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STATE OF THE ART REVIEW
Ischaemic heart disease

Cardiovascular disease in women: traditional and sex-specific risk factors

Yolande Appelman [1], Martha Gulati [2], Jeanine E. Roeters van Lennep [3], Leslee J. Shaw [4], and C. Noel Bairey Merz [2,*]

[1]Department of Cardiology, Amsterdam University Medical Centers, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands; [2]Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; [3]Department of Internal Medicine, Erasmus MC Cardiovascular Institute, Erasmus MC University Medical Center, Rotterdam, Netherlands; and [4]Department of Medicine (Cardiology), Blavatnik Family Women's Health Research Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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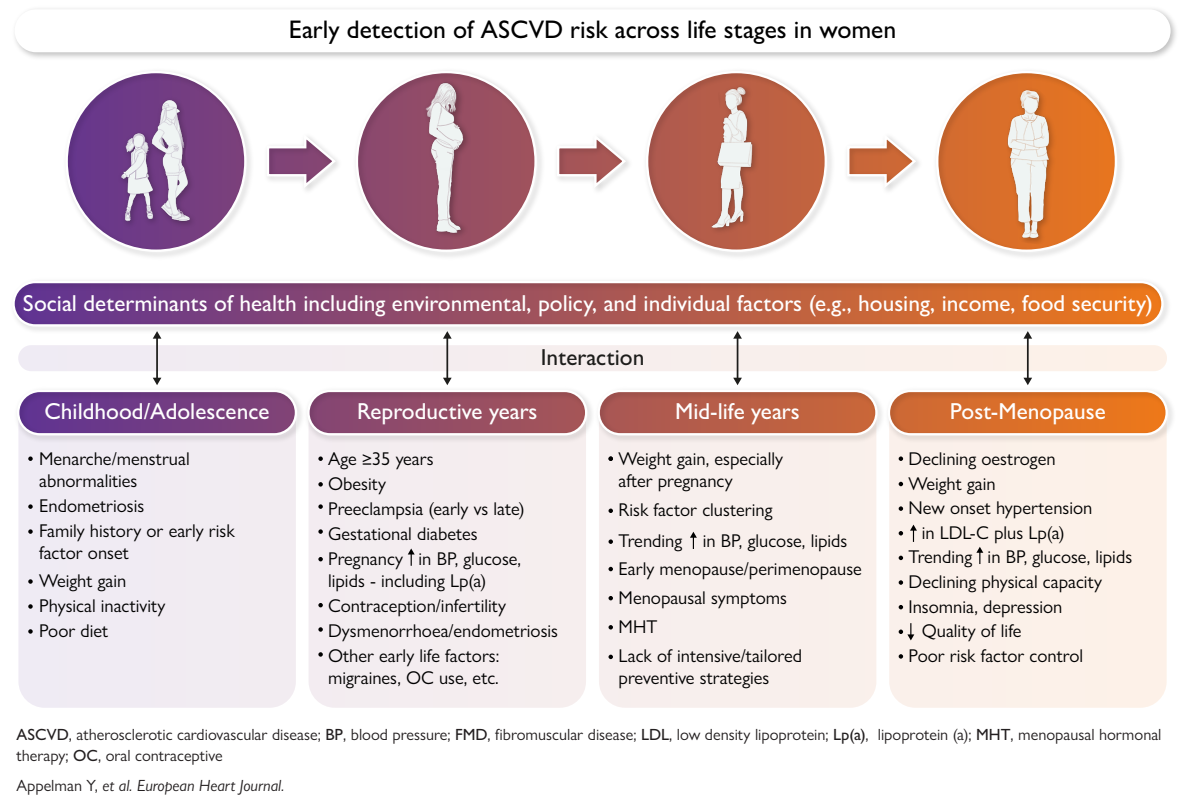
Graphical Abstract



Traditional and Sex-specific Risk Factors for Cardiovascular Disease in Women. Emerging literature of Traditional and Sex-specific Risk Factors to improve CVD prevention, detection, diagnosis, and treatment for women. ASCVD, atherosclerotic cardiovascular disease; FMD, fibromuscular disease; BP, blood pressure; OC, oral contraceptive; MHT, menopausal hormonal therapy.

* Corresponding author. Email: noel.baireymerz@cshs.org

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Abstract

Cardiovascular disease (CVD) accounts for more deaths in women than breast cancer, lung cancer and chronic lung disease combined, with a comparable mortality to that of men. Many women and physicians do not identify CVD as a major morbidity and mortality in women, resulting in significant delays in diagnosis and treatment. While advances have been made in the diagnosis, treatment and outcomes of CVD in women, there often remains insufficient evidence to guide effective, lifesaving care of women. This review of sex-specific and traditional CVD risk and risk-enhancing factors in women identifies areas of knowledge gaps to consider for investigation. A focus on the coronary vasculature reveals physiological differences of clinical relevance which can be interrogated. Inspection of and addressing disadvantage and gender bias in both the medical and lay communities should continue to be addressed. As CVD results from traditional risk factors and emerging risk-enhancing factors, a focus on the detection of preclinical cardiovascular disease may be of particular importance for women. Unique risk markers originate early in pre-menopausal women, as this is considered a healthy period of life. Awareness and implementation of the existing knowledge of sex-specific risk factors and sex-specific thresholds to educate women and physicians are needed. The anticipated life course of women supports a broadening focus on CVD toward that of lifelong care and emphasize key transitional stages for women—early risk factor onset, pregnancy, menopausal transition, and so on. This review is a call to action to re-envision a health system approach for lifespan prevention, detection, and treatment pathways to reduce CVD risk in women.

Keywords Sex • Risk factors • Women • Heart disease

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Introduction

According to the World Health Organization, cardiovascular disease (CVD) is the leading cause of death globally.[1–3] In the United States and Europe, CVD accounts for more deaths in women than breast cancer, lung cancer and chronic lung disease combined.[4,5] Of the 931 578 CVD deaths in the US in 2021, approximately 47% occurred in women (439 729 deaths).[6] Most cardiovascular deaths in women were due to CVD and myocardial infarction (MI), but also from heart failure and stroke.[7] Death rates due to ischemic heart disease (IHD) among younger women, ages 35–54, appear to be rising compared to declines observed in men.[8] Many lay women, as well as physicians, do not identify IHD as a prominent cause of morbidity and mortality in women, contributing to delays in diagnosis and intervention. The Lancet Women and CVD Commission emphasized the need to reduce the global burden of CVD in women by 2030, emphasizing the substantial knowledge gaps in CVD prevention, treatment, research and access to care for women.[9]

Traditional risk factors contribute to a woman's risk for developing clinically significant CVD. However, traditional risk stratification using a variety of scoring systems provides ineffective risk classification for the short-term and long-term or lifetime risk for women. In general, women have a high average lifetime risk for CVD, recognizing that nearly one in two women will have CVD over the course of their lives, reinforcing the need for sex-specific risk assessment. Consideration of a number of risk-enhancing factors uniquely relevant to CVD in women is being investigated as potential tools for more precise sex-specific risk assessment for women across the lifespan. We review this emerging literature and provide suggestions for ongoing work needed to improve CVD prevention, detection, diagnosis, and treatment for women (*Graphical Abstract*).

Sex differences in traditional cardiovascular risk factors

Traditional risk factors for CVD are well established, however, sex differences exist that are not fully appreciated (*Figure 1*).

Diabetes mellitus

CVD is the leading cause of morbidity and mortality in patients with diabetes. Type 1 and Type 2 diabetes (T1DM, T2DM) have a greater cardiovascular risk, especially increased risk of MI, heart failure, and stroke in women vs men.[10–15] Gestational diabetes CV risk begins to emerge within a decade post-partum.[16–19]

The Swedish National Diabetes Registry compared 33 170 persons with T1DM to 164 698 controls matched on age, sex and county and demonstrated that women with T1DM had an excess risk of acute myocardial infarction (AMI) and CAD compared with men at all ages.[12] The excess risk for AMI was substantially lower among those with good glycemic control and the absence of renal complications, but less so in women. Women with T1DM appear to have an excess risk of IHD compared with men, but not an excess of cerebrovascular disease.[13,14]

Women with T2DM have an estimated 25–50% greater risk of CVD compared with men with T2DM.[11,20–22] The prospective population-based U.K. Biobank study included 471 998 persons (56% women) and demonstrated a 50% excess risk of cardiovascular events in women vs men.[20] A large meta-analysis including 64 cohorts and over 858 000 persons also demonstrated that women with T2DM had a 40% excess risk of CAD compared with afflicted men.[22] Although there are documented disparities in the medical management of T2DM in women vs men, this alone does not explain the excess female risk.[11] Conversely, the retrospective analysis of the Clinical Practice Research Datalink in England examined 79 985 persons (45% women) observed that women with T2DM were less prescribed lipid-lowering agents and ACE-inhibitors vs their male counterparts, there was no excess risk based with women.[23] T2DM occurs in women at a relatively higher BMI than in men, perhaps exposing women to a longer exposure to insulin resistance and metabolic dysfunction.[22,24] This has been proposed as one of the potential mediators of endothelial dysfunction, which is often more severe in women with impaired glucose tolerance vs men.[24,25]

Hypertension

Hypertension is the most prevalent risk factor for CVD. Younger women, ages 43–46, have a lower prevalence of hypertension compared with men, but there is a reversal after the ages of 61–64, with more

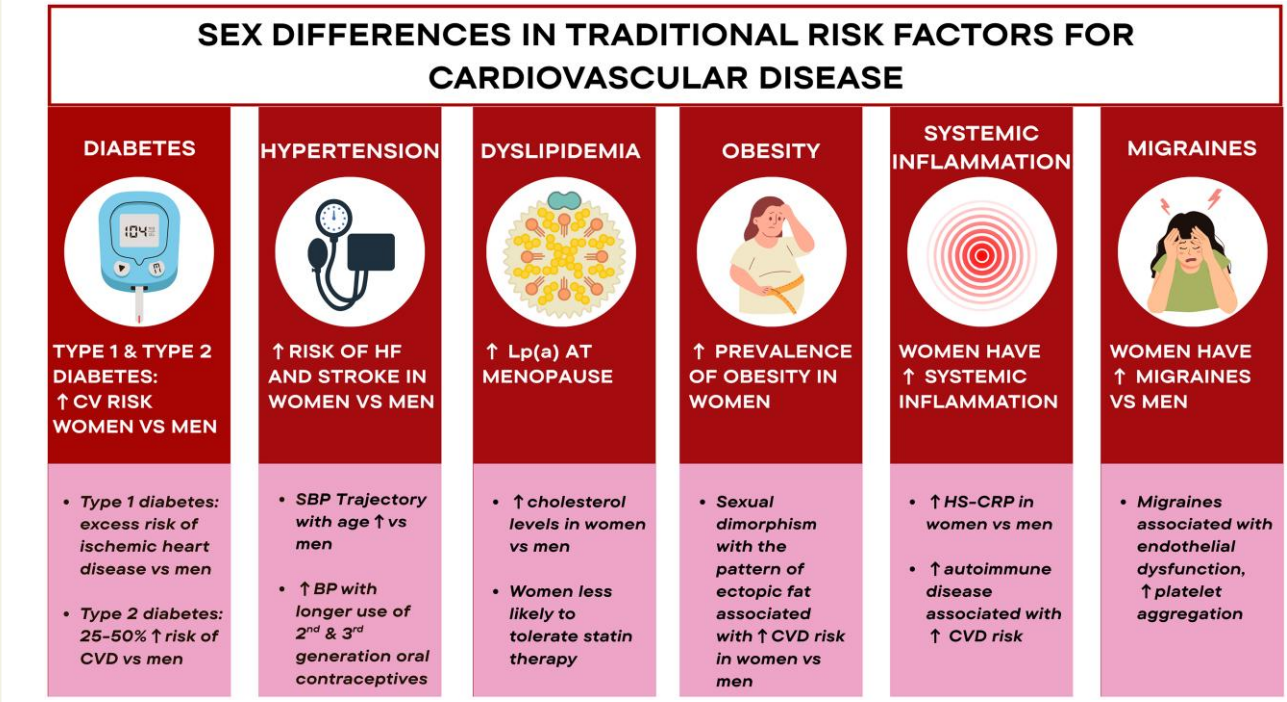

Figure 1 Sex Differences in Traditional Risk Factors for Cardiovascular Disease. There are sex (biological) differences in traditional risk factors, including those related to diabetes, hypertension, dyslipidemia, obesity, systemic inflammation, and migraines. CV, Cardiovascular; CVD, Cardiovascular Disease; HF, Heart Failure; HS-CRP, high sensitivity C-reactive protein; Lp(a), Lipoprotein (a) SBP, Systolic Blood Pressure

older women with hypertension.[26] Although women are more likely than men to have their blood pressure controlled, only one in four women with hypertension have their blood pressure controlled.[6]

Ageing increases the risk of hypertension in both men and women, but there are significant sex differences in blood pressure trajectories, particularly for the changes in systolic blood pressure. Although systolic blood pressure is lower in women at younger ages, the rate of increase is greater among women than men, with blood pressure increasing more rapidly in women with age, which was demonstrated using four large U.S. based cohorts and included over 32 000 adults.[27] These biological differences in the blood pressure trajectory may explain the pathophysiological differences of the effect of hypertension, in addition to the sex differences in responsiveness to antihypertensive medications. To date, it remains uncertain if thresholds for blood pressure diagnosis and treatment should differ by sex.[28]

Sex-specific factors need to be considered when assessing hypertension risk. Oral contraceptives impact hypertension risk, as demonstrated in a large pooled meta-analysis observed a 13% increase for every 5 years of use.[29] Not all oral contraceptives are the same, and the risk appears to be greater with second and third-generation oral contraceptives, raising the risk two- to three-fold. Fourth-generation progestin pills do not appear to elevate blood pressure, and those containing drospirenone may lower blood pressure through their antimineralocorticoid effects.[30,31]

Hypertension is associated with an increased risk of numerous forms of CVD, but its presence increases the relative risk for heart failure in women compared with men, particularly for the development of heart failure with preserved ejection fraction.[32] Women with hypertension have a greater lifetime risk of stroke than men, and women are more likely than men to have a history of hypertension when presenting with a stroke.[33]

Dyslipidemia

Lipid levels change during the life course both in women and men. Until approximately 25 years and after 55 years, low-density lipoprotein cholesterol (LDLC) levels are higher in women.[34] Overall cholesterol levels are higher for women compared with men, based on the NHANES data from 2017 to 2020 [4.9 mmol/L (190 mg/dL) vs 4.75 mmol/L (183.9 mg/dL)].[6] Undertreatment of dyslipidemia in women, in both primary and secondary prevention, is well-documented.[35–37] Additionally, women are also more likely to decline statins or discontinue therapy due to experiencing side effects.[37,38]

LDL-C increases during the menopausal transition. Although there is an ongoing debate about whether these changes are due to chronological ageing or reproductive ageing, the increase in LDLC is most likely related to menopause-related changes.[39,40] Moreover, lipoprotein (a) [Lp(a)] increases in women at the time of menopause, in contrast with men.[41,42]

Obesity

Obesity, defined as a BMI $\geq$ 30 kg/m^{2,} is epidemic worldwide, with the global age-standardised prevalence of obesity estimated to be 18.5% in women and 14% in men in 2022.[43] Obesity is both a chronic disease and a risk factor for CVD. The Nurses' Health Study demonstrated that obesity was the strongest predictor for T2DM in women, those with a BMI $\geq$35 kg/m^2 had a 40-fold greater relative risk for diabetes than women with a BMI < 23 kg/m^2.[44] Visceral obesity measures may be a better assessment of clinical obesity and target organ involvement,[45] and there is evidence of sexual dimorphism with the pattern of ectopic fat in the abdomen, pericardium and neck associated with greater CVD risk women compared with men.[46]

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Systemic inflammation

Women have higher baseline levels of systemic inflammation compared with men, and evidence of this can be assessed by high-sensitivity C-Reactive Protein (hsCRP), in addition to other biomarkers.[47] HsCRP has been demonstrated to be a strong independent predictor of CVD risk in several trials, including the Women's Health Study, and the combined use of hsCRP, LDL-C and lipoprotein(a) effectively predicted cardiovascular events.[48,49]

Autoimmune diseases

Autoimmune diseases occur more often in women and may accelerate atherosclerosis and IHD.[50] In a large UK study of over 22 million people from three large cohort studies, they examined those with autoimmune diseases compared to a matched group free of autoimmune diseases. They demonstrated that women with autoimmune disease had a higher risk of incident CVD, compared with age-matched controls (23.3 events/1000 patient-years, compared to 15.0/1000 patient-years, HR = 1.56, 95% CI: 1.52–1.59).[50] This risk increased progressively with the number of autoimmune diseases present. Systemic sclerosis, Addison's Disease, systemic erythematous lupus, and T1DM had the highest CVD risk. The increased presence of traditional risk factors in patients with systemic inflammation does not completely account for the increased risk of CVD in patients with autoimmune diseases.[51]

Migraine headaches

Migraine headaches are the third most prevalent condition worldwide and disproportionately affect women, with two-thirds of persons suffering from chronic migraines being women.[52,53] Migraines have been associated with an increased risk of CVD in both men and women.[54–56] The American Migraine Prevalence and Prevention study examined 120 000 U.S. households and demonstrated a strong association between migraines with or without an aura and CVD risk factors and CVD.[57] Those with migraines have an increase in traditional CVD risk factors[58,59] and a demonstrated association of migraines with generalized endothelial dysfunction[60] and increased platelet aggregation.[61,62] Additionally, some have suggested that the chronic use of non-steroidal anti-inflammatory drugs (NSAID) in some patients with migraines could contribute to increased CVD risk, although recent data from the Danish nationwide population cohort showed that this increased CVD risk was not explained by NSAID-associated CVD risks.[63]

Cardiovascular-kidney-metabolic syndrome

There is increasing recognition of the interaction between the cardiometabolic risk factors and chronic kidney disease. The interconnectedness and clustering of these risk factors have been recognized in new risk score assessments.[64] Cardiovascular-kidney-metabolic syndrome has risen over time, but has a lower prevalence in women compared with men (15.2% vs 22.4% Stage 3 CKM in 2018, based on the National Health and Nutrition Examination Survey).[65] Nonetheless, women have excess mortality compared with men at all stages of CKM.[65] The exact mechanism for these differences remains unclear.

Lifestyle Risk Factors. Sex differences in lifestyle risk factors are often underappreciated. (*Figure 2*)

Tobacco use

Cigarette smoking remains the leading preventable cause of cardiovascular deaths. There is significant geographic variability in tobacco use worldwide, with three times as many men smoking compared with women. Europe has the highest prevalence of tobacco use among adults (28%), in addition to some of the highest rates of tobacco use in adolescents.[66] Although the prevalence of smoking is lower in women compared with men, it may be more detrimental in women than in men. Women who smoke die 14.5 years earlier than non-smoking women, and men who smoke die 13.2 years earlier than non-smoking men.[67] Unique to women is the combined use of oral contraceptives

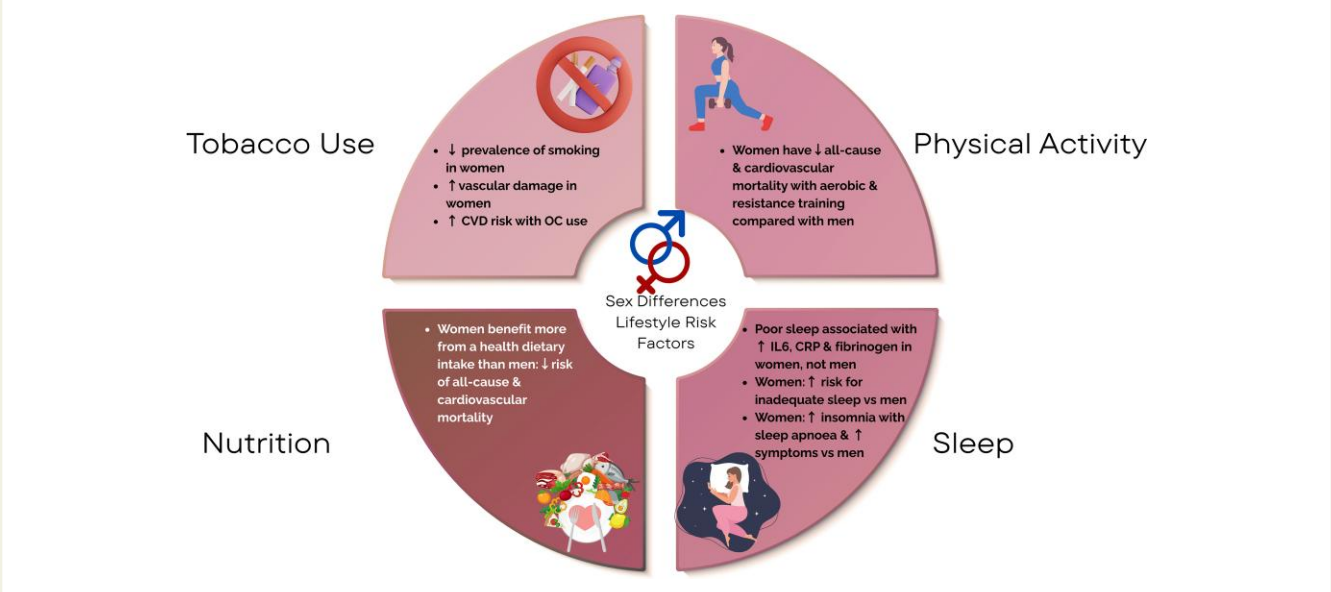

Figure 2 Sex Differences in Lifestyle Risk Factors for Cardiovascular Disease. There are sex (biological) differences related to lifestyle risk factors, including those related to tobacco use, physical activity, nutrition, and sleep, that need to be considered when assessing cardiovascular risk. CVD, Cardiovascular Disease; CRP, C-reactive protein; IL-6, Interleukin-6; OC, oral contraceptives

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with cigarette use, which further elevates the risk of AMI, attributed to the pro-thrombotic effects of both substances.[68]

Additional attention to the use of e-cigarettes is required when assessing CVD risk. The use has increased in women in the U.S. from 3.3% in 2016% to 4.3% in 2018, and the potential cardiovascular consequences of this are unknown.[69] The use of e-cigarettes appears not to differ in women compared with men in Europe (2.4% vs 2.5%) but varies by country, ranging from 0.6% in Spain to 7.2% in England when assessed in 2017–2018.[70]

There are also newer tobacco contacting products known as 'heat-not-burn' products that are touted as safer alternatives to either cigarettes or e-cigarettes, as they heat tobacco rather than combusting it. They lack any data to support claims of reduction of harm, yet are targeting both young consumers and women.[71]

Recent data from Europe suggests female adolescents are more likely to have tried or used cigarettes compared with males, whereas adolescent males were more likely to have tried or used e-cigarettes.[72]

Physical activity

Physical activity is associated with improved cardiovascular health, but inactivity is increasingly common. Women are less likely to meet physical activity guideline recommendations compared with men (20% vs 28%), and activity declines with age. When physical activity measurements do not account for domestic activities such as cooking, cleaning, childcare and informal care, these tools may underestimate true physical activity. Recent work has demonstrated sex differences in the benefit of physical activity.[73] In a study of over 400 000 adults, women derived greater gains in all-cause and cardiovascular mortality risk reduction compared with men from the same dose of leisure-time physical activity.[73]

Nutrition

Although dietary recommendations to preserve cardiovascular health are the same for both women and men, there is some evidence of sex-specific differences in benefits from dietary intake. In the NHANES study, a representative sample of the U.S. population demonstrated that females benefited more from a healthy dietary intake than males, with a reduced risk of all-cause and cardiovascular mortality.[74] In an analysis of the National Health and Nutrition Examination Survey (NHANES) from 2009 to 2018 of 22 761 participants (52% women), women had higher (better) health factor scores compared with men, but had lower (worse) health behavior scores using Life's Essential 8.[75] Despite a lower overall health behavior score in women, women had a healthier diet score compared with men. The adherence to a healthier diet in women compared with men has been demonstrated in other large population studies.[74,76] In the National Institutes of Health-AARP Diet and Health Study (237 036 men and 179 068 women), the association of high potassium intake and lower sodium–potassium ratio had a stronger reduction in mortality in women, compared with men.[76]

Sleep

Sufficient sleep is inversely associated with CVD and its risk factors.[77] There is a rise in inadequate sleep (less than 7 h), with a third of adults reporting inadequate sleep, with more women reporting poor sleep compared with men.[78,79] Women may be at greater risk for non-optimal sleep due to changing reproductive hormones that may affect sleep in women. Inadequate sleep is associated with excess inflammation, with poor sleep quality associated with increases in IL-6, CRP and fibrinogen in women but not in men.[80,81]

Obstructive sleep apnea (OSAS) can disrupt sleep and affect the quality of sleep, and is associated with an increased risk of CVD.[82] Although OSAS is more prevalent in men, when untreated, it is associated with an increased risk of hypertension, CAD, stroke, heart failure, and atrial fibrillation in women. Women with OSAS have shorter apneic episodes, lower apnea-hypopnea index scores, but prolonged partial upper airway obstruction than men.[83] When longer apneic episodes occur, they are associated with more severe oxygen desaturation in women compared with men. Women experience more insomnia because of the sleep apnea symptoms and are more likely to be symptomatic compared with men.[83] Because of these sex differences in presentation, women with sleep disordered breathing are often underdiagnosed and undertreated compared with men. Untreated sleep apnea in women is associated with 3.5 times greater risk of dying from CVD, but this risk reduces to the same as women without sleep apnea with appropriate treatment and continuous positive airway pressure.[84]

Sex-specific risk enhancers in women

Sex-specific risk factors in women can be broadly divided into reproductive factors (menstrual cycle, Infertility, PCOS) and uterine-related risk factors(endometriosis and leiomyomas) (*Figure 3*), and pregnancy-related risk factors (*Figure 4*). Some of these risk factors are interconnected, such as infertility and polycystic ovary syndrome (PCOS), and small for gestational age, premature birth, and hypertensive disorders of pregnancy (HDP). If a woman has multiple sex-specific risk factors, the multiplicative nature of this risk is unknown.

Menstrual-cycle related

During the menstrual cycle, female sex hormones such as estrogen and progesterone levels fluctuate. Several studies showed that even these subtle variations increase the risk of CVD events. Several studies report that premenopausal women have a higher risk of an acute coronary syndrome (ACS) during or immediately after menses.[85–88] However, these are only small studies as premenopausal ACS is rare. Moreover, recording the phase of the menstrual cycle during admission for ACS is not part of routine care but should be part of a thorough history in young women. Also, the effect of the phase of the menstrual cycle phase on specific subtypes of ACS, such as MI with no obstructive coronary artery (MINOCA) disease or spontaneous coronary artery dissection (SCAD), is unknown.

Functional hypothalamic amenorrhea (FHA) is a form of anovulation that results in chronic hypoestrogenemia in addition to infertility in young women, particularly in those with anorexia.[89] FHA can be prolonged from months to years, and an emerging study has identified endothelial dysfunction in women with FHA.[90]

Infertility

There is an association between infertility and CVD risk.[91–93] The results are diverse due to variable definitions of infertility and also the underlying causes of infertility. The Nurses' Health Study showed that infertility, defined as trying to become pregnant for >1 year without success, was common and reported by 27.6% of the participants. Compared with gravid women who had not reported infertility,

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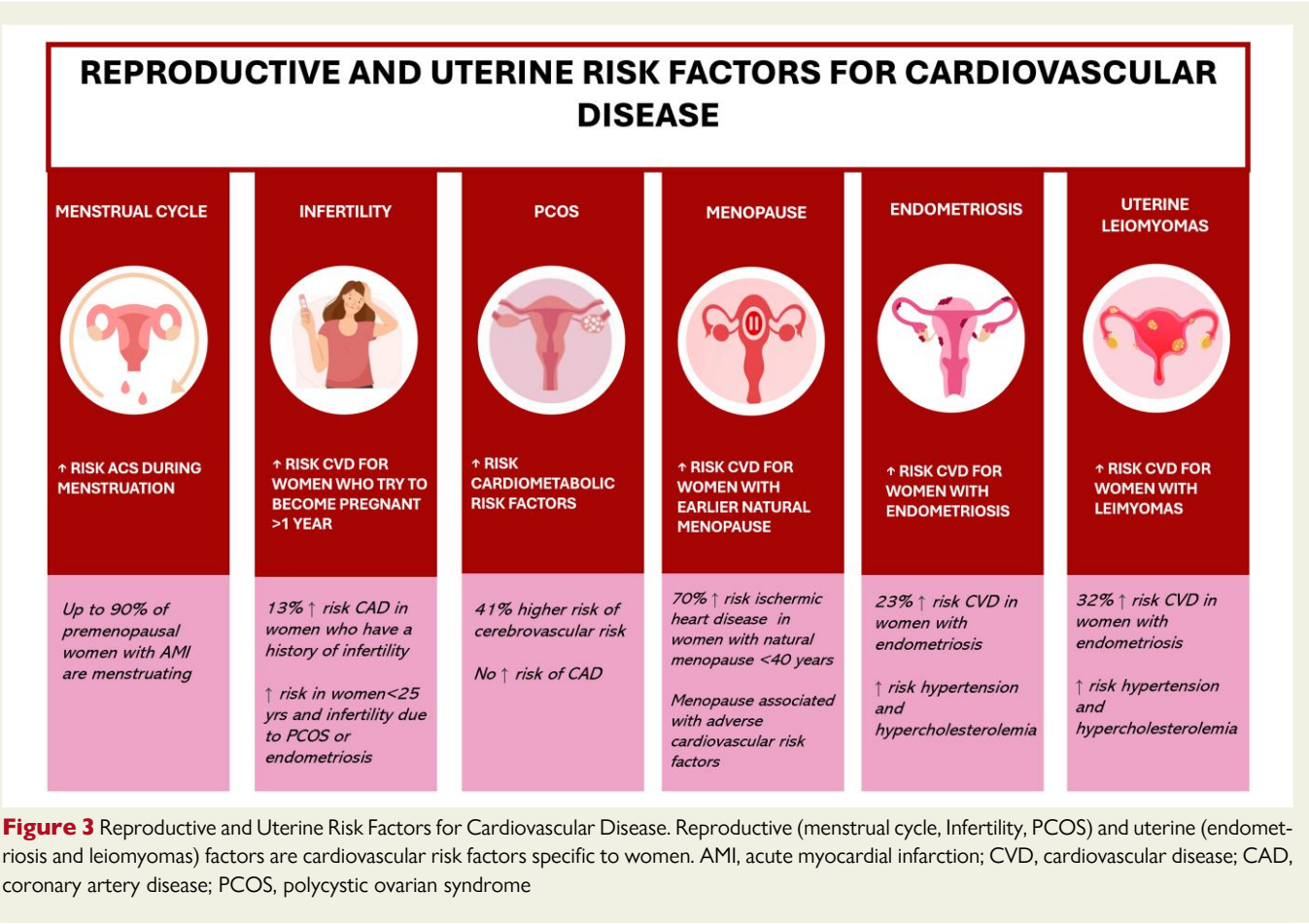

Figure 3 Reproductive and Uterine Risk Factors for Cardiovascular Disease. Reproductive (menstrual cycle, Infertility, PCOS) and uterine (endometriosis and leiomyomas) factors are cardiovascular risk factors specific to women. AMI, acute myocardial infarction; CVD, cardiovascular disease; CAD, coronary artery disease; PCOS, polycystic ovarian syndrome

women with a history of infertility had a 13% higher risk of CAD. This risk was stronger in women who reported experiencing infertility at younger ages (≤ 25 years) and in women whose infertility was attributed to ovulatory disorders, which included PCOS or having endometriosis.[94]

Polycystic ovarian syndrome (PCOS)

PCOS is the most common endocrine disorder in women of reproductive age, with a prevalence of 6–20%, depending on which diagnostic criteria are applied. PCOS is associated with clustering of cardiometabolic risk factors, including obesity, insulin-resistance/diabetes type 2, hypertension and an atherogenic lipid profile with low HDL-C levels and high triglyceride levels and in some studies also increased LDL-C levels.[95]

Interestingly, a meta-analysis showed that women with PCOS, despite a diagnosis of cardiometabolic risk factors, did not have a significantly higher risk of non-fatal CAD events but did have a 41% higher risk of non-fatal cerebrovascular events.[95] A hypothesis to explain this unexpected finding is that the risk of CAD is less than what would be expected of their risk profile is as women with PCOS have less menstrual cycle-related fluctuations of estrogen levels and a slightly higher age of menopause.

Another meta-analysis showed that lifestyle interventions are effective in reducing cardiometabolic risk factors in women with PCOS.[96] Therefore, timely lifestyle intervention aimed at women with PCOS is important to reduce the long-term exposure to cardiometabolic risk factors.

Menopause

Age of natural menopause is inversely associated with CVD risk.[97,98] Women with premature ovarian insufficiency, defined as a natural menopause before the age of 40 years, have an approximately 1.7-fold increased risk of fatal or non-fatal IHD risk compared to women who had their menopause at 50–54 years of age.[98] However, it is uncertain if early menopause is a marker or a risk factor of CVD, as a recent Mendelian randomization study did not find evidence for a causal relation between age of natural menopause and CAD.[99] Moreover, iatrogenic early menopause as a result of risk-reducing salpingo-oophorectomy (RRSO) seems not associated with increased cardiovascular risk, which is also evidenced by a recent study showing that the prevalence of coronary artery calcium was not increased in women who had a RRSO ≤ 45 years compared to women who had an RRSO ≥ 54 years or age-matched controls from the general population.[100] Also timing of RRSO is variable, and generally, they wait until post-reproduction, which is mostly 40 years and older. These women are at elevated breast cancer risk and largely cannot receive estrogen post-surgery.[101]

The menopausal transition is accompanied by adverse metabolic changes, including increased body weight, accumulation of visceral fat, reduced insulin sensitivity, elevated systolic blood pressure, and a more atherogenic lipid profile characterized by an increase in LDL-C and Lp (a) as well as impaired HDL functionality.[102]

The effect of menopausal hormonal therapy (MHT) on CVD risk is complicated, as it is affected by the timing and type of MHT. Initiation of MHT early after menopause is likely to have beneficial effects on CVD risk. Moreover, the type of estrogen and mode of administration

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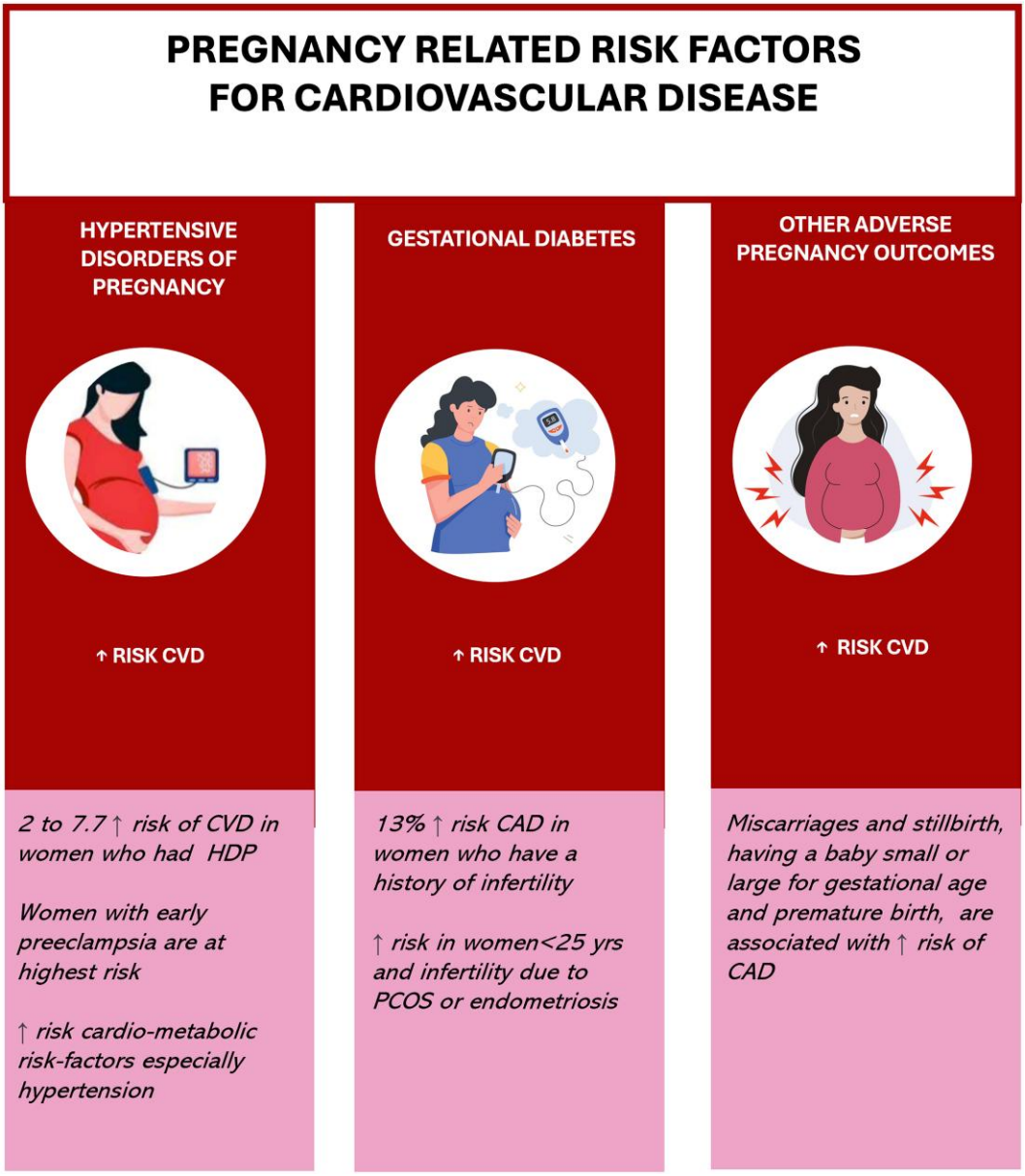

Figure 4 Pregnancy-related risk factors for cardiovascular disease. Hypertensive Disorders of pregnancy, gestational diabetes and other adverse pregnancy outcomes, such as miscarriage and stillbirth, having a baby small or large for gestational age and premature birth, are cardiovascular risk factors specific to women. CVD, cardiovascular disease; HDP, hypertensive disorders of pregnancy; CAD, coronary artery disease; PCOS, polycystic ovarian syndrome

are important.[103] Fourth generation subcutaneous bioequivalent estrogens are currently recommended as MHT as they have the most favourable safety profile. Currently, MHT is indicated in women with a premature menopause or to alleviate menopausal symptoms, including vasomotor symptoms and 'brain fog' and genitourinary syndrome, but not for reducing CVD risk.[103]

Endometriosis

Endometriosis is characterized by endometrial-like tissue outside the uterus, inducing a local inflammatory response leading to chronic pelvic pain, fatigue, dysmenorrhea, menorrhagia, dyspareunia and infertility. The prevalence of endometriosis appears to be similar to or lower in Black women compared to White women; however, diagnostic bias, inequities in access to health care, and potential variations in disease presentation may collectively contribute to the underdiagnosis of endometriosis among Black women.[104] Endometriosis is associated with an increased risk of hypercholesterolemia and hypertension.[105] Women with endometriosis have a 23% higher risk of developing CVD compared to women without endometriosis.[106] The proposed biological pathway is that chronic inflammation, coupled with additional risk factors, leads to accelerated atherosclerosis.[107–109] However, more large-scale studies are needed, especially to explore the pathophysiological consequences of longstanding inflammation.

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Uterine leiomyomas

Uterine leiomyomas are the most common benign gynaecological tumours originating from the uterine smooth muscle tissue, affecting up to two-thirds of women of reproductive age.[110] The most common symptom is menorrhagia, other symptoms include chronic pelvic pain, pelvic pressure leading to urinary incontinence and dyspareunia. Uterine leiomyomas are more common and more symptomatic in Black women compared to women of other ethnicities.[104] Black women disproportionately face a variety of exposures throughout the life course that may contribute to their higher incidence, prevalence, and severity of uterine fibroids, such as daily stress, including exposure to perceived racism and environmental and occupational exposures, including beauty products.[104]

Uterine leiomyomas are associated with chronic inflammation and hypertension.[111] Women with uterine leiomyomas have a 32% increased risk of MI, which was attenuated when women had surgical treatment.[112] The proposed biological pathway is that, in addition to the higher prevalence of hypertension, the long-term exposure to chronic inflammation leads to accelerated atherosclerosis.[107] However, also for uterine leiomyomas, more large-scale studies are needed, as well as studies to unravel the pathophysiological mechanisms.

Pregnancy-related risk factors

Pregnancy can be regarded as a natural cardiovascular stress test early in life. Therefore, having an adverse pregnancy outcome (hypertensive disorders of pregnancy (HDP), gestational diabetes, miscarriage and stillbirth, having a baby small or large for gestational age and premature birth) 'flags' women who are at increased cardiovascular risk, which should prompt timely cardiovascular prevention. The early years postpartum are largely ignored for women with preeclampsia or gestational diabetes, but represent a time where heart failure and other CVD event risk emerges,[19,113] even more so for those with early or severe preeclampsia.[114]

Hypertensive disorders of pregnancy

HDP include gestational hypertension, preeclampsia, HELLP syndrome and eclampsia and are the main cause of maternal death in high-income countries.

Approximately 5–15% women experience an HDP, which is increasing due to the older age of pregnancy and the increased prevalence of pre-pregnancy hypertension, diabetes, and obesity, which are all risk factors for developing HPD. Ethnic disparities in the prevalence and outcome of HDPS are described. Black women are reported to have an almost 2-times increased risk of developing pre-eclampsia, while a slightly decreased risk of preeclampsia is reported in women of East Asian.[115] Women who had an HDP have a 2 to 7.7 times increased risk of developing IHD.[116] However, HDPs are also associated with an increased risk of developing heart failure, atrial fibrillation and cardiac valve diseases.[117] Women who had early pre-eclampsia, often defined as <34 weeks of gestation, which is often accompanied by premature birth and having a baby small for gestational age, have the highest risk of developing future cardiovascular events.[116] At the short term, women who have had a HDP have an increased risk of developing hypercholesterolemia, diabetes and especially hypertension. Within 10 years, 32% of women who had an HDP developed hypertension in their forties.[118] But women who had severe preeclampsia have an even higher risk of developing hypertension: 41.5% had an increased blood pressure 1 year after delivery.[119]

Women who had HDP have an increased burden of subclinical atherosclerosis, substantiated by increased carotid media thickness,[120] and a higher coronary artery calcium score compared to age-matched controls.[121] Recent Mendelian randomization studies showed that HDPs are causally related to CVD, underscoring that HDP is a risk factor and not merely a risk marker.[122,123] The exact pathophysiology of HDPs and how they relate to CVD is still not fully elucidated, but chronic inflammation and abnormal endothelial function are likely involved.[124,125] A strategy of targeting a blood pressure of less than 140/90 mm Hg was associated with better pregnancy outcomes than a strategy of reserving treatment only for severe hypertension, with no increase in the risk of small-for-gestational-age birth weight.[126].

Gestational diabetes mellitus

Approximately 10% of pregnant women develop gestational diabetes.[127] Obesity pandemic prevalence is increasing at an alarming rate. Women who have gestational diabetes more often develop other pregnancy complications, including HDP, preterm birth and having a baby large for gestational age.[128] Postpartum, they are at increased risk of developing cardiometabolic risk factors, not restricted to T2DM, but also hypertension and hypercholesterolemia.[129,130] Women who had GDM and developed T2DM have an approximately two times increased risk of developing cardiovascular events, but also women who do not have postpartum T2DM have a 1.56 times higher risk of cardiovascular events.[19]

Not only mothers who had gestational diabetes, but also their offspring have an increased risk of long-term CVD, highlighting an intergenerational-genetic effect.[131]

Other adverse pregnancy outcomes

Many adverse pregnancy outcomes (APOs), including miscarriages and stillbirth, having a baby small or large for gestational age and premature birth, are associated with an increased risk of developing cardiovascular future diseases.[132] Recent evidence suggests the elevation in Lp(a) heightens risk for stillbirth, which may be due to effects on the vasculature leading to foetal hypoxia, but also to the thrombotic effect of Lp(a).[133]

Women who have multiple APOs have an even further increased risk for future CVD. At <10 years of delivery, the risk of IHD is 2.26 times increased for women who had three APOs, compared to 1.29 times for a woman with one APO.[134] The specific pathophysiological pathways by which APOs lead to CVD are not known, but a Mendelian Randomization study showed APOs and CVD are driven by shared genetic liabilities.[135]

X chromosome

X inactivation is the epigenetic mechanism to compensate for the extra X chromosome women have compared to men. This X-inactivation is expected to be random, leading to a balanced exposure to the paternal and maternal X chromosomes. Preferential X inactivation to one of the X chromosomes is called skewed X-X- X-inactivation and has been linked to multiple diseases, including autoimmune diseases and cancer.[136]

A recent study showed that skewed X-inactivation was observed in almost 50% of the atherosclerotic carotid plaques and 67% of the blood samples of women with cerebrovascular disease.[137] Moreover, women with skewed plaques had a 46% higher risk of developing peripheral arterial events.[137] X-inactivation has not been studied widely in CVD research, but could be an important sex-specific mechanism in atherosclerosis.

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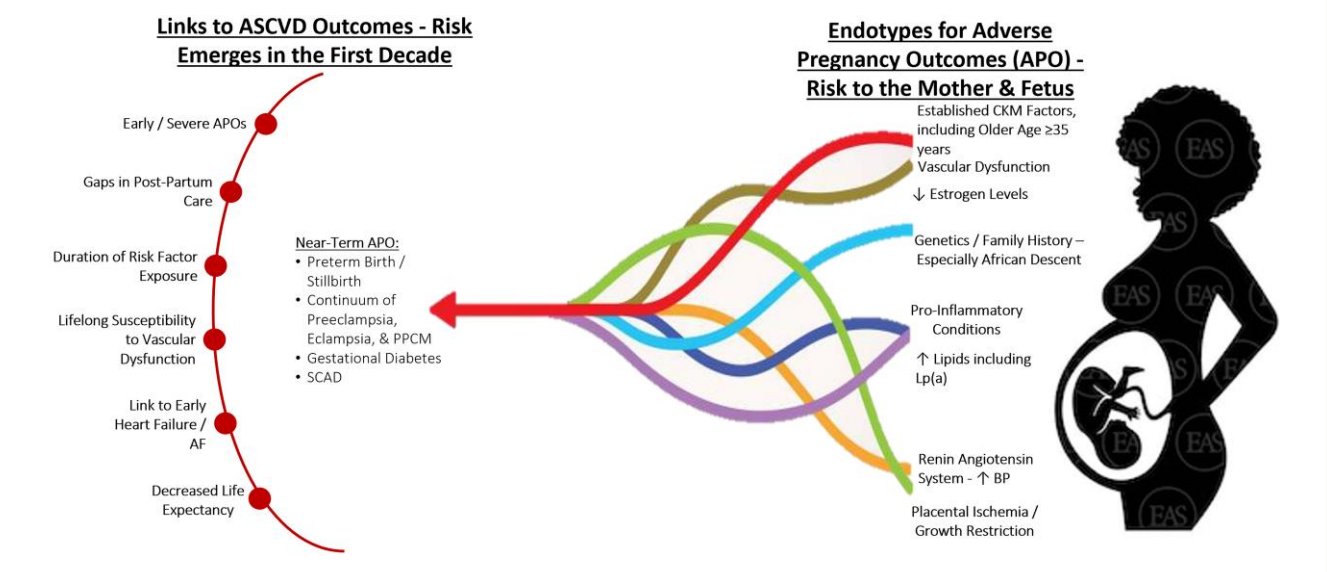

Figure 5 Pregnancy-related risk factors for cardiovascular disease. Emerging literature of Traditional and Sex-specific Risk Factors to improve CVD prevention, detection, diagnosis, and treatment for women. APO, Adverse Pregnancy Outcomes; PPCM, Peripartum Cardiomyopathy; AF, Atrial Fibrillation; CKM, Cardiovascular-Kidney Metabolic; Lp(a), Lipoprotein(a); BP, Blood Pressure; ASCVD, atherosclerotic cardiovascular disease; SCAD, spontaneous coronary artery dissection

Potential strategies for prevention, detection and management

The complexity of CVD in women presents unique obstacles to timely and accurate risk detection. In premenopausal women, many harbingers of CVD risk are apparent but often do not prompt regular screening over their lifespan. The transition to menopause and older years brings with it additional unfavourable trends in CVD risk, but often does not result in intensified care and minimizes opportunities for meaningful improvements in clinical outcomes. Preventive care, however, is evolving toward earlier detection and treatment of atherosclerotic CAD, which covers the early life stages where risk becomes apparent in younger women up until CVD assessment in older women.[138] In this section, we highlight key subgroups of women not traditionally considered at-risk along varied life stages and inclusive of diverse specialities to devise prompt and targeted preventive care pathways (*Figure 5*).

Screening across critical life stages for women

Clinicians should generally understand how risk factor measures change throughout stages of a woman's life, with notably worsening trends for blood pressure, weight, lipids, and Lp(a) through the menopausal transition.[139] Weight gain also occurs at predictable life stages, including pregnancy, through the menopausal transition, and into a woman's older years. Following pregnancy, flagging weight gain (or the failure to lose weight) is a sentinel moment for the physician to re-focus the woman on the untoward consequences of unhealthy obesity—including diabetes, hypertension, infertility, sleep disorders, and breast cancer (to name a few).[140] Risk factors continue to worsen with ageing, such that up to 80% of older women are hypertensive.[141]

Regular CVD screening is generally recommended for young to older women, generally every 1–5 years, depending on the risk strata of the patient. For the preventive cardiologist, there is an unexpectedly high prevalence of cardiovascular risk factors before age 50 years. For example, 1 in 8 are hypertensive, 1 in 6 have dyslipidemia, and 1 in 3 are obese, respectively.[141–143] It is this longer duration of risk factor exposure which is a major determinant of atherosclerotic CAD risk, and, as such, detection and lifestyle changes for women with early onset hypertension or diabetes, along with those who are overweight or obese, are essential to preserve lifelong health.[141,144] The concept of early intervention and lifelong prevention is the current mantra for early CVD risk assessment in young women, yet challenges with adherence exist.[145,146]

Pregnancy, including reproductive infertility, represents a critical phase for screening to guide not only those at-risk for pregnancy complications (e.g. preeclampsia and gestational diabetes) but also long-term risk of chronic conditions contributing to CVD and heart failure risk.[113] It is essential that we target more intensified care of women with pregnancy-related complications to improve their course for future pregnancies, but also improve their lifelong risk of CVD. Collaborative relationships must be developed between maternal and fetal medicine specialists and CV medicine to care for the woman during pregnancy, but also to devise strategies for post-partum care.[113] Too often, a focus on CV care can easily be supplanted by other family and work-related priorities during a woman's reproductive years.

Chronic autoimmune disorders, more prevalent in women, also form an important group of women at an elevated CVD risk, including rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome. Any women's centre should create pathways of care for the rheumatologist to facilitate early screening of CVD risk for women with autoimmune disorders. Inflammation also plays a shared role in CVD with endometriosis and dysmenorrhea.[114] This shared endotype should be a flag to those identified pre-menopausal, most often by their gynaecologist. Gynaecologists would also be those caring for women entering menopause early (<40 years of age), who should also be

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flagged as higher CVD risk. Other groups of women referred to gynecologic oncologists for RRSO present unique challenges as they promptly enter menopause. Women generally wait to undergo RRSO following reproduction (or after age 40 years). However, CVD risk is often not a focus of the surgical plan to reduce breast and ovarian cancer risk, and the CV specialist would add considerably to discussions regarding healthy lifestyle changes and intensified preventive care, as needed.[147] Like other specialities, there needs to be a more defined link between gynaecology and CV medicine.

For all physicians, there needs to be more detailed risk detection pathways for the peri- and post-menopausal woman, and not only care for those with vasomotor symptoms. Women generally receive minimal education as to what to expect in terms of CVD health in their post-menopausal years. Women should understand how weight, blood pressure, and cholesterol (including lipoprotein(a)) change with menopause. And when combined with declining physical functioning, there is a further exacerbation of CVD risk. An essential component of care for the older woman is education to intensify lifestyle changes (i.e. healthy diets, weight loss, decreased salt intake, and increasing physical activity) to attenuate risk as well as optimize well-being.

Imaging of atherosclerotic CAD in asymptomatic women

The cornerstone of CVD risk is the use of a variety of scores that provide assessment of low to high-risk women, now inclusive across ages 30–79 years.[148] There are greater limitations with the pooled-cohort equations CVD risk score and the Systematic Coronary risk Evaluation (SCORE), including SCORE2, compared with the Predicting the Risk of cardiovascular EVENTs (PREVENT) risk score. The PREVENT score was developed and validated, with 56% of participants being women, in a more contemporary population, and more inclusive of younger ages.[148] All of these scores are the basis for risk-based treatment—especially for hypertension and dyslipidemia—yet evidence supports that there are significant limitations to the accuracy of risk scores in women, which are primarily influenced by age and do not include sex-specific risk factors.[149–153] From a recent analysis, underestimation of risk in women was reported in 3 of the 4 cohorts, with discordance ranging from −31% to −81%.[154] Moreover, from the Trøndelag Health Study (31 946 participants), traditional risk factors included in the NORRISK 2 and European SCORE 2 models were not predictive of risk in women.[155] As such, a risk score may leave the clinician with residual uncertainty as to a woman's true CVD risk. Recognition of risk-enhancing features (e.g. preeclampsia, premature menopause) has been shown to improve detection of at-risk women, but a sizeable proportion of other women are often missed and under-recognised as to their true CVD risk.

Imaging is especially helpful for those in whom the risk in a woman remains uncertain. Candidates for imaging of subclinical atherosclerosis, such as with coronary artery calcium (CAC), include women with risk factors achieving intermediate risk status, but also those with lower risk with female-specific risk-enhancing factors.[156] However, from the CAC Consortium, one in four women ≤50 years of age had detectable CAC.[157] More evidence is required to understand thresholds and drivers for early atherogenesis in women.

Evidence supports that CAC markedly improve the risk classification of low to high-risk women beyond clinical risk scores.[157,158] The extent of CAC is a powerful predictor of an array of CVD events[157,159] A CAC score of 100 or higher is generally considered high risk and should be followed with intensified preventive care. Across subgroups, Black and Hispanic women with a CAC score of ≥100 have a significantly higher risk of CV mortality than other women.[158] Moreover, women with more extensive CAC in multiple vessels have a higher CV mortality risk than men.[157] Using CAC to guide preventive care has been shown to improve treatment adherence and reduce atherosclerotic plaque progression.[160,161] Although CAC scores are often used to guide the use of lipid-lowering therapy,[156] evidence also supports that a patient's knowledge of their score enhances overall adherence and improved health behaviours.[161,162]

There is emerging data on the concept of opportunistic CVD screening to identify additional women with imaging measures of arterial calcification. Applying this approach, imaging performed for other clinical indications may be used to identify calcification in arterial beds. Breast arterial calcification (BAC) is commonly visualized on screening mammography in ∼1 in every 6 women. The presence of BAC heightens the risk of CVD events by as much as 50%.[163,164] There are also AI-based algorithms for quantification of CAC from a routine chest CT that have been validated to prognosticate AI-CAC findings akin to those of routine scores.[165,166] These two examples identify the importance of optimizing available data within the electronic health record and how AI-based imaging approaches may be used to supplement risk factor scores. The cost of imaging is often a hurdle, particularly for women. Programs which provide CAC at no cost have demonstrated increased representation of women, as compared with standard testing requiring out-of-pocket costs, as noted in the CLARIFY (Community Benefit of No-charge Calcium Score Screening Program) registry.[167]

Screening approaches in women have largely been 'me too' and emulating risk markers established in predominantly male cohorts. It is time to re-focus risk assessments to highlight novel markers targeting a) mechanistic pathways (e.g. inflammation), b) lengthy risk exposures (e.g. early age at menarche), or c) unique disease biomarkers, such as thyroid-stimulating hormone.[155] None of the risk-based approaches incorporates a thorough reproductive, gynecologic, and menopausal history, which is key to unique drivers of risk in women. Novel risk approaches may be improved when inclusive of genetic variants which alter across the life course (e.g. Lp(a) increases during pregnancy and into menopause) for women (not men). Additional consideration could be given to the role of polygenic risk scores, focusing on inherited susceptibility and trajectories for CVD, such as for endometriosis, obesity, Type 2 diabetes, and PCOS. Moreover, gene by sex interactions may identify unique influences for targeted treatment pathways and risk-based thresholds. Given the disproportionate influence of social determinants, a more comprehensive assessment of exposomic factors should be considered to assess the totality of environmental exposures (e.g. air pollution and social determinants) in altering a woman's disease risk. We can also learn from conditions disproportionately afflicting women, such as Alzheimer's disease, where there is a strong overlap in risk markers—especially for lipids and obesity.

Our screening approaches have largely focused on the detection of those at high risk who are targeted for preventive care. Yet, sex differences in variability of drug efficacy and side effect profiles are not entrenched within the preventive evaluation. Pharmacokinetics are influenced by adiposity, liver function, and hormonal status, to name a few, which would support sex differences for common CV preventive drugs.[168] These factors would also influence side effects in women, especially those well described for ACE inhibitors and statins.[169] Although costs of care are often identified as barriers to utilization in women, pharmacogenetic differences between women and men are often unknown. For example, the etiology of sex-related differences in platelet reactivity influences therapeutic effectiveness for antiplatelet therapy,

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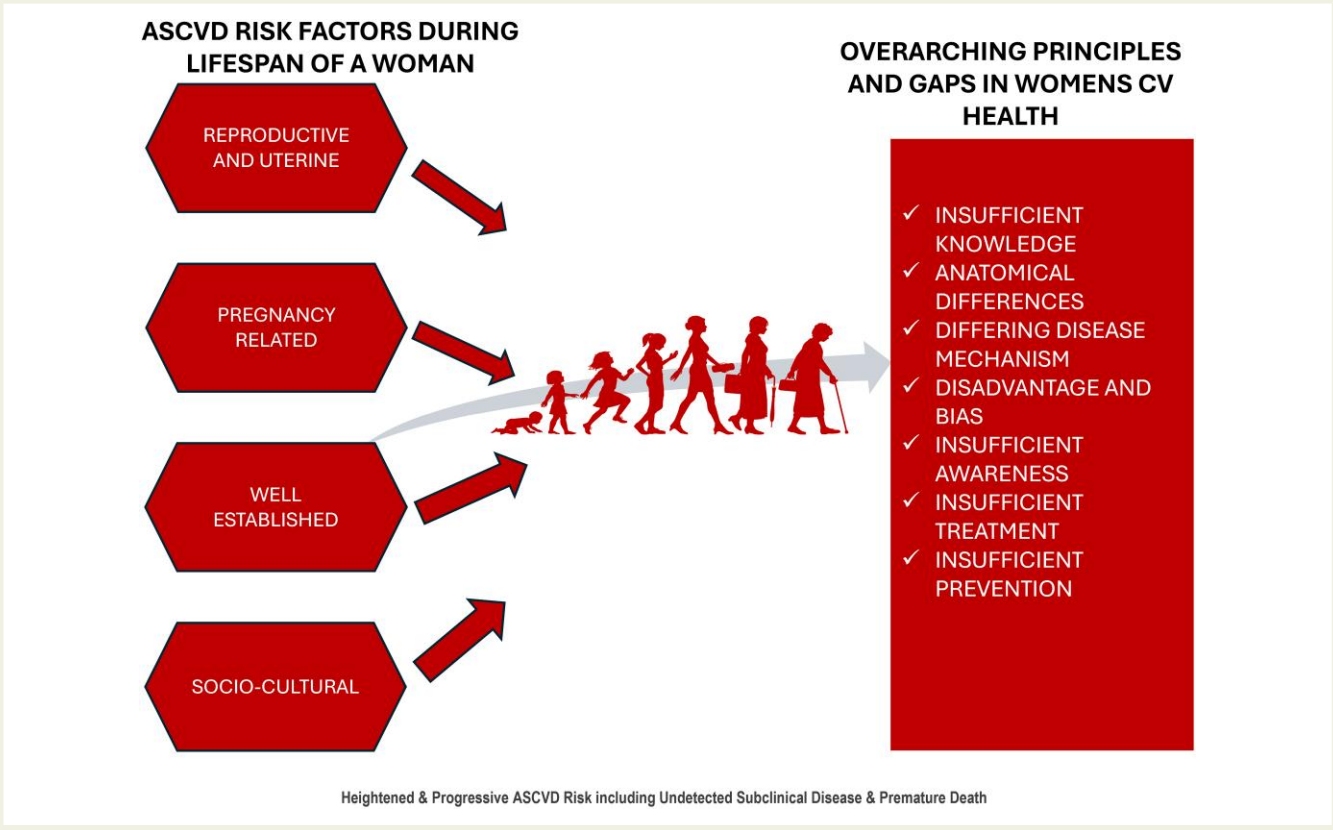

Figure 6 ASCVD risk factors during the lifespan of a woman and overarching principles and gaps in women's CV health. Heightened & Progressive ASCVD Risk, including Undetected Subclinical Disease & Premature Death. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular

such as for aspirin, remains ill-described.[170] A new approach would re-create pathways of care with consideration of the factors influencing drug effectiveness and side effects. One example is the difference in side effects between oral and transdermal MHT, which illustrates how bypassing liver metabolism reduces adverse side effects. Moreover, a polygenic risk score, such as for venous thromboembolic risk, may further define factors contributing risk of complications.

Multidisciplinary approaches to risk detection in women

This section highlights the dramatic extent to which CV care must evolve for better targeting and treatment to reduce CVD risk in women. Any women's centre should evolve toward inclusivity of multiple specialities (e.g. diabetologists, rheumatologists, obstetrics, gynaecology, reproductive science, infectious diseases, and others) who may attract key at-risk women and also form the basis for collaborative care to optimise a woman's health. There are also other conditions which have a higher prevalence in women (e.g. Alzheimer's disease) who may benefit from expanded programs inclusive of CVD screening. Thus, the collaboration across specialities is a key component to optimize population health for women.

Evolving approaches to risk detection in women

Our historic approach has focused on post-menopausal women, perhaps presenting with newly diagnosed risk factors. A key concept is emerging that these traditional approaches occur too late along life's continuum to make a meaningful difference in a woman's life.[138] There are means by which our electronic health record could be programmed to nudge the physician toward identification of unfavourable risk factor trends. Digital health platforms using applications can also be devised that are oriented to women across critical life stages to enhance education and guide a woman's health-seeking behaviours, along with supportive guidance from their primary care provider, including the gynaecologist. There is also a strong need to proactively engage in primordial prevention using community outreach and governmental policies supporting broad public education and neighbourhood screening—especially as risk is often socioeconomically patterned.[171] By 2050, there are projections for marked increases in the prevalence of obesity, diabetes, and hypertension impacting a large proportion of women across the globe, which should serve as a call to action for the CV community to devise widespread programs for CVD prevention.

Conclusions

CVD remains the leading cause of death in women, surpassing the combined mortality from breast cancer, lung cancer, and chronic respiratory diseases, and is on par with mortality rates observed in men. Nevertheless, there continues to be a widespread underrecognition—by both healthcare professionals and women themselves—of CVD as a major health threat for women. This lack of awareness often contributes to missed or delayed diagnoses and inadequate early intervention. Although advancements have been made in improving the diagnosis and treatment of CVD in women, significant knowledge gaps still exist (*Figure 6*). Emerging perspectives suggest that conventional clinical

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strategies may be initiated too late in a woman's life to have optimal impact. A more proactive approach is needed—one that considers the full trajectory across the lifespan of a woman's health and emphasizes early risk assessment and ongoing care. Critical phases such as the onset of risk factors in early adulthood, pregnancy, and the menopausal transition should be key focal points in a more comprehensive care model. This review highlights both established and sex-specific risk factors that influence cardiovascular health in women and underscores the urgent need for further research. Such work could improve predictive strategies and long-term outcomes. Ultimately, a shift in healthcare systems is required—moving towards a life-course approach that integrates prevention, timely detection, and personalized treatment plans tailored to women's unique cardiovascular risks, in order to reduce overall disease burden and improve quality of life.

Supplementary data

Supplementary data are not available at the *European Heart Journal* online.

Declarations

Disclosure of Interest

CNBM serves on the board of directors of iRhythm and receives stock. YA has received a research grant from the Dutch Heart Foundation. MG has served on advisory boards for Medtronic, Novartis and New Amsterdam. JRVL received an investigator-initiated grant from Novartis, paid to the department. LJS receives honorariums from Heartflow for speaking.

Data Availability

No data were generated or analysed for or in support of this paper.

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