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Sex-specific differences in cardiovascular risk factors and implications for cardiovascular disease prevention in women

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Abstract

Cardiovascular disease (CVD) is the leading cause of mortality for women globally. Sex differences exist in the relative risks conferred by traditional CVD risk factors, including diabetes, hypertension, obesity, and smoking. Additionally, there are female-specific risk factors, including age of menarche and menopause, polycystic ovary syndrome, infertility and the use of assisted reproductive technology, spontaneous pregnancy loss, parity, and adverse pregnancy outcomes, as well as female-predominant conditions such as autoimmune diseases, migraines, and depression, that enhance women's cardiovascular risk across the lifespan. Along with measurement of traditional risk factors, these female-specific factors should also be ascertained as a part of cardiovascular risk assessment to allow for a more comprehensive overview of the risk for developing cardiometabolic disorders and CVD. When present, these factors can identify women at elevated cardiovascular risk who may benefit from more intensive preventive interventions, including lifestyle changes and/or pharmacotherapy such as statins. This review describes sex differences in traditional risk factors and female-specific / female-predominant risk factors for CVD and examines the role of coronary artery calcium scores and certain biomarkers that can help further risk stratify patients and guide preventive recommendations.

Keywords

women's cardiovascular health; risk factors; sex differences; prevention; pregnancy; menopause; autoimmune disease; migraine

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and premature death in women in the United States (U.S.) and worldwide. Despite substantial efforts to decrease CVD over the last five decades, 1 in 3 women continue to die from CVD (1). In the U.S., there was a 7% increase in CVD rates in middle-aged women between 2013–2017, likely related to rising trends in obesity and other cardiometabolic risk factors (1,2). The development of CVD in women is further impacted by disparities in traditional cardiovascular risk factors, the presence of female-specific risk factors, and female-predominant high-risk conditions (3–5). The early detection and management of these risk factors can decrease morbidity and mortality while improving the overall quality of women's health (6,7).

In this review, we highlight sex differences in traditional risk factors including diabetes, hypertension, obesity, and smoking, as well as female-specific risk factors including age of menarche and menopause, polycystic ovary syndrome (PCOS), infertility and the use of assisted reproductive technology (ART), spontaneous pregnancy loss, parity, and adverse pregnancy outcomes (APOs). We also address female-predominant conditions such as autoimmune diseases, migraines, and depression that independently increase the risk of CVD. Lastly, this review looks at the role of the use of coronary artery calcium (CAC) scores and biomarkers to help further risk stratify patients and guide preventive recommendations. These topics are also discussed in the paper by Kerkhof and Tona (8).

Of note, in this review, we refer to "women" as was described in the original studies reviewed. This gender assignment was presumably made based on female sex assigned at birth. While addressing the cardiovascular health of individuals who are transgender, non-binary, or gender fluid is an important area of much needed research and preventive efforts, it is beyond the scope of this review (9). In this special issue, cardiovascular disease in transgender individuals is discussed in the review by Murphya et al. (10).

2. Sex differences in traditional risk factors

While women and men mostly share traditional risk factors for CVD, the relative impact of risk factors is variable in part due to biological sex differences and in part due to behavioral practices. Sex differences in circulating lipids and lipidomes are discussed in the reviews by Holven and Roeters van Lennep and Tabassum et al. (11, 12). Notably, women with a history of diabetes, smoking, and hypertension have a greater relative risk for CVD compared to men with the same risk factors. Specifically for diabetes, although men have a higher prevalence of diabetes, analyses have shown that the presence of diabetes increases cardiovascular risk by approximately 3–7-fold in women as compared to 2–3-fold in men (13,14). The incidence of CVD-related mortality, myocardial infarction, heart failure, and stroke are all higher among women with diabetes compared to men with diabetes (15,16). Though the underlying cause for this difference is unknown, proposed hypotheses include a higher body mass index (BMI), greater systemic inflammation, worse glycemic control, and higher risk profile burden of women at the time of diabetes diagnosis compared to men (15).

Tobacco use is another significant modifiable risk factor with differential impacts on CVD risk for women and men (17,18). A meta-analysis of over three million individuals demonstrated that except for women aged 30–44 years, female smokers had a 25% greater risk of CVD than male smokers (19). Oral contraceptives also increase the risk of CVD in women who smoke (20). Other risk factors such as obesity and hypertension have been increasing in prevalence among women compared to men. The Framingham study showed that women with obesity have an increased risk of coronary heart disease (CHD) of 64% compared to 46% among men with obesity (21). The prevalence of hypertension is higher among women above the age of 60 compared to men, presumable due in part to the loss of endogenous estrogens during menopause (22). Furthermore, hypertension is less well-controlled in older women than men, another factor contributing to increased CVD risk (22,23).

3. Menarche age

Menarche, the onset of menstruation, signals the beginning of the reproductive stage in a woman's life. Several large-cohort studies have found associations between early age of menarche and increased risk of CVD as well as associated risk factors such as metabolic syndrome, obesity, and diabetes (5). With regards to all-cause mortality, studies have shown a 2–4% reduction in mortality for each year of delayed menarche as well as associations between early age of menarche and ischemic heart disease and stroke (24,25). A large study from the United Kingdom (UK) Biobank found an independent association between those who had menarche at <12 years of age and increased risk of CVD and heart failure (26,27). There is also evidence from analysis of another UK population-based cohort to suggest a U-shaped relationship between age of menarche and CVD, whereby both early and late menarche are associated with poor cardiovascular outcomes (28). In that study, women with menarche at ≤ 10 years of age and menarche at ≥17 years of age had increased risk of CHD, as well as cerebrovascular and hypertensive disease (28). These findings were corroborated in a recent study where early and late menarche were associated with major adverse cardiac events (29); however, interestingly, there is unclear association between lifetime estrogen exposure and CVD events, which suggests that there may be additional mechanisms underlying the role and timing of menarche in cardiovascular health (30). Specifically, earlier menarche has been related to obesity and metabolic syndrome (31,32). Later menarche, on the other hand, has been linked to PCOS, as well as decreased lifetime estrogen exposure, which may at least partially explain its association with increased CVD (30,33).

4. Early menopause

The onset of menopause that occurs early (<45 years of age), affecting up to 10% of women, or premature (<40 years of age), affecting 1% of women, is an emerging risk factor for adverse cardiovascular outcomes in women (34). Furthermore, some authors have encouraged using a continuum of menopause age rather than a prespecified cut-off for risk stratification (35). Starting in the 1970s, loss of estrogen at menopause has been hypothesized to play an essential role in the increased incidence of CVD in postmenopausal women (36). Both the 2021 European Society of Cardiology (ESC) Prevention Guideline

and the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Prevention Guideline have also incorporated premature menopause as a “risk-enhancing” or “risk-modifying” factor for atherosclerotic CVD (ASCVD) to guide patient risk assessment (34,37). Early menopause has been associated with an increased risk of CHD, stroke, and heart failure (5,27,38). In a recent large cohort of postmenopausal women, premature natural and surgical menopause was additionally associated with traditional ASCVD risk factors (hypertension, hyperlipidemia, diabetes), as well as aortic stenosis, atrial fibrillation, and venous thromboembolism (VTE) (35). This CVD risk associated with premature menopause was also observed after adjustment for prevalent risk factors, suggesting that premature menopause may not only be comorbid with traditional risk factors, but may also increase the risk of developing additional cardiovascular risk factors (35). The mechanism driving the relationship between early menopause and CVD is thought to be related to the deficiency in protective endogenous estrogens and an increase in endogenous androgens (39). It is possible that natural versus surgical premature menopause may have differing cardiovascular risk. Although no dedicated study has selectively investigated this, a secondary analysis showed significant differences in risk between natural and surgical menopause, but those observed differences did not persist in fully adjusted models and were likely limited by reduced statistical power (35). An improved understanding of the differences in a gradual versus abrupt loss of ovarian hormones may influence risk prediction and improve guidance in implementing CVD prevention strategies.

5. Polycystic ovary syndrome

PCOS is the most common endocrine disorder that affects reproductive-aged women with a global prevalence between 5–13% (40). It is complex and heterogenous in presentation with features including ovulatory dysfunction, hyperandrogenism, insulin resistance, and cystic morphology of ovaries by ultrasound (41). Women with PCOS often have irregular menstrual cycles, which menstrual irregularity is also independently associated with CVD (42). Furthermore, PCOS is a leading cause of infertility. During pregnancy, PCOS is associated with greater risk of preeclampsia, gestational diabetes, and cardiovascular complications at delivery (43). Women with PCOS have an increased risk of developing metabolic syndrome and associated diseases including type 2 diabetes (T2D), hypertension, and dyslipidemia (44). Specifically, women with PCOS are 4 times more likely to develop T2D and 2–3 times more likely to develop metabolic syndrome compared to women without PCOS (45–47). Notably, the ESC Prevention Guideline highlights PCOS as a sex-specific “risk-modifier” that increases women’s risk for future T2D (34).

Hyperandrogenism, an important feature of PCOS, may drive some of the insulin resistance, as well as increase the risk for atherosclerosis (39,48). Several studies have demonstrated increased risk of CAC, a marker of subclinical atherosclerosis, in women with PCOS (40,49), and a meta-analysis reported women with PCOS as being twice as likely to have CAC compared to women without PCOS (49). Although there has been mixed evidence, a recent meta-analysis of ten studies found a ~30% increased risk of CVD events among women with PCOS (50). This increased cardiovascular risk associated with PCOS appears to be greater among women of reproductive age, compared to those after menopausal transition (51).

Aggressive cardiometabolic risk factor modification should be a routine aspect of care for patients with PCOS. This includes lifestyle modifications, the addition of metformin for insulin resistance, obesity management with consideration of use of the glucagon-like peptide 1 receptor agonists, diabetes screening, annual blood pressure checks, fasting lipid panel, and screening for additional psychosocial issues such as eating disorders, smoking, depression, and anxiety (40). Oral contraceptives are the first line therapy to address the hyperandrogenic state (41).

6. Infertility and the use of assisted reproductive technology

The use of ART to address infertility in women is growing worldwide; this is an umbrella term encompassing several different types of procedures including ovarian stimulation, fresh embryo transfer, frozen embryo transfer, and pre-implantation genetic testing (43). The use of ART is associated with increased cardiovascular risk; this is most likely due to the higher prevalence of established cardiovascular risk factors among women with infertility such as advanced maternal age, chronic hypertension, diabetes, obesity, and PCOS (43). A retrospective analysis using the National Inpatient Sample found that women who had undergone ART to conceive were older at the time of delivery and had a higher prevalence of hypertension, gestational diabetes, and dyslipidemia (43). In this study, ART was found to be an independent predictor of peripartum cardiovascular complications such as preeclampsia / eclampsia and cardiac arrhythmias when compared with natural conception; however, it was not associated with increased risk of peripartum cardiomyopathy or acute coronary syndrome (43). A large prospective study of post-menopausal women found that self-reported history of infertility was associated with a nearly 20% increased risk of developing future heart failure compared to women without a history of infertility, and this was driven by future risk of heart failure with preserved ejection fraction and not heart failure with reduced ejection fraction (52). Interestingly, the association of infertility and heart failure was not explained by existing cardiovascular risk factors (e.g. hypertension, diabetes, obesity, increased 10-year ASCVD risk score) or infertility-related risk factors (e.g. irregular menstrual cycle, early menopause, thyroid disease) (52). The mechanisms underlying the association between infertility, ART and CVD are likely multifaceted and needs further investigation. Hypothalamic pituitary axis dysregulation and subsequent estrogen deficiency has been implicated in the development of future heart failure and CVD (53). Both low concentrations of estradiol found in infertility and ovarian hyperstimulation in ART have been linked with angiotensin-renin-aldosterone system derangements and endothelial dysfunction (54,55). It is not yet clear how different modes of ART are associated with peripartum or future risk of CVD. Women undergoing ART should be evaluated for CVD risk factors and monitored for cardiovascular complications during pregnancy and beyond.

7. Spontaneous pregnancy loss

Spontaneous pregnancy loss which refers to miscarriages and stillbirths has been known to be associated with an increased risk of CVD (26). While pregnancy loss is linked with the presence of cardiometabolic risk factors, a large cohort study recently demonstrated that women with pregnancy loss had a 1.2-fold increase in CHD and stroke independent of other

risk factors including hypertension, hypercholesterolemia, and T2D (56,57). Furthermore, the risk of CVD was increased up to 2-fold with recurrent pregnancy losses and was higher if pregnancy loss occurred earlier in reproductive lifespan (56,58). In contrast, in a cohort of women from the UK Biobank experiencing miscarriages was not associated with incident heart failure; however experiencing 1 or recurrent stillbirths was associated with a 20% and 43% greater risk of incident heart failure compared to having no history of stillbirth (27).

One proposed mechanism linking spontaneous pregnancy loss with CVD is endothelial dysfunction. Endothelial dysfunction has been linked to development of atherosclerosis and CVD in women as well as with pregnancy loss as a result of poor placental function (59). There are also associations between recurrent miscarriages and prothrombotic genotypes that could potentially increase future risk of thrombotic disease including CHD and stroke (60). Women with recurrent pregnancy losses should be screened for underlying etiologies including anatomical abnormalities, genetic chromosomal testing of parents and fetal products, endocrinopathies, antiphospholipid syndrome, and thrombophilia if there is a history of VTE.

8. Parity

Parity, the number of live births, is another reproductive factor that affects women's cardiovascular health in later life. In a systemic review and meta-analysis of ten prospective studies, ever parity was inversely related to CVD mortality with a potential non-linear J-shaped dose-response relationship (61). In the UK Biobank, compared to women who had 1–2 live births, having 3–4 children or >4 children was associated with 9 and 24% greater risk of incident heart failure, respectively. In that same cohort, there was also excess heart failure risk for having a younger maternal age (<21 years) at first live birth (27).

Interestingly, parity may not be a CVD risk factor unique to women, as a prior study showed an increase CVD risk in men with higher parity (62). Comparisons between women and men are useful in distinguishing between biological or lifestyle/sociocultural contributions to adverse outcomes relating to pregnancy. Using the British Women's Heart and Health Study and the British Regional Heart Study, authors found a similar J-shaped association between number of children and CVD in both sexes, although in men, that association was attenuated to a higher degree after adjustment for obesity and metabolic risk factors (63). Several lifestyle and biological mechanisms for this relationship have been posited and investigated. Multiparity is associated with worse health behaviors in later life, which is supported by findings of worse CVD outcomes in both men and women at higher parity (64). Moreover, multiparity may have an adverse effect on metabolic syndrome and body composition. Indeed, compared to nulliparous women, women with a higher number of children had a higher BMI, waist circumference, higher blood pressure, as well as adverse changes in adipokine profile (64,65). Another proposed mechanism related parity with sex hormones independent of body composition. In a multi-ethnic population without baseline CVD, greater parity was associated with a more androgenic sex hormone profile, namely a higher testosterone to estrogen ratio, even after adjusting for BMI (66).

9. Adverse pregnancy outcomes

APOs have emerged as an important contributor to heart disease in younger women and confer increased CVD risk that persists into later life, far beyond the pregnancy period (4,5,67). These include complications such as hypertensive disorders of pregnancy, gestational diabetes, intrauterine growth restriction, small-for-gestational age delivery and preterm delivery.

Hypertensive disorders of pregnancy, including preeclampsia, complicate 5–10% of all pregnancies, with a recent increase in incidence associated with rising cardiometabolic disorders in younger women (68,69). Studies have demonstrated that women with a history of preeclampsia have substantially higher risk of maternal and fetal morbidity and mortality (70,71). These women notably have elevated risk of future CVD, with large meta-analyses demonstrating 2–4 times higher risk among women with a history of preeclampsia compared to women with normotensive pregnancies – a risk which remains persistently elevated over at least four decades of follow-up (71). Women with preeclampsia are also at elevated risk of CVD risk factors such as chronic hypertension and diabetes (72,73).

Similarly, gestational diabetes is also associated with increased CVD risk. About 15–30% of women with gestational diabetes develop T2D within the first 10 years postpartum (73,74). They are also twice as likely to develop other cardiometabolic disorders such as hypertension and dyslipidemia (15,75). A large meta-analysis demonstrated that women with gestational diabetes are 1.7-fold more likely to develop CVD (76).

Other APOs have also been linked to heightened CVD risk. Preterm delivery was associated with an almost 2-fold increased risk of CVD mortality in a recent meta-analysis (76). Preterm birth may also increase risk for chronic hypertension, T2D, and dyslipidemia, although data are more mixed for associations with the latter two risk factors (75).

Currently, there are no strong data on interventions to prevent long-term CVD among women with history of APO. Pharmacologic interventions may further be limited by safety concerns in women of reproductive age who may wish to breastfeed or conceive for an additional pregnancy. Optimal strategies to prevent CVD should likely focus on lifestyle efforts such as adhering to healthy diets, increasing physical activity, and maintaining optimal cardiometabolic health measures (37). Among women 40–75 years of age who are estimated to be at borderline or intermediate risk of ASCVD using the Pooled Cohort Equations, a history of an APO, such as preeclampsia, is considered to be a risk-enhancing factor that would favor initiation of statin therapy per the ACC/AHA Prevention Guideline (37). Similarly, the ESC Prevention Guideline also considers preeclampsia and pregnancy-associated hypertension as “risk modifiers” that increase women’s risk of future CVD (34).

10. Autoimmune diseases

Women are more likely to have autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), which are risk factors for the development of CVD. These autoimmune diseases have also been identified in the ACC/AHA and ESC Prevention Guidelines as risk-enhancing or risk-modifying factors that would favor more

intensified preventive efforts such as statin therapy (34,37). The higher levels of systemic inflammation seen in autoimmune conditions promotes endothelial dysfunction, arterial stiffness, premature atherosclerosis, coronary microvascular dysfunction, and advanced plaque instability (77,78). During pregnancy, women with SLE are at heightened risk for cardiovascular complications including preeclampsia and stroke (79). Long-term, individuals with SLE have a 2.6-fold higher risk of developing CVD compared to the general population (80). Furthermore, analysis from the Framingham Offspring study suggests that reproductive-aged women with SLE are 50 times more likely to have a myocardial infarction compared to individuals in the same age range (81). SLE disease activity and duration has been associated with accelerated atherosclerosis (82). Notably, Black women are more likely to develop SLE as well as lupus nephritis, and disease activity is worse among Black women as compared to White women (83). Furthermore, Black women with SLE have a 2-fold increased risk of developing carotid plaque as a manifestation of subclinical CVD (84).

Individuals with RA are also twice as likely to develop CVD with 50% higher mortality from CVD compared to individuals without RA (85,86). As such, the ESC Prevention Guideline recommends multiplying estimated CVD risk by a factor of 1.5 for patients with RA (34). CVD risk was found to be higher in individuals with RA who spent longer in flare states (87). Interestingly, patients with RA present with a paradoxical lipid profile whereby there is a suppression of total and low-density lipoprotein cholesterol (LDL-C) as a likely consequence of high-grade inflammation (88). While glucocorticoids are often used in the acute period to manage flares, high cumulative exposure to glucocorticoids in patients with SLE or RA is associated with significantly higher CVD risk even after accounting for disease activity (80,89). In individuals with RA, the usage of methotrexate and tumor necrosis factor (TNF)-inhibitor therapy are associated with decreased CVD risk, and hydroxychloroquine is associated with decreased risk of diabetes (90–92). CVD risk can be decreased in individuals with autoimmune diseases such as SLE and RA by decreasing autoimmune disease activity to the extent possible with appropriate therapy, encouraging lifestyle modifications and statin therapy if necessary, and addressing other common comorbidities such as hypertension, dyslipidemia, and kidney disease.

Inflammatory bowel disease (IBD) including Crohn’s disease and ulcerative colitis are also associated with almost 20% increased risk of CVD (93). Moreover, women with IBD are at higher risk of developing CVD compared to men with IBD regardless of age (93). Inflammation at large has been postulated as a causal driver of atherothrombosis (94). As an example of this, certain anti-inflammatory agents such as canakinumab, an IL-1β monoclonal antibody, and colchicine have been shown to decrease cardiovascular events in patients with established CVD (95,96). The 2021 ESC Prevention Guideline and 2019 ACC/AHA Prevention Guideline both discuss the need to consider chronic inflammatory conditions when deciding whether to start preventive interventions for CVD risk reduction (34,37).

11. Migraines

Migraines are more common in women than men, and specifically, the prevalence of migraines with visual aura is present in 2–10% of women as compared to 1–4% of men

(97). There is at least a 2-fold increased risk of ischemic stroke in patients with migraines with visual auras, and this has been well-established in the literature (98). The phenomenon of visual auras is thought to be related to cortical spreading depression, a wave of slowly propagating neuronal and glial depolarization, which can be triggered by microvascular ischemia, alterations to cerebral blood flow, vasoreactivity, and vascular dysfunction (99). These same pathways are often implicated in the development of cerebrovascular disease and ischemic stroke (99). Moreover, migraines with aura are associated with increased risk of CVD including 1.7-fold increased risk of coronary revascularization and 2.3-fold increased risk of cardiovascular death (100). These risks can be compounded by other lifestyle habits such as smoking and medications such as combined hormonal contraceptives; however, data are limited (34). Although given the younger mean age of patients affected with migraines, the absolute contributing risk of migraine to CVD is small at individual level, but the ESC Prevention Guideline notes that the high global burden of migraines makes it a relevant consideration when discussing cardiovascular prevention at the population level (34).

12. Depression and anxiety

Psychological factors, both favorable and unfavorable, has been linked to CVD risk, illustrating the importance of the “Mind-Body-Heart” connection (101). Approximately 7% percent of the adult U.S. population experiences depression each year, and unfortunately, depression is twice as common in women compared to men (102). A prospective study demonstrated that depression is an independent risk factor for CVD in women, and furthermore, there is some evidence to suggest that the strength of association between depression and CHD is greater than that conferred by traditional risk factors (103). Another study looking at individuals with CHD found that higher psychological distress was associated with the development of CVD in women only and not men (104). Women are also more likely to be exposed to adverse childhood events which are more strongly associated with the development of cardiometabolic risk factors and CVD compared to men (105,106). Depression affects the overall stress response and inflammatory state of the body in addition to affecting neurohormonal pathways. Furthermore, depression is also associated with many aspects of lifestyle including smoking, alcohol use, substance use, poor diet, and lack of exercise (107). Mental health has far-reaching implications for women’s health, and the management of depression and other psychosocial issues should be a priority with regards to CVD prevention. The ESC Prevention Guideline specifically recommends that mental health disorders that confer functional impairment or decreased use of the healthcare system be considered as influencers of CVD risk (34).

13. Approach to risk assessment: coronary artery calcium scoring and biomarkers

CAC, assessed by non-contrast cardiac computed tomography, is a marker of atherosclerotic disease burden and highly prognostic of ASCVD risk, independent of traditional risk factors (108,109). The CAC score predicts risk of ASCVD events over a 10-year period in women in a graded fashion (109). Although, at a given age, women are less likely to have prevalent

CAC than men, when present, CAC is associated with a greater relative risk of CVD in women compared to men (110,111). Furthermore, data from a multi-ethnic cohort found that CAC presence (CAC > 0) was associated with future CVD risk among women determined to be “low-risk” per the Framingham Risk Score, with a 5-fold increased risk compared to women with no detectable CAC (112). As such, recent guidelines have recommended the use of CAC to help refine risk stratification in asymptomatic populations in cases where risk is otherwise uncertain to help guide preventive interventions such as statin therapy (37,113).

One emerging risk marker in women is breast arterial calcification (BAC), which is medial artery calcification that can be found incidentally on mammogram. BAC has been shown to be associated with the CAC score (114), as well as future CVD risk (115,116). A recent meta-analysis of 10 studies found that BAC was an independent predictor of CHD with 2.4-fold increased risk (116). The detection of BAC might encourage additional CVD risk factor screening, and consideration of obtaining a CAC score.

While calcium scores and other cardiovascular imaging techniques have given us powerful tools beyond the classic framework for risk assessment in women (117), biomarkers may also be helpful in this regard as well (118). High-sensitivity C-reactive protein (hsCRP) predicts future CVD risk in women, independent of lipids (119), and as such as been incorporated in some risk calculators such as the Reynolds Risk Score for women (120). The ACC/AHA Prevention Guideline considers lipid related biomarkers such as persistently elevated triglycerides (≥ 175 mg/dL), lipoprotein (a) (≥ 50 mg/dL or 125 nmol/L), and/or apolipoprotein B (≥ 130 mg/dL) as risk-enhancing factors elevating patients into a higher risk group that may favor the initiation of statin therapy (34). Furthermore, the ACC/AHA Prevention Guideline also considers elevated hsCRP (≥ 2 mg/L) to be an independent risk-enhancing factor (37). Although high-sensitivity troponins and natriuretic peptides have also been established to confer prognostic information on future CVD risk in asymptomatic populations, the ACC/AHA Prevention Guideline does not specifically endorse recommendations for their measurement in the asymptomatic population (37). The 2021 ESC Prevention Guideline also notes that cardiac biomarkers are promising, but state that further work is needed before they can be incorporated as part of routine CVD risk assessment (34). However, a persistently unexplained elevation of cardiac troponin or natriuretic peptide would be a marker of Stage B Pre-Heart Failure per the ACC/AHA Heart Failure Guideline (37,121).

14. Conclusion

A comprehensive approach to risk assessment and prevention of cardiometabolic and cardiovascular diseases in women is necessary to address increasing rates of CVD in women (Figure 1). Traditional cardiovascular risk factors manifest differently in women compared to men, and these differences have implications for management and clinical outcomes. Furthermore, discussion of female-specific risk factors such as pregnancy-related conditions and adverse outcomes, PCOS, infertility, and the use of ART need to be integrated into conversations on primary and secondary CVD prevention. Lastly, the management of underlying conditions such as autoimmune diseases (i.e., SLE, RA, inflammatory bowel disease), migraines, depression, and other psychosocial stressors are integral to

cardiovascular health given the high associated risk of CVD. Identification of any of the above “red-flags” of risk could serve as an opportunity to intensify preventive efforts including lifestyle modifications and pharmacotherapies such as lipid-lowering medications (e.g., statins) and possibly aspirin, to hopefully reduce CVD morbidity and mortality in women.

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References

1. Tsao CW, Aday AW, Almarzooq ZI et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation 2023.
2. Curtin SC. Trends in Cancer and Heart Disease Death Rates Among Adults Aged 45–64: United States, 1999–2017. Natl Vital Stat Rep 2019;68:1–9.
3. Cho L, Davis M, Elgendy I et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. Journal of the American College of Cardiology 2020;75:2602–2618. [PubMed: 32439010]
4. Elder P, Sharma G, Gulati M, Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention. Am J Prev Cardiol 2020;2:100028. [PubMed: 34327455]
5. O’Kelly AC, Michos ED, Shufelt CL et al. Pregnancy and Reproductive Risk Factors for Cardiovascular Disease in Women. Circ Res 2022;130:652–672. [PubMed: 35175837]
6. Holtzman JN, Kaur G, Hansen B, Bushana N, Gulati M. Sex differences in the management of atherosclerotic cardiovascular disease; Atherosclerosis in press
7. Antza C, Gallo A, Boutari C, Ershova A, Murat Gurses K, Lewek J, et al. Prevention of Cardiovascular Disease in Young Adults: focus on gender differences. A collaborative review from the EAS Young Fellows. Atherosclerosis in press
8. Kerkhof PLM and Tona F. Sex differences in diagnostic modalities of atherosclerosis in the macrocirculation. Atherosclerosis in press
9. Streed CG Jr., Beach LB, Caceres BA et al. Assessing and Addressing Cardiovascular Health in People Who Are Transgender and Gender Diverse: A Scientific Statement From the American Heart Association. Circulation 2021;144:e136–e148. [PubMed: 34235936]
10. Murphya CN, Dellesa C, Daviesa E, Connelly PJ; Cardiovascular Disease in Transgender Individuals, Atherosclerosis in press
11. Holven KB, Roeters van Lennep, Sex differences in lipids: a life course approach. Atherosclerosis in press
12. Tabassum R, Widén E, Ripatti S. Effect of biological sex on lipidomic profiles human circulating lipidome: an overview of the literature. Atherosclerosis in press
13. Bancks MP, Akhabue E, Rana JS et al. Sex differences in cardiovascular risk factors before and after the development of type 2 diabetes and risk for incident cardiovascular disease. Diabetes Research and Clinical Practice 2020;166:108334. [PubMed: 32702469]
14. Recarti C, Sep S, Stehouwer C, Unger T. Excess cardiovascular risk in diabetic women: a case for intensive treatment. Current hypertension reports 2015;17:1–6.
15. Broni EK, Ndumele CE, Echouffo-Tcheugui JB, Kalyani RR, Bennett WL, Michos ED. The Diabetes-Cardiovascular Connection in Women: Understanding the Known Risks, Outcomes, and Implications for Care. Curr Diab Rep 2022;22:11–25. [PubMed: 35157237]
16. Angoulvant D, Ducluzeau PH, Renoult-Pierre P et al. Impact of gender on relative rates of cardiovascular events in patients with diabetes. Diabetes & metabolism 2021;47:101226. [PubMed: 33454437]

17. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet (London, England) 2011;378:1297–305. [PubMed: 21839503]
18. Grundtvig M, Hagen TP, German M, Reikvam A. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. Eur J Cardiovasc Prev Rehabil 2009;16:174–9. [PubMed: 19247184]
19. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. The Lancet 2011;378:1297–1305.
20. Gallucci G, Tartarone A, Lerose R, Lalinga AV, Capobianco AM. Cardiovascular risk of smoking and benefits of smoking cessation. Journal of thoracic disease 2020;12:3866. [PubMed: 32802468]
21. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Archives of internal medicine 2002;162:1867–1872. [PubMed: 12196085]
22. Kovell LC, Harrington CM, Michos ED. Update on Blood Pressure Control Among US Adults With Hypertension. Jama 2021;325:586–587.
23. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. Jama 2005;294:466–472. [PubMed: 16046653]
24. Jacobsen B, Oda K, Knutsen S, Fraser G. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976–88. International journal of epidemiology 2009;38:245–252. [PubMed: 19188208]
25. Jacobsen BK, Heuch I, Kvåle G. Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. American journal of epidemiology 2007;166:1431–1437. [PubMed: 17875585]
26. Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart 2018;104:1069–1075. [PubMed: 29335253]
27. Zhu F, Qi H, Bos M, Boersma E, Kavousi M. Female Reproductive Factors and Risk of New-Onset Heart Failure: Findings From UK Biobank. JACC Heart failure 2023.
28. Canoy D, Beral V, Balkwill A et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. Circulation 2015;131:237–244. [PubMed: 25512444]
29. Lee JJ, Cook-Wiens G, Johnson BD et al. Age at Menarche and Risk of Cardiovascular Disease Outcomes: Findings From the National Heart Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. Journal of the American Heart Association 2019;8:e012406. [PubMed: 31165670]
30. Mishra SR, Chung HF, Waller M, Mishra GD. Duration of estrogen exposure during reproductive years, age at menarche and age at Menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: a systematic review and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology 2021;128:809–821. [PubMed: 32965759]
31. Lakshman R, Forouhi N, Luben R et al. Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. Diabetologia 2008;51:781–786. [PubMed: 18320165]
32. Lakshman R, Forouhi NG, Sharp SJ et al. Early age at menarche associated with cardiovascular disease and mortality. The Journal of Clinical Endocrinology & Metabolism 2009;94:4953–4960. [PubMed: 19880785]
33. Carroll J, Saxena R, Welt CK. Environmental and genetic factors influence age at menarche in women with polycystic ovary syndrome. Journal of Pediatric Endocrinology and Metabolism 2012;25:459–466. [PubMed: 22876539]
34. Visseren FLJ, Mach F, Smulders YM et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European heart journal 2021;42:3227–3337. [PubMed: 34458905]
35. Honigberg MC, Zekavat SM, Aragam K et al. Association of premature natural and surgical menopause with incident cardiovascular disease. Jama 2019;322:2411–2421. [PubMed: 31738818]

36. Kannel WB, Hjortland MC, McNAMARA PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. Annals of internal medicine 1976;85:447–452. [PubMed: 970770]
37. Arnett DK, Blumenthal RS, Albert MA et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–e646. [PubMed: 30879355]
38. El Khoudary SR, Aggarwal B, Beckie TM et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation 2020;142:e506–e532. [PubMed: 33251828]
39. Zhao D, Guallar E, Ouyang P et al. Endogenous Sex Hormones and Incident Cardiovascular Disease in Post-Menopausal Women. J Am Coll Cardiol 2018;71:2555–2566. [PubMed: 29852978]
40. Guan C, Zahid S, Minhas AS et al. Polycystic ovary syndrome: a “risk-enhancing” factor for cardiovascular disease. Fertil Steril 2022;117:924–935. [PubMed: 35512976]
41. Teede HJ, Misso ML, Costello MF et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018;110:364–379. [PubMed: 30033227]
42. Solomon CG, Hu FB, Dunaif A et al. Menstrual cycle irregularity and risk for future cardiovascular disease. The Journal of Clinical Endocrinology & Metabolism 2002;87:2013–2017. [PubMed: 11994334]
43. Zahid S, Khan MZ, Gowda S et al. Trends, Predictors, and Outcomes of Cardiovascular Complications Associated With Polycystic Ovary Syndrome During Delivery Hospitalizations: A National Inpatient Sample Analysis (2002–2019). Journal of the American Heart Association 2022;11:e025839. [PubMed: 35708290]
44. Teede HJ, Hutchison S, Zoungas S, Meyer C. Insulin resistance, the metabolic syndrome, diabetes, and cardiovascular disease risk in women with PCOS. Endocrine 2006;30:45–53. [PubMed: 17185791]
45. Rubin KH, Glintborg D, Nybo M, Abrahamsen B, Andersen M. Development and risk factors of type 2 diabetes in a nationwide population of women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism 2017;102:3848–3857. [PubMed: 28938447]
46. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction update 2010;16:347–363. [PubMed: 20159883]
47. Lim S, Kakoly N, Tan J et al. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. Obesity reviews 2019;20:339–352. [PubMed: 30339316]
48. Adams MR, Williams JK, Kaplan JR. Effects of androgens on coronary artery atherosclerosis and atherosclerosis-related impairment of vascular responsiveness. Arteriosclerosis, thrombosis, and vascular biology 1995;15:562–570. [PubMed: 7749870]
49. Osibogun O, Ogunmoroti O, Kolade OB et al. A Systematic Review and Meta-Analysis of the Association Between Polycystic Ovary Syndrome and Coronary Artery Calcification. Journal of women’s health (2002) 2022;31:762–771.
50. Zhao L, Zhu Z, Lou H et al. Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis. Oncotarget 2016;7:33715. [PubMed: 27220885]
51. Oliver-Williams C, Vassard D, Pinborg A, Schmidt L. Risk of cardiovascular disease for women with polycystic ovary syndrome: results from a national Danish registry cohort study. Eur J Prev Cardiol 2020:2047487320939674.
52. Lau ES, Wang D, Roberts M et al. Infertility and risk of heart failure in the Women’s Health Initiative. Journal of the American College of Cardiology 2022;79:1594–1603. [PubMed: 35450577]
53. Takefuji M, Murohara T. Corticotropin-releasing hormone family and their receptors in the cardiovascular system. Circulation Journal 2019;83:261–266. [PubMed: 30584229]
54. Murphy E Estrogen signaling and cardiovascular disease. Circulation research 2011;109:687–696. [PubMed: 21885836]

55. Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. Journal of assisted reproduction and genetics 2010;27:121–128. [PubMed: 20140640]
56. Wang Y-X, Mínguez-Alarcón L, Gaskins AJ et al. Pregnancy loss and risk of cardiovascular disease: the Nurses' Health Study II. European Heart Journal 2022;43:190–199. [PubMed: 34718507]
57. Horn J, Tanz LJ, Stuart JJ et al. Early or late pregnancy loss and development of clinical cardiovascular disease risk factors: a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology 2019;126:33–42.
58. Oliver-Williams CT, Heydon EE, Smith GC, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. Heart 2013;99:1636–1644. [PubMed: 23539554]
59. Germain AM, Romanik MC, Guerra I et al. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? Hypertension (Dallas, Tex : 1979) 2007;49:90–5. [PubMed: 17116761]
60. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. Archives of internal medicine 2004;164:558–563. [PubMed: 15006834]
61. Li W, Ruan W, Lu Z, Wang D. Parity and risk of maternal cardiovascular disease: A dose–response meta-analysis of cohort studies. European journal of preventive cardiology 2019;26:592–602. [PubMed: 30567461]
62. Moazzeni SS, Toreyhi H, Asgari S, Azizi F, Tehrani FR, Hadaegh F. Number of parity/live birth (s) and cardiovascular disease among Iranian women and men: results of over 15 years of follow-up. BMC Pregnancy and Childbirth 2021;21:1–11. [PubMed: 33388035]
63. Lawlor DA, Emberson JR, Ebrahim S et al. Is the association between parity and coronary heart disease due to biological effects of pregnancy or adverse lifestyle risk factors associated with child-rearing? Findings from the British Women's Heart and Health Study and the British Regional Heart Study. Circulation 2003;107:1260–1264. [PubMed: 12628945]
64. Ogunmoroti O, Osibogun O, Kolade OB et al. Multiparity is associated with poorer cardiovascular health among women from the Multi-Ethnic Study of Atherosclerosis. Am J Obstet Gynecol 2019;221:631 e1–631 e16.
65. Rodriguez CP, Ogunmoroti O, Quispe R et al. The Association Between Multiparity and Adipokine Levels: The Multi-Ethnic Study of Atherosclerosis. Journal of women's health (2002) 2021.
66. Kazzi B, Ogunmoroti O, Rodriguez CP et al. Parity history and later life sex hormone levels in the Multi-Ethnic Study of Atherosclerosis (MESA). Canadian Journal of Cardiology 2022;38:1893–1900. [PubMed: 36087657]
67. Choi E, Kazzi B, Varma B et al. The Fourth Trimester: a Time for Enhancing Transitions in Cardiovascular Care. Current cardiovascular risk reports 2022:1–11. [PubMed: 36465151]
68. Hutcheon JA, Lisonkova S, Joseph K. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best practice & research Clinical obstetrics & gynaecology 2011;25:391–403. [PubMed: 21333604]
69. Hogan MC, Foreman KJ, Naghavi M et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. The lancet 2010;375:1609–1623.
70. Minhas AS, Ogunwole SM, Vaught AJ et al. Racial Disparities in Cardiovascular Complications With Pregnancy-Induced Hypertension in the United States. Hypertension (Dallas, Tex : 1979) 2021;78:480–488. [PubMed: 34098730]
71. Wu P, Haththotuwa R, Kwok CS et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes 2017;10.
72. Boucheron P, Lailler G, Moutengou E et al. Hypertensive disorders of pregnancy and onset of chronic hypertension in France: the nationwide CONCEPTION study. European heart journal 2022;43:3352–3361. [PubMed: 34643681]

73. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ 2020;369:m1361. [PubMed: 32404325]
74. Lee AJ, Hiscock RJ, Wein P, Walker SP, Permezel M. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. Diabetes care 2007;30:878–83. [PubMed: 17392549]
75. Parikh NI, Gonzalez JM, Anderson CAM et al. Adverse Pregnancy Outcomes and Cardiovascular Disease Risk: Unique Opportunities for Cardiovascular Disease Prevention in Women: A Scientific Statement From the American Heart Association. Circulation 2021;143:e902–e916. [PubMed: 33779213]
76. Grandi SM, Filion KB, Yoon S et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications: systematic review and meta-analysis. Circulation 2019;139:1069–1079. [PubMed: 30779636]
77. Faccini A, Kaski JC, Camici PG. Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases. European heart journal 2016;37:1799–1806. [PubMed: 26912605]
78. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Annals of the rheumatic diseases 2011;70:8–14. [PubMed: 21109513]
79. Zahid S, Mohamed MS, Wassif H, Nazir NT, Khan SS, Michos ED. Analysis of Cardiovascular Complications During Delivery Admissions Among Patients With Systemic Lupus Erythematosus, 2004–2019. JAMA Netw Open 2022;5:e2243388. [PubMed: 36445710]
80. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. American journal of epidemiology 2012;176:708–719. [PubMed: 23024137]
81. Manzi S, Meilahn EN, Rairie JE et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. American journal of epidemiology 1997;145:408–415. [PubMed: 9048514]
82. Roman MJ, Shanker B-A, Davis A et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. New England Journal of Medicine 2003;349:2399–2406. [PubMed: 14681505]
83. Feldman CH, Hiraki LT, Liu J et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum 2013;65:753–63. [PubMed: 23203603]
84. Rhew EY, Manzi SM, Dyer AR et al. Differences in subclinical cardiovascular disease between African American and Caucasian women with systemic lupus erythematosus. Translational Research 2009;153:51–59. [PubMed: 19138649]
85. Peters MJ, Van Halm VP, Voskuyl AE et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis Care & Research: Official Journal of the American College of Rheumatology 2009;61:1571–1579.
86. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Care & Research 2008;59:1690–1697. [PubMed: 19035419]
87. Myasoedova E, Chandran A, Ilhan B et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. Annals of the rheumatic diseases 2016;75:560–565. [PubMed: 25637001]
88. Myasoedova E, Crowson CS, Kremers HM et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Annals of the rheumatic diseases 2011;70:482–7. [PubMed: 21216812]
89. Davis III JM, Maradit Kremers H, Crowson CS et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis & Rheumatism 2007;56:820–830. [PubMed: 17330254]
90. Wasko MCM, Hubert HB, Lingala VB et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama 2007;298:187–193. [PubMed: 17622600]

91. Micha R, Imamura F, von Ballmoos MW et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. The American journal of cardiology 2011;108:1362–1370. [PubMed: 21855836]
92. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti–tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. Arthritis care & research 2011;63:522–529. [PubMed: 20957658]
93. Singh S, Singh H, Loftus EV Jr, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2014;12:382–393. e1. [PubMed: 23978350]
94. Quispe R, Varghese B, Michos ED. Inflammatory Diseases and Risk of Atherosclerotic Cardiovascular Disease: A New Focus on Prevention. In: Shapiro MD, editor Cardiovascular Risk Assessment in Primary Prevention. Cham: Springer International Publishing, 2022:247–270.
95. Tardif J-C, Kouz S, Waters DD et al. Efficacy and safety of low-dose colchicine after myocardial infarction. New England journal of medicine 2019;381:2497–2505. [PubMed: 31733140]
96. Ridker PM, Libby P, MacFadyen JG et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). European heart journal 2018;39:3499–3507. [PubMed: 30165610]
97. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. Neurological Sciences 2020;41:429–436. [PubMed: 32845494]
98. MacClellan LR, Giles W, Cole J et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. Stroke 2007;38:2438–2445. [PubMed: 17690308]
99. Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. The Lancet Neurology 2010;9:309–317. [PubMed: 20170844]
100. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener H-C, Buring JE. Migraine and risk of cardiovascular disease in women. Jama 2006;296:283–291. [PubMed: 16849661]
101. Levine GN, Cohen BE, Commodore-Mensah Y et al. Psychological Health, Well-Being, and the Mind-Heart-Body Connection: A Scientific Statement From the American Heart Association. Circulation 2021;143:e763–e783. [PubMed: 33486973]
102. Hedden SL. Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health: Substance Abuse and Mental Health Services Administration, Department of …, 2015.
103. O'Neil A, Fisher AJ, Kibbey KJ et al. Depression is a risk factor for incident coronary heart disease in women: An 18-year longitudinal study. J Affect Disord 2016;196:117–24. [PubMed: 26921864]
104. Pimple P, Lima BB, Hammadah M et al. Psychological distress and subsequent cardiovascular events in individuals with coronary artery disease. Journal of the American Heart Association 2019;8:e011866. [PubMed: 31055991]
105. Suglia SF, Koenen KC, Boynton-Jarrett R et al. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the American Heart Association. Circulation 2018;137:e15–e28. [PubMed: 29254928]
106. Korkeila J, Vahtera J, Korkeila K et al. Childhood adversities as predictors of incident coronary heart disease and cerebrovascular disease. Heart 2010;96:298–303. [PubMed: 20194205]
107. Vaccarino V, Bremner JD. Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. Neuroscience & Biobehavioral Reviews 2017;74:297–309. [PubMed: 27496672]
108. Michos ED, Blaha MJ, Blumenthal RS. Use of the Coronary Artery Calcium Score in Discussion of Initiation of Statin Therapy in Primary Prevention. Mayo Clinic proceedings 2017;92:1831–1841. [PubMed: 29108840]
109. Budoff MJ, Young R, Burke G et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). European heart journal 2018;39:2401–2408. [PubMed: 29688297]

110. Shaw LJ, Min JK, Nasir K et al. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium. European heart journal 2018;39:3727–3735. [PubMed: 30212857]
111. Minhas A, Cubero Salazar I, Kazzi B et al. Sex-Specific Plaque Signature: Uniqueness of Atherosclerosis in Women. Current cardiology reports 2021;23:84. [PubMed: 34081222]
112. Lakoski SG, Greenland P, Wong ND et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as “low risk” based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). Archives of internal medicine 2007;167:2437–2442. [PubMed: 18071165]
113. Orringer CE, Blaha MJ, Blankstein R et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. Journal of clinical lipidology 2021;15:33–60. [PubMed: 33419719]
114. Maas AH, van der Schouw YT, Atsma F et al. Breast arterial calcifications are correlated with subsequent development of coronary artery calcifications, but their aetiology is predominantly different. European journal of radiology 2007;63:396–400. [PubMed: 17360140]
115. Quispe R, Al-Rifai M, Di Carlo PA et al. Breast Arterial Calcium: A Game Changer in Women’s Cardiovascular Health? JACC Cardiovascular imaging 2019;12:2538–2548. [PubMed: 30878429]
116. Osman M, Regner S, Osman K et al. Association Between Breast Arterial Calcification on Mammography and Coronary Artery Disease: A Systematic Review and Meta-Analysis. Journal of women’s health (2002) 2022;31:1719–1726.
117. Bullock-Palmer RP, Michos ED, Gaballa D, Blankstein R. The Role of Imaging in Preventive Cardiology in Women. Current cardiology reports 2022.
118. Sweeney T, Quispe R, Das T, Juraschek SP, Martin SS, Michos ED. The Use of Blood Biomarkers in Precision Medicine for the Primary Prevention of Atherosclerotic Cardiovascular Disease: a Review. Expert Rev Precis Med Drug Dev 2021;6:247–258. [PubMed: 34423130]
119. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. The New England journal of medicine 2000;342:836–43. [PubMed: 10733371]
120. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. Jama 2007;297:611–9. [PubMed: 17299196]
121. Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology 2022;79:1757–1780. [PubMed: 35379504]

HIGHLIGHTS

- The relative risk for cardiovascular disease (CVD) conferred by traditional cardiovascular risk factors (i.e., diabetes, hypertension, obesity, and smoking) is greater in women as compared to men.
- Female-specific risk factors (i.e., age of menarche and menopause, polycystic ovary syndrome, infertility and the use of assisted reproductive technology, spontaneous pregnancy loss, parity, and adverse pregnancy outcomes), as well as female-predominant conditions (i.e., lupus, rheumatoid arthritis, depression), confer additional CVD risk.
- Comprehensive assessment of risk factors and the selective use of coronary artery calcium scores and/or biomarkers can help stratify a women's CVD risk and guide prevention efforts, including lifestyle modifications and the initiation of pharmacotherapy such as a statin when appropriate.

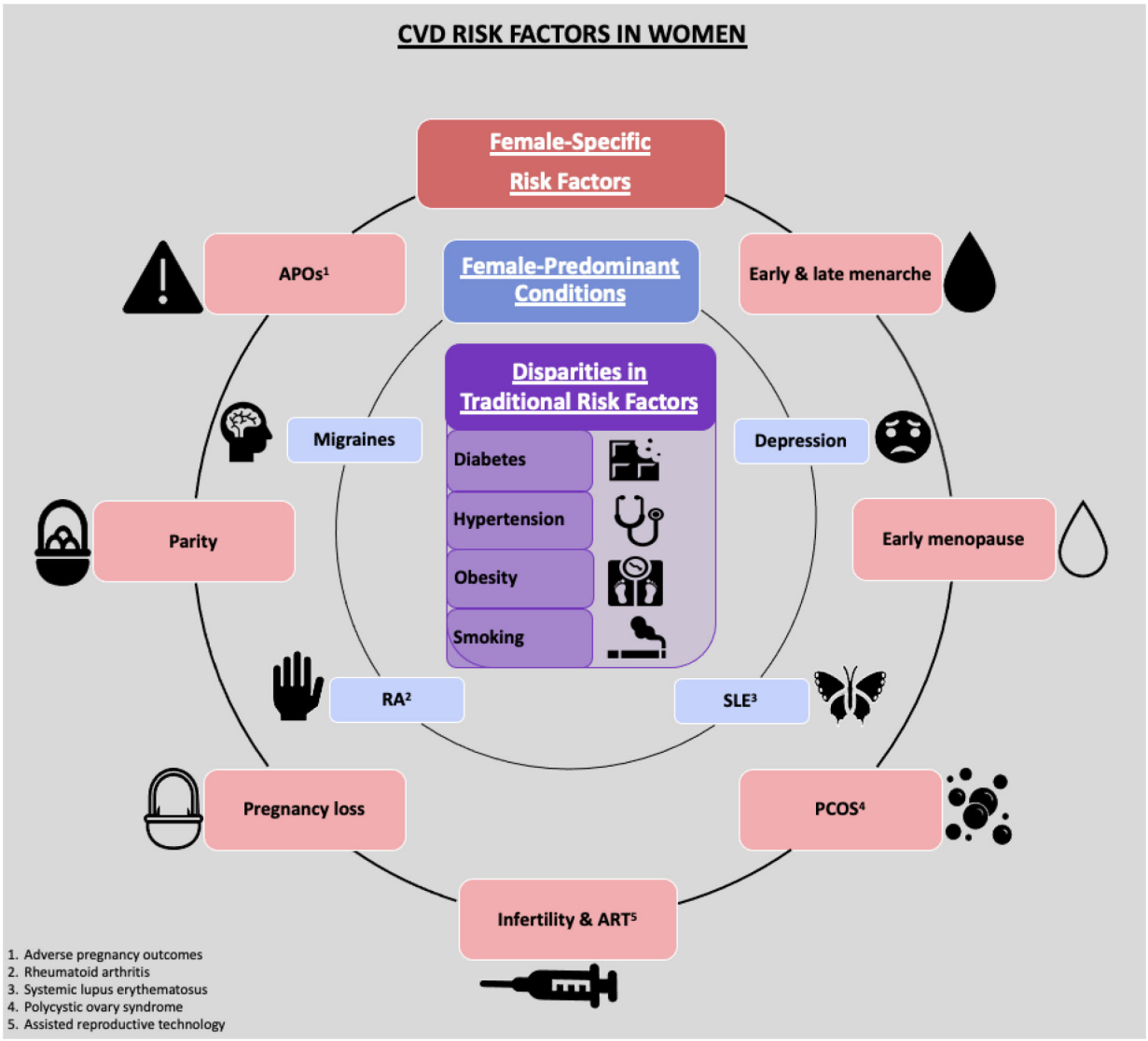

Fig. 1:
CVD risk factors in women.