

## COMPENDIUM ON LIFELONG CARE IN WOMEN: APPLYING A SEX- AND GENDER-LENS TO PRACTICE

# Sex-Specific Factors Influencing Obesity in Women: Bridging the Gap Between Science and Clinical Practice

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**ABSTRACT:** Obesity in women is a significant public health issue with serious implications for cardiovascular-kidney-metabolic syndrome and cardiovascular disease. This complex challenge is influenced by physiological, hormonal, socioeconomic, and cultural factors. Women face unique weight management challenges due to hormonal changes during pregnancy, perimenopause, and menopause, which affect fat distribution and increase cardiovascular-kidney-metabolic syndrome risk. Current clinical guidelines often overlook these sex-specific factors, potentially limiting the effectiveness of obesity management strategies in women. This review explores the sex-specific aspects of obesity's pathophysiology, epidemiological trends, and associated comorbidities, focusing on cardiovascular and metabolic complications. This review synthesizes literature on obesity in women, emphasizing sex-specific factors influencing its development and progression. It examines the limitations of body mass index as an obesity measure and explores alternative classification methods. Additionally it investigates the relationship between obesity and comorbidities such as diabetes, hypertension, and dyslipidemia, with a focus on postmenopausal women. Obesity in women is linked to increased risks of cardiovascular-kidney-metabolic syndrome and cardiovascular disease. Hormonal fluctuations throughout life contribute to weight gain and fat distribution patterns specific to women, increasing cardiovascular disease risk. Effective obesity management strategies in women must account for these sex-specific variations. Postmenopausal women are particularly affected by obesity-related complications. Lifestyle interventions, pharmacotherapy, and bariatric surgery have shown efficacy in weight management, though success rates vary. Addressing obesity in women requires a comprehensive approach that considers sex-specific physiological factors, life-stage challenges, and sociocultural barriers. Integrating precision medicine and emerging therapies offers potential for more personalized and effective interventions. Personalized strategies that consider women's biological and life-stage challenges can enhance obesity management and improve cardiovascular outcomes. Future research and clinical practice should focus on developing tailored strategies that address women's unique vulnerabilities to obesity and its associated health risks and on validating sex-specific interventions to improve obesity management in women.

**Key Words:** body mass index ■ kidney ■ pregnancy ■ public health ■ weight gain

Both nationally and globally, obesity in women is an escalating public health concern with far-reaching implications, particularly related to cardiovascular-kidney-metabolic (CKM) syndrome and cardiovascular disease (CVD).<sup>1</sup> CKM syndrome includes both the risk for CVD and existing CVD and connects obesity, diabetes, chronic kidney disease, and CVD, including heart failure, atrial fibrillation (AF), coronary heart disease, stroke, and peripheral artery disease.<sup>1</sup> Despite the growing body of evidence

highlighting the importance of addressing obesity in women, current clinical guidelines often do not fully account for the unique physiological and hormonal dynamics at play in women.<sup>2</sup> Women experience distinct challenges related to weight management due to life stage-specific hormonal fluctuations during pregnancy, perimenopause, and menopause.<sup>3,4</sup> These periods are associated with shifts in fat distribution, such as increased intrahepatic adiposity, which is closely tied to heightened CKM syndrome.<sup>3,5,6</sup>

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## Nonstandard Abbreviations and Acronyms

<b>AF</b>	atrial fibrillation
<b>BMI</b>	body mass index
<b>CAD</b>	coronary artery disease
<b>CBT</b>	cognitive behavioral therapy
<b>CKM</b>	cardiovascular-kidney-metabolic
<b>CVD</b>	cardiovascular disease
<b>GIP</b>	gastric inhibitory polypeptide
<b>GLP-1</b>	glucagon-like peptide-1
<b>HFpEF</b>	heart failure with preserved ejection fraction
<b>LDL-C</b>	low-density lipoprotein cholesterol
<b>OR</b>	odds ratio
<b>PCOS</b>	polycystic ovary syndrome
<b>SELECT</b>	Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity
<b>SES</b>	socioeconomic status
<b>SGBG</b>	sex hormone-binding globulin
<b>WC</b>	waist circumference

Obesity, a multifactorial chronic condition defined by excessive fat accumulation posing health risks, is commonly assessed using body mass index (BMI), calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). BMI, while simple, cost-effective, and useful for tracking population trends, has significant limitations. It does not measure fat distribution, misclassifies muscular or large-boned individuals, and overlooks physical fitness and metabolic health. BMI thresholds also vary across populations, with ethnic groups like South Asians at higher risk even at lower BMI levels. Obesity is traditionally classified as overweight (BMI, 25–29.9  $\text{kg}/\text{m}^2$ ) or into 3 obesity classes (BMI,  $\geq 30$   $\text{kg}/\text{m}^2$ ). Alternative classifications consider factors such as metabolic status (eg, metabolically healthy versus unhealthy obesity), central adiposity (waist circumference [WC]), and muscle-fat composition (sarcopenic obesity). While obesity is a recognized driver of comorbidities like diabetes, hypertension, and dyslipidemia, how these conditions affect women, especially post-menopause, requires further exploration.<sup>4,7,8</sup> The cardiovascular risks associated with obesity differ significantly between men and women, primarily due to hormonal, metabolic, and structural differences. Women tend to accumulate more subcutaneous fat during their reproductive years, but this shifts to intra-abdominal fat post-menopause, increasing their risk for CVD.<sup>9</sup> Obesity management strategies that do not account for these sex-specific variations may be less effective in women.<sup>10</sup>

This review aims to fill these gaps by focusing on sex-specific factors that influence obesity in women.

The American Heart Association emphasizes the need to close the gap between obesity science and clinical practice, citing barriers like insufficient clinician training, limited access to care, and policy restrictions.<sup>11</sup> Understanding these sex-specific influences is essential for improving health outcomes and reducing obesity-related complications, particularly CKM and CVD, which disproportionately affects women post-menopause. By applying a sex-specific approach, this review will provide insights into how prevention, diagnosis, and treatment of obesity in women can be better tailored to address these differences. Personalized interventions that consider the biological and life-stage challenges women face will enhance the effectiveness of obesity management and improve cardiovascular outcomes.<sup>12</sup> Tailoring clinical strategies for women is essential for addressing the disproportionate impact of obesity on their health, especially in light of their unique vulnerability to CVD.<sup>13</sup>

## EPIDEMIOLOGY AND DEMOGRAPHICS

### Global and Regional Prevalence of Obesity in Women

Obesity in women has become a significant global public health issue, with notable regional disparities. In high-income countries, such as the United States, Canada, and the United Kingdom, obesity prevalence among women ranges from over 30% to  $>40\%$ , reflecting long-term dietary shifts, urbanization, and sedentary lifestyles.<sup>1,14</sup> For example, in the United States, the prevalence of obesity among adult women exceeds 40%, and similar trends are observed in European nations, though these rates vary across regions.<sup>14,15</sup> By comparison, in low- and middle-income countries, while obesity rates remain lower overall, they are rising rapidly. This increase is associated with urbanization, reduced physical activity, and the adoption of Western dietary patterns. Countries such as South Africa and Saudi Arabia have seen obesity rates in women rise dramatically, with some regions reporting rates exceeding 30% to 40% in the last 2 decades.<sup>16,17</sup> The growing obesity epidemic among women in these regions highlights the need for targeted interventions that consider both socioeconomic and cultural factors.

### Age-Related Trends

Obesity rates vary significantly across age groups, with middle-aged and postmenopausal women showing the highest prevalence.<sup>18</sup> Women aged 40 to 59 years experience a higher prevalence of obesity compared with younger age groups, with rates exceeding 40% in several high-income countries. This trend is linked to metabolic slowdowns, hormonal changes, and decreased physical activity during middle age.<sup>18</sup> Postmenopausal women

are particularly vulnerable due to a decline in estrogen levels, which leads to an increase in intra-abdominal fat, associated with higher risks of CKM syndrome.<sup>19</sup> In younger women, while obesity rates are rising, they tend to remain lower than in older women, but lifestyle factors such as unhealthy dietary patterns and sedentary behavior are contributing to a steady increase.<sup>20</sup> This pattern suggests a need for early intervention strategies that target younger age groups before the onset of more serious health risks associated with obesity later in life.

### Racial and Ethnic Disparities

In the United States, racial and ethnic disparities in obesity are well-documented, with non-Hispanic Black and Hispanic women experiencing disproportionately higher obesity rates compared with their White and Asian counterparts.<sup>21</sup> Non-Hispanic Black women have the highest obesity rates at 54.8%, followed by Hispanic women at 50.6%, compared with 38.0% for non-Hispanic White women and 14.8% for non-Hispanic Asian women.<sup>22</sup> Non-Hispanic Black women are 4.6× more likely to underestimate their BMI compared with Non-Hispanic White women and 29% less likely to use dieting or professional assistance for weight loss. Similarly, Mexican American women are 29% less likely to seek professional help for weight loss. Weight misperception is also more prevalent among non-Hispanic Black women, with 28.6% underestimating their weight compared with 15.9% of Hispanic women and 12.9% of non-Hispanic White women.<sup>23</sup> Black and Hispanic women are also more likely to begin pregnancy with obesity or develop gestational diabetes, exacerbating risks.<sup>18,22</sup> These disparities are driven by a combination of possible genetic predisposition and more importantly, socioeconomic status (SES) and environmental factors, such as access to healthy foods and health care.<sup>22</sup>

In contrast, Asian women generally have lower obesity rates, but those living in Western countries face an increasing risk, as they adopt Western dietary patterns and lifestyles.<sup>24</sup> Indigenous American Indian/Alaska Native women also experience some of the highest obesity rates, influenced by historical socioeconomic inequalities and limited access to health care and nutritious foods.<sup>25</sup> Given the interaction of multiple factors shaping obesity outcomes, effective obesity prevention and management requires addressing not just individual behaviors but broader social determinants of health.<sup>22</sup>

### PATHOPHYSIOLOGY OF OBESITY IN WOMEN

Estrogen plays a crucial role in fat distribution in women, particularly in the regulation of subcutaneous fat accumulation. Before menopause, higher estrogen levels

contribute to fat storage in peripheral areas such as the hips and thighs, which is considered less harmful in terms of CKM syndrome and overall cardiovascular risk.<sup>26</sup> However, as women transition through menopause and estrogen levels decline, there is a notable shift in fat distribution toward central or intra-abdominal adiposity.<sup>27</sup> This shift is linked to an increased risk of CKM and CVD, as hepatic fat is associated with higher levels of inflammation, insulin resistance, and dyslipidemia, all of which contribute to atherosclerosis, CKM syndrome, and diabetes. This association has been well-established in postmenopausal women, where intra-abdominal fat increases significantly as estrogen levels decline.<sup>26</sup> The hormonal changes during menopause exacerbate metabolic health issues. With the loss of estrogen, women often experience weight gain, reduced energy expenditure, and changes in fat metabolism, making it more challenging to maintain a healthy weight.<sup>28</sup> This shift toward central obesity during menopause heightens the risk of developing conditions such as hypertension, type 2 diabetes, and coronary artery disease (CAD).<sup>29</sup> In postmenopausal women, the use of weight-promoting medications, including antidepressants,  $\beta$ -blockers, insulin, and glucocorticosteroids, is associated with significant increases in BMI and WC. Women taking at least 1 such medication experienced greater increases in BMI (0.37 versus 0.27 kg/m<sup>2</sup>;  $P=0.0045$ ) and WC (1.10 versus 0.89 cm;  $P=0.0077$ ) over 3 years compared with nonusers, with a clear trend showing greater weight gain as the number of medications increased.<sup>30</sup> Antidepressants and insulin were the most strongly linked to weight gain, with BMI increases up to 0.39 units in certain subgroups.  $\beta$ -Blockers contributed to weight gain by reducing energy expenditure and exercise tolerance, while insulin and glucocorticosteroids increased fat mass and central adiposity.<sup>30</sup>

Genetic predispositions can play a critical role in obesity, with numerous genes influencing fat storage, metabolism, and appetite regulation. Variants in genes like *FTO* and *MC4R* have been strongly associated with increased BMI and adiposity in women, impacting how the body regulates energy balance and fat accumulation.<sup>31,32</sup> These genetic factors can contribute to differences in obesity rates and how individuals respond to interventions such as diet or exercise. In addition to genetic predispositions, epigenetic factors—modifications that do not alter the DNA sequence but affect gene expression—are crucial in understanding obesity risk.<sup>33</sup> Environmental factors like diet, physical activity, and stress can induce epigenetic changes that influence fat storage and metabolic processes, particularly in women. For example, maternal obesity and gestational diabetes can lead to epigenetic changes in offspring, predisposing them to obesity later in life.<sup>34</sup> This is particularly significant for women, as epigenetic mechanisms often interact with hormonal fluctuations across

different life stages (eg, pregnancy, menopause), further influencing obesity risk.<sup>35</sup>

Pregnancy is a critical period that can significantly impact a woman's long-term weight and risk of obesity. Excessive gestational weight gain is a major contributor to postpartum weight retention, which can persist for years and lead to long-term obesity.<sup>36</sup> On average, women retain 0.5 to 3 kg of weight in the postpartum period, but excessive weight gain during pregnancy can lead to much larger retention, increasing the risk of future obesity and associated metabolic diseases.<sup>37</sup> Gestational weight gain beyond recommended guidelines, particularly among women who start pregnancy with a higher BMI, compounds this risk. Retention of this weight is often linked to behavioral and metabolic changes that occur during pregnancy, such as reduced physical activity and altered metabolism, which persist postpartum.<sup>38</sup>

Addressing these issues involves both preventive and interventional strategies. Managing weight gain during pregnancy through regular physical activity, dietary monitoring, and adherence to gestational weight gain guidelines is key to reducing long-term risk.<sup>39</sup> Postpartum, strategies such as breastfeeding, which has been shown to aid in weight loss, as well as structured exercise programs and lifestyle interventions, can be effective in promoting weight reduction and minimizing long-term weight retention.<sup>40,41</sup> A 2-year cohort study of 305 mother-child pairs found that 23.6% had concurrent excess body weight at the 2-year mark. Breastfeeding for <2 months significantly increased the likelihood of excess body weight, with mothers 2.9× (odds ratio [OR], 2.9 [95% CI, 1.1–8.1]) and children 2.4× (OR, 2.4 [95% CI, 1.1–5.1]) more likely to be overweight compared with those breastfed for at least 6 months.<sup>42</sup> A 3-year study of 1051 women found that weight gain was higher in the no-lactation group (+5.6 kg) versus lactation (+4.4 kg) or nonpregnant women (+2.5 kg). Lactation also improved low-density lipoprotein cholesterol (LDL-C; +6.7 mg/dL in no lactation versus −0.8 mg/dL for ≥3 months). Lactation ≥3 months may reduce adverse metabolic changes and coronary heart disease risk by 14% to 21%.<sup>43</sup> A systematic review and meta-analysis of 8 studies involving over 1.19 million parous women found that breastfeeding is associated with an 11% reduced risk of CVD, a 14% lower risk of coronary heart disease, a 12% reduced risk of stroke, and a 17% reduced risk of fatal CVD.<sup>44</sup>

## CARDIOVASCULAR IMPLICATIONS OF OBESITY IN WOMEN

Obesity plays a significant role in the development of CVD in women by affecting various metabolic pathways. One of the key mechanisms is insulin resistance, which is commonly heightened in women with excess adiposity,

especially hepatic fat. Insulin resistance is often accompanied by dyslipidemia, characterized by elevated triglycerides and LDL-C levels, along with reduced high-density lipoprotein cholesterol, all of which contribute to atherosclerosis and CAD.<sup>45</sup> Postmenopausal women are particularly vulnerable, as the loss of estrogen leads to a shift from subcutaneous to intra-abdominal fat accumulation, further exacerbating these risks. Estrogen has a protective effect on lipid metabolism, and its decline during menopause results in a worsened lipid profile, heightening the risk of CVD, leading to a 20% to 25% increase in LDL-C and a 10% to 20% increase in triglycerides, alongside a 20% decrease in insulin sensitivity, a 2-fold increase in intra-abdominal fat within 5 years, a 50% prevalence of metabolic syndrome, and a 4-fold increased risk of type 2 diabetes.<sup>46,47</sup>

Additionally, the decline in estrogen is associated with increased blood pressure, as estrogen influences vascular tone and endothelial function. This hormonal change during menopause leads to higher rates of hypertension, a major contributor to heart disease in women.<sup>48</sup> Hypertension is twice as prevalent in postmenopausal women compared with premenopausal women, with studies indicating a 3- to 4-mm Hg increase in systolic and diastolic blood pressure regardless of age or BMI.<sup>49</sup> The combined effects of dyslipidemia, hypertension, and insulin resistance create a perfect storm for developing CKM syndrome, including atherosclerosis and myocardial infarction.

Obesity, particularly in postmenopausal women, also increases the risk of heart failure with preserved ejection fraction (HFpEF). HFpEF is more common in women, and its prevalence is rising in those with obesity. The increased intra-abdominal fat and systemic inflammation caused by obesity leads to myocardial stiffness and diastolic dysfunction, hallmarks of HFpEF.<sup>50</sup> The hormonal and metabolic shifts that occur during menopause further compound this risk, making women with obesity more susceptible to HFpEF.<sup>51</sup> The risk increases sharply within 5 to 6 years after menopause.<sup>52</sup>

Obesity impacts cardiovascular health in women differently than in men, largely due to physiological and hormonal differences. Women with obesity are more likely to develop HFpEF, a condition characterized by stiffening of the heart muscle and impaired diastolic function.<sup>50,53</sup> HFpEF is particularly prevalent among postmenopausal women with obesity, as estrogen deficiency accelerates the accumulation of intra-abdominal fat, which contributes to systemic inflammation and myocardial stiffness.<sup>50</sup> This differs from men, who more commonly experience heart failure with reduced ejection fraction, which is primarily driven by ischemic heart disease.<sup>53</sup>

In women, obesity is linked to a significantly greater risk of AF.<sup>54</sup> For example, studies show that women with obesity or overweight have a 41% higher risk of developing AF compared with those maintaining a normal BMI.<sup>54</sup>

Specifically, young women with obesity face double the risk (hazard ratio [HR], 2.04), while women with extreme obesity face more than triple the risk (HR, 3.50) of AF compared with normal-weight women.<sup>54</sup> Elevated inflammation and oxidative stress in women with obesity lead to atrial fibrosis and electrical abnormalities, contributing to this excess AF risk.<sup>54</sup>

Women with obesity are at greater risk of coronary microvascular disease due to altered vasomotor function and inflammatory responses. The release of proinflammatory cytokines and adipokines from expanded adipose tissue in obesity contributes to coronary microvascular dysfunction, particularly affecting myocardial perfusion in postmenopausal women.<sup>55</sup> Data from the Framingham Heart Study show that obesity raises the risk of CAD by 64% in women compared with 46% in men. Women with BMI  $\geq 30$  kg/m<sup>2</sup> are 2× to 3× at higher risk of developing CAD.<sup>1</sup> Elevated leptin levels, associated with obesity, are higher in women and linked to a 46% increase in the occurrence of coronary events. Postmenopausal women face a 2-fold higher risk of CAD due to hormonal changes, and central obesity is associated with a 34% increase in CAD for every 10-cm increase in WC.<sup>1,46</sup> A study of 115 886 women found that had obesity was significantly associated with a greater heart disease risk. Women with the highest BMI ( $\geq 29$  kg/m<sup>2</sup>) had over 3× the risk of heart events compared with the leanest group (BMI,  $< 21$  kg/m<sup>2</sup>), with 70% of these events linked to obesity. Moderate weight gain (BMI, 25–28.9 kg/m<sup>2</sup>) raised risk by 80%, and weight gain after age 18 doubled the risk.<sup>56</sup>

Small dense LDL-C levels were significantly higher in individuals with obesity (BMI,  $\geq 25$  kg/m<sup>2</sup>). Participants with higher body weight showed a 15% to 20% increase in small dense LDL-C levels, a 50% rise in plasma triglycerides, and a 15% reduction in HDL cholesterol, forming what is known as the atherogenic lipid triad. Around 58% of individuals with obesity exhibited a small dense LDL-C–dominant (pattern B) lipid profile, compared with 19% of those with lower body weight, underscoring its role as a marker of cardiovascular risk in relation to body weight.<sup>57</sup>

The relationship between obesity, CKM syndrome, and CVD is particularly pronounced in women, especially post-menopause. Obesity, a key component of CKM syndrome, contributes to a cluster of conditions such as insulin resistance, hypertension, dyslipidemia, and central adiposity, all of which significantly elevate the risk of CVD in women. Postmenopausal women are especially vulnerable due to the decline in estrogen, which exacerbates intra-abdominal fat accumulation and metabolic dysfunction, increasing their susceptibility to atherosclerosis, CAD, and other cardiovascular conditions.<sup>53</sup> Overall, CKM syndrome, more common in women with obesity, further elevates these risks by worsening lipid profiles, blood pressure, and glucose metabolism.<sup>58</sup> This interplay highlights the critical need for targeted interventions to address both obesity and CKM syndrome in

reducing CVD risk in women, particularly during and after menopause.<sup>58,59</sup>

## LIFESTYLE INTERVENTIONS FOR WEIGHT MANAGEMENT

Nutritional strategies tailored for women are crucial in managing obesity and reducing CVD risk. Importantly, a calorie deficit is essential for weight loss, achieved by consuming fewer calories than the body utilizes daily, increased physical activity, or a combination of both. The American Diabetes Association recommends using nutritional plans that promote weight loss through calorie restriction, regardless of the specific macronutrient composition of the diet.<sup>59</sup> While calorie counting is a common approach, diets like Paleolithic (Paleo) and Mediterranean can naturally create a calorie deficit without explicit tracking. Dietary interventions such as low-calorie diets, the Mediterranean diet, and the Paleo diet have shown effectiveness, particularly for postmenopausal women facing unique metabolic challenges.<sup>60</sup> The Mediterranean diet, which emphasizes whole grains, vegetables, fruits, nuts, legumes, olive oil, and moderate fish and dairy consumption, has been extensively studied for its impact on cardiovascular health and weight management, particularly in women. Research indicates that adherence to the Mediterranean diet leads to significant weight loss, reduced WC, and improved metabolic health, especially in postmenopausal women. The Mediterranean diet helps in reducing cardiovascular risk factors, such as hypertension, insulin resistance, and dyslipidemia, while also promoting anti-inflammatory effects. These benefits are largely attributed to the diet's high content of unsaturated fats, fiber, and antioxidants, which support better fat metabolism and overall health outcomes.<sup>61,62</sup>

Similarly, the Paleolithic diet, comprising vegetables, fruit, nuts, fish, meat, and eggs and excluding dairy, grain-based foods, legumes, extra sugar, and nutritional products of industry (including refined fats and refined carbohydrates), has demonstrated benefits in weight loss and metabolic health.<sup>60</sup> A randomized trial in postmenopausal women with obesity found that a Paleolithic diet (n=27) led to a greater reduction in fat mass and abdominal obesity compared with a Nordic Nutrition Recommendations diet (n=22) after 6 months, though the differences between the 2 groups diminished after 24 months.<sup>60</sup> The Paleolithic diet also resulted in significant decreases in triglyceride levels, highlighting its potential in managing CVD risk.<sup>63</sup> A study on postmenopausal women with obesity found that a high-protein diet (1.2 g/kg per day) during weight loss preserved 45% more lean mass but reduced improvements in muscle insulin sensitivity compared with a standard-protein diet (0.8 g/kg per day).<sup>64</sup>

Physical activity is widely recognized as a critical component of effective weight loss interventions and long-term weight maintenance, particularly in women with overweight and obesity. Increases in physical activity during periods of dietary energy restriction have been shown to significantly accelerate weight loss outcomes. Studies indicate that a reduction in sedentary time coupled with increased physical activity results in faster weight loss and contributes to the success of weight management programs.<sup>65,66</sup> Exercise alone contributes modestly to weight loss but can still be effective under certain conditions. Supervised exercise programs can achieve 3.9 to 5.2 kg weight loss over 10 months with significant effort, such as burning 400 to 600 calories per session, 5 days a week, often requiring  $\geq 7$  h/wk, far exceeding the 150 min/wk general health recommendations.<sup>67</sup> To maintain weight loss, consistent physical activity is essential. Studies recommend  $\geq 250$  min/wk of moderate-intensity exercise or an energy expenditure of 1500 to 2000 calories/wk, with active individuals showing significantly less weight regain over time.<sup>67</sup>

The timing of increased physical activity is also important, as changes made early in the intervention process appear to be particularly influential. Individuals who increased their activity levels within the first 2 weeks of dietary restriction saw better long-term outcomes. This early engagement in physical activity often leads to sustained improvements, reinforcing its significance as an integral part of any weight management strategy.<sup>65</sup>

Cognitive behavioral therapy (CBT) and social support are key components in effective weight management for women, especially those with obesity. CBT helps individuals restructure negative thought patterns related to eating and body image, leading to healthier behaviors like mindful eating and regular physical activity. Research shows that CBT reduces gestational weight gain in pregnant women and supports sustained weight loss by promoting goal setting and self-monitoring. Social support from family, friends, or support groups further enhances weight management by providing motivation, accountability, and emotional support, which is crucial for overcoming setbacks and maintaining long-term success (defined as  $>12$ –18 months). Together, CBT and social support address both the psychological and social aspects of weight loss, making them particularly effective for women managing obesity.<sup>68</sup>

## PHARMACOTHERAPY FOR OBESITY IN WOMEN

Anti-obesity medications have become essential tools for managing obesity and related conditions, especially for women with comorbidities such as polycystic ovary syndrome (PCOS), hypertension, and diabetes. The Food

and Drug Administration has approved 6 medications for long-term obesity management, including GLP-1 (glucagon-like peptide-1) receptor agonists (semaglutide and liraglutide), tirzepatide (a dual GLP-1/GIP [gastric inhibitory polypeptide] receptor agonist), phentermine-topiramate, naltrexone-bupropion, and orlistat. These medications function through different mechanisms, such as appetite suppression, delayed gastric emptying, and fat absorption inhibition, achieving various levels of weight loss. Anti-obesity medications are prescribed as an adjunct to lifestyle modifications like reduced-calorie diets and increased physical activity for individuals with obesity (BMI,  $\geq 30$  kg/m<sup>2</sup>) or overweight (BMI,  $\geq 27$  kg/m<sup>2</sup>) with weight-related comorbidities such as hypertension, diabetes, or dyslipidemia.<sup>69</sup>

For instance, tirzepatide has shown up to 21% weight reduction, while semaglutide achieves around 14.9% weight loss in clinical trials. Additionally, metformin, although not specifically approved for weight loss, is often prescribed off-label to improve insulin sensitivity, particularly in women with PCOS, showing modest weight loss and metabolic improvements.<sup>70,71</sup>

Women, particularly those with conditions such as PCOS, have demonstrated significant improvements in weight and metabolic parameters when anti-obesity medications are combined with lifestyle modifications. In clinical trials, GLP-1 receptor agonists and orlistat were the most effective for reducing BMI and improving reproductive outcomes by modulating hormonal profiles.<sup>72,73</sup> Incretin therapies such as semaglutide and liraglutide, in addition to promoting weight loss, helped lower testosterone levels and increase SHBG (sex hormone-binding globulin), which can lead to enhanced ovulation rates and improved fertility in women with obesity-related reproductive challenges.<sup>73</sup> GLP-1 receptor agonists like semaglutide commonly cause gastrointestinal side effects, such as nausea and diarrhea, but these are typically mild, transient, and occur during dose escalation, with long-term tolerability demonstrated by low discontinuation rates (4.3%).<sup>74</sup> Of note, tirzepatide significantly reduces the bioavailability of oral hormonal contraceptives, unlike other GLP-1 receptor agonists.<sup>75</sup>

Phentermine/topiramate extended-release (Qsymia) combines a sympathomimetic appetite suppressant (phentermine) and an antiepileptic agent (topiramate) achieving significant weight loss. Clinical trials such as EQUIP, CONQUER, and SEQUEL demonstrated weight reductions of up to 10.9% with high doses over 52 to 108 weeks, alongside improvements in metabolic parameters such as blood pressure, lipids, and glucose levels.<sup>76</sup> Although Qsymia has been associated with increased heart rate in some cases, no significant long-term cardiovascular risks have been observed.<sup>77</sup> Additionally, a study involving 13 972 adults found that long-term phentermine use ( $>12$  months) led to 7.4% greater weight loss at 24 months compared with short-term use, with

no increased risk of CVD or death over 3 years.<sup>78</sup> Qsymia is contraindicated in pregnancy due to the risk of oral cleft formation from topiramate exposure during the first trimester.<sup>76</sup> Women of childbearing potential must use contraception and undergo regular pregnancy tests.<sup>76</sup>

Naltrexone/bupropion ER (Contrave) has shown significant efficacy for weight loss, achieving an average reduction of 5% to 9% in body weight over 56 weeks in clinical trials. Clinical trials confirm its cardiovascular safety, showing no increased risk of major adverse cardiovascular events, with rates of 2.7% in treated patients versus 2.8% for placebo after 121 weeks and major adverse cardiovascular events+ rates of 3.7% versus 3.8%. It is contraindicated in individuals with seizure disorders, uncontrolled hypertension, or chronic opioid use due to associated risks.<sup>79</sup>

Orlistat led to a weight loss of 4.65 kg and reduced BMI by 1.91 kg/m<sup>2</sup> over 24 weeks, significantly outperforming placebo. It also decreased WC and LDL-C. Common side effects were mild gastrointestinal issues, including loose stools and oily spotting.<sup>80</sup> According to a national cohort study from an electronic Clinical Practice Research Datalink, 36 876 patients with obesity who underwent a course of orlistat therapy demonstrated a lower risk of adverse cardiovascular events compared with propensity score matched controls who did not receive orlistat therapy over a median of 6 years of follow-up.<sup>81</sup> In terms of cardiovascular outcomes, anti-obesity medications offer substantial benefits beyond weight loss. Semaglutide and liraglutide have shown reductions in cardiovascular events such as heart attacks, strokes, and major adverse cardiovascular events, even in patients without diabetes. For instance, semaglutide was found to reduce the risk of cardiovascular death by 20% in the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity). Additionally, these drugs improve cholesterol profiles (reducing LDL-C), lower blood pressure, and decrease inflammatory markers like C-reactive protein, making them beneficial for managing cardiovascular risk in women with obesity.<sup>70,77</sup> In 2024, Wegovy (semaglutide) was approved by the Food and Drug Administration to reduce the risk of cardiovascular death, heart attack, and stroke in adults with obesity or overweight and CVD. In a trial involving over 17 600 participants (inclusion criteria age  $\geq 45$  years, BMI  $\geq 27$  kg/m<sup>2</sup>, prior myocardial infarction, stroke, or peripheral arterial disease with claudication and ankle-brachial index  $< 0.85$ , prior revascularization, or amputation), the major cardiovascular events occurred in 6.5% of those treated with Wegovy, compared with 8% in the placebo group.<sup>71</sup>

## BARIATRIC SURGERY IN WOMEN

Bariatric surgery has been shown to significantly improve cardiovascular outcomes in women with obesity, even

among the elderly Medicare population.<sup>82</sup> The procedure is associated with a reduction in both all-cause and cardiovascular mortality. Specifically, bariatric surgery reduces the risk of heart failure, myocardial infarction, and stroke. In a systematic review and meta-analysis of 39 studies, bariatric surgery decreased the incidence of heart failure by 50% (n=26 002), myocardial infarction by 42% (n=101 536), and stroke by 36% (n=86 601).<sup>83</sup> These findings suggest that bariatric surgery not only helps with weight loss but also offers substantial long-term cardiovascular protection for women, particularly those at high risk for CVD.<sup>83</sup>

Obesity significantly affects female fertility by disrupting the hypothalamic-pituitary-ovarian axis, leading to conditions such as anovulation, infertility, menstrual irregularities, and complications in pregnancy. Bariatric surgery, the most effective long-term treatment for obesity, is shown to improve these reproductive outcomes by promoting weight loss and regulating hormonal profiles. Studies have highlighted that post-surgery, women experience improvements in menstrual cycles, ovulation, and fertility, particularly in conditions like PCOS. Additionally, bariatric surgery reduces pregnancy-related complications such as gestational diabetes, hypertension, and fetal macrosomia. The American College of Obstetricians and Gynecologists recommended delaying pregnancy for 12 to 24 months post-surgery to optimize health outcomes for both the mother and the child.<sup>84</sup>

According to a randomized trial of patients with obesity with indication for Roux-en-Y gastric bypass (n=60), the psychosocial impacts of bariatric surgery on women, particularly regarding mental health, were significant.<sup>84</sup> The research revealed a marked improvement in mental health, as evidenced by a reduction in depressive symptoms and an increase in general well-being post-surgery.<sup>84</sup> This was demonstrated through improvements in the Patient Health Questionnaire and Beck Depression Inventory scores in women who underwent Roux-en-Y gastric bypass. Additionally, there was a substantial enhancement in several domains of the 36-Item Short Form Health Survey, which measures health-related quality of life across dimensions such as bodily pain, vitality, and social functioning. These improvements underscore the positive psychological outcomes for women post-surgery, including a decrease in depression and enhanced overall quality of life.<sup>85</sup>

An umbrella analysis of 28 meta-analyses evaluated 82 health-related outcomes associated with bariatric surgery. The results showed significant benefits, including a 50% reduction in cardiovascular mortality (OR, 0.50 [95% CI, 0.35–0.71]) and a 79% decrease in gestational diabetes (OR, 0.21 [95% CI, 0.12–0.36]). However, it increased the risk of suicide 4-fold (OR, 4.15 [95% CI, 3.20–5.38]), fractures by 20% (relative risk [RR], 1.20 [95% CI, 1.15–1.26]), and perinatal complications like small-for-gestational-age births (OR, 2.18 [95% CI, 1.41–3.38]).<sup>86</sup>

## SPECIAL CONSIDERATIONS IN OBESITY MANAGEMENT FOR WOMEN

When managing obesity in women, special considerations must be made for conditions such as pregnancy, PCOS, and menopause, as these factors can significantly influence treatment choices. During pregnancy, weight management is complex and requires a careful balance to ensure maternal and fetal health. Excessive weight gain during pregnancy increases the risk of complications such as gestational diabetes, preeclampsia, and delivery complications. Therefore, obesity management strategies for pregnant women should focus on healthy weight maintenance rather than aggressive weight loss, incorporating moderate physical activity and tailored dietary interventions. The goal is to prevent excessive weight gain while avoiding harm to the developing fetus.<sup>87,88</sup>

In women with PCOS, obesity is a key factor that intensifies the risk of insulin resistance, hyperandrogenism, and reproductive issues such as infertility. Effective weight management can substantially improve both metabolic and reproductive health outcomes for women with PCOS. Studies demonstrate that a weight reduction of as little as 5% to 10% can help restore ovulation and fertility, as well as reduce the risks associated with endometrial cancer and CVDs.<sup>89–91</sup> Therefore, lifestyle interventions, including dietary modifications, exercise, and sometimes pharmacotherapy, are typically recommended as initial treatments to address weight issues in patients with PCOS. These interventions aim to improve insulin sensitivity and lower androgen levels, which are critical to reducing the metabolic and hormonal imbalances associated with the syndrome. Furthermore, weight loss can also alleviate symptoms related to hyperandrogenism, thus contributing to both immediate and long-term health improvements in women with PCOS.<sup>92,93</sup>

Notably, eating disorders including binge eating disorder and night eating syndrome are prevalent in women; however, these are exacerbated with PCOS, creating a vicious cycle that aggravates both obesity and the hormonal disturbances associated with PCOS.<sup>99</sup> These eating disorders are often enhanced by emotional stress related to PCOS symptoms like hirsutism, infertility, and insulin resistance, which further disrupt the brain's reward system. Effective treatment of obesity in PCOS women must address both physical and psychological factors, as untreated emotional or binge eating can hinder weight management.

The treatment of binge eating disorder involves a combination of pharmacotherapy, psychotherapy, and emerging therapies. Among pharmacological treatments, lisdexamfetamine is the first-line Food and Drug Administration–approved medication, shown to significantly reduce binge episodes while improving obsessive-compulsive symptoms. Other effective medications include methylphenidate, which reduces binge episodes and BMI. Anticonvulsants such as topiramate and zonisamide,

particularly in combination with CBT, show promise for reducing binge episodes and promoting weight loss.<sup>94</sup>

Cultural, socioeconomic, and psychosocial factors play critical roles in shaping obesity management strategies for women. Cultural norms influence body image, perceptions of beauty, and food habits, which can affect women's willingness to seek obesity treatment. In some cultures, societal pressure to conform to specific body ideals can either encourage or discourage weight loss efforts depending on local norms.<sup>95</sup>

SES also profoundly impacts obesity management. Women from lower-income backgrounds often face significant barriers, such as limited access to healthy food, health care, and exercise opportunities for safe physical activity. The financial strain can lead to higher consumption of low-cost, high-calorie, nutrient-poor foods, contributing to higher obesity rates. Affordability remains a significant issue for anti-obesity medications like semaglutide, costing \$1500 per month. Only 20% of insured adults have coverage, with no support from Medicare and limited Medicaid coverage in a few states. Among semaglutide-eligible adults, 11.9% are uninsured, 33.6% have low income, and 38.9% lack higher education. These barriers disproportionately affect low-SES groups, particularly 29.3% of Hispanic and 14.7% of Black adults who are uninsured, highlighting the need for equitable access to these treatments.<sup>96</sup>

Moreover, women with lower SES are more likely to experience stress, anxiety, and depression, which are risk factors for emotional eating and obesity.<sup>97</sup> This mental health burden further complicates weight management strategies and makes it more difficult to maintain healthy lifestyle changes.<sup>98</sup> Additionally, a long-term consequence of obesity among lower SES women portends a greater risk of their children developing obesity.<sup>97</sup> On the other hand, in the Look AHEAD trial (Action for Health in Diabetes), Black and Hispanic women with type 2 diabetes achieved substantial weight loss, but their outcomes were slightly lower compared with non-Hispanic White women. At year 1, Black and Hispanic women lost an average of 6.8% and 8.1% of their body weight, respectively, while non-Hispanic White women lost 9.1%. By year 8, Black and Hispanic women sustained losses of 6.3% and 5.8%, compared with 5.5% for non-Hispanic White women.<sup>99</sup> Despite socioeconomic challenges, Black and Hispanic women matched or surpassed White women in long-term engagement, with higher group session attendance and reliance on culturally adapted strategies like daily self-weighing for Black women and group support for Hispanic women, underscoring the importance of tailored interventions for equitable outcomes.<sup>99</sup>

## FUTURE DIRECTIONS AND EMERGING THERAPIES

The incretin-based pharmacological approaches show great promise in providing more effective treatments

for weight management, including the emerging investigational triagonist retatrutide, a GLP-1/GIP/glucagon receptor, and cagrisema, which is a combination agent that includes semaglutide and cagrilintide. Emerging combination therapies are being explored to optimize metabolic pathways and improve long-term outcomes for individuals with obesity.<sup>14,100</sup>

The future of obesity management is set to evolve significantly with advancements in pharmacotherapy, precision medicine, and digital health. Precision medicine is another key frontier, leveraging genetic and microbiome profiling to tailor obesity treatments to individual patients.<sup>101</sup> This approach allows clinicians to consider unique genetic factors, microbiome composition, and metabolic profiles when designing personalized interventions. By focusing on individual biological markers, precision medicine has the potential to significantly enhance treatment efficacy and minimize adverse effects.

Moreover, digital health and telemedicine are transforming the way obesity is managed. These tools provide opportunities for remote monitoring, personalized feedback, and real-time support, allowing patients to engage in their weight loss journey with greater flexibility and access to care. Telemedicine applications enable health care providers to deliver more personalized interventions, monitor progress continuously, and adjust treatment plans as needed, thereby improving patient outcomes in weight management.<sup>102</sup> This integration of digital health tools makes obesity care more accessible, scalable, and patient centered.

## CONCLUSIONS

Obesity in women is a multifaceted challenge that intersects with diverse physiological, hormonal, socioeconomic, and cultural factors, necessitating a tailored approach to its management. This review highlights the sex-specific nuances of obesity's pathophysiology, its epidemiological trends, and its associated comorbidities, particularly cardiovascular and metabolic complications. Lifestyle interventions, pharmacotherapy, and bariatric surgery provide effective strategies for weight management, but their success often hinges on addressing unique life-stage challenges and societal barriers faced by women. Emerging therapies and the integration of precision medicine offer promising directions for the future, enabling more personalized and equitable care.

The Table summarizes the key findings and management strategies, offering a concise reference for clinicians aiming to optimize outcomes for women with obesity. By leveraging these insights, health care providers can better address the complex interplay of biological, psychological, and social determinants of health, ultimately reducing the burden of obesity and its complications in women.

**Table. Obesity Management Strategies for Women—Summary**

Obesity in women is a global health concern, particularly related to CKM syndrome. Women face unique challenges in obesity management due to hormonal changes during pregnancy, menopause, and life stages. Tailored strategies are essential to improve outcomes.
Obesity prevalence in women is rising globally, with disparities across regions and populations. Middle-aged and postmenopausal women show higher rates, and racial/ethnic groups such as non-Hispanic Black women face disproportionately high rates due to socioeconomic and cultural factors.
Hormonal changes, especially estrogen decline post-menopause, lead to increased visceral fat and heightened cardiovascular risks. Genetic and epigenetic factors, along with pregnancy-related weight retention, exacerbate obesity in women.
Obesity drives cardiovascular risks like insulin resistance, dyslipidemia, hypertension, and heart failure, particularly HFpEF in postmenopausal women. Sex-specific differences in cardiovascular outcomes necessitate tailored interventions.
Mediterranean and Paleolithic diets, physical activity, and CBT are effective strategies. Early engagement in lifestyle changes and reducing sedentary behavior significantly improve outcomes.
Medications like GLP-1 receptor agonists, phentermine/topiramate, and naltrexone/bupropion show promise. Tailoring treatments to women-specific comorbidities, like PCOS, enhances effectiveness.
Bariatric surgery improves weight, cardiovascular outcomes, and fertility while reducing pregnancy complications. Risks include increased fracture and perinatal complications; timing post-surgery is critical for pregnancy planning.
Conditions like PCOS and menopause, eating disorders, and socioeconomic factors require targeted interventions. Culturally sensitive and equitable access to treatments can address disparities.
Innovations in pharmacotherapy, precision medicine, and digital health are transforming obesity management. Personalized approaches based on genetics and digital monitoring improve long-term outcomes.

CBT indicates cognitive behavioral therapy; CKM, cardiovascular-kidney-metabolic; GLP-1, glucagon-like peptide-1; HFpEF, heart failure with preserved ejection fraction; and PCOS, polycystic ovary syndrome.

## ARTICLE INFORMATION

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