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State-of-the-Art Review

Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention

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A B S T R A C T

Cardiovascular disease (CVD) remains the leading cause of death in women in the United States and globally, with heart disease actually on the rise among middle-aged women in the United States. This disease burden can be reduced by prioritizing a preventive approach to cardiovascular health. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of CVD contains important updates for delivery of primary prevention and also highlights early menopause and pre-eclampsia as two female-specific risk factors that enhance CVD risk. Additionally other female-specific risk factors including early menarche, polycystic ovarian syndrome, multi-parity, other adverse pregnancy outcomes, and hormone therapy also influence women's CVD risk throughout their lifespan. It is vital that both women and healthcare clinicians are made aware of this information as it has lifesaving potential. This review aims to (1) Introduce the key points of the 2019 ACC/AHA Guideline (2) Highlight the evidence for the female-specific risk factors for refining CVD risk assessment and (3) Discuss the impact of the female-specific risk enhancing factors on primary prevention interventions such as statin therapy. This approach will be able to more personalize risk assessment in women, with an emphasis on the importance of shared decision making in building authentic partnerships between clinicians and women patients throughout their lifespan.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally. Moreover, it results in high healthcare costs and lost productivity. This disease burden can be reduced by prioritizing a preventive approach to cardiovascular health, which can be enhanced by considering factors unique to women vs men. Sex refers to biological difference between males and females; while gender refers to sociocultural roles and behaviors and individual identity. Both sex and gender interact to influence cardiovascular health in women and the implementation of cardiovascular prevention strategies.

CVD accounted for 418,665 deaths in women in 2017 in the United States (U.S.) [1]. Back in the late 1990's, CVD deaths in women in the U.S. exceeded 500,000/year and were much greater than in men. Since that time, much initial progress was made, with steep declines in CVD deaths in women after the year 2000, in part driven by intensive women-specific preventive efforts and awareness campaigns [1]. Some of these efforts include the American Heart Association (AHA)'s Go Red for Women campaign and the publication of women-specific guidelines for CVD prevention by the AHA, first in 1999 and last updated in 2011 [2]. An updated summary of those primary prevention guidelines for women was recently put forth by the American College of Cardiology (ACC) in 2020 [3].

Unfortunately, more work still needs to be done. Since 2010, tracking along with the developing epidemic of obesity and type 2 diabetes (T2DM), there has been a concerning plateauing or even slight rise in CVD mortality in women (as well as in men). In fact, middle aged women (age 45–65) experienced the greatest relative increase in heart disease death rates between 2011 and 2017 [4]. This worrisome pattern is an indication that more intensive preventive efforts are still sorely needed. Prevention of CVD is not only focused on preventing atherosclerotic CVD (ASCVD), which includes fatal and non-fatal coronary heart disease (CHD), stroke, and peripheral arterial disease, but also preventing heart failure and atrial fibrillation.

Unfortunately women remain under-represented in clinical trials for preventive therapies such as lipid-lowering and cardiometabolic drugs, which limits the generalizability of trial results regarding efficacy and safety for this subgroup [5,6]. Additionally, women are less likely to be treated with guideline-recommended therapy such as statins, and even when offered statins, women are more likely to decline or discontinue therapy [7]. Women may be more likely to underestimate their CVD risk and over-estimate their risk for side effects [8], leading to

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underutilization of preventive therapies. Additionally even among statin-treated women, residual risk can remain; newer non-statin therapies offer opportunities for further intensification of prevention strategies in high risk women [9]. Cardiovascular risk is less often discussed with women resulting in missed opportunities for prevention [10].

There are sex-differences in the risk conferred by several traditional CVD risk factors, such as diabetes and smoking, in women compared to men [3]. Additionally there are unique risks for women that men do not experience. This review will discuss current approaches to CVD primary prevention in women, specifically the female-specific risk-enhancing factors, some of which were included in 2019 ACC/AHA Guideline on the Primary Prevention of CVD [11]; others of which were recently highlighted in the 2020 ACC review of primary prevention in women [3]. These factors include early menarche, polycystic ovarian syndrome (PCOS), multiparity, adverse pregnancy outcomes, premature menopause, and other hormonal factors (Fig. 1). These female-specific risk-enhancing factors are significant as they play an instrumental role in determining ASCVD risk and thus will influence the treatment plan including commencement of statin therapy. Pivotal times in a women's reproductive health throughout her lifespan also serve as prime opportunities for early CVD preventive interventions. Thus, it is imperative that both clinicians and women are aware of these risk factors.

1.1. The 2019 ACC/AHA guideline on primary prevention of CVD

In 2019, the ACC/AHA released an updated Guideline for the primary prevention of CVD [11]. The Guideline recommendations can be summarized into 9 key topic areas, framed together by a global "ABCDE" approach to prevention: 1) Assessment of CVD risk; 2) Aspirin therapy; 3) Blood pressure management; 4) Cholesterol management; 5) Cigarette smoking and other tobacco products cessation; 6) Diet; 7) Diabetes treatment and prevention; 8) Exercise and physical activity; 9) Obesity and weight management. Furthermore, the value of patient-centric care is highlighted throughout the guideline with 3 over-arching themes: 1) including a team-based approach to prevention; 2) addressing the social determinants of health which influence delivery and adherence to preventive recommendations; and 3) emphasizing the importance of shared decision making in building an authentic partnership between clinicians and patients.

1.2. The ACC/AHA primary prevention guideline applied to women

A healthy lifestyle through one's lifespan is the foundation for all preventive efforts. But when considering adding pharmacological therapy, a core tenet of preventive guidelines is to match the intensity of preventive efforts to the absolute risk of the patient. To guide risk-based decisions, the 2019 ACC/AHA Guideline recommends starting with a 10-year assessment of ASCVD risk, estimated by the race- and sex-specific pooled cohort equations (PCE), for adults aged 40–75 years [11]. For younger individuals age 20–59, who are not at high short-term risk, a lifetime risk can be estimated using the same PCE tool.

Low risk individuals (<5% 10-year risk) can generally be managed by lifestyle modifications alone, while for high risk individuals (≥20%), high intensity statin therapy is recommended in addition to lifestyle. Statin therapy is also recommended for adults with LDL-C ≥190 mg/dL, regardless of their 10-year risk given high lifetime risk associated with severe primary hypercholesterolemia. Adults over the age of 40 years with diabetes are also recommended for statin therapy for ASCVD prevention. For those without diabetes who have low-density lipoprotein cholesterol (LDL-C) of 70–189 mg/dL and 10-year risk ≥7.5–20% (intermediate risk), statin therapy is also generally recommended, but additional information and clinician-patient risk discussion is particularly needed for this group. Ten-year ASCVD risk estimation is the start of the conversation with patients, but not the end. Unfortunately these risk assessment tools, which are based on traditional CVD risk factors and derived from older cohort data, have the potential to both under-estimate [12,13] and over-estimate [14,15] risk in women.

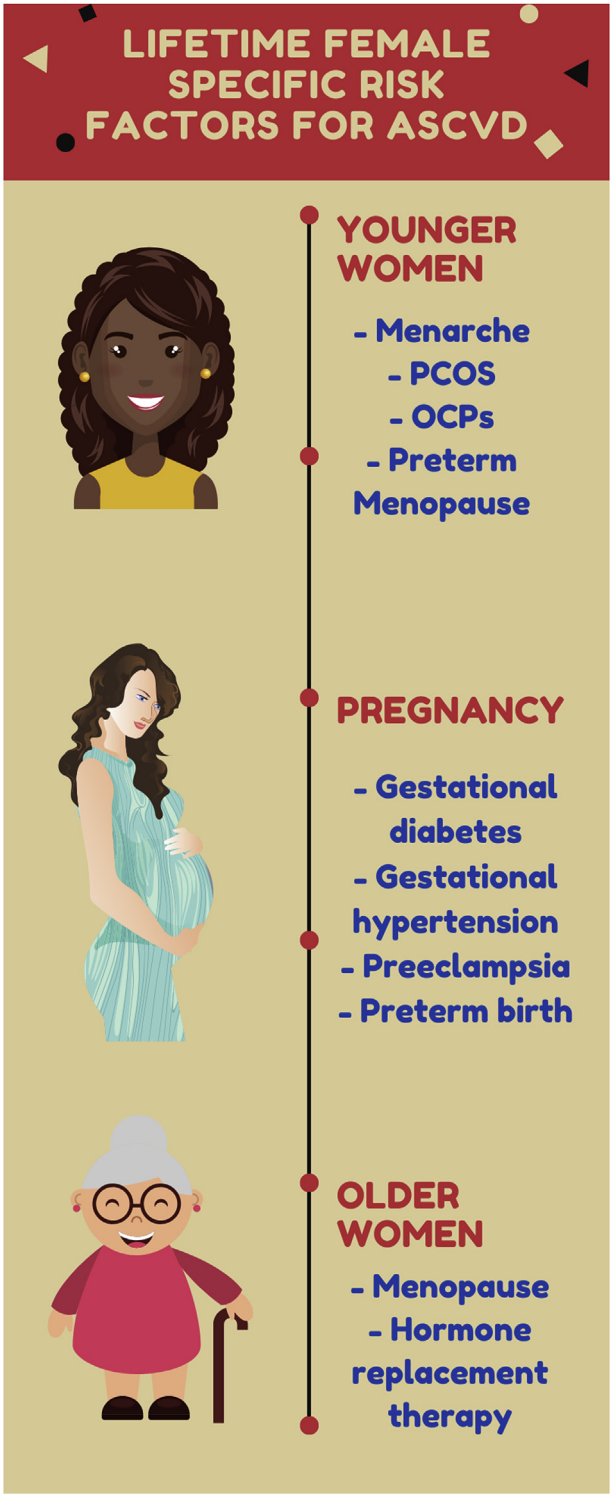

Fig. 1. Infographic showing the risk-enhancing factors for ASCVD across the lifespan of women.

Many high risk women under the age of 40 years old are not identified because the currently available tools were developed and validated in older populations, i.e. >50 years of age [16,17]. Furthermore, women develop CVD at older ages than men, resulting in lower risk estimates. Risk scores that use a time-based framework can lead to underestimation of risk. For example, one study demonstrated a significant association between cumulative exposure to hyperlipidemia in young adulthood and subsequent CHD risk despite the younger persons not meeting statin

therapy criteria by the 10-year risk score [18]. Notably, the focus on older age groups may further be harmful as it fails to include the younger population, which due to its sheer size, indicates a higher population burden who may benefit from an opportunity for earlier intervention [19]. Alternative solutions that have been proposed include using a lifetime risk score, or using age and sex-specific CVD thresholds to guide cholesterol treatment recommendations [20].

The 2019 ACC/AHA Guideline acknowledged the limitations of term-based (10-year) risk assessment and recommended that for adults at borderline (5% to <7.5%) and intermediate (≥7.5% to <20%) risk, the following risk enhancing factors should be assessed and utilized to modify the ASCVD estimate: family history of premature ASCVD, primary hypercholesterolemia, metabolic syndrome, persistently elevated triglycerides, chronic kidney disease, chronic inflammatory conditions, high risk race/ethnicity such as South Asian ancestry, and if measured, elevation in specific biomarkers such as high-sensitivity C-reactive protein, apolipoprotein B, and lipoprotein (a) [Lp(a)] [11]. Additionally, the ACC/AHA Guideline specifically highlights female-specific risk factors including a history of premature menopause and a history of pre-eclampsia [11]. These female-specific factors will be further discussed in the sections below.

It should be recognized that to date studies have not shown that inclusion of pregnancy-related factors improve current risk prediction models after including conventional CVD risk factors [16,17]. However, although these studies used population-based cohorts, they primarily included women beyond their reproductive years in the sample populations, which may in part explain the lack of positive findings. Ideally, future registries should include sample populations that are closer to the target populations intended for screening and intervention of CVD risk following an adverse pregnancy outcome.

The 2019 ACC/AHA Guideline acknowledges that even after assessment of 10-year risk by PCE score and assessment of these clinical risk-enhancing factors, there can still be uncertainty for patients and clinicians about the net benefit of initiating pharmacological preventive therapy, such as statins. If uncertainty remains as to the level of risk and value of preventive therapy, further evaluation with coronary artery calcium (CAC) by non-contrast CT can be employed to better determine ASCVD risk [11]. Coronary artery calcium is a good surrogate marker of total burden of atherosclerotic plaque and can predict future CVD risk, even independently of age, sex, and other traditional risk factors [21]. CAC has proven to be an effective and reliable tool in revising risk estimation both upwards and downwards after PCE assessment. Notably, the CAC score improves risk prediction in women, even for those deemed to be at low risk by traditional risk scoring estimates [22–24]. The presence of a CAC score of 0 indicates a very low risk of incident CVD event in next 5–10 years and statin therapy thus could be deferred or postponed; on the other hand any non-zero score indicates the presence of coronary atherosclerosis where statin therapy could be considered and would be recommended for high scores such as ≥100 Agatston units or ≥75th age-sex percentile. The use of age-sex percentiles may be more applicable to women who have lower CAC scores on average compared to men.

This rest of this narrative will focus on a deeper-dive into reviewing the female-specific risk enhancing factors that can refine ASCVD risk estimation and guide treatment decisions for statin therapy. For further information about the other prevention topic areas (diet, physical activity, tobacco cessation, weight management, blood pressure management, diabetes management, and selective use of aspirin), please refer to the 2019 ACC/AHA Guideline where these topics are discussed in detail [11].

1.2.1. Risk factors for ASCVD associated with younger women

1.2.1.1. Polycystic ovarian syndrome. Polycystic ovarian syndrome (PCOS) is a disorder characterized by hyperandrogenism and menstrual irregularities [25]. Women affected by PCOS have a heightened risk of developing diabetes due to associated insulin resistance, central obesity and hypertension. This adverse cardiovascular risk profile in women with PCOS may lead to premature atherosclerosis [26,27]. Women with PCOS have been shown to have increased risk for CVD events [28]; although it is debated whether this is independent of the above CVD risk factors or not [25]. Regardless, implementation of lifestyle management can help mitigate some of this risk.

Once a woman is diagnosed with PCOS, clinicians should be judicious and proactive by pursuing aggressive CVD risk factor management. For example, blood pressure and body mass index (BMI) should be measured regularly as per the guidelines. At diagnosis, measurement of lipids to establish a baseline as well as testing for diabetes via oral glucose tolerance test, fasting glucose and obtaining the hemoglobin A1c should be performed. If impaired oral glucose tolerance is detected, yearly screening for diabetes should be done. If the woman has normal glucose tolerance, diabetes screening should be done at least every 2 years [29].

1.2.1.2. Hormone contraceptive use. The use of combination estrogen/progestin oral contraceptive (OCP) elevates the possibility of developing a thrombotic stroke or myocardial infarction. In general, because women of child-bearing age are at low CVD risk, this excess risk conferred by OCPs is very minimal and is offset by the benefits of avoiding an unplanned pregnancy. However, risk conferred by OCP does increase with the age of woman, smoking, hypercoagulable states, and with higher estrogen doses. The risk is approximately 1.6-fold increased with the highest risk associated with pills with >50 microgram of estrogen [30]. Notably, OCP use is not an independent risk factor for ASCVD risk long term [31]. The risk of stroke is increased when women use OCPs and also have other risk factors. These risk factors include smoking, hypertension, hyperlipidemia, diabetes, obesity and migraine/aura [29]. A meta-analysis found that the safest oral form of hormonal contraception with regard to the OCP pill was the one containing levonorgestrel and 30 microgram of estrogen [30]. Thus, consideration should be given for this formulation, especially if other risk factors are present and OCP is absolutely required. Consideration should be given to progestin-only pills or intra-uterine delivery systems if patient is above age 35 and has other ASCVD risk factors [31].

Regarding the use of OCPs, healthcare professionals and female patients should be aware that use of OCP could contribute to ASCVD risk, employ strategies to reduce the likelihood of ASCVD by mitigating other risk factors through preventive efforts, and avoid estrogen-based OCPs in women at highest CVD risk in favor of other progestin-only or non-hormonal contraception.

1.2.1.3. Menarche. Early menarche is associated with a higher risk of adverse CVD outcomes [32]. Results from the Women's Ischemia Syndrome Evaluation (WISE) study demonstrated that in comparison to women with menarche at age 12 years, there was an approximately 4-fold adjusted increased risk for major adverse cardiac events for menarche ≤10 years [hazard ratio (HR) 4.53 (95% CI 2.13–9.64)] [33]. There is also an increased risk with late menarche ≥15 years. Increased BMI and other behavioral/lifestyle factors may be one trigger for onset of early menarche. Additionally, genetic studies are being undertaken to better understand the reasons as to why age at menarche affects CVD risk but currently the underlying mechanism is thought to be linked to weight and height [34]. Age of menarche has potential to be used as a screening tool to identify women at greater risk of CVD. Attention should be placed on optimizing women's cardiovascular risk profile and encouragement of healthy lifestyle.

1.2.1.4. Primary ovarian insufficiency. Primary ovarian insufficiency (POI) is a clinical condition defined by loss of ovarian activity before the age of 40 years [35]. It is characterized by amenorrhea or oligomenorrhea, high levels of follicle-stimulating hormone (FSH) and low estradiol and anti-Mullerian hormone levels [36]. It is thought to be due to genetic

mutations, such as an autosomal recessive FSH receptor mutation [37], or an inactivating ALA 189Val mutation [38]. The incidence of POI is 0.01% in women younger than 20, 0.1% in women younger than 30, and approximately 1% of women younger than 40 [39].

POI is associated with a shortened life expectancy with the main cause of mortality being identified as CVD. POI can result in reduced vascular endothelial function, an early marker of atherosclerosis [40]. Hormone therapy (HT) has been shown to improve the endothelial function in as short as 6 months [41]. Estrogen also improves cholesterol metabolism which in turn decreases formation of atherosclerotic plaque and reduces coronary constriction via catecholamine modulation [42].

Hormone therapy is essential in the treatment of women with POI, so as to mitigate the adverse effects of hypoestrogenism and prevent CVD. It is recommended that HT formulations that most closely resemble normal ovarian hormone production be employed and continued until the average age of natural menopause, which is approximately 50 years [40].

Healthcare providers should be aware of POI to aid in a timely diagnosis, the counselling of patients on the various health problems due to estrogen deficiency and prompt initiation of HT. The relationship between POI and CVD, underscores the importance of careful documentation of women's menstrual history; investigating the age of menarche, frequency of menses and family history so as to identify POI in a timely fashion. Women with POI should also be advised to optimize lifestyle risk factors such as diet, exercise and abstaining from tobacco in order to further protect their cardiovascular health.

1.2.1.5. Fertility therapy. Greater numbers of women, mostly age 35–39 years, who suffer from infertility are electing fertility therapy to increase their chance of a pregnancy [43]. Fertility therapy, however, has been shown to have adverse cardiovascular outcomes. The pathophysiology is thought to be due to fertility therapy generating thrombosis, vascular injury from ovarian hyperstimulation and activation of the renin-angiotensin system [44,45]. Moreover, vascular injury can be worsened in women who undergo multiple fertility cycles or those who have miscarriages [46,47].

There is also added risk for CVD in women who fail fertility therapy. One cohort study investigated this, defining fertility therapy failure as cycles of treatment that were not followed by a subsequent newborn delivery within 1 year [48]. The results revealed that women who failed fertility therapy were 19% more likely to develop adverse cardiovascular health outcomes as compared to the group in which fertility therapy was successful [48]. There was a marked increase in numbers of cases of heart failure and ischemic stroke. Furthermore, the most substantial risk for cardiovascular event or mortality was during the first year of follow up after the failure of fertility therapy [48].

Women who fail fertility therapy should undergo close surveillance for the development of risk factors for CVD and cardiovascular morbidity. It is of paramount importance that clinicians and patients know about this risk as more women with comorbidities are utilizing fertility therapy [49], as well as more women partaking in oocyte cryopreservation for future fertility [50]. Research is being done to looks at the utility of renin angiotensin inhibitor therapy [51]. For prevention of thromboembolism, there is the potential for the use of antiplatelet agents [52].

1.2.2. Risk factors for ASCVD associated with pregnancy

1.2.2.1. Hypertensive disorders of pregnancy: eclampsia, preeclampsia, gestational hypertension. A history of preeclampsia was highlighted as a CVD risk-enhancing factor in the 2019 ACC/AHA Prevention Guideline and other reviews [3,11,53,54]. Preeclampsia is a pregnancy specific disorder which results in hypertension and multi-organ dysfunction, after 20 weeks' gestation [55]. It is a leading cause of maternal mortality globally, affecting 2–8% of all pregnancies [55]. A recent meta-analysis linked preeclampsia with a four-fold increased risk of heart failure development and a two-fold increase in CHD, stroke and death due to CVD, after adjusting for age, BMI and diabetes mellitus [56]. Another study demonstrated that women with a history of preeclampsia have accelerated subclinical coronary atherosclerosis [57].

Hypertensive disorders of pregnancy (HDP), which includes gestational hypertension, preeclampsia and eclampsia, have been shown to be linked to accelerated cardiovascular aging and a multitude of cardiovascular conditions such as valvular heart disease. This link can be explained by the enhanced risk of developing chronic hypertension after HDP, as highlighted by a large study from UK biobank [58].

The pathophysiology of preeclampsia is thought to include placental ischemia and increase in anti-angiogenic milieu leading to vascular and endothelial damage [59]. Consequently, this can result in systemic hypertension and end-organ hypoperfusion. This damage may persist and manifest as CVD in the future, even more than a decade after the pre-eclamptic pregnancy [54,55]. An association between early onset of pre-eclampsia and an increased risk of metabolic syndrome development has also been shown [60]. The CHAMPS (Cardiovascular Health After Maternal Placental Syndrome) study demonstrated a 12-fold increase in CVD risk for women with a history of preeclampsia and metabolic syndrome as compared to women with neither of these conditions [61]. Notably, risk factors for development of preeclampsia, also fit the risk profile for CVD such as dyslipidemia, obesity, chronic hypertension and insulin resistance [56].

Moreover, the 2011 AHA Guideline for the Prevention of CVD in Women also discussed gestational hypertension as a risk factor for CVD [2]. Gestational HTN is defined as the development of hypertension (blood pressure >140/90 mmHg on 2 separate occasions) after 20 weeks of gestation with no evidence of proteinuria or preeclampsia. Gestational HTN is thought to contribute to the consequent development of hypertension, diabetes, CVD and heart failure [56].

Lifelong monitoring of cardiovascular risk factors, particularly blood pressure and diabetes, in women with a history of preeclampsia is required. In the postnatal appointments, cardiovascular risk assessments should be performed, and interventional measures implemented as necessary. Patient education about lifestyle modification to reduce risk should be prioritized. Early identification of these high-risk women can preclude future CVD events with timely prevention efforts. Furthermore, for the prevention of preeclampsia, evidence suggests the use of low dose aspirin, which has been shown to be safe [62]. Multi-disciplinary collaboration between obstetrics, cardiology, and primary care can improve delivery of CV preventive care for these high risk women, including of implementation of dedicated post-partum cardiology clinics [63].

1.2.2.2. Preterm delivery. Preterm delivery is defined as delivery before 37 weeks of gestation. Approximately 10% of pregnancies are affected by preterm delivery in the U.S. annually [64,65]. Preterm delivery has been shown to increase the risk of CVD development in mothers [65]. Studies and subsequent meta-analyses have demonstrated that the occurrence of a preterm delivery is associated with a 2-fold increased risk of future CVD events [66,67]. The highest future CVD risk was among women who delivered very prematurely before 32 weeks of gestation. Women with a history of preterm delivery are also more likely to develop chronic hypertension, T2DM, and hypercholesterolemia, with a more pronounced risk in the first 10 years following the preterm delivery [68].

Preterm delivery is an independent predictor of CVD [69]. Thus, it can be used as prognostic tool for CVD, identifying women who can benefit from early screening, prevention and treatment. Primary care providers should take into account preterm delivery in workup of patients' CVD risk level. Interventions to reduce the risk of having a preterm delivery should also be performed. This includes diet and exercise management plans and weight reduction.

1.2.2.3. Gestational diabetes. The 2011 AHA guidelines for the prevention of CVD in women discussed gestational diabetes mellitus (GDM) as a

critical risk factor for CVD [2]. Gestational diabetes mellitus is characterized as the presence of raised blood glucose during pregnancy, normally associated with insulin resistance. GDM independently increases the risk of the development of CVD, as well as increases the risk of the development of T2DM, a known risk factor for adverse cardiovascular health outcomes [70]. If a woman develops gestational diabetes, she has an 8-fold increased risk of acquiring T2DM [71]. Gestational diabetes also results in a 63% higher odds of incident CVD and an absolute risk increase of 2.8% [72]. This study that included 8127 parous women aged 20 years or older, also revealed that there was a significant association between a history of GDM and a lower serum level of high density lipoprotein cholesterol (HDL-C). Of note, adjustments for BMI, modestly attenuated the associations described above [72].

Increased awareness of the heightened risk of developing T2DM and CVD after GDM, can change clinical practice and positively alter the trajectory of the impacted women's lives. It provides an opportunity to further investigate and utilize lifestyle (dietary, exercise) and pharmacological interventions that can decrease the likelihood of CVD complications in the affected women. One meta-analysis demonstrated that GDM confers a 2.3-fold increased risk of CVD in the first decade postpartum [70]. This emphasizes the urgency and the importance of early surveillance and risk modification.

1.2.2.4. Parity. Greater parity, or number of live births, is independently associated with risk for development of CVD in several observational studies; however the mechanism which is not fully understood [73–75]. During pregnancy, there are normal physiologic changes that influence CV risk factors of lipids, glucose, and weight), along with additional stressors such as endothelial dysfunction, inflammation, and hemostatic processes. Women may gain weight with each subsequent pregnancy, with multi-parous women being more likely to have an elevated BMI [76]. These factors may lead to an increased risk of incident CVD later in life. Prior work from Multi-Ethnic Study of Atherosclerosis found that multiparous women, particularly those with history of $\geq$5 live births were less likely to have ideal cardiovascular health at middle to older ages [76] and have worse arterial function later in life [77]. In the Dallas Heart Study, higher parity was also associated with increased CAC [78].

More attention needs to be placed on the mother's health after each pregnancy, and some of the risk conferred by multi-parity could be potentially mediated by more intensive lifestyle changes. Mothers need more support and resources, including help with childcare, to be able to prioritize their own well-being. Family-centric approaches that optimize healthy diet and physical activity should be encouraged, which benefit both children and adults.

1.2.3. Risk factors for ASCVD associated with older women

1.2.3.1. Menopause. Cardiovascular risk accelerates after menopause due to withdrawal of endogenous estradiol levels, which can worsen many traditional CVD risk factors including body fat distribution, impairment of glucose tolerance, adverse changes in lipid profile, elevations in blood pressure, endothelial dysfunction and increased sympathetic tone, which all have detrimental effects on arterial/cardiovascular function [79]. In regard to lipids, at the time of menopausal transition, women experience increases in total cholesterol, LDL-C, very low density lipoprotein cholesterol (VLDL-C), and triglycerides, and a decrease in HDL-C [80,81]. The atherogenic index (total cholesterol/HDL-C ratio) is significantly higher in post-menopausal women as compared to premenopausal women [80]. However, conversely, an elevated HDL-C may not be cardioprotective among post-menopausal women [82], which may lead to false reassurance and underestimation of women's risk.

In pre-menopause state, estrogen contributes to cardio-protection through several mechanisms including the maintenance of a healthy lipoprotein profile. This is evident by the negative correlation of estrogen levels with total cholesterol, LDL-C, triglycerides, and VLDL-C while positively correlated with HDL-C. Estrogen alters vascular tone by producing nitrous oxide resulting in stabilization of endothelial cells, enhancement of antioxidant effects and modification of fibrinolytic protein; however, this cardio-protection is lost with menopause. Women with higher androgen levels relative to estrogen after menopause are at greater risk of endothelial dysfunction, atherosclerosis, and subsequent CVD events [83–85].

Menopause is an event that all women experience during their lifetime. However, of particular concern is when menopause comes prematurely (<45 years), with early menopause being linked to an increased risk of CVD even independently of traditional CVD risk factors [86,87]. The enhanced risk occurs regardless if menopause onset was natural or surgically induced [86]. [See above discussion in the younger women section about premature ovarian failure (POI) which is associated with increased cardiovascular risk too.] A recent pooled meta-analysis including over 300,000 women found a graded association of CVD risk depending on timing of menopause. Compared to women with menopause at age 50–51 years, the risk for younger women were as follows: <40 years [HR 1.55 (95% CI 1.38–1.73)], age 40–44 [HR 1.30 (1.22–1.39), age 45–49 [HR 1.12 (1.107–1.18)] [88].

Early menopause can identify women who are at greater risk of developing ASCVD, and this is highlighted as a risk-enhancing factor in the 2019 ACC/AHA Primary Prevention Guideline [11]. Thus, women with early menopause may benefit from aggressive CVD primary prevention and consideration of assessment of CAC to refine risk if decisions for statin therapy are unclear. They would also benefit from strategies to reduce the likelihood of premature menopause such as following a healthy lifestyle and smoking avoidance. Smoking is linked to earlier onset of menopause, with smokers undergoing menopause 2 years prior to non-smokers [86].

1.2.3.2. Post-menopausal hormone therapy. As mentioned above, post-menopausal women are at greater risk of developing CVD as compared to premenopausal women, which is thought to be due to the lower levels of endogenous estrogens [79]. Multiple observational studies has suggested that menopausal hormone therapy (MHT) has cardioprotective potential [89]. This effect was further enhanced if MHT is started early after menopause [90]. One study underscored a possible mechanism for this effect; by demonstrating that MHT use led to a substantial reduction in pro-thrombotic Lp(a). Lp(a) is associated with an increased risk of CHD [89]. A 2006 meta-analysis outlined the reduction in risk factors for CHD such as abdominal obesity, insulin resistance, lipids, and blood pressure with MHT use. However, there was a caveat that while oral agents resulted in larger beneficial effects than transdermal agents, they can adversely affect C-reactive protein and protein C, which was not seen with transdermal agents [90].

It is still however unclear as to what modification of sex hormones is most suitable for CVD risk reduction. Unfortunately, randomized clinic trials such as the Women's Health Initiative (WHI) failed to confirm beneficial effect of MHT on CVD events, and risks even exceeded benefits in that trial [91]. For this reason, MHT is not recommended for the sole purpose of CVD prevention. Notably, the trials included women who on average were at older ages and more distant from the menopause transition. Additionally, the trials focused on conjugated equine estrogen and medroxyprogesterone acetate [92,93]. The beneficial effects may be dependent upon the formulation for MHT of which there are many various strengthens of estrogen and progestin [94]. Thus, more research is ideally needed on the use of MHT in post-menopausal women for primary prevention of CVD, particularly for those in the peri-menopausal transition; however, it is unlikely there will ever be another large scale randomized clinical trial conducted to replace the findings from the WHI.

The use of MHT to decrease CVD risk remains controversial. Estrogen therapy has the potential to prevent subclinical atherosclerosis if given to women closer to their menopausal transition [95]. However, the CVD

preventive benefit of MHT if given later in menopause is significantly reduced and may even be harmful in this setting [93]. At this point, MHT is not recommended for CVD prevention, but is reasonably safe to administer to women 50–59 years free of clinical CVD in efforts to manage vasomotor symptoms. Therefore, it should be a shared decision making process between clinician and patient to determine if to utilize MHT. If a woman's CVD risk is uncertain before starting MHT, the use of CAC may be helpful to refine risk estimation further.

1.2.3.3. Transgender individuals. Accounting for 0.6% of adults in the U.S., the transgender population has unique CVD risks, with a higher risk of myocardial infarction compared to the cisgender population [96]. Efforts must be made to better understand the CVD risk factors in this population, so as to promote better health. Data from a large gender clinic in the Netherlands reported that transwomen receiving transgender hormone therapy (THT) (typically estrogens) had an increased risk of venothromboembolism and stroke, while transmen receiving THT (testosterone) had an increased risk of myocardial infarction, compared to their cis-counterparts [97]. Transmen receiving testosterone therapy are at risk for elevated blood pressure, lipid derangements and insulin resistance. Given risk of venothromboembolism in transwomen, lower doses of transdermal estrogen is preferred [96]. One study indicated that there is a protective effect of progestin therapy in transgender women due to decreased blood pressures [98]. Other studies show that transgender men and women may have other prevalent risk factors for CVD such as diabetes and being overweight[99] and social stressors; so it is not entirely clear from these observational studies how much of the excess CVD risk is due to the THT itself or due to other risk factors in this population. More research needs to be done as most studies thus far look at younger transgender adults, thus lacking generalizability to older cohorts who are more likely to have CVD. Additionally, there are limited randomized control studies comparing the different THT formulations [96]. Since THT is an important part of gender identity, it is not recommended to withhold hormone therapy but rather to screen for and address CVD risk factors in this population to help mitigate their excess risk.

2. Conclusions

Despite substantial progress over the past two decades, more recent trends in the increased prevalence of obesity and diabetes have slowed or even reversed prior reductions in CVD mortality in women. Thus, more work remains to be done to further improve cardiovascular health in women. Healthcare professionals should be cognizant of female-specific risk factor that enhance women's risk for ASCVD [100]. These include adverse pregnancy outcomes (e.g., hypertensive disorders of pregnancy, gestational diabetes) and hormonal factors (e.g. PCOS, POI, infertility treatment, early menarche, early menopause, and use of hormone therapies (OCPs, MHT, or THT). These "red" flags of risk warrant more intensive primary preventive efforts, notably lifestyle changes and closer monitoring for progression of CVD risk factors. The use of statin therapy should be employed for higher risk women. When women's risk is uncertain after calculation of 10-year ASCVD risk and consideration of these female-specific and other risk-enhancing factors, assessment for the presence of subclinical atherosclerosis by measurement of CAC is a helpful tool to refine CVD upwards or downward and guide shared decision making about preventive therapies.

For other preventive recommendations to manage CV risk factors, the 2019 ACC/AHA Primary Prevention Guideline provides a useful "ABCDE" framework. Finally, disparities in socioeconomic factors are key drivers of CVD risk and should not be overlooked. None of these preventive efforts will be successful without paying attention to patients' access to health insurance, transportation, availability of healthy food sources, safe neighborhoods for physical activity, and freedom from violence and abuse. Preventive therapy should be leveraged in the context of building successful clinician-patient partnerships towards a shared goal of CV health promotion, with recommendations individualized for a given patient.

Declaration of competing interest

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References

[1] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. Circulation 2020;141(9):e139–596.
[2] Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the american heart association. Circulation 2011;123(11):1243–62.
[3] Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(20):2602–18.
[4] 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(6):1–8.
[5] Khan SU, Khan MZ, Raghu Subramanian C, Riaz H, Khan MU, Lone AN, et al. Participation of women and older participants in randomized clinical trials of lipid-lowering therapies: a systematic review. JAMA Network Open 2020;3(5). e205202.
[6] Khan MS, Shahid I, Siddiqi TJ, Khan SU, Warraich HJ, Greene SJ, et al. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US food and drug administration approval of novel cardiometabolic drugs. J.Am. Heart Assoc 2020;9(11). e015594.
[7] Nanna MG, Wang TY, Xiang Q, Goldberg AC, Robinson JG, Roger VL, et al. Sex differences in the use of statins in community practice. Circ.Cardiovasc.Qual.Outcome 2019;12(8). e005562.
[8] Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, et al. Patient-reported reasons for declining or discontinuing statin therapy: insights from the PALM registry. J.Am. Heart Assoc 2019;8(7). e011765.
[9] Mosca L, Navar AM, Kass Wenger N. Reducing cardiovascular disease risk in women beyond statin therapy: new insights 2020. J Wom Health 2020. https://doi.org/10.1089/jwh.2019.8189.
[10] Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, et al. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO study. J Am Coll Cardiol 2015;66(18):1949–57.
[11] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 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(11):e596–646. 2019.
[12] Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. Atherosclerosis 2006;184(1):201–6.
[13] Michos ED, Vasamreddy CR, Becker DM, Yanek LR, Moy TF, Fishman EK, et al. Women with a low Framingham risk score and a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. Am Heart J 2005;150(6):1276–81.
[14] DeFilippis AP, Young R, McEvoy JW, Michos ED, Sandfort V, Kronmal RA, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. Eur Heart J 2017;38(8):598–608.
[15] Amin NP, Martin SS, Blaha MJ, Nasir K, Blumenthal RS, Michos ED. Headed in the right direction but at risk for miscalculation: a critical appraisal of the 2013 ACC/AHA risk assessment guidelines. J Am Coll Cardiol 2014;63(25 Pt A):2789–94.
[16] Timpka S, Fraser A, Schyman T, Stuart JJ, Åsvold BO, Mogren I, et al. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction in middle-aged women. Eur J Epidemiol 2018;33(10):1003–10.
[17] Markovitz AR, Stuart JJ, Horn J, Williams PL, Rimm EB, Missmer SA, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. Eur Heart J 2019;40(14):1113–20.
[18] Navar-Boggan AM, Peterson ED, D'Agostino RB, Neely B, Sniderman AD, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. Circulation 2015;131(5):451–8.
[19] Sniderman AD, Thanassoulis G, Williams K, Pencina M. Risk of premature cardiovascular disease vs the number of premature cardiovascular events. JAMA Cardiology 2016;1(4):492–4.
[20] Navar-Boggan AM, Peterson ED, D'Agostino Rb Sr, Pencina MJ, Sniderman AD. Using age- and sex-specific risk thresholds to guide statin therapy: one size may not fit all. J Am Coll Cardiol 2015;65(16):1633–9.

[21] Michos ED, Blaha MJ, Blumenthal RS. Use of the coronary artery calcium score in discussion of initiation of statin therapy in primary prevention. Mayo Clin Proc 2017;92(12):1831–41.
[22] Budoff MJ, Young R, Burke G, Jeffrey Carr J, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J 2018;39(25):2401–8.
[23] Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi AA, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. J Am Med Assoc 2016;316(20):2126–34.
[24] Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, 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). Arch Intern Med 2007;167(22):2437–42.
[25] Osibogun O, Ogunmoroti O, Michos ED. Polycystic ovary syndrome and cardiometabolic risk: opportunities for cardiovascular disease prevention. Trends Cardiovasc Med 2019;S1050-1738(19):30128–38.
[26] Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Endocrinol Metabol 2004;89(11):5454–61.
[27] Orio Jr F, Palomba S, Cascella T, De Simone B, Di Biase S, Russo T, et al. Early impairment of endothelial structure and function in young normal-weight women with polycystic ovary syndrome. J. Clin. Endocrinol.Metabol 2004;89(9):4588–93.
[28] Glintborg D, Rubin KH, Nybo M, Abrahamsen B, Andersen M. Cardiovascular disease in a nationwide population of Danish women with polycystic ovary syndrome. Cardiovasc Diabetol 2018;17(1):37.
[29] Gill SK. Cardiovascular risk factors and disease in women. Med Clin 2015;99(3):535–52.
[30] Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev 2015;(8):Cd011054.
[31] Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012;366(24):2257–66.
[32] Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. J.Am. Heart Assoc 2017;6(11).
[33] Lee JJ, Cook-Wiens G, Johnson BD, Braunstein GD, Berga SL, Stanczyk FZ, 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. J.Am. Heart Assoc 2019;8(12). e012406.
[34] Luijken J, van der Schouw YT, Mensink D, Onland-Moret NC. Association between age at menarche and cardiovascular disease: a systematic review on risk and potential mechanisms. Maturitas 2017;104:96–116.
[35] Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod 2016;31(5):926–37.
[36] Fortuno C, Labarta E. Genetics of primary ovarian insufficiency: a review. J Assist Reprod Genet 2014;31(12):1573–85.
[37] Aittomaki K, Lucena JL, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J, et al. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell 1995;82(6):959–68.
[38] Aittomaki K, Herva R, Stenman UH, Juntunen K, Ylostalo P, Hovatta O, et al. Clinical features of primary ovarian failure caused by a point mutation in the follicle-stimulating hormone receptor gene. J. Clin. Endocrinol.Metabol 1996;81(10):3722–6.
[39] Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol 1986;67(4):604–6.
[40] Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril 2016;106(7):1588–99.
[41] Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. J Clin Endocrinol Metabol 2004;89(8):3907–13.
[42] Sarrel PM, Lindsay D, Rosano GM, Poole-Wilson PA. Angina and normal coronary arteries in women: gynecologic findings. Am J Obstet Gynecol 1992;167(2):467–71.
[43] Stephen EH, Chandra A, King RB. Supply of and demand for assisted reproductive technologies in the United States: clinic- and population-based data, 1995-2010. Fertility and Aterility 2016;105(2):451–8.
[44] Binder H, Dittrich R, Einhaus F, Krieg J, Muller A, Strauss R, et al. Update on ovarian hyperstimulation syndrome: Part 1–Incidence and pathogenesis. Int J Fertil Women's Med 2007;52(1):11–26.
[45] Hassan E, Creatsas G, Mastorakos G, Michalas S. Clinical implications of the ovarian/endometrial renin-angiotensin-aldosterone system. Ann N Y Acad Sci 2000;900:107–18.
[46] Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001;357(9273):2002–6.
[47] Ranthe MF, Andersen EA, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Pregnancy loss and later risk of atherosclerotic disease. Circulation 2013;127(17):1775–82.
[48] Udell JA, Lu H, Redelmeier DA. Failure of fertility therapy and subsequent adverse cardiovascular events. Can Med Assoc J 2017;189(10):E391–7.
[49] Somigliana E, Peccatori FA, Filippi F, Martinelli F, Raspagliesi F, Martinelli I. Risk of thrombosis in women with malignancies undergoing ovarian stimulation for fertility preservation. Hum Reprod Update 2014;20(6):944–51.
[50] Petropanagos A, Cattapan A, Baylis F, Leader A. Social egg freezing: risk, benefits and other considerations. Can Med Assoc J 2015;187(9):666–9.
[51] Ata B, Yakin K, Alatas C, Urman B. Dual renin-angiotensin blockage and total embryo cryopreservation is not a risk-free strategy in patients at high risk for ovarian hyperstimulation syndrome. Fertil Steril 2008;90(3):531–6.
[52] Bates SM. Anticoagulation and in vitro fertilization and ovarian stimulation. Hematol.Am.Soc.Hematol.Educ. Progr. 2014;2014(1):379–86.
[53] Hauspurg A, Ying W, Hubel CA, Michos ED, Ouyang P. Adverse pregnancy outcomes and future maternal cardiovascular disease. Clin Cardiol 2018;41(2):239–46.
[54] Ying W, Catov JM, Ouyang P. Hypertensive disorders of pregnancy and future maternal cardiovascular risk. J.Am. Heart Assoc 2018;7(17). e009382.
[55] Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol 2014;63(18):1815–22.
[56] Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ.Cardiovasc.Qual.Outcome 2017;10(2).
[57] Zoet GA, Benschop L, Boersma E, Budde RPJ, Fauser B, van der Graaf Y, et al. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. Circulation 2018;137(8):877–9.
[58] Honigberg MC, Zekavat SM, Aragam K, Klarin D, Bhatt DL, Scott NS, et al. Long-term cardiovascular risk in women with hypertension during pregnancy. J Am Coll Cardiol 2019;74(22):2743–54.
[59] LaMarca B, Amaral LM, Harmon AC, Cornelius DC, Faulkner JL, Cunningham Jr MW. Placental ischemia and resultant phenotype in animal models of preeclampsia. Curr Hypertens Rep 2016;18(5):38.
[60] Stekkinger E, Zandstra M, Peeters LLH, Spaanderman MEA. Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome 2009;114(5):1076–84.
[61] Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet 2005;366(9499):1797–803.
[62] Roberge S, Odibo AO, Bujold E. Aspirin for the prevention of preeclampsia and intrauterine growth restriction. Clin Lab Med 2016;36(2):319–29.
[63] Sharma G, Lindley K, Grodzinsky A. Cardio-obstetrics: developing a niche in maternal cardiovascular health. J Am Coll Cardiol 2020;75(11):1355–9.
[64] Joyce A. Martin MPH, Brady E. Hamilton, PhD., Michelle J.K. Osterman, M.H.S., Anne K. Driscoll, Ph.D, and Patrick Drake, M.S., reportDivision of vital statistics. National vital statistics report, births: final data for 2017. Contract No.: 8..
[65] Tanz LJ, Stuart JJ, Williams PL, Rimm EB, Missmer SA, Rexrode KM, et al. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. Circulation 2017;135(6):578–89.
[66] Rich-Edwards JW, Klungsoyr K, Wilcox AJ, Skjaerven R. Duration of pregnancy, even at term, predicts long-term risk of coronary heart disease and stroke mortality in women: a population-based study. Am J Obstet Gynecol 2015;213(4).518.e1-.e8.
[67] Wu P, Gulati M, Kwok CS, Wong CW, Narain A, O'Brien S, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. J.Am. Heart Assoc 2018;7(2).
[68] Tanz LJ, Stuart JJ, Williams PL, Missmer SA, Rimm EB, James-Todd TM, et al. Preterm delivery and maternal cardiovascular disease risk factors: the nurses' health study II. J Wom Health 2019;28(5):677–85.
[69] Heida KY, Velthuis BK, Oudijk MA, Reitsma JB, Bots ML, Franx A, et al. Cardiovascular disease risk in women with a history of spontaneous preterm delivery: a systematic review and meta-analysis. Eur. J.Prev. Cardiol. 2016;23(3):253–63.
[70] Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia 2019;62(6):905–14.
[71] Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373(9677):1773–9.
[72] Shostrom DCV, Sun Y, Oleson JJ, Snetselaar LG, Bao W. History of gestational diabetes mellitus in relation to cardiovascular disease and cardiovascular risk factors in US women. Front Endocrinol 2017;8:144.
[73] Parikh NI, Cnattingius S, Dickman PW, Mittleman MA, Ludvigsson JF, Ingelsson E. Parity and risk of later-life maternal cardiovascular disease. Am Heart J 2010;159(2):215–21. e6.
[74] Peters SA, van der Schouw YT, Wood AM, Sweeting MJ, Moons KG, Weiderpass E, et al. Parity, breastfeeding and risk of coronary heart disease: a pan-European case-cohort study. Eur. J.Prev. Cardiol. 2016;23(16):1755–65.
[75] Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, et al. Number of pregnancies and the subsequent risk of cardiovascular disease. N Engl J Med 1993;328(21):1528–33.
[76] Ogunmoroti O, Osibogun O, Kolade OB, Ying W, Sharma G, Vaidya D, et al. Multiparity is associated with poorer cardiovascular health among women from the Multi-Ethnic Study of Atherosclerosis. Am J Obstet Gynecol 2019;221(6):631 e1–e16.

[77] Vaidya D, Bennett WL, Sibley CT, Polak JF, Herrington DM, Ouyang P. Association of parity with carotid diameter and distensibility: multi-ethnic study of atherosclerosis. Hypertension 2014;64(2):253–8.
[78] Sanghavi M, Kulinski J, Ayers CR, Nelson D, Stewart R, Parikh N, et al. Association between number of live births and markers of subclinical atherosclerosis: the Dallas Heart Study. Eur. J.Prev. Cardiol. 2016;23(4):391–9.
[79] Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric 2007;10(Suppl 1):19–24.
[80] Reddy Kilim S, Chandala SR. A comparative study of lipid profile and oestradiol in pre- and post-menopausal women. J Clin Diagn Res 2013;7(8):1596–8.
[81] Jensen J, Nilas L, Christiansen C. Influence of menopause on serum lipids and lipoproteins. Maturitas 1990;12(4):321–31.
[82] El Khoudary SR, Ceponiene I, Samargandy S, Stein JH, Li D, Tattersall MC, et al. HDL (High-Density lipoprotein) metrics and atherosclerotic risk in women. Arterioscler Thromb Vasc Biol 2018;38(9):2236–44.
[83] Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, et al. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). J. Cardiovasc.Comput. Tomogr. 2019;13(1):41–7.
[84] Mathews L, Subramanya V, Zhao D, Ouyang P, Vaidya D, Guallar E, et al. Endogenous sex hormones and endothelial function in postmenopausal women and men: the multi-ethnic study of atherosclerosis. J Wom Health 2019;28(7):900–9.
[85] Zhao D, Guallar E, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, et al. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. J Am Coll Cardiol 2018;71(22):2555–66.
[86] Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause 2012;19(10):1081–7.
[87] Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart 2018;104(13):1069–75.
[88] Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health 2019;4(11):e553–64.
[89] Gregersen I, Hoibraaten E, Holven KB, Lovdahl L, Ueland T, Mowinckel MC, et al. Effect of hormone replacement therapy on atherogenic lipid profile in postmenopausal women. Thromb Res 2019;184:1–7.
[90] Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metabol 2006;8(5):538–54.
[91] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. J Am Med Assoc 2002;288(3):321–33.
[92] Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women's health initiative randomized trials. J Am Med Assoc 2017;318(10):927–38.
[93] Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. J Am Med Assoc 2007;297(13):1465–77.
[94] Shufelt CL, Merz CN, Prentice RL, Pettinger MB, Rossouw JE, Aroda VR, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study. Menopause 2014;21(3):260–6.
[95] Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, et al. Estrogen therapy and coronary-artery calcification. N Engl J Med 2007;356(25):2591–602.
[96] Streed CG, Harfouch O, Marvel F, Blumenthal RS, Martin SS, Mukherjee M. Cardiovascular disease among transgender adults receiving hormone therapy: a narrative review. Ann Intern Med 2017;167(4):256–67.
[97] Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. Circulation 2019;139(11):1461–2.
[98] Pyra M, Casimiro I, Rusie L, Ross N, Blum C, Keglovitz Baker K, et al. An observational study of hypertension and thromboembolism among transgender patients using gender-affirming hormone therapy. Transgender Health 2020;5(1):1–9.
[99] Caceres BA, Jackman KB, Edmondson D, Bockting WO. Assessing gender identity differences in cardiovascular disease in US adults: an analysis of data from the 2014-2017 BRFSS. J Behav Med 2020;43(2):329–38.
[100] Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS. The use of sex-specific factors in the assessment of women's cardiovascular risk. Circulation 2020;141(7):592–9.