivation and ability to gain access to, understand, and use information

in ways that promote and maintain good health.[133] Poor health literacy is not solely a problem for LMICs, but is also present in high-income countries. For example, a German study reported lower health literacy in women than in men for patients with cardiovascular disease (41·8% *vs* 46·7%).[134] Although another study found poorer health literacy in men than in women, it also suggested sex and gender-related differences in predictors for poor health literacy at an older age, including educational attainment, adolescent cognitive and non-cognitive skills, and rate of cognitive decline from the middle to later life.[135] Further research is needed to investigate sex and gender-related differences in predictors of poor health literacy. In technology-rich environments such as the USA, approximately a third of adults were categorised as having basic or less than basic health literacy, with 12% of women having less than basic health literacy.[136] Health literacy is necessary to ensure that women are equipped to participate in cardiovascular disease self-care, including treatment adherence and behavioural modifications to reduce cardiovascular disease risk. This Commission endorses organisations dedicated to promoting education for girls and women globally, and best practices, such as standardising health information using culturally tailored communication mechanisms, to reduce cardiovascular disease risk among women.[137,138]

*Environmental risk factors*

Evidence is growing that air pollution substantially increases the risk of cardiovascular disease.[139] The European Society of Cardiology (ESC) released an expert position paper on air pollution and cardiovascular disease,[140] providing an overview of all evidence for increased risk of coronary artery disease, heart failure, cardiac arrhythmias or cardiac arrest, and cerebrovascular disease or thromboembolism. Air pollution results in higher oxidative stress and inflammation, which might affect plaque progression, endothelial dysfunction, impaired fibrinolysis, platelet hyper-reactivity, and possibly also arrhythmogenesis. A study of 1816 women who were postmenopausal and without previous cardiovascular disease indicated that long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death.[141] Another study suggested that roadway proximity to living accommodation was associated with elevated and statistically significant risks of sudden cardiac death and fatal coronary heart disease in women, even after adjusting for other cardiovascular risk factors.[142] The main source of indoor air pollution is smoke from domestic cooking using solid fuels such as wood. Women are more likely than men to be affected by high amounts of particulate matter and carbon monoxide produced by cooking on indoor stoves.[143] The effect of environmental and indoor pollution on the cardiovascular health of women is uncertain and warrants further investigation.

*Socioeconomic and cultural status, race, and poverty*

Women are disproportionately affected by disparities in the distribution of wealth, income, and access to resources that affect cardiovascular health and wellbeing. Data from the GBD Study[2] found that in countries with a low Socio-demographic Index women have higher age-adjusted mortality than men.[2] Women, especially women with minority ethnicity, are also over-represented among people living in poverty in high-income countries, with associated negative effects on health and access to care.[144,145] The inverse relationship between socioeconomic status and cardiovascular disease risk and mortality, is well established.[146–149] A large meta-analysis found that low income, low levels of education, and living in disadvantaged areas are strongly associated with cardiovascular risk in women.[150] Similarly, an analysis from the 2006 Health and Retirement Study[151] found a strong association between low socioeconomic status and six of seven cardiovascular risk factors in women older than 50 years. Another study suggested a strong relationship between low socioeconomic status and metabolic syndrome in women.[152] In addition, data from the Jackson Heart Study[153] in 5301 African American people showed that adult socioeconomic position was more consistently associated with cardiovascular disease risk in women than in men: age-adjusted hazard ratios for low versus high wealth were 2·14 (95% CI 1·39–3·29) in women and 1·06 (95% CI 0·62–1·81) in men ($p_{interaction}$=0·0224).

Many factors (including low levels of education) contribute to an increased cardiovascular risk associated with socioeconomic deprivation in women. These factors are associated with poor health literacy and can influence unhealthy behaviours, such as smoking, poor diet, and low amounts of physical activity. Commercial advertising of fast or processed food, and the lower cost of unhealthy food in comparison with healthy food, promote food options that contribute to higher energy and fat intakes,[154] which are associated with obesity and metabolic disorders, including diabetes and dyslipidaemia. Women with low socioeconomic status also have considerable chronic stress and depression, are disproportionally affected by intimate partner violence and domestic abuse, and are more likely to be single parents with little time to seek medical treatment and preventive care, compared with their male counterparts.[155] In addition, there is evidence that menopause occurs earlier in women with a low than a high socioeconomic status, which in turn is associated with increased cardiovascular risk.[156] Women with low socioeconomic status in both low-income and high-income countries have suboptimal medical care and inadequate health-care coverage, which is further compounded by race and ethnicity.[148,157] For example, in the USA, despite Medicaid expansions that reduced the number of uninsured US women, continued efforts to repeal the Affordable Care Act have especially put Black

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women and Latinas at risk of losing health coverage.[145] Although studies suggest that women generally have higher amounts of interaction with health-care systems than men, these encounters can often be restricted to gynaecological or obstetric visits and are less likely to be characterised by optimal care that includes cardiovascular disease prevention, treatment, and specialist referral.[158]

Traditional roles (eg, carer for children, older parents, or other family members), domestic duties, and cultural norms might also restrict women in their pursuit of healthy lifestyles, being physically active, and practising self-care. It is not only in low socioeconomic status populations that responsibilities associated with a caretaker role can contribute to a lower likelihood of women seeking optimal and specialised medical care.

The COVID-19 pandemic has shown inexorably how the socioeconomic status and the cultural role of the woman in society affect the physical and mental health and wellbeing of women globally (panel 1; figure 5).

Public health and clinical interventions should address simultaneously the multiple cardiovascular disease risk factors that frequently coexist in women with low socioeconomic status, and health-care providers should receive training on how to adapt their practices to accommodate vulnerable populations (figure 6).[170] At the same time, women's cardiovascular health and well-being are shaped profoundly by public policy, income inequality, social immobility, and women's social status and role in society.[157,171,172] Access to health care, social inclusion, and community outreach and education in socioeconomically deprived regions could reduce the burden of cardiovascular disease in women.

This Commission recommends giving policy attention to low socioeconomic status populations in both high-income countries and LMICs. Proximal policies that provide health insurance coverage and access to care, including preventive and treatment services, are important factors in reducing cardiovascular risk.[170] Distal policies can also have an important effect, such as policies that endorse access to smoke-free environments and heart-healthy foods, and that address education, employment, time off work to look after family and dependants, housing, and safe environments. Most importantly, programmes that support universal health coverage are likely to improve cardiovascular health outcomes among women from socioeconomically deprived regions.

### *Panel 1*: Women, cardiovascular disease, and COVID-19

Data on COVID-19 point towards similar infection rates between the sexes, but higher death rates in men than in women.[159] However, global COVID-19 data is often missing information on sex. Many countries do not report COVID-19 cases and deaths disaggregated by sex, according to the Global Health 5050 research initiative.[160] More importantly, information on testing by sex is not available, although the numbers of infections are largely dependent on testing strategies in different countries and regions.[161]

Nevertheless, it is without a doubt that COVID-19 affects women differently to men. Although the effect of sex hormones might be partly responsible for sex-related differences in the inflammatory response to SARS-CoV-2 (the virus causing COVID-19), sex and gender have an important role in other effects on health associated with the COVID-19 pandemic. Specifically, domestic violence against women has increased during lockdown.[162] Also, compared with men, women are more likely to be responsible for childcare, now that many schools have been closed, and women's jobs are more likely to be at risk. Data on the effect of these issues on women's mental and physical health are deficient. Even before the pandemic women were doing 3 times as much unpaid care and domestic work as men globally.[163] It was found that these factors can restrict women from pursuing a healthy lifestyle, practising self-care, and seeking treatment for cardiovascular disease. Although it can be estimated that these inequalities have only become worse since the onset of the pandemic, the data to prove this are missing. Governments are under great pressure to react to the global threat, and might focus on flattening the infection and death rate curves, but the pandemic's social and socioeconomic effects represent major threats to the health and wellbeing of women, and are neither acknowledged nor addressed.

In addition to understanding the pathophysiological mechanisms of COVID-19 and the sociocultural consequences of the pandemic, collecting sex-disaggregated data and obtaining sex-related biological factors is also important for the development of effective treatment and prevention. For example, it has been shown that women are less likely than men to accept vaccination.[161] Although women have a more effective response they also report more adverse reactions to vaccines, compared with men.[161,164] With regards to treatment, the angiotensin-converting enzyme 2 (ACE2) receptor has an important role in the infection route of SARS-CoV-2 and might also be a key factor in the mechanisms leading to severe myocardial injury associated with COVID-19.[165] Understanding sex differences in ACE2-receptor density and activity might help to develop effective treatment strategies.[166] Although there is no proven effective treatment of COVID-19 so far, the off-label use of certain drugs, especially in the early phase of the pandemic, carried the risk of serious side-effects. For example, adverse events associated with chloroquine and hydroxychloroquine include arrhythmias and sudden cardiac death,[161,167,168] and women might have been affected disproportionally because of their increased risk of drug-induced torsade de pointes compared with men.[169] The COVID-19 pandemic once again emphasises the importance of collecting sex-disaggregated data and sex-related biological factors to improve disease treatment and prevention and ensure equitable care globally. The pandemic provides a unique opportunity to investigate and better understand sex-specific pathophysiological mechanisms, but also acute and long-term consequences resulting from the aspects of gender inequality aggravated by the pandemic on health and wellbeing of women.

## Cardiovascular risk assessment in women

Cardiovascular disease risk estimation remains challenging, especially in women. Although numerous prediction models exist, validity is often limited by small sample size and the specific characteristics of the population that they are derived from. This results in these tools having low validity for use in particular populations, including young women and minority populations. Although the risk for cardiovascular events in young women remains low at population level, individual women could have a high relative risk. Using sex-specific and age-specific cardiovascular disease risk thresholds, and incorporating novel measures of subclinical disease (eg, coronary calcium scoring) into risk assessment, might improve the guidance for preventive measures.[13,173]

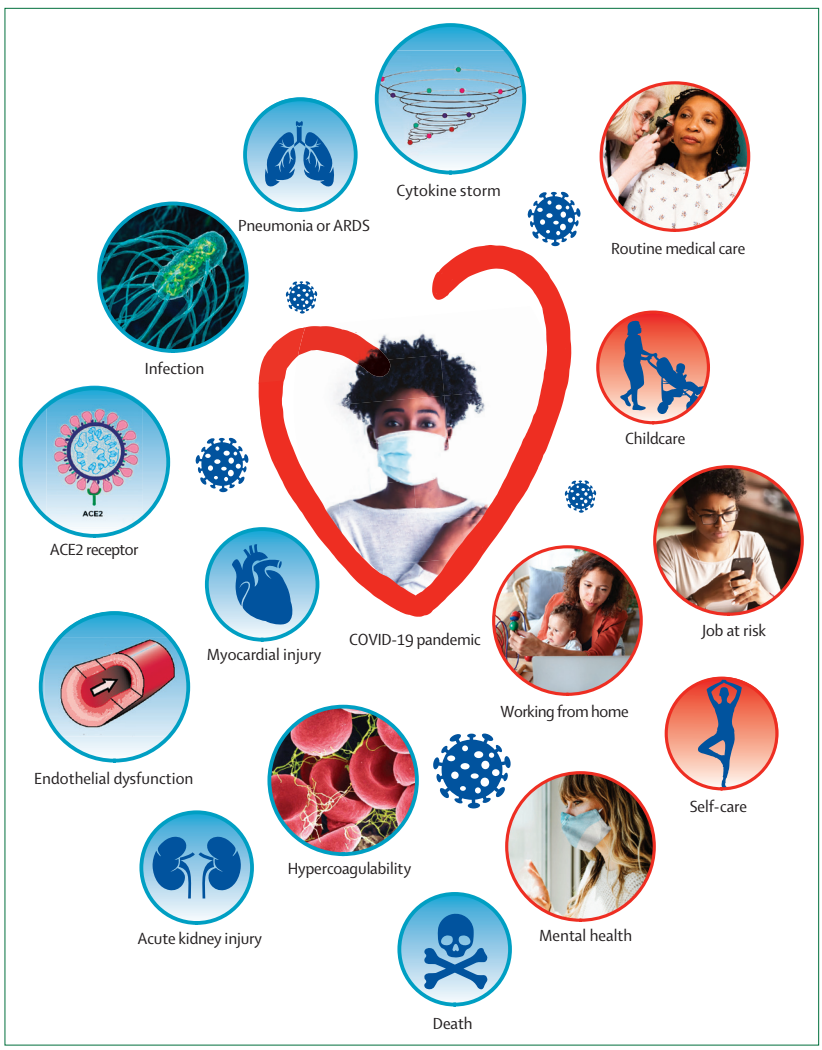


***Figure 5:*** **Women, cardiovascular disease, and COVID-19**
The COVID-19 pandemic provides a powerful example of how sex-related biological factors (blue border) underpinning SARS-CoV-2 infection and gender-associated factors (red border) can interact to negatively affect women's cardiovascular health. ACE2=Angiotensin-converting enzyme 2. ARDS=Acute respiratory distress syndrome.

It remains uncertain how to include and consider sex-specific and under-recognised factors in risk calculators, and women might be especially affected by these limitations of current risk prediction tools. Although some guidelines note the dearth of evidence about the role of sex-specific factors in cardiovascular risk prediction and disease,[174] others mention premature menopause and pregnancy-related disorders as risk enhancing factors,[175,176] whereas another report on cardiovascular risk prediction tools does not mention (female) sex at all.[177] Increased attention to these knowledge gaps is urgently needed, to address the complex relationship of particular sex-specific factors and cardiovascular risk prediction. Meanwhile, because of a higher lifetime risk of stroke in women than in men, the use of cardiovascular risk calculators should be preferred to the use of risk prediction tools that consider only cardiac events.[178]

However, the limitations of current risk prediction models are only one side of the problem. Although marked improvements have been achieved over the past 2 decades, awareness about cardiovascular disease risk among women themselves, and among their health-care providers, remains suboptimal.[7,179] Younger women and women from minority ethnic backgrounds are especially unaware of the risk and, in a survey from 2014, only 39% of primary care physicians rated cardiovascular disease in women as the top concern after weight and breast health.[7] Furthermore, only 22% of primary care physicians and 42% of cardiologists felt extremely well prepared to assess cardiovascular disease risk in women, and only 16% of primary care physicians and 22% of cardiologists said they comprehensively implemented cardiovascular disease prevention guidelines when treating women. Although most of these professionals were aware of the atherosclerotic cardiovascular disease risk assessment calculator,[180] only around a half of each group indicated that they used it.[7] A subsequent analysis of survey data suggested an actual decline in awareness about heart disease was the leading cause of death among women from 2009 to 2019, particularly among Hispanic women, non-Hispanic Black women, and younger women.[8]

Despite the great success of various campaigns and initiatives, further efforts are needed to increase awareness about cardiovascular disease risk in women. There is an unmet need for a cardiovascular disease risk calculator that considers sex-specific risk factors. We consider the risk calculator to be an important next step to support education and access to care, and to enhance our ability to prevent cardiovascular disease in women.

### Prevention of cardiovascular disease in women

The physicians who directly take care of women remain underused for addressing cardiovascular risk and educating women about their risk. Integrated care programmes for women, with multidisciplinary treatment from a range of providers at the different stages of the process, are needed. It is particularly important for risk assessment and cardiovascular disease prevention efforts to identify and promote methods that encourage health-care providers to assess, and to empower women to recognise, cardiovascular disease risk. As seen in other fields, community health workers could be invaluable agents for supporting cardiovascular disease screening and identifying women at risk of cardiovascular disease (figure 6).[181] Further investigation on the sex-specific effects of preventive measures for cardiovascular disease is required.

## Overview of disease states

### Ischaemic heart disease

Ischaemic heart disease is the leading cause of death in women worldwide. Although research on sex-specific pathophysiology of ischaemic heart disease has increased


***Figure 6*: Changing the perceptions of cardiovascular disease in women by recognising the populations most likely to be affected by social, cultural, and economic factors that can indirectly increase risk**

Shaping interventions and initiatives to target the reduction of cardiovascular disease in women requires identification of those women who are the most susceptible globally, including those who might not have traditionally been viewed as being at high risk, such as younger women.

over the past 2 decades, women remain under-represented in clinical trials, registries, and pathological studies. As a result, knowledge about the specific pathophysiological mechanisms and the spectrum of ischaemic heart disease manifestation in women is suboptimal, and reliance on male-pattern diagnostic criteria most likely contributes to delayed or deferred diagnosis of ischaemic heart disease in women. Emerging evidence points to substantial differences between women and men with ischaemic heart disease, in pathophysiology, clinical presentation, risk factor patterns, quality of care, and outcomes. This section summarises important women-specific aspects of ischaemic heart disease; for key points and recommendations by disease see panel 2.

### *Ischaemia with no obstructive coronary artery disease*

Symptoms and signs of ischaemia without obstructive disease in the epicardial coronary arteries, known as ischaemia with non-obstructive coronary arteries

(INOCA), are more common in women than men, with especially high prevalence among women aged 45–65 years.[182–184] The prevalence of INOCA is dependent on the study population and the diagnostic approach, and might be underestimated. The Women's Ischemia Syndrome Evaluation study[185] enrolled women referred

### *Panel 2*: Key points and recommendations by disease

**Ischaemic heart disease**

*Ischaemia with non-obstructive coronary arteries (INOCA)*

- INOCA is not a benign condition and is associated with increased risk for adverse cardiac events
- A large international study using a standardised diagnostic algorithm is required to better understand the epidemiology of women with INOCA
- Further research is required to investigate underlying mechanisms of INOCA and define approaches to its evaluation and treatment

*Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA)*

- Understanding the mechanisms of the underlying disease in women presenting with MINOCA is essential in providing therapeutic options
- Randomised controlled trials are urgently needed to investigate treatment options and secondary prevention strategies in women with MINOCA
- This Commission endorses the request by the American Heart Association for a MINOCA-specific International Classification of Diseases, 10th Revision code, which would facilitate research and help hospitals to pursue higher amounts of reimbursement for additional diagnostic studies in this patient population

*Spontaneous coronary artery dissection (SCAD)*

- Further research is urgently needed to address uncertainties about prevalence and treatment of SCAD as well as post-SCAD lifestyle modifications and medical therapies
- Initiatives such as the EURObservational Research Programme and other SCAD registries are crucial to improve our understanding of the disease

*ST-segment elevation myocardial infarction (STEMI)*

- The general underestimation of cardiovascular risk in women needs to be addressed
- Continuing efforts are needed to provide guideline-recommended treatment to women with STEMI
- Further research is mandated to investigate potential biological sex differences as underlying reasons for the sex-related mortality gap in STEMI

**Heart failure**

- The overwhelming increase in the incidence of heart failure with preserved ejection fraction in women with few therapeutic options underlines the importance of further research in this area
- Evidence points towards sex-specific target doses in heart failure therapies and should be validated in prospective, sex-specific, dose-finding studies
- Cardiac resynchronisation therapy should be offered to women with a clinical indication
- Women are more susceptible than men to cardiogenic shock after myocardial infarction; further research is urgently needed to investigate the underlying mechanisms
- Further research is needed to better understand the observed sex differences in the transplantation field

*Takotsubo syndrome*

- International research collaborations with access to large registries should be established to improve diagnosis and treatment of women with takotsubo syndrome
- Clinicians should be equipped to recognise, identify, and treat serious complications and outcomes of takotsubo syndrome

*Peripartum cardiomyopathy*

- Large-scale multicentre prospective registries and randomised controlled trials are warranted to examine the benefit of standard heart failure treatments as well as the role of emerging therapies in women with peripartum cardiomyopathy
- A global collaboration between specialised centres is crucial to investigate pathophysiology, prognosis, diagnosis, and treatment

**Arrhythmia**

*Ventricular tachyarrhythmia and sudden cardiac death*

- Comprehensive global data collection to identify accurate sudden cardiac death rates in women is needed
- Women are more likely to have sudden cardiac arrest at home and lower likelihood of bystander resuscitation even in public places than men; awareness campaigns are warranted and resuscitation programmes need to be expanded to train the community to recognise and respond to sudden cardiac death
- The true benefit of implantable cardioverter-defibrillator therapy in women is not well known and needs to be investigated

*Atrial fibrillation*

- Atrial fibrillation is an important underlying cause of stroke in women, yet many women are not diagnosed or treated
- Because women with atrial fibrillation present at an older age and with more comorbidities than men, dedicated studies in women are needed to develop treatment strategies for reducing the risk of stroke while minimising the risk of bleeding
- The under-representation of women in clinical trials for rhythm and rate control for atrial fibrillation as well as left atrial appendage occlusion devices needs to be addressed

(Continues on next page)

(Panel 2 continued from previous page)

**Vascular disease**

*Stroke*

- Women have poor stroke-related outcomes
- Early diagnosis and treatment of hypertension should be implemented across the globe to reduce mortality due to stroke in women
- Comprehensive data collection is needed to identify and address sex-related gaps in access to care and treatment
- Rehabilitation programmes tailored for women might reduce sex-related differences in functional limitations and quality of life after stroke

*Vascular dementia*

- Dementia is a growing global health change that affects considerably more women than men
- Preventive strategies that identify women at higher risk earlier in life and target modifiable metabolic risk factors might delay vascular dementia in women and should be emphasised

*Peripheral arterial disease*

- Peripheral arterial disease remains underdiagnosed and undertreated in women worldwide, but especially in low-income and middle-income countries
- Further efforts are needed to increase awareness about the high prevalence of peripheral arterial disease in women
- Allied health-care providers need to be involved in screening for peripheral arterial disease using easy, quick, and non-invasive tools such as ankle–brachial index measurements to increase the probability of establishing a diagnosis and ensure patient referral

**Valvular heart disease**

- Evaluation of women with calcific aortic stenosis across racial and ethnic populations should be provided, with prompt treatment according to guideline recommendations for symptomatic and severe aortic stenosis
- Sex-related disparities in diagnosis and treatment should be investigated and avoided to reduce morbidity and mortality for women with mitral valve disease
- Transcatheter mitral valve replacement might be a treatment option in women with mitral valve calcification who are not deemed surgical candidates, although further clinical trials are needed to define the best treatment strategy

**Cardiovascular disease and pregnancy**

- Cardiovascular disease is a major contributor to late maternal death worldwide
- Late maternal death is not well documented and is therefore a neglected issue
- Global estimates of access to surgery and treatment of congenital heart disease in women are missing and few data exist on pregnancy outcomes in women with uncorrected congenital heart disease; studies and registries addressing these knowledge gaps are urgently needed
- Cardio-obstetrics is an emerging multidisciplinary team approach and crucial for optimal care for women with cardiovascular disease during pregnancy

**Rheumatic heart disease**

- Prevalence of rheumatic heart disease remains high in some regions of the world, and young women of childbearing age are disproportionately affected
- Multidisciplinary cooperation combined with appropriate preconception counselling and antenatal care is crucial to reduce complications from rheumatic heart disease in pregnancy
- It is essential to raise awareness about, and create political incentives to address, rheumatic heart disease and its implications as part of an integrated rheumatic heart disease prevention and control programme that targets women in low-income and middle-income countries affected by this disease

**Cardiovascular disease and cancer**

- Further studies are needed to improve risk assessment, optimise screening and surveillance, identify preventive measures, and investigate treatment options for cardiovascular disease associated with cancer treatments
- This Commission endorses the interdisciplinary field of cardio-oncology as a crucial resource in reducing cardiovascular disease among female cancer survivors

for coronary angiography and found that 547 (62%) of 883 had no obstructive coronary artery disease. Even in patients enrolled in the ISCHEMIA trial,[186] who all had suspected stable ischaemic heart disease and moderate or severe ischemia on stress imaging testing, the proportion with non-obstructive coronary artery disease based on coronary CT angiography findings was 353 (34·4%) of 1022 women (compared with 378 [11·3%] of 3353 men).

INOCA is not a benign condition; it is associated with increased risk for major adverse cardiovascular events compared with a reference population without ischaemic heart disease[187] and prompt diagnosis and treatment are therefore important. Diagnostic approaches based on detecting coronary stenosis often fail in women (because women more often than men have ischaemia with no or non-obstructive coronary artery disease), which contributes to delayed diagnosis or misdiagnosis. If coronary stenosis is not detected and INOCA is not diagnosed, many women are mistakenly presumed to have no heart disease and are offered no specific management, even though they might be at increased risk of adverse cardiac events.

Although the pathophysiology of angina symptoms in INOCA remains poorly understood, it has been proposed that coronary microvascular dysfunction, or epicardial vessel spasm, or both, have important roles.[188,189] Although

epicardial vessel spasm is more common in men than in women,[190] women represent up to 70% of patients with coronary microvascular dysfunction.[191] In coronary microvascular dysfunction, structural remodelling of the microvasculature, or vasomotor disorders affecting the coronary arterioles, or both, can lead to signs and symptoms of ischaemia (microvascular angina) owing to fixed reduced microcirculatory conductance, or dynamic arteriolar obstruction, or both.[189,192] The multiple underlying mechanisms of coronary microvascular dysfunction and their relative contributions to angina symptoms are still unclear and need further investigation.[184,193–196]

Coronary microvascular dysfunction can be detected via invasive or non-invasive testing.[184] Diagnostic criteria have been proposed[192,197] but there is too little evidence to make strong guideline recommendations or to standardise diagnosis.[184] Similarly, management strategies for INOCA are not well defined, mostly because there is insufficient evidence about treatments to improve coronary microvascular dysfunction. In the CorMicA trial[198] (151 patients, 74% women) stratified medical therapy (guided by measurements taken at invasive coronary testing) improved angina symptoms and quality of life in patients with no obstructive coronary artery disease compared with guideline-directed medical therapy and antianginal therapies according to the preference of the treating cardiologist. In addition to important lifestyle changes, such as cardiovascular risk factor modification (eg, weight loss and stress management),[189,194] potential medical therapies for coronary microvascular dysfunction include β blockers, short-acting nitrates, calcium antagonists, and angiotensin-converting enzyme inhibitors for symptom relief.[194,199] Aggressive modification of risk factors and treatment with aspirin and statins should be pursued in patients with non-obstructive coronary artery disease, but can also be considered in patients with angiographically normal coronary arteries and diagnosed coronary microvascular dysfunction, because of the high prevalence of atherosclerotic plaque found by coronary intravascular ultrasound studies in these patients.[194,199–201] Newer anti-ischaemic therapies (eg, ivabradine or ranolazine), anti-inflammatory medications, or proprotein convertase subtilisin/kexin type 9 inhibitors have not yet been investigated in women with coronary microvascular dysfunction, but might also represent treatment options.

Further research is urgently needed to build an evidence base for robust guidelines on diagnosis and treatment, and to better understand the pathophysiological mechanisms that predispose women to coronary microvascular dysfunction. For now, proposed diagnostic algorithms and a simplified classification of the clinical spectrum of coronary microvascular dysfunction, considering the severity of atherosclerosis (none or non-obstructive) and associated cardiovascular risk factors, might help to accurately identify and appropriately treat INOCA in women.[188,189,194]

This Commission has identified gaps in knowledge for the prevalence, diagnosis, treatment, and outcomes of INOCA in women, and recommends that societies and stakeholders support and fund further research in this area.

### *Myocardial infarction in the absence of obstructive coronary artery disease*

Although obstructive coronary artery disease with plaque rupture remains the predominant cause of myocardial infarction, an analysis of 27 large clinical trials and registries reported an overall prevalence of 6–15% of patients with myocardial infarction with no evidence of obstructive coronary artery disease.[202,203] The term myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) represents a condition that is caused by coronary mechanisms (eg, coronary artery dissection, coronary spasm, and coronary emboli), or is mimicked by myocardial disorders (eg, myocarditis, takotsubo syndrome, and other cardiomyopathies) or non-cardiac conditions (eg, pulmonary embolism).[204,205] The most recent diagnostic criteria incorporate the Fourth Universal Definition of Myocardial Infarction and exclude myocarditis and takotsubo syndrome from the final diagnosis of MINOCA.[206,207]

MINOCA is more common in women than men (10·5% *vs* 3·4%; p<0·0001), although outcomes are similar for both sexes.[208] Studies suggest better outcomes for patients with MINOCA than for patients who have acute myocardial infarction with obstructive coronary artery disease.[202,208,209] By contrast, one study found that major adverse cardiovascular events were similar in patients with MINOCA and patients with single-vessel or double-vessel coronary artery disease, although these findings were limited by a low study follow-up rate and small sample size.[210] Patients with MINOCA are at considerable risk of non-cardiac mortality.[211,212] Furthermore, approximately 25% of patients with MINOCA have ongoing angina, which according to registry data was equivalent to the prevalence in patients with acute myocardial infarction and obstructive coronary artery disease.[213] Of note, in this study, depression and self-reported avoidance of care because of cost were independently associated with angina in patients without obstructive coronary artery disease.[213] Strategies are urgently needed to raise awareness about the prognostic implications of accurate diagnosis and treatment of MINOCA, and the importance of continued patient counselling and care.

A working diagnosis of MINOCA should only be considered in those patients with a definite acute myocardial infarction, non-obstructive disease on coronary angiography, and no other underlying clinical entity resulting in myocardial injury without ischaemia.[207] Different diagnostic algorithms have been proposed, with cardiac MRI being considered an important investigational tool to exclude myocarditis, takotsubo syndrome, and other cardiomyopathies.[206,207] In the

absence of advanced imaging, diagnosis is typically made on clinical grounds.[207] Other investigations include provocative spasm testing, screening for thrombophilia disorders, and intravascular ultrasound if other diagnoses are ruled out. In a prospective observational study to investigate underlying causes of MINOCA in women, 301 women with a clinical diagnosis of myocardial infarction were enrolled, and MINOCA was diagnosed in 170 (56%). If invasive coronary angiography revealed less than 50% stenosis in all major arteries, the study protocol mandated doing multi-vessel optical coherence tomography followed by cardiac MRI. An ischaemic cause was identified in 63·8% of women, a non-ischaemic cause in 20·7%, and no mechanism was identified in 15·5%.[203]

The AHA scientific statement on MINOCA acknowledged the difficulty of identifying and tracking patients with MINOCA in the absence of a specific diagnostic code.[207] An International Classification of Diseases, 10th Revision MINOCA-specific code would not only facilitate research but also help hospitals to pursue higher amounts of reimbursement for additional diagnostic studies in this patient population.[207] Randomised controlled trials to investigate treatment options for secondary prevention in patients after MINOCA are needed urgently.

In women presenting with MINOCA, understanding the mechanisms of the underlying disease is essential in providing therapeutic options. Consideration of non-atherosclerotic causes of myocardial infarction is key to improving health outcomes of women globally.

*Spontaneous coronary artery dissection*

Spontaneous coronary artery dissection is a comparatively rare cause of myocardial infarction that represents 1–4% of all acute coronary syndromes,[214,215] but is increasingly recognised as an important cause of acute myocardial infarction in women younger than 50 years.[216] The true prevalence is uncertain because it is often underdiagnosed, and its clinical presentation ranges from mild chest pain to sudden cardiac death. Spontaneous coronary artery dissection is defined as a non-traumatic, non-iatrogenic, and non-atherosclerotic separation of the coronary artery wall, either by spontaneous intimal rupture or by rupture of vasa vasorum within the vessel wall.[217] This rupture results in the accumulation of intramural haematoma in the false lumen that can compress the true lumen, causing myocardial ischaemia or infarction. Studies have reported spontaneous coronary artery dissection as the cause of myocardial infarction in 25–35% of women younger than 50 years, and up to approximately 25% of women younger than 60 years.[218–220] Spontaneous coronary artery dissection is also the most common cause (up to 43%) of myocardial infarction associated with pregnancy, primarily occurring in the third trimester or post partum.[221] Conventional cardiovascular risk factors are absent for many patients with spontaneous coronary artery dissection. Underlying disorders and factors that could predispose women to spontaneous coronary artery dissection include fibromuscular dysplasia (50–86%),[222–224] connective tissue disorders (5%), systemic inflammatory diseases (5–12%), hormonal therapy use (eg, oestrogen, progesterone, gonadotrophin, clomifene, or fertility treatment), and multiple previous pregnancies.[225–227] Conditions that increase intracoronary shear stress, such as physical and emotional triggers, might precipitate spontaneous coronary artery dissection.[228]

Spontaneous coronary dissection can be missed on coronary angiography, and intravascular imaging is an important diagnostic tool. Assuming timely evaluation via coronary angiography and accurate diagnosis, patients with spontaneous coronary artery dissection generally do well with conservative management. Revascularisation with percutaneous coronary intervention or coronary artery bypass surgery is recommended if high-risk features are present (ie, left main dissection, ongoing ischaemia, haemodynamic instability, or sustained ventricular arrhythmias).

The risk of recurrent events after spontaneous coronary artery dissection is substantial, as shown by the Canadian Spontaneous Coronary Artery Dissection cohort study.[228] The study showed that women with spontaneous coronary artery dissection during the post-partum period have a 2·8 times increased risk of in-hospital major adverse events, whereas women with connective tissue disorder have an 8·7 times increased risk for major adverse cardiovascular events within 30 days of admission to hospital.[228] To minimise risk of recurrent events after spontaneous coronary artery dissection, cardiac rehabilitation is recommended, preferably with a modified protocol avoiding heavy isometric exercise and intense aerobic activities.[229] Other strategies to prevent recurrent events include minimising emotional triggers, avoiding hormonal therapy (ie, oestrogen, progesterone, and β-human chorionic gonadotropin), and avoiding future pregnancies.[214] The EURObservational Research Programme study[230] has been designed to assess the optimal medical therapies and interventional strategies for spontaneous coronary artery dissection, and should increase knowledge about this condition.

Spontaneous coronary artery dissection is an important and underdiagnosed cause of acute coronary syndromes in women. Diagnosis is usually with intravascular imaging, and treatment is based on a conservative approach at first. Women with this condition are at high risk of recurrent ischaemic events and require close follow-up. This Commission supports further research and education on the diagnosis and treatment of spontaneous coronary artery dissection.

*STEMI*

STEMI in women is usually caused by a ruptured plaque and thrombus formation, and is the most acute

manifestation of coronary heart disease. In STEMI, differences related to sex and gender are especially pronounced, and include (but are not restricted to) the following: women present later than men after STEMI, have a longer time from presentation to definitive therapy, and are less often treated with guideline-recommended therapies.

The gold standard STEMI treatment is primary percutaneous coronary intervention, if the procedure can be done within 120 min of first medical contact at a well equipped centre with experienced interventional cardiologists and skilled support staff.[204,231] Several factors are barriers to timely presentation and appropriate treatment. Studies suggest that women are more likely to delay help-seeking and presentation than men,[232,233] which could be attributable to a low awareness of personal risk, misinterpretation of symptoms, barriers to accessing care, fear, or embarrassment.[234,235] At least one European study showed that emergency ambulance services place a lower priority on transporting women who present with possible STEMI than men.[236] Although the reasons for this finding are unclear, women with STEMI commonly present with symptoms other than chest pain (including pain in the jaw, neck, and shoulder, or fatigue and nausea), which might be a contributing factor.[237] Furthermore, cardiovascular risk is often underestimated in women, who more often have missed diagnosis of STEMI prehospital than men, which then necessitates interhospital transfer to a facility capable of doing percutaneous coronary intervention and delayed reperfusion.[238]

Once the diagnosis has been made, women are less likely than men to receive acute reperfusion therapy[239,240] and evidence-based pharmacological treatment, including dual antiplatelet therapy, statins, and β blockers.[239] In addition to differences in risk profile (including older age, higher prevalence of risk factors, and comorbidities), these sex-related gaps in treatment could contribute to the higher in-hospital mortality in women than in men. A nationwide cohort study in both England and Wales found that an estimated 8243 (95% CI 8111–8375) women's deaths could have been prevented during the study period, if they had received treatment (as defined by the ESC Acute Cardiovascular Care Association quality indicators) similar to that received by men.[241] Other studies showed that comprehensive STEMI protocols can help to reduce sex disparities in quality of care and outcomes.[242,243] Although many studies[239,242,244–246] suggest that the sex-related mortality gap in STEMI is because of differences in baseline characteristics and treatment disparities, substantial evidence suggests that additional factors, such as biological sex differences, contribute to worse outcomes in women than in men.[247,248] An analysis of the International Survey of Acute Coronary Syndromes in Transitional Countries registry found that higher 30-day mortality for women than men with STEMI persisted after adjustment for clinical characteristics, angiographic disease severity, primary percutaneous coronary intervention, and medications used at admission, driven by the excess risk in women aged 60 years or younger.[247] Similar findings of worse outcomes in women than in men, even after multivariate adjustment, were documented by other studies,[248] with particularly poor outcomes in women younger than 50 years in one study,[249] but not in another.[250] The mechanisms causing excess mortality in women compared with men are not clear, but could partly be explained by the findings of another analysis showing that prehospital delay of more than 1 h was associated with poorer 30-day survival in women than in men.[251] These findings suggest that women are more susceptible to prolonged untreated ischaemia, and might explain the higher risk of heart failure and cardiogenic shock after STEMI in women than in men.[249,252] A pooled patient-level analysis showed longer reperfusion delay, higher mortality, and a higher risk of heart failure hospitalisation in women than men; however, it found no evidence of an interaction between sex and infarct size or left ventricular ejection fraction, regarding risk of death or heart failure hospitalisation.[253] There is an urgent need to investigate this matter further and to reduce the time lag between symptom onset and hospital presentation in women with STEMI.

Although overall STEMI reperfusion rates have increased over the past 2 decades and remarkable systems of care have been established in most high-income countries, substantial challenges persist in LMICs, and in rural and isolated communities, which might especially affect women.[254]

Initiatives to raise awareness among both women and health-care providers about STEMI in women have contributed to a reduction in sex-related disparities in STEMI care, and should be continued to further mitigate adverse outcomes in women. The major goals of STEMI care in women include: reducing the time from symptom onset to seeking and receiving treatment; providing guideline-recommended treatment; and improving systems of care in underserved, rural, and isolated communities. Further research is needed to investigate biological sex differences as underlying reasons for the sex-related mortality gap in STEMI.

### *Young women and acute myocardial infarction*

Worrying trends have been seen in young women during recent years; data from the USA and Europe documented an increase in hospital admissions with acute coronary syndrome in women younger than 55 years (21% in 1995–99 *vs* 31% in 2010–14; p<0·0001), with a 3·6% mean annual increase in STEMI between 2004 and 2014.[4,5] Indeed, studies point to gaps in risk perception and discussion among young women. The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients study[255] showed that women were less likely than men to be told they were at risk for heart disease or

to have a health-care provider discuss risk modification with them before their index event.

Many studies have shown excess mortality and higher risk for adverse outcomes in young women with myocardial infarction compared with similarly aged men. An early study found that in patients younger than 50 years, the mortality rate during hospitalisation because of myocardial infarction was more than twice as high for women as it was for men.[249] This difference in mortality rates decreased with increasing age, and was no longer significant after the age of 74 years. Limitations of this study include the fact that it predates the era of routine invasive management, and also it did not differentiate between STEMI and non-ST-segment elevation myocardial infarction. STEMI and non-ST-segment elevation acute coronary syndrome differ considerably in treatment strategies and outcomes, so it might be useful to analyse them separately. Although prompt revascularisation is key for the improvement of outcomes in STEMI, in non-ST-segment elevation acute coronary syndrome, treatment strategy decisions are dependent on clinical presentation and risk assessment. Although studies found that women with non-ST segment acute coronary syndrome generally have similar or decreased adjusted mortality risk when compared with men,[256–258] an analysis investigating the relationship between age, sex, and type of myocardial infarction found excess mortality in young women regardless of the type of myocardial infarction, and a survival benefit for older women with non-ST-segment elevation myocardial infarction compared with their male counterparts.[259] Studies that only included patients with ST-elevation myocardial infarction confirmed an excess mortality risk in women younger than 60 years[247] and 55[260] years. A high prevalence of diabetes, obesity, and other risk factors has been documented and might have a pathophysiological role in the occurrence of myocardial infarction in young women and in the associated excess mortality risk.[261] A small study of young (≤61 years) patients hospitalised within the previous 8 months with myocardial infarction found that compared with men, women had lower income and education, and higher amounts of depression, post-traumatic stress disorder, and perceived stress.[262] The women in this study population had twice the risk of developing mental stress-induced myocardial ischaemia compared with men. An aspect worth further investigation was derived from a prospective observational cohort study in young patients hospitalised for acute coronary syndrome. This study suggested that roles and personality traits traditionally associated with female gender were predictors of increased risk of recurrent major adverse cardiac events, independent of patient sex.[263] Further research is urgently needed to investigate these and other sex and gender-related factors to improve cardiovascular disease risk assessment, prevention, and treatment in young women. Education of health-care providers and of women themselves is needed to tackle the general underestimation of cardiovascular risk in women, especially in young women. Early detection and treatment of established and emerging cardiovascular risk factors is key to addressing the increasing burden of cardiovascular disease in young women.

## Heart failure

### *Chronic heart failure*

Even though the overall incidence of heart failure is similar for women and men, pronounced sex differences are seen in specific heart failure phenotypes (eg, heart failure with preserved ejection fraction *vs* heart failure with reduced ejection fraction; ischaemic *vs* non-ischaemic cardiomyopathy; takotsubo syndrome; and peripartum cardiomyopathy).[264,265] Women are strikingly over-represented among patients with heart failure with preserved ejection fraction, especially in the oldest age categories.[266,267] By contrast, men are at higher risk of heart failure with reduced ejection fraction.[268] In the USA, women outnumber men by around 2:1 among patients with incident heart failure with preserved ejection fraction. Epidemiological data for 2762 incident heart failure cases occurring between 2000 and 2010 showed an increase in the overall proportion of heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction, from 48% in 2000–03 to 52% in 2008–10.[267] At the same time, the incidence of heart failure with reduced ejection fraction decreased more sharply than it did for heart failure with preserved ejection fraction in women (–61% in 2000 *vs* –27% in 2010), but not in men (–29% in 2000 *vs* –27% in 2010).[267] A population-based study from the UK investigating heart failure outcomes between 1998 and 2017 saw worrying trends in women, with faster increases in rates of admission to hospital because of heart failure and slower decreases in mortality than in men.[269] The study authors hypothesised that these patterns probably reflected worsening severity of heart failure or an absence of effective therapies for heart failure in women compared with men, because of the increased prevalence of heart failure with preserved ejection fraction.[269] Although there are multiple drug and device therapies for the treatment of heart failure with reduced ejection fraction, there are none approved for heart failure with preserved ejection fraction.

Several risk factors are prevalent among women with heart failure, including hypertension, which triples heart failure risk.[270] Studies found that the excess risk of heart failure associated with diabetes is greater in women than in men,[271] and obesity is a stronger risk factor for heart failure with preserved ejection fraction than for heart failure with reduced ejection fraction, especially in women, and the risk of heart failure with preserved ejection fraction associated with hypertension and obesity is more pronounced in women who are African American than are White.[272,273]

Morbidity for heart failure is high, mainly owing to a high symptom burden and frequent hospitalisations, and 5-year survival was 44% according to a UK analysis published in 2019.[274] Women with heart failure were also found to have a more impaired quality of life, or higher incidence of depression, or both, compared with men.[275,276] Although the prognosis of patients with heart failure with reduced ejection fraction has improved over time, the alarming fact remains that up to now no treatments have been found to improve the prognosis of patients with heart failure with preserved ejection fraction.

*Pharmacotherapy for heart failure*

Many therapies have been investigated and proven to be effective in patients with heart failure with reduced ejection fraction. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin form the cornerstone of heart failure with reduced ejection fraction medical therapies.[277,278] In addition, SGLT2 inhibitors reduce the risk of worsening heart failure or death from cardiovascular causes.[279,280] The efficacy of these drugs was shown in large randomised controlled trials, in which women were largely underrepresented (20–25% of the participants). Although analyses of pooled patient-level data have found consistent benefits of various heart failure therapies for women and men,[281,282] large, statistically powered clinical trials are needed to confirm benefits in both sexes for key outcomes. Sex differences in pharmacokinetics and pharmacodynamics are currently not considered in the guidelines, which recommend up-titration to target doses that are similar in both men and women. However, in some studies, β blockers showed greater pharmacodynamic effects in women, resulting in a larger decrease in heart rate and blood pressure, compared with men on similar doses.[283,284] The optimal doses for heart failure therapies in men and women with heart failure with reduced ejection fraction were studied in the BIOlogy Study to Tailored Treatment in Chronic Heart Failure,[285] a prospective, multinational, European heart failure cohort, and the Asian Sudden Cardiac Death in Heart Failure registry,[285] a prospective multinational Asian heart failure cohort. In both the European and the Asian cohorts, women with heart failure with reduced ejection fraction had the lowest risk of death or hospitalisation for heart failure if taking β blockers plus either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, all at half the guideline-recommended doses, with no further decrease in risk with taking the full doses.[285] These findings could have important implications for sex-specific target doses in heart failure and should be validated in prospective, sex-specific dose-finding studies.

By contrast, therapeutic approaches for heart failure with preserved ejection fraction are restricted to treating underlying comorbidities, such as hypertension. An important finding published in 2020 comes from the sub-analysis on sex differences in the PARAGON-HF trial,[286] which compared sacubitril–valsartan versus valsartan in patients with heart failure with preserved ejection fraction. In women, sacubitril–valsartan was more effective than valsartan in reducing the composite endpoint of heart failure hospitalisation or cardiovascular death, but in men no difference between treatment groups was found, suggesting a significant sex–treatment interaction. Of note, the beneficial effect in women was driven by a reduction in heart failure hospitalisation associated with sacubitril–valsartan. The effect of treatments for heart failure with preserved ejection fraction might differ between women and men and should be the target of large prospective investigations.

The overwhelming increase in the incidence of heart failure with preserved ejection fraction in women, which has few therapeutic options, underlines the importance of further research in this area and calls for a dedicated all-female study on the treatment with sacubitril–valsartan.

*Cardiac resynchronisation therapy*

Implantation of biventricular pacemakers, known as cardiac resynchronisation therapy, has the potential to improve symptoms, morbidity, and mortality in carefully selected patients with heart failure.[277] Sex-stratified evaluation of cardiac resynchronisation therapy has repeatedly been suggested to be at least similarly or even more beneficial in women than in men.[287,288] For instance, the MADIT-CRT trial[289,290] found that cardiac resynchronisation therapy had greater benefits in women than in men regarding heart failure symptoms and death, and found evidence of reverse left ventricular remodelling. Furthermore, women respond to cardiac resynchronisation therapy at QRS durations that are shorter than in men.[291,292] This benefit might be associated with smaller body and heart size in women.

According to an analysis from the Swedish Heart Failure Registry, cardiac resynchronisation therapy was similarly underused in both women and men.[293] By contrast, an analysis of data from the AHA's Get With The Guidelines—Heart Failure quality initiative programme found that eligible women were less likely to receive a cardiac resynchronisation therapy compared with their male counterparts in recent study periods (2008–11 and 2012–14).[294]

Cardiac resynchronisation therapy is known to reduce morbidity and mortality in selected patients with heart failure and might be offered to women less often than to men, although evidence suggests it provides more beneficial effects in women than in men.[290,294] Adequately powered randomised controlled trials are needed to evaluate sex-specific outcomes associated with resynchronisation therapy to improve outcomes in women with heart failure.

For more on the **AHA's Get With The Guidelines—Heart Failure programme** see https://www.heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-heart-failure

*Acute heart failure and cardiogenic shock*

Cardiogenic shock is the leading cause of death in patients with acute myocardial infarction. Studies have found that women are more susceptible than men to cardiogenic shock after acute coronary syndrome.[249,252] Women are also more likely than men to have mechanical complications such as ventricular septal rupture (7·7% *vs* 3·5%, p=0·003) and severe mitral regurgitation (11·4% *vs* 7·1%, p=0·014),[295] which might also contribute to the increased risk of cardiogenic shock.

Early revascularisation has been shown to significantly reduce short-term mortality due to cardiogenic shock in both women and men.[295,296] An analysis of data from the Should We Emergently Revascularise Occluded Coronaries for Cardiogenic Shock registry, showed no significant difference between women and men for in-hospital mortality (63·4% *vs* 59·3%, OR 1·16, 95% CI 0·87–1·55; p=0·25) in patients presenting with cardiogenic shock in the setting of acute myocardial infarction, after adjustment for differences in patient demographics and treatment approaches.[295] Conversely, a report from the International Survey of Acute Coronary Syndromes in Transitional Countries registry[297] published in 2019 found that compared with men, women were more susceptible to de-novo heart failure after STEMI and remained at higher risk of 30-day mortality, even if analysis was restricted to patients undergoing primary percutaneous coronary intervention. The report authors concluded that women's increased risk of developing de-novo heart failure and the associated worse survival compared with men were key features that explain the sex-related mortality gap after STEMI. Conversely, the absence of a sex-related mortality gap in non-ST-segment elevation acute coronary syndrome might be related to the generally lower occurrence of cardiogenic shock and heart failure in non-ST-elevation acute coronary syndrome than in STEMI, mostly owing to low occurrence of cardiogenic shock in patients with unstable angina.[297–299]

Data suggest that the early percutaneous placement of a mechanical ventricular support device in acute myocardial infarction complicated by cardiogenic shock might improve survival in women compared with men. The Impella 2·5 (Abiomed, Danvers, MA, USA) is a miniaturised, catheter-based, intravascular blood pump that supports the circulatory system. An analysis of data from the Catheter-based Ventricular Assist Device Registry (180 patients, 27·2% women) reported that the survival benefit of implanting an Impella 2·5 pre versus post percutaneous coronary intervention was greater in women than in men, but the interaction between patient sex and timing of implantation was not significant (p=0·07).[300] Women were also as likely as men to survive to hospital discharge despite being older (71·0 [SD 12·8] years *vs* 63·8 [13·0]; p=0·001) and having higher Society of Thoracic Surgeons mortality scores (27·9 [17·0] *vs* 20·8 [16·8]; p=0·01). No differences in bleeding rates were seen between the sexes.[300] These data suggest a potential benefit of early haemodynamic stabilisation in women, but this warrants further investigation and underscores the need for increasing the representation of women in clinical studies addressing the management of cardiogenic shock.

*Takotsubo syndrome*

Takotsubo syndrome is a syndrome of acute and reversible left ventricular systolic dysfunction. Patients usually present with chest pain and electrocardiographic changes characteristic of acute coronary syndrome (including ST elevation on electrocardiogram), but without angiographically obstructive coronary artery disease, and characteristically have reversible left ventricle apical ballooning. The global improvements in triaging and rapid transportation of patients with symptoms of acute coronary syndrome to the catheter laboratory have led to increasing recognition of the phenomenon, which is estimated to account for 1–2% of all patients,[301] but up to 7·5% of female patients,[302,303] with acute coronary syndrome presentation. Takotsubo syndrome occurs almost exclusively in women and is often triggered by emotional or physical stress. More than 90% of reported cases occur in postmenopausal women who are aged 58–75 years.[304,305] Enhanced sympathetic activity is thought to be crucial to Takotsubo syndrome with elevated concentrations of catecholamines documented in patients with the condition.[304,305]

Diagnosis typically requires echocardiogram, troponin concentration, coronary angiography, and serial assessment of systolic left ventricular function. Cardiovascular MRI, if available, can also be helpful.[306] Despite the rapid recovery of left ventricular function, the incidence of complications is substantial. In the International Takotsubo Registry,[307] 21·8% of patients had a combined endpoint of serious in-hospital complications (ie, death, ventricular tachycardia, ventricular thrombus, or ventricular rupture) at rates equal to or higher than most patients with acute coronary syndrome. Cardiac arrest has been estimated to occur in 5·9% of patients with takotsubo syndrome;[308] mortality from any cause is reported at 5·6% per patient-year, and major adverse cardiovascular events are reported at 9·9% per patient-year.[309] Patients are typically managed as per acute coronary syndrome pathways, with supportive care for haemodynamic and electrical instability, but with minimisation of catecholamines and consideration of intravenous levosimendan or mechanical support.[306,310,311] The use of angiotensin-converting enzyme inhibitors has been associated with improved survival at 1 year, with no associated benefit seen with the use of β blockers.[309]

*Peripartum cardiomyopathy*

Peripartum cardiomyopathy is defined as an idiopathic pregnancy-related left ventricular dysfunction, diagnosed

at the end of pregnancy or in the months after delivery, without any other identifiable cause.[312] Peripartum cardiomyopathy is a transglobal occurrence, although incidence varies by geography and incidence data are incomplete. A review of the worldwide incidence of peripartum cardiomyopathy found the highest incidence in Africa (from 1:100 to 1:1000 births), followed by Haiti (1:300), and Pakistan (1:840).[313,314] Estimated incidence in the USA is reported to be between 1:1000 and 1:4000 births,[315,316] with the highest incidence among African American women (>40%) and the lowest among Hispanic women.[316] Incidence appears to be rising, possibly because of increased awareness and diagnosis, rising maternal age, changing demographics, and rising numbers of multiple gestation pregnancies.[316]

The precise mechanisms resulting in peripartum cardiomyopathy remain undefined, and further research on the pathophysiology of this disease is urgently needed.

Although patients typically present with symptoms and signs of heart failure, there is an overlap with symptoms of normal pregnancy; clinicians might therefore fail to recognise peripartum cardiomyopathy, or diagnose the condition late in the clinical course. The potential complications and consequences of missed or late diagnosis include cardiogenic shock, thromboembolism, and arrhythmias.[317]

Few studies have specifically focused on management approaches in peripartum cardiomyopathy; therefore, management recommendations are based on expert consensus opinion and extrapolated from other forms of heart failure. Although many heart failure therapies are contraindicated during pregnancy, most heart failure agents can be used post partum according to standard heart failure guideline recommendations.[277] On the basis of sparse data suggesting beneficial effects of bromocriptin,[318–320] the ESC gives a weak recommendation (class IIb, level of evidence B) for considering bromocriptine treatment,[319] although in the USA, bromocriptine is regarded as an experimental treatment.[321] Data from adequately powered randomised controlled trials are urgently needed to evaluate the risk and benefit of this medication. Inotropic support (eg, dopamine, dobutamine, levosimendan, or milrinone) could be considered in patients with severe hypotension or signs of cardiogenic shock. However, in a small study of 27 patients, seven participants who were treated with dobutamine had a worse outcome than patients who did not receive dobutamine, and therefore it cannot be excluded that catecholamines might aggravate myocardial damage.[322] Temporary circulatory support (with intra-aortic balloon pump, Impella, or extracorporeal membrane oxygenation) has been used successfully in patients with peripartum cardiomyopathy and cardiogenic shock, and should be considered early in patients with haemodynamic instability despite inotropic support.[321,323]

In patients with severely reduced left ventricular ejection fraction, New York Heart Association classification class III or IV patients are discouraged from breastfeeding, to avoid high metabolic demand and enable early optimal heart failure treatment.[318,324] Additionally, future pregnancies are precluded because of the increased morbidity and mortality risk with subsequent pregnancies, especially in women with persistent left ventricular dysfunction.[325–327]

Prospective data suggest that left ventricular function typically improves within 6 months to 5 years for the majority of peripartum cardiomyopathy patients on standard medical therapy, although a substantial proportion of women can have major events or persistent severe cardiomyopathy.[328] A systematic review and meta-analysis published in 2019 reported mortality as high as 9% (14% in LMICs *vs* 4% in high-income countries).[329]

Peripartum cardiomyopathy is an important cause of maternal death that is under-recognised and seldom recorded as a cause of maternal death. An interdisciplinary approach to managing this condition is essential, and global collaboration between specialised centres is crucial to investigate pathophysiology, prognosis, diagnosis, and treatment.

### *Mechanical circulatory support devices*

In patients with severely symptomatic end-stage heart failure, mechanical circulatory support devices should be considered in both the acute and chronic setting as a bridge to transplantation, a bridge to recovery, or as destination therapy.[277,278] To now, the majority (approximately 80%) of these devices have been implanted in men, because a smaller body surface area in women is of concern and a suspected contributor to higher complication rates.[330] However, techniques are improving, and devices are getting smaller than the earlier versions, and at least one analysis found that continuous-flow left ventricular assist devices were associated with similar survival rates for patients with a body surface area equal to or lower than 1·5 m² (68% women) and patients with an area higher than 1·5 m² (20% women).[331] Data from the same registry found that treatment with a continuous-flow left ventricular assist device showed a better survival benefit in women with peripartum cardiomyopathy than in women with other causes of advanced heart failure.[332] However, the survival benefit was likely to be related to younger age and lower rates of comorbidities in the study group with peripartum cardiomyopathy.[332]

Further research and robust outcomes data on mechanical circulatory support devices for various clinical indications in women are urgently needed.

### *Heart transplantation*

Heart transplantation is an option for patients with end-stage heart failure fulfilling specific eligibility criteria.[277] Although no randomised controlled trials exist, there is consensus that heart transplantation, when eligibility criteria are met, markedly increases survival, exercise capacity, and quality of life compared with conventional treatment.[277] However, this therapy

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requires a multidisciplinary team in centres of excellence and an ample supply of organ donations, which are not widely available, especially in LMICs in which these resources are desperately needed. Importantly, women are far less likely than men to be considered eligible for transplantation and represent only 25% of heart transplantations.[333] Post-transplantation data show that women have a slightly better prognosis than men, with a median survival of 12·2 years, compared with 11·4 years for men.[333] Although sex-matched transplants are associated with better outcomes for both women and men, and sex-mismatched transplants and oversizing or undersizing of the transplanted heart appear to be important prognostic factors, observed sex differences in the transplantation field are not yet fully understood.[333,334]

## Arrhythmia

### *Sex differences in electrophysiology*

Distinct electrophysiological parameters increase the risk of life-threatening arrhythmia in women. Cellular electrophysiological sex differences have been seen for the action potential sodium, calcium, and potassium currents, which affect both depolarisation and repolarisation. Many studies come from animal research, in which the ion currents affecting repolarisation have been fairly well established as showing sex differences. The causes of these differences are not well understood, although female ventricular myocytes are smaller and contract more slowly than male myocytes do.[335–338] Women are known to be at greater risk for sudden arrhythmic death in the heritable long QT2 syndrome (*KCNH2* gene),[339–341] and at higher risk for drug-related proarrhythmia from medications that block the delayed rectifier potassium current in the cardiomyocyte channel.[342] Such medications don't only include antiarrhythmic drugs, but also other cardiovascular and non-cardiovascular medications, such as medications used to treat depression and other mental illnesses, antimicrobials, antifungals, antihistamines, and opiate blockers (eg, methadone). Another example is hydroxychloroquine, which has widely been used in combination with azithromycin in the treatment of patients with COVID-19 during the early phase of the pandemic. Health-care providers might be unaware of these risks and might not consider drug–drug interactions, which could heighten the risk of QT prolongation and ventricular tachyarrhythmia, especially in women.[343,344]

### *Ventricular tachyarrhythmia and sudden cardiac death*

Sudden cardiac death is defined as a sudden collapse without spontaneous pulse or respirations, occurring within 1 h of a stable clinical status, and which is not due to non-cardiac causes. Sudden cardiac death is a major public health problem with wide global incidence, although sex-specific estimates vary depending on data sources. In the USA (in which estimates are limited by non-mandatory reporting, inadequate reporting, differences in definitions, and scant autopsy data[345]) there were an estimated 366 494 cases in 2016, with approximately 178 823 (48·8%) occurring in women.[264] The documented overall decline in the incidence of sudden cardiac deaths has been less pronounced among women than men.[346] An earlier study even documented an increase in sudden cardiac death in young women.[347] The potential years of life lost because of sudden cardiac death in women is higher than for any individual cancer in women or for other causes of death in women,[348] and sudden cardiac death contributes substantially to mortality in women with and without coronary artery disease.

Although coronary artery disease is the most common cause of sudden cardiac death,[349] sudden cardiac death appears to occur more often in women than in men, and in patients without obstructive coronary artery disease[350] or with a non-ischaemic cause,[351] making well established modifiable cardiovascular risk factors less sufficient predictors in women. Women have less ventricular tachycardia or ventricular fibrillation documented as the first rhythm identified (19·4% women *vs* 26·7% men), which reduces the likelihood of survival compared with men.[352] Data are inconsistent with regard to outcomes in women compared with men;[353] nevertheless, women are less likely to have sudden cardiac arrest that is witnessed by a bystander and are more likely to have a sudden cardiac arrest at home, reducing the potential for identifying and treating a shockable rhythm and contributing to poorer outcomes.[352,354] Even when out-of-hospital cardiac arrest is witnessed, bystander resuscitation is done less often in women than in men (69·2% *vs* 73·9%; p<0·001).[355]

Implantable cardioverter defibrillator therapy is indicated to prevent death from ventricular tachyarrhythmia. However, women have largely been under-represented in randomised clinical trials[356] that have identified appropriate candidates (16–29%), and subgroup analyses on sex differences were therefore limited by the small sample sizes. A meta-analysis of randomised controlled trials did not show any mortality benefit in women,[357] whereas analyses of observational and registry data found similar benefits in women and men treated with implantable cardioverter-defibrillator therapy for primary,[358] and primary or secondary, prevention of sudden cardiac death.[359] Another analysis from registry data showed that implantable cardioverter defibrillators were less likely to deliver appropriate therapies, and also had a greater risk of complications, in women than in men.[360] Robust data are urgently needed to evaluate the risk–benefit ratio of implantable cardioverter-defibrillator therapy in women. Currently women meeting criteria for indicated implantable cardioverter defibrillator therapy should be considered equally to men for these life-saving therapies,[361,362] although data suggest that eligible women are less likely to be referred for implantable cardioverter-defibrillator therapy than their male counterparts.[359]

### *Atrial fibrillation*

Atrial fibrillation is a global disease and the most commonly diagnosed cardiac arrhythmia, with prevalence increasing. Globally, it is estimated by GBD data[1] from the Institute for Health Metrics and Evaluation that 29·4 (95% UI 22·4–37·3) million women have atrial fibrillation; however, this is likely to be an underestimation.

Although atrial fibrillation incidence is higher among men than women, the estimated lifetime risk of atrial fibrillation is similar for both because of women's longer life expectancy. Lifetime atrial fibrillation risk for women in North America and Europe is 23·0% at age 40 years, and 22·2% at age 55 years.[363,364] Lifetime risk of atrial fibrillation for women in China was found to be 21·1% at age 55 years, which was higher than for men of the same age (16·7%).[365] Overall, women with atrial fibrillation are older than men, with the majority (74%) aged 70 years or older.

Structural properties such as atrial cardiomyocyte changes, fibrosis, mixed cardiomyocyte changes and fibrosis, or non-collagen infiltration can account for atrial myopathy and atrial fibrillation progression in women.[366] Other factors seen to affect the atrium include inflammation and primary atrial amyloid. The latter is known to be associated with age and female sex.[367] In an MRI study of 908 patients (34·8% women) with atrial fibrillation, both older age and female sex were independent predictors of atrial fibrosis, which has been shown to be associated with elevated stroke risk.[368] Globally, women with atrial fibrillation have higher prevalence of hypertension, valvular heart disease, and increased body-mass index than men. The consequences of atrial fibrillation include premature death, stroke, heart failure, and diminished quality of life. Studies found that morbidity and mortality associated with atrial fibrillation are higher in women compared with men, even after adjustment for baseline risk.[369,370] These shifts in atrial fibrillation epidemiology and population attributable risks warrant investigation as part of a strategy to reduce morbidity and mortality associated with atrial fibrillation in women.

### *Medication and catheter ablation for atrial fibrillation: rate and rhythm control*

Heart rate and rhythm control are pivotal to reducing symptoms related to atrial fibrillation and to preventing tachycardia-induced cardiomyopathy, although few studies have been powered to investigate sex-specific outcomes for these strategies. Subgroup analyses in the AFFIRM trial[371] investigated outcomes of rate versus rhythm control and reported no sex-specific differences in mortality between treatment with antiarrhythmic drugs and treatment with rate control drugs. During the past 15 years, catheter ablation with isolation of the pulmonary veins, with or without additional ablation strategies, has emerged as an alternative to antiarrhythmic drugs for the reduction of recurrent atrial fibrillation. For instance, the CASTLE-AF trial[372] showed that catheter ablation was associated with a reduction in all-cause and cardiovascular mortality when compared with standard medical therapy (rate or rhythm control). The sex-specific subgroup analysis on the primary endpoint of all-cause mortality or heart failure hospitalisation found no significant interaction between sex and randomised treatment assignment. Subsequently, the larger CABANA trial[373,374] did not show a reduction in all-cause mortality associated with catheter ablation compared with medical therapy (rate or rhythm control), but did show a significant reduction in the combined endpoint of death or cardiovascular hospitalisation, and for atrial fibrillation recurrence, associated with catheter ablation compared with medical therapy (rate or rhythm control), with no significant differences in treatment effects between women and men for all these outcomes. Of note, the prespecified per-protocol sensitivity analysis showed a significant reduction in all-cause mortality for patients who received ablation within 12 months of random allocation. Although no interaction between sex and treatment strategies were shown, the small sample sizes of the sex-specific subgroup analyses do not allow for any definitive conclusion with regards to the benefits of these therapies in women. The marked uptake overall in atrial fibrillation ablation has been much less pronounced in women, and women receive this treatment at a higher age compared with men.[375,376] Sex-specific research in this field is needed to provide the best possible care for women with atrial fibrillation.

### *Stroke prevention in atrial fibrillation*

It is well established that women with atrial fibrillation have a higher stroke risk than men do.[377,378] Analyses of registry data also suggest that strokes related to atrial fibrillation are more severe in women than they are in men.[379] As a result, stroke prediction, the use of risk calculators (eg, $CHA_2DS_2VAS_C$ score for prediction of stroke risk or the $SAMeRT_2R_2$ score for prediction of international normalised ratio control with a vitamin K antagonist), and the use of anticoagulants for stroke prevention are crucial.[380–382] Direct oral anticoagulants have a favourable risk–benefit profile compared with warfarin, and analyses have shown that direct oral anticoagulants have similar efficacy and safety in women and in men.[383] Nevertheless, direct oral anticoagulants need to be adjusted for renal insufficiency, which can contraindicate use of these agents in older women, who often have chronic kidney disease. Despite the availability of therapies with demonstrable efficacy and safety, globally women with atrial fibrillation are less likely to be prescribed oral anticoagulants than men.[384] As women with atrial fibrillation are older and have multiple comorbidities, they are also at risk of bleeding with oral anticoagulants (panel 3). Such characteristics lead to undertreatment of patients with atrial fibrillation, especially women, and expose them to risk of stroke.

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Left atrial appendage occlusion is considered an option for patients who cannot take warfarin safely and have a contraindication for direct oral anticoagulants. Several devices are available in North America and Europe, including the WATCHMAN (Boston Scientific, Marlborough, MA, USA), AMPLATZER (Abbott, Plymouth, MN, USA), and LARIAT (SentreHEART, Redwood City, CA, USA) devices. However, women are under-represented in left atrial appendage occlusion device studies.[385–388] Large randomised trials (eg, CATALYST [NCT04226547], CHAMPION-AF [NCT04394546] and OPTION [NCT03795298]) have been initiated to compare left atrial appendage occlusion versus non-vitamin K antagonist oral anticoagulants in patients with a standard risk of bleeding, and it will be pertinent to do sex-specific analyses in these studies to delineate benefits for women.

Atrial fibrillation is an important underlying cause of stroke in women, yet many women are not diagnosed or treated for atrial fibrillation. This disparity contributes to morbidity and mortality of women globally and should be addressed with large-scale studies. The Heartline study will investigate whether the use of new technology such as health apps on mobile devices is capable of reducing stroke risk by detecting atrial fibrillation earlier. The Heartline study plans to enrol large numbers of patients older than 65 years to further evaluate this important issue. The Apple heart study[389] showed the ability to include patients in a timely way in a large-scale study. This Commission endorses the use of technology-based diagnostic tools to reach out to an increasingly broad and inclusive population to identify atrial fibrillation and deploy treatment options for patients at risk for ischaemic stroke.

### *Panel 3*: Women and the increased risk of bleeding

Treatment of cardiovascular disease is often associated with the administration of antithrombotic, or anticoagulant therapies, or both. Examples include dual antiplatelet therapy after acute coronary syndrome, or stent implantation, or both, intravenous anticoagulation during interventional or surgical procedures for coronary artery or valvular heart disease, and oral anticoagulants for the prevention of stroke in atrial fibrillation or valvular thrombosis and thromboembolism after mechanical valve replacement. Higher risk of bleeding in women than men associated with these therapies has been reported throughout the literature. In addition, significant mortality risk has been associated with these bleeding events. Underlying reasons for the increased risk of bleeding in women compared with men include older age and higher prevalence of comorbidities at presentation with cardiovascular disease. However, inherent sex-related factors might also have a role. Although evidence increasingly indicates that pharmacodynamics differ between women and men, anticoagulation and antiplatelet doses are rarely sex-specific. These undifferentiated doses might be implicated in higher bleeding complications and suggest that dose should be adapted to suit women-specific pharmacodynamic profiles. In addition, the use of strategies such as radial artery access for percutaneous coronary intervention has been shown to significantly reduce bleeding and mortality, especially in women. Although the evidence base clearly supports routine radial access in women, a slower uptake of radial access has been documented in women than in men. Further effort is needed to improve bleeding avoidance strategies, and to ensure their implementation in women with cardiovascular disease.

## Vascular disease

### *Stroke*

Ischaemic stroke is the second most common cause of cardiovascular disease death in women worldwide, and the number one cause of cardiovascular disease death in women in southeast Asia and high-income Asia-Pacific.[390] Data from the 2019 US Heart Disease and Stroke Statistics showed that 58·2% of total stroke deaths occurred in women.[264] Although women have a lower age-adjusted stroke incidence than men, they have a higher lifetime stroke risk. Stroke incidence seems to be affected by age and race, with higher stroke incidence in women aged 25–34 compared with similarly aged men, and higher stroke prevalence with increasing age; at age 85 years or older, stroke occurs in around 3 times as many Black women as Black men, and in twice as many White women as White men.[391,392] In countries with a rapidly ageing population, stroke effect on women is likely to increase.[391] Projected data from the US Census Bureau suggest an increase of excess stroke deaths in women from 32 000 in 2000 to nearly 68 000 in 2050.[391]

Although accurate data collection in women with stroke is very much missing, especially in countries at the earlier stages of industrialisation and economic development, a review of data from studies worldwide suggests a sex-related gap in access to treatment and care.[393] Sex-related differences have also been documented in diagnostic and treatment procedures for stroke. For instance, a European study found that after adjusting for age, women were less likely to receive brain imaging, carotid ultrasound, and echocardiograms than men were.[394] Also, women were less likely to receive alteplase than men, even after adjustment for factors including age.[391,395,396]

For more on the **Heartline study** see https://www.heartline.com/

Advanced age has been identified as one of the major drivers of higher mortality, but pre-stroke functional limitations and stroke severity also contribute to worse survival and functional outcomes in women than in men.[397] For example, analysis of data on 4228 first-stroke cases from the International Stroke Outcomes Study[398] found lower pooled health-related quality of life after stroke in women than in men. Depression in women is an additional factor to consider in post-stroke outcomes. Before stroke, women are more likely than men to have pre-existing depression that increases risk of stroke and is associated with increased morbidity and mortality after stroke.[399,400] Women who have a stroke are also more likely to live alone than men, which reduces their chance of returning home and back into their community, which could increase their social isolation and decrease recovery after stroke.[401]

Data from the UK Biobank showed that hypertension was more strongly associated with the risk of any stroke and stroke subtypes in women than in men.[402] Preventive measures with early diagnosis and treatment of

hypertension and elevated cholesterol should be implemented across the globe to reduce mortality due to stroke in women. Comprehensive data collection is also needed, to identify and address sex-related gaps in access to health care worldwide. Rehabilitation programmes that are more effective and which have been tailored for women might reduce sex-related differences in functional limitations and quality of life after stroke.

### *Dementia*

Vascular dementia caused by cerebrovascular disease or impaired cerebrovascular blood flow is the second most common form of dementia after Alzheimer's disease in terms of incidence and prevalence.[403,404] Dementia overall is a growing global health change and affects considerably more women than men. More women than men both have dementia (27·0 million *vs* 16·8 million in 2016) and die from dementia. Between 1990 and 2016, the number of dementia-related deaths increased by 148%, with 1·5 million (95% UI 1·3 million to 1·8 million) deaths in women versus 0·8 million (95% UI 0·7 million to 1·0 million) deaths in men in 2016.[405] Although women typically live longer than men, dementia is not an inevitable part of ageing, and excess dementia-related deaths are not attributable to women's longer life expectancy. Analysis of GBD data[405] identified hypertension, obesity, high fasting plasma glucose, smoking, and high intake of beverages sweetened with sugar as the main risk factors associated with dementia. Preventive strategies that identify women at higher risk earlier in life and target modifiable metabolic risk factors in women might delay vascular dementia and should be emphasised.

### *Peripheral arterial disease*

The global prevalence of peripheral arterial disease in women is increasing at alarming rates, especially in younger women. Worldwide, women represent more than half (52·2%) of patients with peripheral arterial disease.[406] Although previous studies have established that peripheral arterial disease prevalence increases with age, subsequent analyses show a rising proportion of peripheral arterial disease among younger women (age <45 years) in LMICs.[406] In addition to established risk factors such as hypertension, diabetes, and smoking, which are more prevalent in LMICs, factors like body-mass index of 30 kg/m² and above and low pulse pressure manifest as risk predictors in LMIC patient populations.[406] Data from the Women's Health Initiative study[407] documented a strong dose–response relationship for smoking as a risk factor for peripheral arterial disease in women. Environmental factors in LMICs (eg, poverty, ongoing industrialisation, and a shift towards sedentary lifestyles) could also be contributing to higher peripheral arterial disease burden in younger women.[408,409] Inadequate access to health care, a lower physician:patient ratio, low awareness among patients and physicians, and social barriers might be additional factors that are contributing to the rising peripheral arterial disease prevalence and mortality trends.

Large studies have established that women are more likely than men to be asymptomatic or to present with sex-specific symptoms, which subsequently increases their risk of delayed presentation with critical limb ischaemia.[410–412] Women are also more likely than men to have complications after revascularisation procedures, including higher rates of wound infections, periprocedural complications, bleeding, and in-hospital mortality,[412–416] and African American women in particular have higher rates of graft failure and limb loss after bypass surgery for limb salvage.[417] Women continue to have higher rates of transfemoral amputation, which can result in poor quality of life and high economic burden.[418]

Worldwide, women remain poorly informed about peripheral arterial disease risk factors and disease modalities.[419–421] Representation of women in major peripheral arterial disease clinical trials has consistently remained at less than 40%, further adding to the dearth of sex-specific evidence-based medicine.[422] In 2012, the AHA released a call to action scientific statement addressing these rising concerns about women with peripheral arterial disease.[423]

Allied health-care providers, especially in LMICs, should be involved in population screening for peripheral arterial disease using quick, easy, and non-invasive tools such as ankle–brachial index measurements. These approaches can help to increase the probability of establishing a timely diagnosis and to ensure patient referral.

Peripheral arterial disease is an indicator of polyvascular disease. Further efforts are needed to increase awareness of diagnosis and treatment for peripheral arterial disease in women. Early diagnosis is crucial to provide optimal treatment (eg, intensified risk factor management) and to improve cardiovascular outcomes in women.

## Valvular heart disease

Valvular heart disease in the USA and Europe is recognised primarily as a manifestation of degenerative processes associated with ageing. In other parts of the world, especially in Oceania, sub-Saharan Africa, and south Asia, rheumatic heart disease remains a common cause of valvular heart disease.[424,425]

### *Calcific aortic stenosis*

Valve degeneration due to progressive fibrosis and calcification is the most common cause of aortic stenosis in women. Without intervention, the prognosis for symptomatic aortic stenosis is poor, and mortality is high, with an average survival of 2 years.[424,426] Although prevalence is similar for women and men, there are crucial epidemiological differences that have the potential to affect outcomes. Women who have surgical aortic valve replacement are usually of advanced age and are therefore often frail, and have high surgical risk because of comorbidities.[427]

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Transcatheter aortic valve replacement has emerged as an alternative treatment for patients with severe, symptomatic aortic stenosis. Initially, transcatheter aortic valve replacement was only indicated in patients deemed too high risk for surgical valve replacement but, subsequently, the indication was expanded to lower-risk populations. Despite older age, worse baseline characteristics, and increased vascular and bleeding complications during transcatheter aortic valve replacement, multiple studies have found higher rates of survival at 1 year after transcatheter aortic valve replacement for women than for men.[428,429] These data reinforce the benefit of transcatheter aortic valve replacement for women with symptomatic severe aortic stenosis, if they have favourable anatomy for this intervention. Although retrospective analysis of a medical claims database (43 822 patients with aortic stenosis) reported that women were more likely to receive transcatheter aortic valve replacement than surgical valve replacement compared with men (39·8% *vs* 32·3%), sex disparities were shown to persist by the smaller proportion of women who were treated at all compared with men (28·7% *vs* 36·0%).[430]

This Commission endorses the screening and evaluation across all races and ethnicities of all women with calcific aortic stenosis, and prompt treatment according to guideline recommendations for symptomatic and severe aortic stenosis.

*Mitral valve disease*

The most common type of mitral valve disease requiring surgical intervention is mitral regurgitation. Studies have shown that women are less likely than men to have mitral valve replacement and have worse postoperative outcomes.[431,432] Women are also less likely to receive mitral valve repair. A study in US Medicare beneficiaries aged 65 years and older documented lower rates of mitral valve repair in women than in men (31·9% *vs* 44·0%).[433] Compared with US patients matched for age and sex, mitral valve repair restored life expectancy for men but not for women.[433] Potential explanations for these findings include worse preoperative characteristics in women, including heart failure and other conditions that suggest longer-standing mitral valve disease.[433] The study investigators hypothesised that referral for surgical intervention might occur later in the disease course for women than for men. A study of 24 977 patients (49% women) having isolated mitral valve repair or replacement showed that young women (age 40–49 years) had 2·5 times higher hospital mortality than their male counterparts.[434] Authors hypothesised that ovarian function in women who were perimenopausal might have contributed to the sex–age interaction. Further research is warranted to investigate the determinants of worse outcomes after mitral valve replacement or repair in women across age groups compared with men.

Mitral annular calcification is a degenerative process of the mitral annulus, is known to increase with age, and is more common in women than in men.[435] Patients with mitral annular calcification are often older, with multiple comorbidities and a high risk of cardiovascular death and all-cause mortality.[435,436] Transcatheter mitral valve replacement using aortic transcatheter heart valves has been used to treat symptomatic patients who are not candidates for standard mitral valve surgery; however, outcomes data are few from retrospective registries and one prospective trial (MITRAL).[437–441] Women account for approximately 70% of the patients enrolled in registries, although it is unclear whether the higher proportion of women enrolled results from a greater prevalence of mitral annular calcification among women or from women being less likely to be considered as surgical candidates because of high risk. Although outcomes have improved, owing to better patient selection and interventions to decrease the risk of left ventricular outflow tract obstruction, further clinical trials are needed to define the best transcatheter treatment strategy for women with mitral annular calcification.

*Rheumatic heart disease*

An entirely preventable condition, rheumatic heart disease is the most common cause of heart failure in children, adolescents, and young adults worldwide,[442,443] with the highest prevalence occurring in women of childbearing age.[444] Acute rheumatic fever is an autoimmune response to *Streptococcus pyogenes* (group A *streptococcus)* that initiates a cascade of carditis, valvulitis, and ultimately permanent heart valve damage and sequelae.[445] Although rheumatic heart disease has been largely eradicated in high-income countries, prevalence remains high in regions and populations that are marked by poverty and economic disadvantage. This shift in the distribution of burden has led to neglect by cardiovascular, infectious disease, and public health agendas. Currently, Africa, southeast Asia, and the western Pacific represent 84% of rheumatic heart disease prevalence and more than 80% of estimated mortality.[425] Prevalence is especially high among women,[446,447] for whom the risk of developing rheumatic heart disease is 1·6–2·0 times higher than for men. Research attributes higher risk to socioeconomic and environmental factors (eg, overcrowding) and sex-specific factors that include pregnancy, exposure to *S pyogenes* through childrearing, inadequate access to health care, and genetics.[445,448–450] The effect of rheumatic heart disease on women is of paramount concern, especially among women in their childbearing years, in whom the morbidity and mortality burden is high. Pregnancy represents a critical period for women in the context of rheumatic heart disease and is discussed in the pregnancy and rheumatic heart disease section.

Measures should continue and be reinforced to raise both awareness about rheumatic heart disease and political incentives to address its implications, as part of

an integrated rheumatic heart disease prevention and control programme that targets women in LMICs.[451,452]

## Cardiovascular disease and pregnancy

Worldwide, 80–90% of women have at least one pregnancy to delivery, which places considerable physiological stress on the cardiovascular system.[47] Although leading causes of maternal mortality such as post-partum haemorrhage and pregnancy-related infections are declining,[453] cases of maternal heart disease are increasing. Maternal cardiovascular disease complicates approximately 1–4% of pregnancies and contributes to approximately 15% of maternal death.[324] According to WHO in 2015, an estimated 303 000 women died while pregnant or within 42 days after the end of pregnancy.[454] Cardiovascular disease appears to be a major contributor to late maternal death (up to 1 year after birth), but this is not well documented, especially in low-income countries, and is therefore likely to be an underestimated and a neglected issue.[455]

Analysis of data from the ESC Registry of Pregnancy and Cardiac disease[456] identified the most prevalent diagnoses in pregnancy as congenital heart disease (57%) and valvular heart disease (29%). With congenital heart disease in high-income countries, access to surgery and medical treatment has resulted in survival to reproductive age, even for women with complex congenital heart disease. Follow-up in tertiary care centres and preconception assessment, plus close monitoring during pregnancy by a multidisciplinary team, are key to reducing maternal death in these women. However, there is little access to surgery, medical treatment, and preconception counselling in low-income countries. Global estimates of access to surgery and treatment are missing, and there are very few data on pregnancy outcomes in women with uncorrected congenital heart disease. ESC EURObservational Research Programme and Registry of Pregnancy and Cardiac disease data on women with uncorrected congenital heart disease showed that coming from an LMIC was associated with higher prepregnancy signs of heart failure, pulmonary hypertension, and cyanosis, plus worse maternal and fetal outcomes, with 3 times the risk of hospital admission for cardiac events and intrauterine growth retardation than in high-income countries.[457]

All women of childbearing age with cardiovascular disease should have risk assessment with the modified WHO classification of maternal risk, as recommended by the 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy.[324] The ESC Guidelines,[324] and the recommendations released by the AHA,[458] provide important guidance about the management of pregnancy in patients with cardiovascular disease, including for decision making about the use of drugs for heart disease in pregnant women.

Cardio-obstetrics is an emerging multidisciplinary team approach for the management of cardiovascular disease during pregnancy. The Commission endorses this team-based approach between cardiologists and obstetricians–gynecologists in caring for women with cardiovascular disease during pregnancy.

### *Pregnancy and rheumatic heart disease*

Although in high-income countries corrected congenital heart disease replaced rheumatic heart disease as the main cause of maternal cardiac complications during pregnancy, rheumatic heart disease remains the number one cause of such complications globally.[459] Analysis of data from the Global Rheumatic Heart Disease Registry[446] on patients anthracyclines (eg, doxorubicin, with rheumatic heart disease living in LMICs showed that many women with rheumatic heart disease are young and of childbearing age (82·5% aged 11–51 years; median age 28 years). The burden of complications from rheumatic heart disease in 76 pregnant women from this cohort was high: 54·8% had mitral stenosis, 49% had heart failure, 27% had atrial fibrillation, and 26% had pulmonary hypertension. Results from the Registry of Pregnancy and Cardiac Disease[460] documented a quite low (1·9%) mortality rate during pregnancy in women with rheumatic heart disease; however, 50% of women with severe mitral stenosis developed heart failure during pregnancy. Two scenarios need additional consideration. The first scenario involves women who present in pregnancy with severe valve lesions (usually mitral valve) that preclude a safe delivery. If they are available, interventions during pregnancy (eg, mitral valvuloplasty) are associated with similar maternal and fetal outcomes to interventions done before pregnancy.[461] The second scenario involves women with rheumatic heart disease who require anticoagulation during pregnancy, such as women with prosthetic heart valves; although warfarin is recommended in such cases, large prospective trials in this population are needed.[324,462–464]

Health systems in endemic areas seldom adequately address the needs of women with severe rheumatic heart disease who are pregnant, likely to become pregnant, or are considering pregnancy.[465,466] Multidisciplinary cooperation, combined with appropriate preconception counselling and antenatal care, are the key measures to improve outcomes in these women.[467] A prospective cohort study[468] in low-resource areas of South Africa found that joint cardio-obstetric care is associated with substantially improved morbidity and mortality for mothers and their children. Although combined cardio-obstetric clinics might not be feasible in many regions, algorithms for cardiac screening could still be applied to identify women at risk of rheumatic heart disease or complications from rheumatic heart disease.[469]

The Commission strongly advocates for preconception counselling and directed care for girls and young women with rheumatic heart disease before and during pregnancy, including decentralised acute rheumatic fever diagnostics that are integrated into prevention

and control programmes aligned with local non-communicable disease targets and efforts.

### Cardiovascular disease and cancer: cardio-oncology for women

As deaths related to cancer have been reduced in women across the world, cardiovascular disease is becoming an important issue in cancer survivorship. The field of cardio-oncology has evolved as an important subspeciality to improve cardiovascular care in female survivors of cancer.

Globally, breast cancer is the most common cancer in women. Treatment options have improved markedly, leading to reduced mortalilty.[470] However, therapies such as anthracyclines (eg, doxorubicin, which is one of the most commonly used chemotherapeutic agent in breast cancer) and trastuzumab (a monoclonal antibody) affect cardiac function and increase the risk of developing heart failure, which has higher mortality than breast cancer itself.[471] Doxorubicin directly affects cardiovascular function, with the potential for type I cardiotoxicity resulting in irreversible damage, whereas trastuzumab can cause type II cardiotoxicity, which is potentially reversible if discovered early.[472]

The incidence of symptomatic heart failure events ranges between 1% and 4% of all patients treated with trastuzumab in the setting of adjuvant chemotherapy, but the incidence of asymptomatic left ventricular dysfunction might be as high as 10–40% in such patients.[473,474] Patients with breast cancer are often treated with a combination of chemotherapy with anthracyclines plus radiotherapy to the chest. Radiotherapy not only increases the likelihood of cardiovascular side-effects from chemotherapy, but is also associated with numerous other adverse cardiovascular outcomes. For instance, left-sided radiation increases the risk of developing coronary artery disease, cardiac death, and death from any cause,[475] not only shortly after exposure, but also for 20 years or more.[476] Radiotherapy to the chest can lead to coronary artery stenosis, damage the pericardium, and cause cardiomyopathy, valvulopathy, conduction abnormalities, atrial fibrillation, ventricular tachycardia, and aortic complications.[477–481] Although these side-effects can manifest slowly over many years, a cohort study published in 2019 showed that the damage can be evident as soon as 1 year after treatment.[482] Therefore, it is important to identify women at risk and to establish prevention strategies before radiotherapy is initiated.

In 2016 the ESC released a position paper on cancer treatments and cardiovascular toxicity that provided support and guidance for health-care professionals involved in cardiovascular monitoring and decision making for patients before, during, and after cancer treatment with potential cardiovascular side-effects.[483] Important measures include routine surveillance imaging during treatment in asymptomatic patients considered to be at increased risk, and early referral to a cardio-oncology team.[483] The American Society of Clinical Oncology recommends rigorous follow-up and management for patients at high risk of developing cardiac dysfunction, including patients receiving high-dose anthracyclines or high-dose radiotherapy with the heart in the treatment area, or receiving a combination of low-dose radiotherapy with the heart in the treatment area plus low-dose anthracyclines.[484]

This Commission endorses the field of cardio-oncology as a crucial resource in reducing cardiovascular disease among female survivors of cancer.

### The under-representation of women and under-reporting of sex-specific data in cardiovascular clinical trials

It is widely acknowledged that appropriate representation of women in clinical trials is crucial to gain knowledge about sex-related differences in optimal treatment and to improve outcomes in patients of both sexes. Historically, women have been under-represented and often excluded from clinical trial participation. In 1977 the FDA recommended that women of childbearing potential should be excluded from phase 1 and early phase 2 drug trials because of drug-related incidents, including the tragedy conferred by giving thalidomide to pregnant women.[485] This policy resulted in the broad exclusion of women from clinical trials and contributed to their subsequent frequent under-representation.[486] Although legislative changes in the 1980s and 1990s mandated the inclusion of women in clinical trials, the enrolment of women has increased only slowly. Indeed, a recent analysis shows that men still predominate overall as cardiovascular clinical trial participants.[487] Between 2010 and 2017, women represented 38·2% of participants in cardiovascular clinical trials, although this representation varied by disease and trial characteristics.[487] The analysis provided participation prevalence ratios (PPRs), with a PPR of 0·8–1·2 suggesting adequate representation of women in trials relative to disease population, a PPR less than 0·8 suggesting under-representation, and a PPR greater than 1·2 suggesting over-representation. The PPR was 0·82 for hypertension and 1·33 for pulmonary arterial hypertension trials, but lower (0·48–0·78) for trials in heart failure, acute coronary syndrome, coronary heart disease, stroke, and arrhythmia.[487] Overall, representation of women has been higher in primary than in secondary prevention trials, with balanced enrolment between women and men in large primary prevention trials.[488–490]

Nevertheless, there is considerable work to be done to investigate why women are under-represented in cardiovascular clinical trial participation, including why women are less likely than men to be considered for screening in trials, and why women might be less likely than men to consider participating.[491] For example, a study in 783 people across 13 US clinical centres examined differences between women and men in willingness to participate in cardiovascular prevention

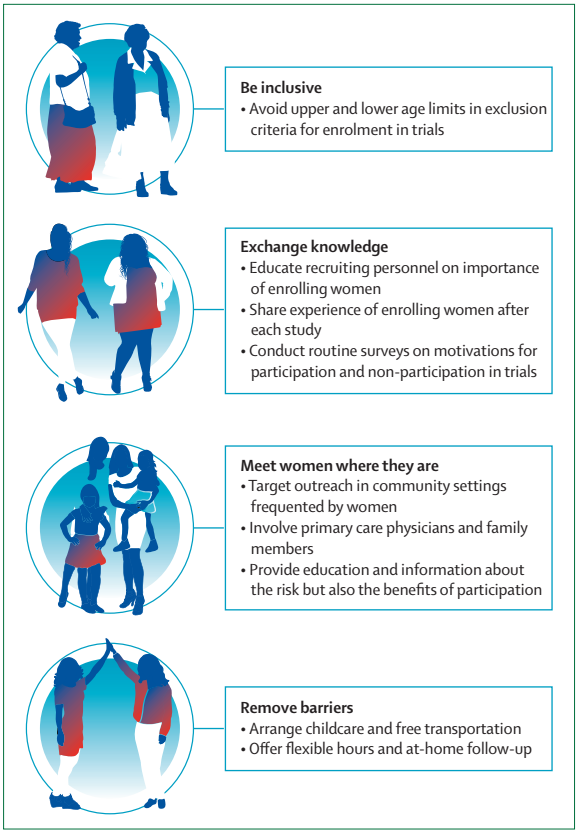


***Figure 7*: Strategies to increase the proportion of women in cardiovascular clinical trials**

studies, and differences in perceived risks and distrust.[492] The study found that women were less willing to participate in clinical trials than men. Although adjustment for sex differences concerning distrust of medical researchers and perceived 10-year risk of myocardial infarction did not alter these results, sex differences in willingness to participate were fully attenuated by adjusting for differences in the perceived probability of experiencing harms and benefits. A Canadian study in 270 women asked participants to comment on the reasons for participating or not participating in the Raloxifene Use For The Heart trial.[493] Major factors included concerns about the burden of participation on health and time. Regarding concerns about time, another study found that women were more likely than men to document caring responsibilities (eg, for grandchildren, other family members, friends, and neighbours) as reasons for not participating in a clinical trial.[494] Further efforts are needed to identify strategies that make participation in clinical trials increasingly accessible and inclusive for women (figure 7).

In addition to the under-representation of women in clinical trials, knowledge gaps on sex-related differences in cardiovascular disease ensue from the absence of sex-specific data reporting. In 1998, the FDA enforced regulatory requirements for reporting clinical data by sex in addition to by age and race. However, despite substantial interest in understanding sex differences in cardiovascular disease, few studies have addressed such issues, and many gaps in our knowledge remain. In 2015, the US National Institutes of Health (NIH) released Consideration of Sex as a Biological Variable in NIH-funded Research,[495] and emphasised that sex and gender should be considered in research design, analysis, and reporting of results. The Sex and Gender Equity in Research Guidelines[496] give specific recommendations on how to include the influence of sex in clinical research. Other organisations, such as the AHA, the Canadian Institutes of Health Research, and the European Commission, have also called for sex and gender analyses in research.

Sex and gender are crucial to the interpretation, validation, and generalisability of research findings, and sex-disaggregated analyses in research and clinical trial design should be mandatory. Enrolling women in clinical trials across the lifespan of women is a key factor in improving cardiovascular outcomes in women.

## Review of specific global areas

Although cardiovascular disease is the leading global cause of mortality for women, there are important geographical differences in the burden of cardiovascular disease. This section provides an overview of region-specific conditions that need to be taken into consideration when identifying and implementing recommendations to prevent and manage cardiovascular disease in women (see panel 4). Although the GBD Study analyses of mortality and risk factors provide data for regions that are defined according to their epidemiological similarity and geographical proximity, in this section, we focus on geographical areas that reflect the regions from which the Commissioners originate.

### Australia and New Zealand

The female population of Australia makes up just over half (51%) of the total population and is characterised by cultural and ethnic diversity: 29% were born overseas, and 3·2% are Aboriginal People and Torres Strait Islander People.[497]

Although the majority of the population live along the coast (71%), there are barriers to equitable health care for people with low income in rural and remote areas, who have less access to specialised cardiac services.[498] Older women (>75 years) living in remote areas of Australia are 3 times less likely than people in urban areas to get a clinically indicated echocardiogram and 4 times less likely to be seen by a cardiologist.[499]

Among Aboriginal and Torres Strait Islander people, more women (59%) than men (41%) have cardiovascular disease.[500] A study in Aboriginal people found that the incidence of heart failure is 2 times higher among women than men.[501] Aboriginal and Torres Strait Islander women are reported to have obesity rates that are

### *Panel 4*: Recommendations by region

**Australia and New Zealand**

- Barriers to equitable health care and access to specialised cardiac services persist for women in low-income and remote areas. Telehealth can address health inequities by delivering cardiovascular health care to women in remote and rural areas.
- Cardiovascular disease prevalence and mortality are especially high in Aboriginal and Torres Strait Islander women. Culturally sensitive primary and secondary prevention programmes are much needed for Indigenous people and women from low-socioeconomic areas, including rheumatic heart disease initiatives, smoking cessation programmes, cardiac rehabilitation, and psychosocial support.

**Asia**

- Misconceptions, restricted education, and cultural beliefs contribute to low awareness about cardiovascular disease risk and risk factors among women in Asia. Culturally sensitive initiatives, national campaigns, and public education activities are needed to increase awareness about cardiovascular risk factors, and morbidity and mortality related to cardiovascular disease in women.
- Traditional roles and responsibilities persist in many parts of Asia, in which women are caretakers of health, often in addition to their domestic duties and employment, and men are decision makers about medical care. A combination of strategic population-based and public policy-based approaches are needed to improve health care for women in Asia, and to enable women to view themselves as decision makers about their own health and health care.

**Eastern Mediterranean region: Middle East and north Africa**

- No governmental measures exist to prevent cardiovascular disease in women. National awareness and screening campaigns are needed to target hypertension and diabetes, and early school programmes should promote a healthy diet and physical activity. It is essential to empower women through education about health and wellbeing.
- Accurate data on cardiovascular disease prevalence and mortality are absent for most countries. Governmental agencies should establish robust health surveillance systems to monitor mortality and morbidity associated with cardiovascular disease in women.

**Europe**

- Cardiovascular disease morbidity and mortality for women from central and eastern Europe are among the highest in the world, in great contrast to data from northern, southern, and western Europe. Coordinated actions and policy coherence across European countries are needed to address health inequalities in the region.
- Smoking remains one of the most salient health concerns for European women. Education, initiatives, and social media campaigns are imperative to prevent smoking among young women.

**Latin America**

- Access to health care is inequitable. Indigenous women and those of African descent have the worst health outcomes and shorter life expectancy because of low awareness and substandard quality of care. Strategies are needed to generate outcomes data and improve health care for these populations.
- Approximately 1 125 000 women of reproductive age are infected with *Trypanosoma cruzi*, the parasite that causes Chagas disease, and rheumatic heart disease is endemic in particular regions. Screening women for Chagas disease and rheumatic heart disease during early reproductive age is an opportunity to prevent Chagas disease transmission and to reduce the risk of cardiovascular disease complications associated with rheumatic heart disease during pregnancy.

**North America**

- The prevalence of metabolic disturbances is high in North American women. Prevention of obesity and obesity-related conditions should be a priority in public health interventions and policy-based approaches, social campaigns, and initiatives targeting girls and women at a young age.
- African American, Hispanic, and Native American or Alaskan Native women carry an excessive cardiovascular risk burden compared with White women, and inadequate health-care coverage remains an issue for women of minority ethnicity or race in the USA. Collaborative efforts to tackle inequalities and identify culturally sensitive strategies for disease prevention and management in women of minority ethnicity or race are urgently warranted.

**Sub-Saharan Africa**

- Too little attention and too few resources are directed at the obesity epidemic that affects women more than men. Further research is needed to investigate how obesity perceptions are shaped by cultural frames and to identify the best way to apply a cultural lens to community-level obesity interventions.
- Women are disproportionally affected by poverty and inadequate access to health care. The exclusion of women from formal education and skills training has substantial implications, not only for socioeconomic development, but also for health literacy, the ability to afford health care, and decision making about health. It is crucial to empower women to self-manage their own health, via education and building up literacy.

1·3 times higher than in non-Indigenous women (73% *vs* 55%),[497] and are more likely to have central obesity than non-Indigenous women.[502] In Aboriginal and Torres Strait Islander women, the absolute rate of smoking is approximately twice that of non-Aboriginal Australian women.[503] Type 2 diabetes prevalence for women living in the lowest socioeconomic areas is twice as high as for women living in the highest socioeconomic areas.[504]

Aboriginal women often have traditional roles as mothers and homemakers, carry a large share of domestic duties, are at increased risk of domestic violence compared with non-Aboriginal women, and have poor access to health care. Aboriginal women have worse health outcomes, a shorter life expectancy, and deaths related to cardiovascular disease occur approximately 10–20 years earlier, compared with non-Indigenous women.[505] Rheumatic heart disease prevalence among Indigenous Australians is one of the highest recorded globally,[506] with approximately 65% of cases affecting Indigenous women.[507] Rheumatic fever also continues unabated among Māori and Pacific Island New Zealanders. Initiatives to prevent severe rheumatic heart disease by screening disadvantaged school-age children using portable echocardiography are important for helping to diagnose girls before they reach childbearing age.[508] However, disparities based on ethnicity are large in acute rheumatic fever and subsequent rheumatic heart disease, and the gap is widening.[508]

### Asia

Asia is a heterogeneous region with an eclectic mix of ethnicities, sociocultural norms, and religions and beliefs, with substantial socioeconomic inequalities and wide gaps in access to health care. Women from south Asia were reported to be at 76% greater risk of cardiovascular disease events than women in Norway, and at 39% greater risk than women in New Zealand.[509] In addition to ischaemic heart disease, the issue of stroke is of huge importance in women of Asia.[510] Hypertension and diabetes have been identified as strong risk factors. The Asia Pacific Cohort Studies Collaboration[511] reported that the proportion of ischaemic heart disease attributable to hypertension is 8–39% in women versus 4–28% in men. The prevalence of hypertension is highest among women from south Asia (38·2% in India),[512] east Asia (30·8% in South Korea),[513] and southeast Asia (25·0% in Malaysia and 20·1% in Singapore).[514,515] This high prevalence is largely attributable to diet (high salt intake in the form of salted fish and shrimp paste) and genetics (predominantly in Indian and Malay people). In addition, rapid urbanisation and an increasingly sedentary lifestyle have resulted in increased prevalence of hypertension and diabetes in Asia.

Misconceptions, restricted education, and cultural beliefs contribute to low awareness about cardiovascular disease risk among women in Asia. For instance, surveys in Singapore found that only 10% of women were aware that cardiovascular disease is the leading cause of death for Singaporean women, and only 8% had discussed topics related to cardiovascular disease with their doctor in the past 12 months.[516] Furthermore, the view of cardiovascular disease as being a man's disease prevails in Asia. Also, many older women who develop cardiovascular disease distrust allopathic medicine and prefer to die in their homes rather than in hospital; cause of death is therefore often misclassified as old age.[517] Finally, traditional roles and responsibilities persist in many parts of Asia, in which women are caretakers of health, often in addition to their domestic duties and employment, whereas men are decision makers about medical care.[518] Gender norms, environmental factors (eg, hot and humid weather conditions), and expectations of religions and beliefs limit the potential for women to engage in physical activities and reinforce the notion that taking time out for physical activity instead of domestic duty is a selfish act.[519]

### The Middle East and north Africa

Rapid transformation in the eastern Mediterranean region from a nomadic to an urban society has led to major changes in lifestyle. However, strict cultural and religious norms prevail in ways that contribute to a considerable cardiovascular disease burden among women. The INTERHEART study,[26] involving Gulf countries, Egypt, and Iran, showed that women with Arab ethnicity present with coronary artery disease 10 years earlier than women in Europe and east Asia.

In the Middle East, the prevalence of obesity is substantially higher in women (30·6%) than in men (16·6%),[520] and is especially high among women in oil-rich countries such as Saudi Arabia (44%).[521] Other than dietary changes, multiple pregnancies are a major cause of obesity in Middle Eastern and north African women, because large families are still socially and culturally favoured in the region. Consequently, women have a high fertility rate along with a short spacing period between pregnancies, which results in the accumulation of body fat.[522] Also, approximately 50% of women are insufficiently physically active compared with 36% of men.[523] Social and physical restrictions on mobility and traditional religious norms define socially acceptable behaviours for women, and place more emphasis on spiritual and religious extracurricular activities than on sports and physical activity.[524]

Although access to undergraduate and graduate programmes has begun to increase,[525] women in Middle Eastern and north African regions have been marginalised from secondary and tertiary education for many years.[526] This restricted access to education has undermined women's health and reinforces a wide gender gap in health and wellbeing. In most Middle Eastern countries,

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cardiovascular mortality among women correlates with years of education, and in some countries (eg, Saudi Arabia), limited physical mobility and restricted autonomy impede women's access to health-care services.[527] For example, the prehospital delay for myocardial infarction admission in Saudi Arabia was reported to be twice as high for women as for men (12·9 h *vs* 5 h).[528] Factors contributing to this delay included requiring a male relative's permission to seek medical help and the inability to travel to hospital unless accompanied by a male relative.[527]

Epidemiological data in the Middle East and north Africa are scarce because of no government funding to support women's health and inadequate disease registries. Also, health-care strategies in the region focus more on therapeutic interventions than on disease prevention.[529]

### Europe

Within the European region, there are wide gaps in cardiovascular disease prevalence and mortality. Central and eastern European countries are among countries with the highest cardiovascular disease burden globally, which contrasts greatly to data from northern, southern, and western Europe.[530] These differences in cardiovascular morbidity, mortality, and risk factor prevalence are based on marked disparities in research funding, effective health interventions, and health-care systems across Europe.[530] Coordinated actions and policy coherence across European countries are needed to address health inequalities in Europe.[531]

Nevertheless, further efforts to decrease cardiovascular risk factors and associated mortality in European women are much needed in all countries. Smoking remains one of the most salient health concerns in Europe.[532] Although overall smoking rates have declined, there are alarming trends, with a relentless increase in smoking among women, especially in young women and girls.[533] According to statistics from EU member states, the proportion of daily smokers is similar between women and men in several northern and western European countries, and higher in women than men in Sweden.[534] In addition, mortality risk attributable to hypertension is higher in women than in men across most of Europe, with the highest rates in women from Estonia.[535] Data on the prevalence of elevated cholesterol in European countries show that elevated cholesterol (defined as total cholesterol ≥5·0 mmol/L) affects 55·8% of the population older than 25 years, with a slightly higher prevalence in women (56·8% women *vs* 55·0% men).[536] A quarter of the European adult population has obesity, with higher prevalence among women (27·1%) than among men (23·4%).[537] WHO data show that in the past 3 decades, mean body-mass index in women increased in most European countries.[538] Participation in recommended amounts of physical activity is low, with inactivity being more common in women than in men (32·4% *vs* 29·0%).

### Latin America

This region has seen rapid but uneven social and financial progress during the past decades.[539] Epidemiological transition resulted in population ageing, urbanisation, smoking, unhealthy diets, and physical inactivity, and contributed to increases in cardiovascular disease mortality in women. Data from the Pan-American Health Organization show that ischaemic heart disease is the leading cause of death in Latin American women.[540] The prevalence of ischaemic heart disease and stroke is estimated to triple in the next 20 years, and women are expected to have higher mortality than men.[541]

Hypertension is considered to be a major public health issue in this region, and is especially prevalent in women with African ancestry living in places like Brazil and the Caribbean.[541] The interaction between an unfavourable lifestyle, genetic inheritance, and epigenetic changes also contribute to high rates of dyslipidaemia in women in this region.[542,543] Data from the INTERHEART Latin American study[63] showed that few women (15·7%) do regular physical activity. Obesity prevalence is 30% higher for women than for men in some regions of Latin America.[544] A shift towards higher intake of high-density food and sweetened beverages,[63] and an increase in smoking have been seen in Latin America, with reported rates of tobacco use among women ranging from 3·4% in Honduras to 33·0% in Chile.[545] With regard to women, smoking rates as high as 37·7% and 43·3% were reported in cities such as Bueno Aires, Argentina, and Santiago, Chile.[546] The ten countries with the highest rates of diabetes in the world include Chile (14%), Mexico (9·7%), and Colombia (8·2%).[547,548] Mexico was reported to have the highest diabetes mortality rate in women in the region.[549] The INTERHEART Latin American study[63] found a higher risk of myocardial infarction in women than in men, associated with higher waist-to-hip ratio, hypertension, and diabetes.

The traditional roles of women in Latin America as mothers and homemakers have been changing during the past decades. Although many women participate in the labour force, they continue to carry a larger share of domestic labour, which can create a barrier to a healthy lifestyle and physical activity.[550] Furthermore, access to health care is inequitable;[551] women who are Indigenous or of African descendant have worse health outcomes and shorter life expectancy than women who are not Indigenous or of African descendant, because of substandard quality of health care, including longer delays in diagnosis and treatment and health-provider discrimination.

In Latin America, approximately 1125 000 women of reproductive age are infected with *Trypanosoma cruzi*, the parasite that causes Chagas disease.[552] Arrhythmias and severe cardiomyopathy are hallmarks of the chronic phase of Chagas disease, and are the most common causes of death in these patients.[553] Rheumatic heart disease is also endemic in Latin American countries

such as Nicaragua, Haiti, and Bolivia, affecting women during their childhood and reproductive life.[554]

*North America*

Cardiovascular disease results in a substantial health and economic burden in the USA.[555] Data from the 2019 AHA report on heart disease and stroke statistics showed that cardiovascular disease (ie, coronary heart disease, heart failure, stroke, and hypertension), was prevalent in 44·7% of women aged 20 years or older, and rates increased with age.[264] An analysis of the WHO Mortality Database found an increase of age-standardised cardiovascular disease death (35–74 years) during 2017 in women in the USA and Canada.[3]

For more on the **WHO Mortality Database** see https://www.who.int/data/data-collection-tools/who-mortality-database

Hypertension prevalence is as high as 58% in women aged 65–74 years,[556] and approximately 30% of women older than 20 years have LDL cholesterol of at least 130 mg/dL. A stunning 67·4% of US women are considered overweight or obese (body-mass index ≥25·0 kg/m²) and 40·7% obese (body-mass index ≥30 kg/m²), with the highest prevalence in African American (56·0%), Hispanic (48·9%), and White (37·9%) women. [557] Approximately 13 million adult women in the USA have diabetes, the majority of whom have type 2 diabetes.[558]

African-American, Hispanic, and Native American or Native Alaskan women in the USA carry an excessive cardiovascular risk burden compared with White women. For instance, the risk ratio (RR) for incident hypertension is significantly higher for African-American women aged 65–74 years than for White women of the same age (RR 1·44; 95% CI 1·24–1·66), and African-American women are more than twice as likely to develop diabetes than White women (2·14, 95% CI 1·86–2·46).[559] The prevalence of any cardiovascular disease in African-American women is much higher than in White women (57·1% *vs* 43·4%),[264] with a ratio of approximately 1·3 (166·3 per 100 000 *vs* 131·9 per 100 000) for the age-adjusted heart disease death rate.[560] Similarly, African-American women have a 50% greater risk of heart failure than White women do.[561,562] Although some study results have indicated lower cardiovascular disease prevalence and mortality in Hispanic women compared with non-Hispanic White women and non-Hispanic Black women, the cardiovascular risk factor burden is higher in Hispanic women than in non-Hispanic White women.[563] Although Hispanic and Latino people are the largest minority ethnic group in the USA, data on cardiovascular disease in this population is severely deficient, and a better understanding of cardiovascular risk profile, morbidity, and mortality of women from various Hispanic-origin groups is urgently needed.[563]

Attention has recently been directed to long-standing racial injustice and discrimination against Black people in the USA by the killings of African-American people at the hands of the police and the subsequent emergence of the Black Lives Matter movement. Inequities between Black and White communities affect almost all aspects of life, including health and access to care. Black women face higher rates of physical violence and psychological abuse than women overall do, and are also affected by inadequate access to health care.[145,564,565]

Indeed, the absence of health-care coverage remains an issue in ethnic and racial minority populations throughout the USA.[566] 573 federally recognised Native American and Alaska Native tribes that include 1·8 million women represent an important medically underserved population. Stroke mortality rates are higher for Native American and Alaska Native women than for White American women, especially among younger women (35–44 years). 21·5% of women in this population smoke tobacco (compared with 13·5% of American women overall),[264] which is one of the major risk factors for cardiovascular disease in North America and one of the most preventable causes of death, stroke, and myocardial infarction.[567,568] Between 2007 and 2009, Native American and Alaska Native women more often self-reported their health as fair or poor than White American women did. Over a third of these Indigenous women stated they had been diagnosed as obese, compared with a quarter of non-Hispanic White women, and Indigenous women also reported high amounts of alcohol use.[569]

At least 2 decades of research on health disparities in the USA point to a complex set of historical, social, and economic factors that contribute to cardiovascular disease in non-White US women (including displacement and cultural trauma among Native American and Alaska Native women),[569] and which are rooted in historic and ongoing inequities.[570] Collaborative efforts in disease prevention and management are urgently warranted.

### Sub-Saharan Africa

Mirroring patterns in high-income countries, hypertension, diabetes, dyslipidaemia, obesity, and physical inactivity are risk factors for cardiovascular disease in women in African countries. However, poverty, malnutrition, migration, uncontrolled fertility, and complications of pregnancy and childbirth also contribute to their cardiovascular risk profile. AIDS/HIV and tuberculosis, and uncorrected congenital heart disease and rheumatic heart disease, are substantial contributors to the high burden of cardiovascular disease in African women.

WHO data report that the African region has the highest global prevalence of uncontrolled hypertension in adults aged 25 years.[571] A population-based cross-sectional study done at six sites in four African countries showed a slightly higher prevalence of hypertension in women (35%, 95% CI 33·7–36·2) than in men (31%, 95% CI 30·0–32·6).[572]

The obesity epidemic is another important health concern in Africa. Analysis from the Heart of Soweto Study[573,574] found a significantly higher proportion of

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obese women than men (55% vs 23%; OR 1·76, 95% CI 1·62–1·91). This study also reported that obesity is associated with poorer outcomes in cardiovascular conditions in women, such as rheumatic heart disease,[449] atrial fibrillation,[575] heart failure,[576] and dyslipidaemia.[577] There are substantial concerns about maternal obesity,[578] childhood obesity,[579,580] and inadequate physical activity in this region, with calls for prevention and control. Communicable diseases remain the core focus of researchers and policy makers within Africa, with inadequate attention and resources being directed at the obesity epidemic and the unabated increase of related chronic, non-communicable diseases.[581] In addition, obesity has a different cultural context in some parts of the region, in which it can reflect increased wealth and prosperity.[579,582] There is also the misconception of so-called healthy obesity, given the weight loss associated with the HIV/AIDS epidemic.[581] There is a need for further research investigating how obesity perceptions are shaped by cultural frames (eg, social, political, and historical) and how best to fit a cultural lens to community-level obesity interventions.[580]

Sub-Saharan Africa countries have increasing tobacco use. Fast population growth and rapidly increasing consumer purchasing power have led to intensive efforts by the tobacco industry to expand African markets, particularly among younger women. The African Tobacco Control Alliance surveyed 79 schools in five countries and found a high density of cigarette sellers on the doorsteps of primary and high schools, raising concerns that tobacco companies are aggressively marketing cigarettes to African school children in an attempt to expand their markets.[583]

Women in Africa also face substantial abuse and violence,[584] and are disproportionally affected by poverty and inadequate access to health care. The exclusion of women from formal education and skills training has serious implications, not only for socioeconomic development but also for health literacy, ability to afford health care, and decision making about health. Rebuilding the fragile health system in sub-Saharan Africa also requires repairing relationships with the international community by focusing on human rights and eliminating corruption; strengthening the health workforce through retention strategies, training, and non-specialist providers; and community engagement.

## Limitations of this Commission article

The following issues should be considered when reading this Commission article. First, it is not a systematic review of a specific research topic but rather a report aiming to capture potential sex-related gaps in cardiovascular disease knowledge, research, prevention, treatment, and access to care. A bias towards highlighting evidence for sex-related differences over reports of neutral findings cannot be excluded. Second, there is only mild emphasis on the important differentiation between sex and gender throughout the Commission article. Although sex relates to biological differences, gender is associated with sociocultural power structures.[585] Both sex and gender are increasingly recognised as important in health behaviour and the development, diagnosis, and management of diseases. Explanations for why this Commission article

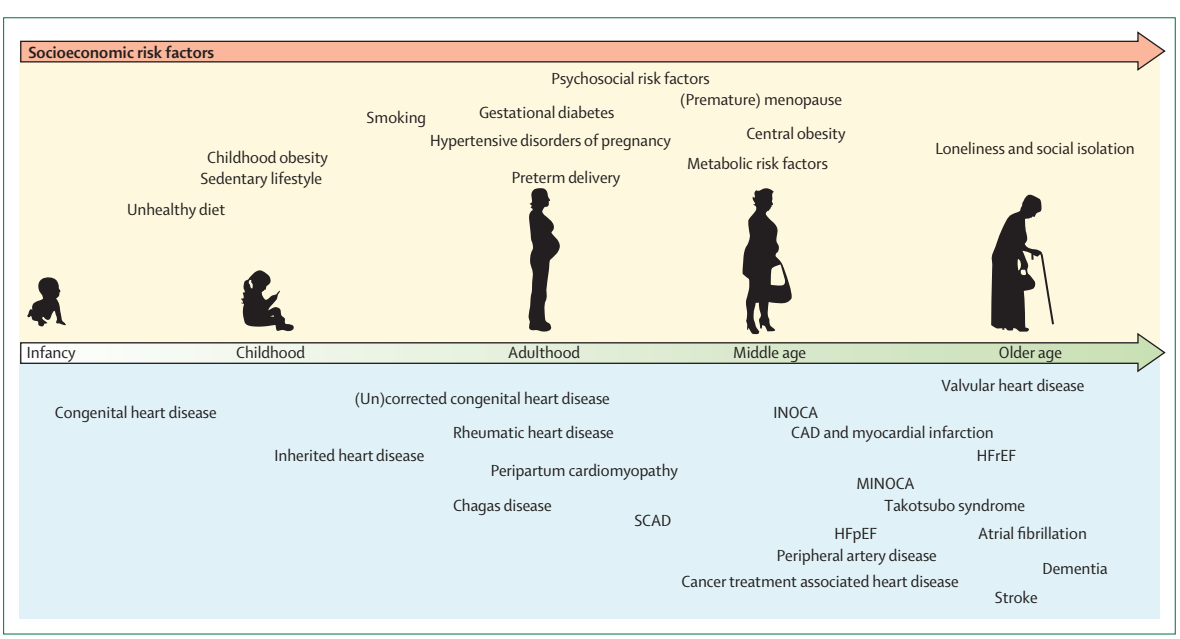


***Figure 8*: Cardiovascular diseases and their risk factors and modifiers during the lifecycle of a woman: opportunities to deliver comprehensive care and intervene**

CAD=coronary artery disease. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. INOCA=ischaemia with non-obstructive coronary arteries. MINOCA=myocardial infarction in the absence of obstructive coronary artery disease. SCAD=spontaneous coronary artery dissection.

### *Panel 5*: Overarching recommendations

**Close knowledge gaps**

Foundational knowledge is still scant concerning the pathogenesis, pathophysiology, and natural history of cardiovascular disease in women. Comprehensive sex-specific data on cardiovascular disease are absent in many regions, and women are under-represented in cardiovascular clinical trials and registries, which has led to uncertainty about the efficacy and safety of many therapies in women compared with men.

- Increase women's involvement in clinical trials; adjust exclusion criteria and partner with a range of stakeholders to investigate and address structural and economic barriers (eg offer flexible hours or at-home follow-up).
- Adhere to policies and guidelines regarding the consideration of sex and gender variables in research design, analysis, and reporting.
- Power cardiovascular clinical trials for sex-specific analyses to identify haemodynamic, pharmacokinetic and pharmacodynamic, and therapeutic norms that are specific to women, and to establish sex-specific treatment algorithms, targets, and appropriate management strategies for women.
- Initiate research studies to explore potential biological pathways that might underpin sex and gender as determinants of cardiovascular health.
- Investigate the effect of sex-specific and under-recognised factors on cardiovascular risk in women, to create the evidence base for improved guideline recommendations for risk factor assessment.
- Establish robust national and regional health-surveillance systems to monitor cardiovascular disease mortality and morbidity in women; integrate these systems with clinical quality registries to improve real-time, region-specific data collection on well established and emerging cardiovascular risk factors, cardiovascular disease management, and cardiovascular disease outcomes for women.
- Fund health services, economics, and outcomes research to establish a clear understanding of global variations in women's access to cardiovascular care.

**Enhance awareness of cardiovascular disease in women**

Education is a crucial resource in raising awareness about cardiovascular disease prevention, risk factor reduction, and intervention among health-care professionals and among women across their life course.

- Develop government-initiated public education activities to increase awareness about morbidity and mortality related to cardiovascular disease in women. Target these activities to specific audiences, including health-care professionals.
- Assess health literacy and cultural sensitivities as a foundation for developing personalised education for women.
- Use and expand both traditional (eg, community health workers) and digital communications media to support education strategies.
- Establish social media campaigns that are targeted specifically towards young women to raise awareness about cardiovascular disease risks.
- Invest in culturally specific and language-specific peer-to-peer programmes for women from minority populations, in which women teach women about positive behaviours that support cardiovascular health and reduce cardiovascular disease risk.
- Use holiday-themed campaigns (eg, February heart month in the USA, Mother's Day) and targeted outreach to places frequented by women (eg, churches, day care facilities, nail spas, hair salons) to heighten awareness about cardiovascular disease in women.
- Consider early education strategies to seed awareness of cardiovascular disease in girls and young women. This is especially important in regions at high risk for cardiovascular disease in pregnancy (eg, areas with high rates of rheumatic heart disease).
- Empower women in all regions through education about health and wellbeing, and establish equal opportunities for higher education, economic activity, and political life.

**Target well established, sex-specific, under-recognised risk factors**

Substantial work on a global scale is necessary to target risk factors associated with cardiovascular disease in women through screening, detection, and early intervention.

- Continue to develop policies that influence individual behaviours and exposures to well established risk factors.
- Strengthen the sex-specific focus of existing global population approaches to cardiovascular risk reduction.
- Develop cardiovascular disease policies that are specific to a region, in line with established global voluntary targets to define priorities, goals, and indicators for public health and community interventions to prevent, reduce, and manage cardiovascular disease in women.
- Enhance and implement women-specific clinical guidelines for cardiovascular disease prevention, and investigate the potential for sex-specific risk factor treatment criteria to improve cardiovascular outcomes in women.
- Scale up healthy heart programmes that target cardiovascular risk factors in women in highly populated and progressively industrialised regions in which cardiovascular disease prevalence is increasing.
- Involve multiple stakeholders (eg, government, health professionals, and patient advocacy organisations) in risk factor reduction policies.

(Continues on next page)

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(Panel 5 continued from previous page)

**Strengthen health-care systems and engage health-care professionals**

Prevention and management of cardiovascular disease in women require robust health-care systems supported by professionals who are aware of, and care about, the specificities of cardiovascular disease in women. It is imperative to create integrated health systems and to engage physicians, health-care workers, and patients as partners in recognising and managing cardiovascular disease in women across the globe.

- Strengthen and support primary care physicians in their key role for screening, guidance, and referral for cardiovascular disease prevention and care.
- Encourage a range of health professionals across relevant specialities (eg, obstetrics and gynaecology, emergency medicine, rheumatology) to routinely screen women with diseases that increase cardiovascular disease risk.
- Equip allied health-care providers (eg, nurses and community health workers) in non-conventional care settings who are involved in other aspects of women's health (eg, breast cancer screening) to initiate discussions with women about, and screen for, cardiovascular disease risk. There is considerable potential for such screening to occur in non-traditional settings and in partnership with a range of non-health-care organisations that are integral to women's lives.
- Create platforms that enable patients to access risk factor screening and assessment (eg, via pharmacies or digital technologies).
- Expand opportunities for women to receive risk factor assessment and management (eg, via community-specific venues such as hair salons, churches, day care facilities, and via cultural ambassadors).
- Invest in strategies to develop culturally competent cardiology care that accommodates religious preferences.
- Invest in novel approaches to care integration that focus on low-income and middle-income countries, and socioeconomically deprived populations.
- Promote, track, and report strategies for increasing the number of women in cardiology in general and in leadership positions (eg, increase the number of female cardiologists on guideline committees).

did not adequately address this issue include the interchangeable use of the terms sex and gender in the literature, which remains an important aspect. In addition, sound and systematic instruments for the analysis of gender in medicine are still needed.[585] Third, this Commission article did not address cardiovascular health in transgender women, owing to the current paucity and quality of data. An upcoming dedicated Series on transgender health by *The Lancet* will provide more information on this topic. Fourth, the overall evidence presented in this Commission article might be dominated by data for White women and high-income countries, reflecting that the current availability of more robust data in women with cardiovascular disease is for these populations and regions. Finally, the level of evidence for the different sections varies substantially. In an effort to provide an overview on the level of evidence for the most important statements of this article, the appendix indicates the level of evidence according to a colour scheme and to the best of our knowledge.

## Looking forwards

This Commission article represents the first attempt to comprehensively summarise the scientific evidence to outline gaps in our understanding of how women are differentially affected by cardiovascular disease and to document crucial disparities across different geographical and demographical settings. As a synthesis of the existing research and the numerous regional parallel efforts underway to better detail the scope of cardiovascular disease in women, this article provides the essential framework for a cohesive global strategy to gather these many strands of research, data collection, and clinical and public health interventions to coalesce around a common goal. Reducing the burden of cardiovascular disease in women by 2030 is an ambitious target, but an imperative and worthy one, especially because despite the heterogeneous patterns of disease and risk factors across countries and contexts, with intervention, much of the risk can be modified and mitigated (figure 8).

The next decade will be a pivotal one for clinical science and public health. The momentum to strive for equity and equality for women more broadly, both socially and culturally, translates into an extraordinary time to invest that same energy into improving women's health. Being the leading killer of women globally, cardiovascular disease must take precedence for our attention and action.

Throughout this article, the Commission has provided a robust, evidence-based, and diverse set of recommendations for strategies to close these knowledge gaps, increase awareness, and improve prevention and care for women with cardiovascular disease. It is both the starting point and a call to action to mobilise and energise the many key stakeholders, health-care professionals, policy makers, and women themselves, to work towards a healthier future (panel 5).

See Online for appendix

**Contributors**

All Commissioners are listed as authors, contributed to the overall concepts and messaging included in this article, and wrote the initial draft. The literature search, the edits of the initial and subsequent drafts, and the written subsequent drafts were prepared by BV with direction from RM and feedback and review from the other authors.

**Collaborators**

Alex Howson edited the initial and subsequent drafts. Maria Alu did the initial compilation of Commission article sections. Eleanor Cooney provided graphic design for figures 4–6 and 7. Deborah Kalkman helped with the literature search and contributed to the section on cardiovascular

disease and pregnancy. Ridhima Goel helped with the literature search and contributed to the section on peripheral arterial disease.
The Commissioners also wish to highlight the contributions of Chanchal Chandramouli for the section on Asia, Bernadet Santema for the section on heart failure, Adrienne O'Neil, Karin Jandeleit-Dahm, Jeroen Hendriks, Jaquelyne T Hughes, Angela Hehir, and Julie-Ann Mitchell for the section on Australia, Ana Girleza Munera for the section on Latin America, and Danny Chan for the sections on Europe, ST-segment elevation myocardial infarction, and cardiogenic shock.

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