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**Metabolism and Target Organ Damage**

**Review**

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# Obesity and diabetes in heart disease in women

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## Abstract

Heart disease remains a major health threat in women. Cardiometabolic risk factors such as obesity and diabetes differentially and adversely impact heart disease risk. Although obstructive coronary artery disease is an important cause of ischemic heart disease in women and is prognostic, women are more likely to have angina and myocardial ischemia without obstructive atherosclerosis, which has been attributed to coronary microvascular dysfunction (CMD). Heart failure with preserved ejection fraction (HFpEF) is another condition that predominates in women. CMD and HFpEF are both associated with cardiometabolic risk factors that are prevalent in women. Women are also more likely to have additional risk-enhancing conditions such as autoimmune dysfunction, chronic inflammation, and sex-specific hormonal factors that adversely influence risk. In this review, we focus on cardiometabolic risk factors of obesity and diabetes in heart disease in women, including ischemic heart disease from CMD, HFpEF, and arrythmias. Team-based care to focus on cardiometabolic risk reduction is needed to alter adverse heart disease outcomes in women. Identification, education, treatment, and active surveillance of these dysmetabolic risk factors are imperative in the primary and secondary prevention of heart disease in women.

**Keywords:** Sex differences, obesity, diabetes, type 2 diabetes mellitus, cardiovascular disease, endothelial dysfunction, inflammation, coronary atherosclerosis, hormone therapy

## INTRODUCTION

Cardiovascular disease (CVD) continues to be the leading cause of death in men and women in the United States (US). According to NHANES data for US adults from 2017 to 2020, the prevalence of CVD (which includes coronary artery disease (CAD), heart failure (HF), stroke, and hypertension) was 48.6% overall and 9.9% when hypertension was excluded[1]. This prevalence increases with age in both men and women. Postmenopausal women have similar CVD prevalence compared to age-matched men; however, in younger premenopausal women, men have higher age-adjusted CVD prevalence. From 1980 to 2010 in the United States, there was a decline in CVD mortality in both men and women. However, in the last decade, there has been an increase in CVD mortality, partly attributed to the rise in cardiometabolic factors such as obesity and diabetes. Even in younger patients aged 30-54 years, an increase in the burden of cardiovascular risk factors such as type 2 diabetes mellitus (T2DM) and hypertension has been accompanied by an increase in hospitalization rates for acute myocardial infarction (MI)[2,3].

Individual cardiometabolic risk factors may also contribute to the development of cardiometabolic syndrome (or metabolic syndrome), which refers to the clustering of risk factors associated with insulin resistance and abdominal obesity that increase the risk for T2DM and CVD. Metabolic syndrome is diagnosed when 3 of 5 risk factors or their equivalents are present: (1) fasting plasma glucose ≥ 100 mg/dL; (2) high-density lipoprotein (HDL-C) cholesterol < 40 mg/dL in males or < 50 mg/dL in females; (3) triglycerides ≥ 150 mg/dL; (4) waist circumference > 102 cm in males or > 88 cm in females; and (5) systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg[1]. Metabolic syndrome is associated with increased CVD risk and has a negative impact on quality of life[4]. NHANES trends from 2011-2016 show a high prevalence of metabolic syndrome, with a 48.6% prevalence in those at least 60 years old and a significant increase in young adults (aged 20-39 years)[5,6].

Although the prevalence of cardiometabolic risk factors like obesity has increased for both men and women, the prevalence is higher in women. The NHANES data show that women have had a higher increase in body mass index (BMI) in recent years compared to men. While men had a decrease in total cholesterol in recent years, women had an increase in mean total cholesterol from 2013 to 2016 compared to 2001-2004. These sex differences in cardiometabolic risk profiles may be one factor that contributes to sex differences in outcomes and prognosis of MI. In addition to a greater risk factor burden, women are less likely to receive treatment for risk factors and heart disease[7]. Cardiometabolic risk factors are also implicated in the syndrome of heart failure with preserved ejection fraction (HFpEF), which is more common in women[8,9]. In this review, we highlight obesity and T2DM as key cardiometabolic risk factors and review the impact on heart disease in women[2].

## CARDIOMETABOLIC RISK FACTORS IN WOMEN

### Obesity

Obesity is a national epidemic and the American Heart Association (AHA) has classified obesity as a major, modifiable risk factor for CVD, which includes CAD, HF, arrhythmias, stroke, venous thromboembolism, and pulmonary hypertension[10-12]. BMI is grouped into three main categories - normal BMI (18-24.9 kg/m$^2$), overweight (25-29.9 kg/m$^2$), and obese (> 30 kg/m$^2$). Obesity can be further broken down into classes 1 to 3, with Class 3 indicating severe obesity and BMI ≥ 40 kg/m$^2$. Recent data from 2017 to 2020 by the NHANES report that the age-adjusted prevalence of overweight or obese United States adults is 71.2%, with 41.4% of United States adults being classified as obese[1]. Recognition of obesity as a major risk factor for CVD is important given the recent shifts in the distribution of BMI in the United States such that the proportion of the population with morbid obesity has increased more than the proportion of overweight or mild obese individuals[1,13]. Excess visceral fat and pericardial fat are prominent risk factors for CVD independent of

traditional measures of obesity[14]. Several risk factors are significantly associated with being overweight and obese. For example, hypertension has a strong association with being overweight (OR = 2.1) and obese (OR =5.2). Diabetes is strongly associated with abdominal obesity (OR = 3.9) in women[15]. It should be noted that while BMI is widely used and easily available, it is not a direct measure of adiposity and includes both fat and muscle mass. BMI not only varies considerably depending on age and sex, but also race/ethnicity, such that lower cut-offs are recommended in South Asian, Chinese, and Japanese populations[11]. Waist circumference is an important measure of abdominal adiposity, and is associated with outcomes within each BMI category[16,17]. Given its prognostic significance, it is recommended that waist circumference measure is obtained and targeted as an important modifiable risk factor[16]. Among women, higher waist circumference values have been associated with a 10%-20% increased risk of MI compared to higher BMI values[18].

In terms of pathophysiology, obesity contributes to the progression of atherosclerotic disease via several mechanisms, including inflammation and reduced availability of nitric oxide[10]. Specifically, visceral adiposity has been associated with increased systemic and vascular inflammation, which in turn leads to progression of atherosclerosis[10]. Insulin resistance plays a role in the increased risk, although it is uncertain whether this is a primary cause of accelerated atherosclerotic disease[11].

Obesity is associated with hormonal and autonomic dysregulation [Figure 1][19]. For example, compression of renal structures by visceral adipose tissue increases sodium reabsorption ahead of macula densa cells in the distal tubule, thereby activating the renin-angiotensin-aldosterone system (RAAS) that partly gives rise to chronic kidney disease and hypertension[20]. Through dysregulation of afferent autonomic receptors, like chemoreceptors, and secretion of adipokines, like leptin, obesity-induced sympathetic activation augments the above risk factors and further contributes to CVD[19-23]. Both visceral and subcutaneous adipose tissues increase with age; however, postmenopausal women have an increased visceral to subcutaneous adipose tissue ratio[24]. Visceral adipose tissue is more strongly associated with cardiometabolic risk factors than subcutaneous adipose tissue in women than in men[25]. Adiposity has been implicated in suppressing GLP-1, which is an enteral hormone with cardioprotective, cardio-restorative, and metabolically stabilizing effects, through alterations in gut microbiota[20,26,27].

Increased visceral fat has been associated with higher cardiovascular risk in both men and women[17,20]. However, there are sex differences in fat distribution, with men having more visceral fat compared to premenopausal women who have more subcutaneous fat[20]. Hormonal differences, as well as genetic and epigenetic factors, contribute to these differences in adipose tissue distribution. Certain regions of the brain, such as the thalamus, amygdala, and ventromedial hypothalamus, control critical processes involved in food metabolism and energy expenditure[28-30]. Prior studies have shown that lesions in these regions of the hypothalamus can cause biological changes such as obesity[30,31]. During a woman's lifespan, estrogen acts on various organs, including the liver, skeletal muscle, brain, adipocytes, and many more, to ensure insulin sensitivity, energy balance, and lipid metabolism. Estrogen acts on the hypothalamic proopiomelanocortin neurons to decrease food consumption. It can also increase energy expenditure by acting on neurons of the ventromedial hypothalamus containing the nuclear receptor steroidogenic factor 1. In the 5th decade of life for most women, estrogen levels begin to drop and this loss of the protective effects of estrogen thus leads to insulin resistance, obesity, T2DM, and increased CVD risk[32-34].

### Diabetes & disorders of insulin resistance

NHANES reports that the prevalence of diagnosed diabetes (both Type 1 and Type 2) among US adults between 2017 and 2020 was 10.6%. Among these adults, 90%-95% had T2DM and 46.4% had prediabetes[1].

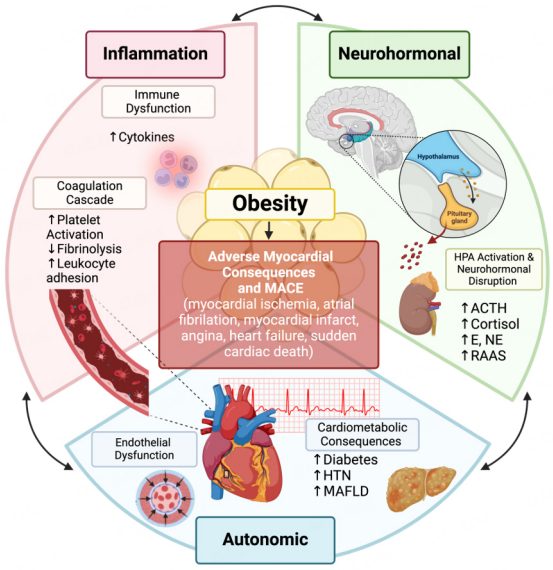


**Figure 1.** Mechanisms implicated in obesity and adverse myocardial consequences. Figure made using biorender.com. Image © Emory University. CC-BY-SA. HPA: Hypothalamic pituitary adrenal; ACTH: Acetylcholine; E, NE: Epinephrine, norepinephrine; RAAS: Renin angiotensin aldosterone system; HTN: Hypertension; MAFLD: metabolic dysfunction-associated fatty liver disease; MACE: Major adverse cardiovascular event.

The risk of T2DM increases with age in both men and women. For women, moreover, there is a stronger obesity-diabetes risk association than for men. Although the prevalence of T2DM in women is slightly lower than men, T2DM confers a 3-to-7-fold increased CVD risk in women compared to a 2-to-3-fold increased CVD risk in men[35,36]. In a systematic review that included studies with pre- and postmenopausal women, Wang *et al.* found that women with T2DM have a 58% increased risk of coronary heart disease and an 8% increased risk of stroke compared to men with T2DM[37]. Compared to women without diabetes, diabetic women are three times more likely to experience a fatal coronary event[38,39]. Diabetic women have higher mortality rates in the presence of established coronary disease compared to diabetic men[40].

Premenopausal women typically have protective effects of estrogen on insulin sensitivity and therefore have lower rates of T2DM and metabolic syndrome. With menopause, the loss of the protective estrogen effects leads to impaired exercise-induced skeletal muscle glucose uptake, hyperglycemia with a high-fat diet, increased LDL and fat mass, and increased circulating inflammatory markers[41,42]. In premenopausal women, however, risk factors such as a history of adverse pregnancy outcomes (e.g., pre-eclampsia, gestational diabetes) are also associated with increased cardiometabolic risk[43,44]. Gestational diabetes confers a 7-fold increased risk of developing T2DM and increases risk of CVD events[45]. Independent of the development of T2DM, there is an association between gestational diabetes mellitus (GDM) and the risk of developing future CVD[46]. Patients diagnosed with GDM had two times the elevated risk of cardiovascular events in the future compared to those without GDM (RR 1.98, 95%CI: 1.57, 2.50)[46]. Even when stratified by patients that did not develop T2DM, having GDM conferred a 56% increased risk of future CVD events (RR 1.56, 95%CI: 1.04, 2.32) and a 2.3 times increased risk in the first postpartum decade (2.31, 95%CI: 1.57, 3.39)[46]. Another study found a 40% increased risk of CVD events in GDM women, of which only 23.3% was explained by subsequent T2DM[47]. It also found a two-fold increase in HF and MI, as well as a 65% increased risk of stroke in these patients[47].

Polycystic ovarian syndrome (PCOS) is another condition that can confer a 4-fold increased risk of T2DM and also increase the risk of CVD[48,49]. Prior research has demonstrated that women with PCOS have a higher risk of heart disease and stroke, and while some studies have shown this association to be independent of BMI, other studies have shown the absolute risk of PCOS to be small[50]. One study that adjusted for these covariates found PCOS patients to still be at higher CVD risk (adjusted HR 1.19, 95%CI: 1.07-1.33)[51]. The discrepancies between prior research could be due to age-related variation, as studies have shown increased CVD risk for PCOS women in their 30s and 40s and no increased risk after the age of 50[51].

### Metabolic associated fatty liver disease

Underlying metabolic dysfunction from conditions such as diabetes and obesity is also associated with the accumulation of fat in the liver. Previously referred to as non-alcoholic fatty liver disease (NAFLD), the term has now changed to Metabolic Associated Fatty Liver Disease (MAFLD) to reflect the underlying metabolic dysregulation and associated hepatic steatosis[52]. Risk factor management of hypertension, diabetes, obesity, and hyperlipidemia is used to manage MAFLD, which can progress to more severe liver diseases such as non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and also the risk of hepatocellular carcinoma. There is heterogeneity in MAFLD-related outcomes, which are influenced by comorbid conditions such as heart failure, chronic kidney disease, chronic inflammation/infection, and underlying liver dysfunction[53]. Women appear to be particularly susceptible to MAFLD after menopause, when there is a rise in cardiometabolic risk factors and the prevalence of MAFLD increases. However, if a younger woman has MAFLD, her risk of heart failure is much higher as reported recently by Wu *et al.*, who found in a prospective cohort study that the risk of heart failure is greater in young women with MAFLD ( age < 45 years) compared to men[54]. Instead of being an "innocent" bystander with fat accumulation in the liver, MAFLD is emerging as an important CVD risk marker that could be a therapeutic target. Interestingly, abnormal gut microbiota have been associated with MAFLD and therapies that target the gut microbiome are being investigated to target underlying inflammation and metabolic dysregulation in MAFLD[55].

## CARDIOMETABOLIC FACTORS AND INFLAMMATION

Cardiometabolic risk factors and chronic inflammation significantly influence heart disease risk[56-60]. These conditions are dynamic throughout life and interact with sex, and may contribute to sex and age-related differences in heart disease. Insulin resistance that leads to T2DM is frequently a byproduct of obesity-induced inflammation, causing adipose tissue dysfunction[61]. Metabolic dysfunction involving factors such as tumor necrosis factor-α, leptin, and adiponectin are associated with increased risk, and serum adiponectin levels are predictive of CVD risk and mortality in men and women[62,63]. Changes in the fat distribution have been implicated as one of the causes of increased IHD menopause. Postmenopausal women have increased visceral fat, which is associated with the development of insulin resistance and impacts inflammatory responses and lipolysis[64]. Low estrogen levels promote a proinflammatory, TH1-driven environment and impact adipose tissue, favoring more visceral fat, thereby increasing CVD risk in postmenopausal women[65]. Additionally, perhaps due to incomplete silencing of sex chromosomes, women are more at risk for CVD driving chronic inflammatory conditions[65]. Due to postmenopausal-induced changes in the nitric oxide pathway, there is also more endothelial dysfunction in post-menopause women[66-68].

Ter Host *et al.* found sex differences in inflammatory pathways in obesity. Among men and women with metabolic syndrome, men had higher levels of inflammatory biomarkers such as interleukin-6 and leptin while women had lower levels of adiponectin, an anti-inflammatory marker[69]. A metabolomic analysis

indicated that metabolic syndrome was associated with valine, leucine, and isoleucine biochemical pathways in both men and women. More studies are needed to understand sex differences in the regulation of inflammatory response in obesity.

## CARDIOMETABOLIC RISK FACTORS AND HEART DISEASE

### Cardiometabolic risk and ischemic heart disease

Ischemic heart disease (IHD) is the leading cause of death for both men and women, and obstructive CAD (stenosis greater than 50% in any major epicardial coronary artery or physiologically significant stenosis by fractional flow reserve testing) is a major cause of ischemia and adverse outcomes in both sexes. It is well known that cardiometabolic risk factors predispose to endothelial dysfunction, which is a precursor for triggering a cascade of events within the arterial wall that lead to atherosclerotic plaque development. Among patients with cardiometabolic risk factors, those with renal dysfunction are at an even higher risk of CAD and heart failure[70]. While obstructive CAD is a major cause of ischemia, symptomatic women with angina and ischemia are more likely to have no obstructive CAD[71]. IHD in women is associated with metabolic risk factors, such as hypertension, T2DM, hyperlipidemia, and obesity, regardless of obstructive CAD[72,73]. These factors trigger inflammation and oxidative stress, and impact endothelial function and coagulation[74,75].

Obesity is an important independent risk factor that contributes to an increased risk of adverse outcomes in both men and women with CAD[76]. In a study by Cho *et al.* of 659 women with chest pain undergoing elective angiography, there was no significant difference in the BMI between patients with and without obstructive CAD. However, the patients with central obesity had a higher prevalence of obstructive CAD (55.5% *vs.* 41%, $P < 0.001$)[77]. The role of visceral fat in the development of more severe coronary disease is felt to be related to the higher degree of insulin resistance seen in these patients[78]. A study using data from the National Cardiovascular Data Registry (NCDR) Action Registry found that women presenting with ST-elevation MI were more likely to be obese or overweight than individuals in the general population. Furthermore, compared to the general population, women with MI are more likely to have class III obesity, which has been shown to increase the risk of mortality after MI. Interestingly, there is a paradox with respect to outcomes of coronary heart disease in obese patients once the diagnosis is established. In general, it has been shown that among those with coronary heart disease, patients with higher BMIs tend to have the lowest mortality[79]. The reasons for this discrepancy have not been clearly elucidated.

The presence of diabetes plays a crucial role in the overall risk of CAD and the outcomes in patients with established disease. In women with obesity, the risk of developing diabetes increases with the severity of obesity[78]. In a study of 84,000 female nurses, obesity was identified as the most important risk factor for the development of diabetes[80]. In a multicenter prospective cohort study examining women hospitalized for MI, the adjusted in-hospital mortality rate for women with diabetes (23.3%) was higher than the mortality rate in women without diabetes (18.9%). Increased risk for adverse events after MI in women with diabetes extended beyond the hospital stay, as the risk of death in women with diabetes was 1.57 times the risk of death in those without diabetes at 1 year[81]. The Framingham Study reported a similar increased risk of adverse events following MI in women with diabetes compared to women without diabetes[82]. In a retrospective study by Gajardo-Navarrete *et al.* comparing CAD in premenopausal and postmenopausal women, postmenopausal women were found to be more likely to have multi-vessel disease (24% in postmenopausal *vs.* 11% in premenopausal; $P < 0.01$). In general, T2DM is more common in postmenopausal women compared to premenopausal women. However, not surprisingly, premenopausal women with T2DM had higher rates of multi-vessel coronary disease[83]. In addition to its impact on the heart, obesity is associated with adverse consequences including hypertension, MAFLD, sleep apnea, and

impaired mobility [Figure 2].

A longitudinal study (over 13 years) of 1,296 non-diabetic and 836 diabetic patients with no CAD showed that women with diabetes had a higher hazard ratio of CHD events compared with men after adjusting for cardiovascular risk factors[84]. Coronary microvascular disease (CMD) is thought to be the main mechanism for adverse outcomes in those with ischemia but no obstructive CAD, and implicated in HFpEF[66,67]. Women with CMD have more physical limitations and lower quality of life compared to men[85]. CMD due to impaired microvascular vasodilation can be detected non-invasively by cardiac positron emission tomography (PET), where myocardial blood flow with rest and stress is calculated. An abnormally low myocardial flow reserve (MFR) is used to diagnose CMD and is prognostic[86]. In a study of 827 patients who underwent cardiac PET, CMD was associated with increased BMI and adverse outcomes[86].

The Nurse's Health Initiative Study showed that women with healthier lifestyles and who are able to control obesity, thus reducing their cardiometabolic risks, have reduced IHD[87]. This highlights the importance of controlling these cardiometabolic risk factors to improve IHD in women[88]. A cross-sectional analysis of 3,849 patients with diabetes showed that women were less likely to be aggressively treated for diabetes and other modifiable risk factors such as high cholesterol and hypertension[89]. While reasons for differences in treatment are not entirely clear, it may be driven by a false perception that women are at lower risk. Lower awareness among both patients and providers that IHD is a leading cause of morbidity and mortality may be contributing to gender bias in treatment and prescriptive practices[90,91]. Women have a longer length of hospital stay and higher in-hospital mortality than men across all age groups for acute MI[2,7].

### Cardiometabolic risk and heart failure

HF continues to increase in prevalence, affecting 6 million Americans and accounting for over 1 million admissions[92]. Approximately one-half of HF patients have reduced left ventricular ejection fraction (HFrEF), while an equal number have HFpEF, defined as ejection fraction ≥ 50%. HFpEF is a multisystem syndrome that impacts multiple other organs including the lungs, skeletal muscles, and kidneys[93]. Specifically, in diastolic HF, cardiometabolic syndrome plays a major role in the underlying pathophysiology. The mean prevalence of diastolic dysfunction in patients with metabolic syndrome is 35%, compared to 11%-27% in the general population. The risk of diastolic dysfunction increases with degree of obesity and with T2DM and prediabetes. Obesity and other cardiometabolic traits carry higher associations with the development of HFpEF *vs.* HFrEF, especially for women[92,94-97].

It is well known that factors such as hypertension, insulin resistance, and obesity are implicated in both systolic and diastolic HF, in both men and women. However, these factors are stronger risk factors for HFpEF in women compared to men. For example, these factors are associated with more left ventricular remodeling and increased mass in women compared to men[98]. Diabetes portends a higher risk of HF in women (5-fold increase) compared to men (2-fold increase)[96]. This is also true of hypertension; women have a 3-fold increased risk compared to 2-fold in men[96]. Kenchaiah *et al.* analyzed the incidence of HF in 5,881 participants in the Framingham Heart Study and found that roughly 14% of HF cases in women can be attributed to obesity, compared to 11% in men[94]. HF risk increases by 7% for every 1-unit increment increase in BMI in women[94-96]. Sex differences in the impact of cardiometabolic factors and myocardial and vascular characteristics predispose women to develop the syndrome of HFpEF over time (smaller left ventricles with less diastolic reserve, more microvascular dysfunction, and impaired ventriculo-arterial coupling)[98].

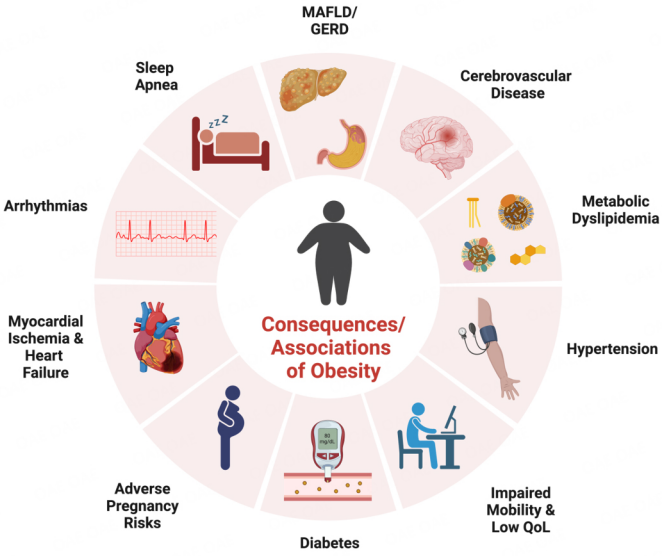


**Figure 2.** Figure made using biorender.com. Image © Emory University, CC-BY-SA. MAFLD/GERD: Metabolic dysfunction-associated fatty liver disease/ Gastroesophageal reflux disease; QoL: Quality of Life.

The presence of risk factors leads to a proinflammatory state that impairs microvascular endothelial function, and results in myocardial remodeling, stiffening, and fibrosis, but pathophysiologic mechanisms and drivers that lead to HFpEF progression are not well understood. In contrast, the pathophysiology behind the development of HFrEF is primarily myocyte damage because of myocardial ischemia/infarction, infection, genetic predisposition, or toxicity. Coronary endothelial dysfunction is present in HFrEF, but it is felt to be a result of the severity of the systolic dysfunction, as opposed to the driving force causing the systolic dysfunction[92,94,97]. Women have more pronounced immune responses, which is felt to explain in part the disproportionate effects of the same risk factors in women and overall higher rates of HFpEF development. Chronic rheumatologic diseases are more prevalent in women (e.g., rheumatoid arthritis, systemic lupus erythematosus) and also associated with microvascular dysfunction and diastolic stiffness. Treatment of autoimmune disorders involves corticosteroids, which are associated with metabolic syndrome and premature atherosclerosis[99,100]. More research is needed to fully understand the pathophysiology of sex differences in HFpEF and its implications in management and outcomes[96].

### Cardiometabolic risk and arrhythmias

The prevalence of dysrhythmia in women is approximately 373 and 59 per 100,000 having atrial fibrillation or ventricular arrhythmia, respectively[101,102]. In the general population, cardiometabolic disease, like obesity, is increasingly recognized as an independent risk factor for arrhythmogenesis. Obesity is the second biggest contributor to atrial fibrillation-accounting for 17.9% of cases in the ARIC study[103]. Women have a 5% increased risk of developing atrial fibrillation with an increase of 1 kg/m$^2$ in BMI[104]. Studies showing increased sudden cardiac death and ICD shocks among obese individuals suggest that obesity predisposes to ventricular dysrhythmias in men and women, who are more susceptible to symptomatic ventricular ectopy[101,105,106]. Multiple mechanisms are implicated in obesity-induced arrhythmias including proinflammatory and pro-fibrotic adipokines, structural remodeling, electrophysiologic remodeling, and associated comorbidities like sleep apnea and hypertension[107-111]. This is evident before the genesis of clinical arrhythmia, as obese individuals have more prolonged PR and QT intervals[107,109]. Due to the association between obesity and arrhythmogenesis, American and European cardiology societies have included weight loss in their guidelines for atrial fibrillation management[112,113]. These guideline changes

have been supported by reduced arrhythmia burden in those receiving obesity-directed therapy, such as bariatric surgery, and those adequately treated for obesity-related comorbidities[114-117].

## PSYCHOLOGICAL STRESS AND CARDIOMETABOLIC RISK

It is important to mention that certain non-traditional risk factors that are more prevalent in women can contribute to significant CVD morbidity and mortality by increasing the risk of certain cardiometabolic risk factors. Job strain in women, for example, has been linked to an increased risk of T2DM while low socioeconomic status increases the risk of obesity[41]. In the Women's Health Study, educated women were less likely to smoke, have hypertension, diabetes, or obesity; a decrease in incident CVD events was observed with increasing levels of education and income[118]. While traditional risk factors implicated in heart disease in women are causal (i.e., hypertension, smoking, dyslipidemia), some factors are associative (i.e., depression) and the exact contribution of psychological risk factors is difficult to determine in isolation. Psychological and psychosocial stress factors are prevalent in women and contribute to increased cardiometabolic risk, partly due to less risk factor control, non-adherence, and lack of access[65,119,120]. The impact of psychological risk factors such as mental stress-induced ischemia, depression, and anxiety in the setting of established traditional risk factors in heart disease in women is an active area of investigation[120-125,65].

Prior studies show up to a 20% increase in CVD mortality among individuals with 4 or more depressive symptoms, and this increase is even greater in urban or rural areas[126]. Many studies show that there are significant sex differences in depression, anxiety, and psychological stressors between men and women. The ratio of major depression is 2:1 when comparing women to men, and it is thought that women are more vulnerable to stressors and discrimination throughout development into adulthood[127]. The prevalence of depression in survivors of acute myocardial ischemia was 19.8% across 10,785 patients from 8 different studies[128]. In the TRIUMPH study, which was a study to understand 1-year mortality among patients with myocardial ischemia, mortality rates were higher in untreated depressive patients compared to treated depressive patients and non-depressed patients[129]. With depression and stress being important risk factors for CVD, it is recommended that depressive symptoms be identified in clinical assessments and treatment should be addressed if necessary to improve CVD risk among at-risk populations[130]. More commonly, women have an interplay between several of these risk factors, which contributes to an enhanced or varied inflammatory response and metabolic dysregulation compared to men[65,131].

## MENOPAUSE AND CARDIOMETABOLIC RISK FACTORS

Menopause is defined as twelve consecutive months of cessation of the menstrual cycle, with an average age of 52 years in the United States. Menopause prior to the age of 40 years is considered premature and under the age of 45 is considered early menopause[34]. The menopause transition can occur 2-7 years before the final menstrual period and is a period of accelerated CVD risk both due to a decline in sex hormone changes and chronological aging[34]. The impact of the menopause transition on CVD risk has been recognized by the AHA in a Scientific Statement, which highlights the importance of addressing cardiometabolic changes in women during this critical transition time in a woman's lifespan[34].

Cardiometabolic risk factors that are more closely associated with the menopause transition include adverse changes to lipoprotein with an increase in total cholesterol, LDL-C, and apolipoprotein B levels. While weight gain is common in midlife, menopause is also associated with a change in body composition from lean to fat mass and acceleration in visceral fat deposition, leading to a transition from a gynoid shape to a central android body shape. Risk factors such as hypertension and insulin resistance increase after menopause, but they also rise with chronological aging. Blood pressure (BP) increases during the

menopausal transition may be related to declining estrogen levels with upregulation of the renin-angiotensin system, production of vasoconstrictive factors such as endothelin, and increased salt sensitivity[132]. Mid-life women are also less likely to be physically active, as shown in the SWAN study where only 7% of mid-life women reported meeting the recommended physical activity guidelines of exercising for 30 min at least 5 days per week, and < 20% consistently maintained a healthy eating pattern[133]. Taken together, studies have found that the menopause transition results in the progression and increase in severity of metabolic syndrome[34,134].

While observational studies have suggested that menopause hormone therapy (HT) may reduce the risk of CVD, it was not until the 1990s that the Women's Health Initiative (WHI) randomized controlled trials began to determine if HT prevented CVD and other chronic diseases. The WHI trials found that oral conjugated estrogen alone or combined with progestin *vs*. placebo was associated with adverse outcomes in women. Results from this trial have led to the understanding that menopause HT is not used for primary prevention or secondary prevention of CVD[135]. Current guidelines recommend the use of menopause HT for the treatment of bothersome vasomotor symptoms or other indications; multiple key factors must be considered before prescribing HT, such as timing of HT initiation and route of HT delivery. The timing hypothesis suggests that the cardiovascular risk associated with the use of HT is lowest when HT is initiated early (< 10 years after menopause) compared to later (> 10 years after menopause)[136,137]. Cardiovascular risk such as VTE has also been shown to be lower in transdermal HT formulations in comparison to systemic formulations[138]. Women with genitourinary symptoms from menopause and significant cardiac risk factors may also be well managed with minimally absorbed low-dose vaginal estrogen therapy[139].

## THERAPY & LIFESTYLE CHANGES

The ACC/AHA guidelines[140] strongly encourage (Class I) risk factor modification for men and women with stable IHD, including adequate blood pressure and cholesterol control, dietary modifications, weight management, daily physical activity, smoking cessation, and statin therapy when indicated. Dietary modifications include increased intake of fresh fruits, vegetables, and low-fat dairy and reduced intake of foods high in cholesterol (to < 200 mg/d) and saturated fat intake (< 7 % of total calories). For overweight or obese patients, an initial weight loss goal should be 5% to 10% from baseline. Due to increased CVD risk with central obesity, patients should be encouraged to achieve a weight circumference of < 102 cm in men and < 88 cm in women. At least 30 to 60 min of moderate-intensity aerobic exercise 5 days a week is recommended, supplemented by an increase in daily lifestyle activities such as performing chores or gardening. Weight loss improves cholesterol levels, lowers blood pressure, and decreases the risk of developing diabetes[141]. Nonpharmacological and pharmacological therapy should be used to encourage smoking cessation[140].

While dietary changes can be part of weight reduction, it is worth noting that men and women do not respond equally to dieting. Prior studies have shown that men have a more advantageous response to a low-calorie diet compared to women, as men are more likely to lose fat mass while women are more likely to lose lean body mass[142]. Pharmacologic therapies to manage weight are used as adjuncts to lifestyle interventions for patients with a BMI of 30 or greater[143]. In particular, the agents containing glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been shown to improve cardiometabolic measures and cardiovascular outcomes[144]. Several studies have cemented an association between GLP-1 RA and weight loss. The SCALE trial showed patients on liraglutide lost a mean of 8.4 kg of weight compared to 2.8 kg in the placebo group at 56 weeks[145]. 63.2% of the liraglutide group lost 5% of body weight and 33.1% lost more than 10% of their body weight[145]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was conducted to study the CVD mortality benefits

conferred by GLP-1 RA drugs and showed a statistically significant lower risk of major adverse cardiovascular events using liraglutide compared to placebo (HR = 0.87; 95%CI: 0.78-0.97), a lower risk of death from cardiovascular causes (HR = 0.78; 95%CI: 0.66-0.93; $P$ = 0.007), and decreased risk of death from any cause in the GLP-1 RA group (HR = 0.85; 95%CI: 0.74-0.97; $P$ = 0.02)[146]. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) showed patients with T2DM on semaglutide improved glycemic control and had a 2.3% absolute risk reduction of a composite of cardiovascular death, nonfatal stroke, and nonfatal MI compared to those on placebo[147]. The Semglutide Effects on Cardiovascular Outcomes in People with Overweight and Obesity (SELECT) trial also showed a protective effect of semaglutide in patients with BMI > 27 and cardiovascular disease without diabetes, wherein these individuals had 8.5% BMI reduction and a 1.5% absolute risk reduction of the above composite outcome compared to those on placebo[148]. In the Study of Tirzepatide in Participants With Obesity or Overweight (SURMOUNT-1), Tirzepatide-a combined agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor-had more pronounced reductions in weight, cholesterol, blood pressure, and hemoglobin A1c compared to placebo[149]. More research is needed to examine sex differences in drug response to newer anti-diabetes/anti-obesity medications.

When lifestyle changes or pharmacological therapies are ineffective, bariatric surgery is considered for individuals with a BMI ≥ 40 or for those with a BMI ≥ 35 with comorbid conditions related to obesity[150]. Surgery in this population poses an additional health risk; however, a recent systematic review and meta-analysis of 39 studies showed a significant benefit on all-cause mortality, incidence of CVD, and cardiac events such as HF, myocardial infarction, or stroke[151]. Following bariatric surgery, up to 70% of individuals have complications or remission of comorbid conditions. Despite the associated risks, a recent cohort study of patients with diabetes and bariatric surgery for obesity found an overall benefit with a 68% reduction in cardiac mortality and a 34% reduction in cardiac events compared to matched controls with nonsurgical management[152]. A longitudinal study across several hundred Swedish facilities also found lower overall mortality and an average 3-year longer life expectancy in individuals who underwent bariatric surgery in place of usual obesity care[153]. Bariatric surgery is an effective method for weight reduction but, most importantly, for lowering ACVD risk factors and related complications. Team-based care to focus on cardiometabolic risk, which includes primary care, preventive cardiologists, endocrinologists, obesity and sleep medicine specialists, nutritionists, psychiatrists, psychologists, and exercise specialists, is needed to alter CVD risk in women.

## CONCLUSIONS

Obesity and diabetes remain significant risk factors for heart disease in men and women, but sex differences exist in the prevalence and impact of these cardiometabolic disorders. These factors are implicated in IHD from obstructive CAD as well as CMD, HFpEF, and arrhythmias. Underlying mechanisms are attributed to inflammation and pro-oxidative state that trigger endothelial damage, cardiomyocyte dysfunction, and ventricular remodeling. These risks highlight the importance of active surveillance, identification, and preventative treatment of these dysmetabolic risk factors in women. Lifestyle and dietary changes, along with pharmacologic advancements like GLP-1 agonists and even surgery, are potential ways for management. Team-based care to focus on cardiometabolic risk is needed to alter CVD risk in women. Identification, education, treatment, and active surveillance of these dysmetabolic risk factors are imperative in the primary and secondary prevention of heart disease in women.

## DECLARATIONS

### Author contributions

Made substantial contributions to writing and editing this review: Fatade YA, Dave EK, Vatsa N, Crumbs TC, Calhoun A, Sharma A, Shufelt CL, Mehta PK

### Availability of data and materials

Not applicable.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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