















# Beyond the conventional risk factors in the management of atherosclerosis in women: a call to action for careful consideration of obesity and inflammation

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Received 11 September 2025; revised 2 February 2026; accepted 17 February 2026; online publish-ahead-of-print 27 April 2026

Handling Editor: Salvatore De Rosa

Conventional risk factors do not completely explain the burden of atherosclerotic cardiovascular disease (ASCVD) in women. Obesity and chronic low-grade inflammation are recognized as important contributors to atherosclerotic risk. This viewpoint explains the role of obesity-driven inflammation in the development and management of atherosclerosis in women. Abdominal obesity promotes a proinflammatory and prothrombotic environment that accelerates atherogenesis. Women with higher inflammatory biomarker levels and experience sex-specific risk-modifying stages, such as polycystic ovary syndrome, pregnancy-related conditions, and menopause, have higher risk for cardiovascular events, including atherosclerosis. We review evidence for antiobesity and anti-inflammatory therapies. Integrating obesity and inflammation into ASCVD care in women requires targeted screening, risk assessment, and sex-stratified research approaches. This viewpoint highlights the relation between obesity and atherosclerosis.

## Keywords

Obesity • Inflammation • Atherosclerosis • Women • Risk factors

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## Introduction and basic concepts

Conventional cardiovascular (CV) risk factors, such as hypertension, dyslipidaemia, diabetes mellitus, smoking, and sedentary lifestyle, form the hallmark of atherosclerotic cardiovascular disease (ASCVD). However, these factors alone do not account for the CV risk observed in women, highlighting the contribution of other risk factors, including obesity and chronic systemic inflammation.<sup>1,2</sup> The Global Burden of Disease (GBD) Obesity Collaborators estimated that the rate of obesity has doubled over the past two decades, with ~39–49% of the world's population (2.8–3.5 billion people) classified as overweight or obese.<sup>3</sup>

Obesity is a multifactorial condition, with its pathogenesis consisting of environmental, socioeconomic, and biological determinants. The conventional definition of obesity relies on body mass index (BMI). While BMI is useful at a population level, it fails to capture sex-specific differences in fat distribution and cardiometabolic risk. Abdominal (central) obesity is assessed by waist circumference (>88 cm in women). It is more accurate to reflect visceral adiposity and is more strongly associated with insulin resistance, endothelial dysfunction, and a proatherogenic inflammatory state.<sup>4</sup> Obesity is a proinflammatory state, characterized by increased levels of inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>5</sup> This inflammatory state exacerbates traditional risk factors, leading to increased risk of CV events.<sup>5</sup> This viewpoint highlights the role of obesity and chronic inflammation in the development of atherosclerosis. By understanding this relationship, targeted interventions can reduce CV events, including atherosclerosis.

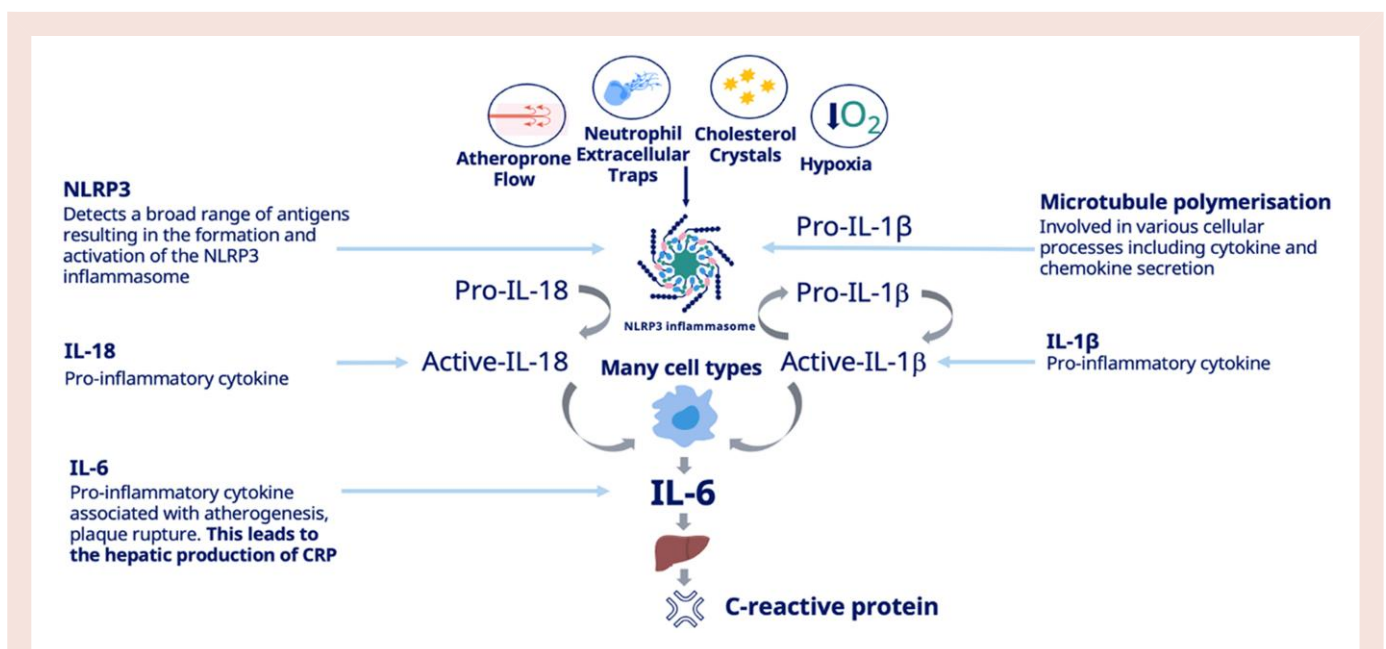
Chronic low-grade systemic inflammation is a key factor in the pathogenesis of ASCVD. Triggers of chronic inflammation include viral infections, rheumatic or autoimmune disorders, cancers, and vascular injury. Vascular injury is interesting as it includes triggers, such as smoking and lipoprotein(A).<sup>6</sup> The

progression and instability of atheroma precipitate acute CV events.<sup>7</sup> In patients with atherosclerosis, cholesterol and oxidized LDL are the main activators of the NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome (Figure 1). These stimuli promote inflammation, oxidative stress, and cell death within the arterial wall. In addition, these crystals cause atheroprone flow (low shear stress, oscillatory flow, and flow separation), which leads to endothelial dysfunction, inflammation, and accumulation of lipids and immune cells in the arterial wall.<sup>8</sup>

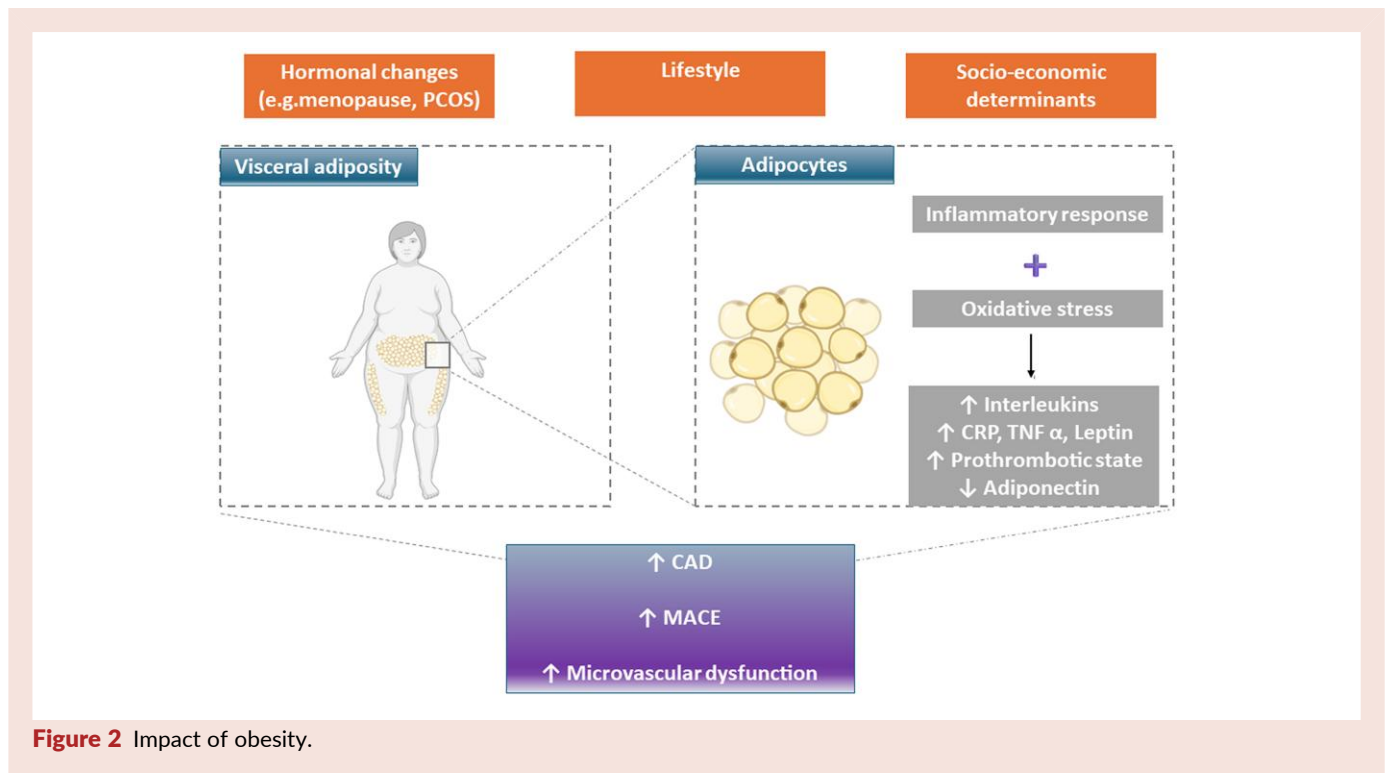
## Interplay between obesity, inflammation, and female-specific conditions across the life course

Obesity represents a complex interplay of factors that result in excess weight and fat accumulation (Figure 2). These factors include neurobiological, genetic, behavioural, socioeconomic, and psychological factors.<sup>9</sup> Excess adipose tissue, especially found with visceral fat deposition, secretes cytokines, such as leptin and adiponectin, and dysregulates the secretion of inflammatory adipocytokines, promoting inflammatory cytokines and the proliferation of proinflammatory macrophages.<sup>10,11</sup> This complex proinflammatory state contributes to increased oxidative stress and the activation of sympathetic pathways, leading to metabolic disturbance and endothelial dysfunction.<sup>12</sup> Dysregulated adipocytokines can induce insulin resistance, endothelial dysfunction, a prothrombotic state, neurohormonal imbalance, and systemic or local inflammation.<sup>13,14</sup> Activation of the inflammation pathway, including TNF $\alpha$ , IL-1, IL-6, and plasminogen activator inhibitor-1, raises insulin resistance, modifies lipid metabolism, increases thrombogenicity, decreases the vasoreactivity of the arterial wall, and increases blood pressure (BP).

In women, the biological consequences are more significant.<sup>15</sup> Premenopausal, nonobese women have lower CV risk compared



**Figure 1** Role of the NLRP3 inflammasome in atherosclerosis. IL, interleukin; NLRP3, NOD (nucleotide oligomerization domain)-, LRR (leucine-rich repeat)-, and PYD (pyrin domain)-containing protein 3; MMP, matrix metalloproteinase; pro-IL, interleukin precursor; VSMC, vascular smooth muscle cells. Ridker PM et al. *Circulation* 2020;141:787–789.



**Figure 2** Impact of obesity.

to men, but obesity significantly worsens a woman's CV risk profile. The role of inflammation can be detected through higher levels of mean C-reactive protein, which are found in obese women compared to obese men.<sup>16</sup> Leptin is another adipokine elevated in obesity, which has a different impact according to sex.<sup>16</sup> Moreover, the protective effect of sexual steroids appears decreased in obesity with a decrease in the oestrogen signalling pathway in endothelial cells, leading to reduced nitric oxide (NO) availability, increased arterial tone, and stiffness.<sup>14</sup> Androgen excess associated with increased adiposity contributes to an unfavourable CV profile. This is also observed in polycystic ovarian syndrome and the postmenopausal state.<sup>17</sup> Increased androgen levels (hyperandrogenism) are associated with obesity, hypertension, insulin resistance, and endothelial dysfunction.<sup>17-19</sup>

## Polycystic ovarian syndrome

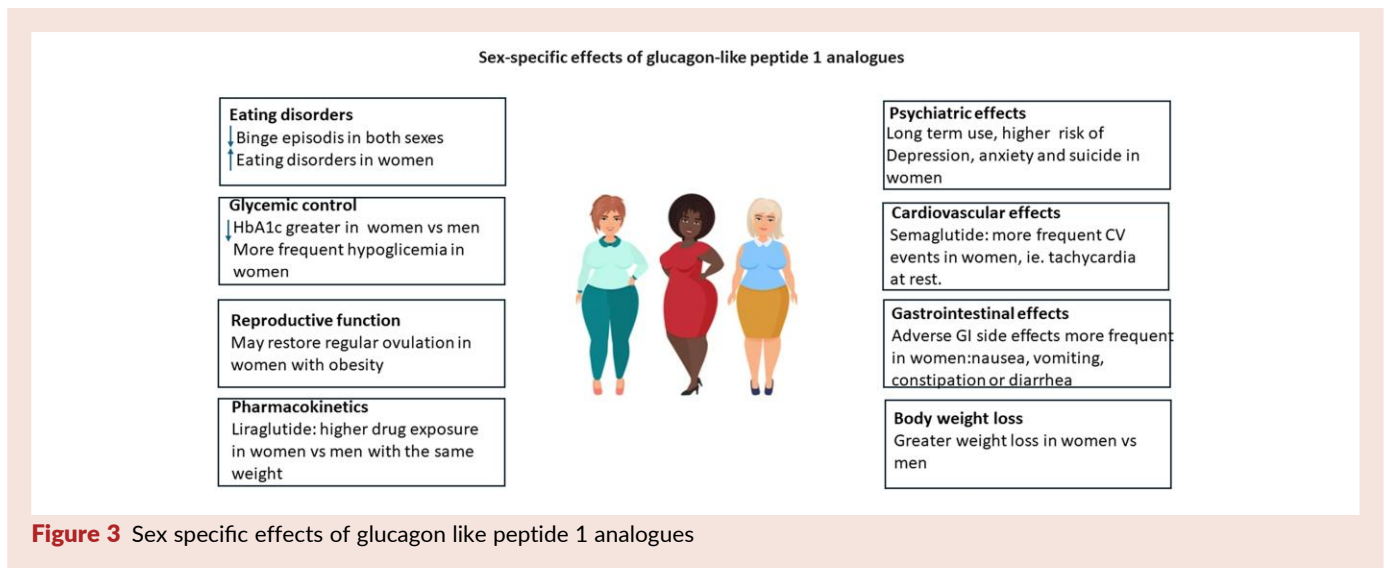
Hyperandrogenism is considered the primary cause of polycystic ovarian syndrome (PCOS). Between 30 and 50% of patients with PCOS present with metabolic syndrome from adolescence.<sup>20</sup> Women with PCOS frequently have an atherogenic lipid profile, characterized by elevated triglycerides (TG), very LDL cholesterol (VLDL-C), LDL cholesterol (LDL-C), and reduced HDL cholesterol (HDL-C) levels. These lipid abnormalities are relatively linked to insulin resistance and reflect metabolic and inflammatory pathways that promote atherosclerosis in women.<sup>21</sup> In a meta-analysis of 30 studies, it was found that women with PCOS have higher LDL-C, non-HDL-C, and TG levels, along with lower HDL-C, compared with age- and weight-matched women without PCOS, even after adjustment for BMI.<sup>22</sup> This highlights that atherogenic dyslipidaemia in women may arise independently of generalized obesity and the importance of sex-specific metabolic risk modifiers.<sup>22</sup> The

dyslipidaemia observed in PCOS is thought to be from obesity, hyperandrogenism, and insulin resistance. Mechanisms that explain dyslipidaemia in PCOS include impaired insulin signalling, increased hepatic production of apolipoprotein B-containing very LDLs, abnormal lipoprotein lipase activity, and androgen receptor-mediated HDL catabolism. Consistent with this, treatment with the androgen receptor antagonist flutamide has been shown to improve lipid profiles in women with PCOS.<sup>23</sup>

## Endometriosis

The most widely accepted theory for pathophysiology of endometriosis is retrograde menstruation, where menstrual blood containing endometrial cells flows through the fallopian tubes into the pelvic cavity. This allows these cells to implant, proliferate, and cyclically bleed.<sup>24-26</sup> Other hypotheses, including contributions from endometrial or bone marrow stem cells, lymphovascular spread, and coelomic metaplasia, have been suggested to explain ectopic lesion locations.

Endometriosis and atherosclerosis have common cellular and molecular features. Both involve chronic inflammation, oxidative stress, endothelial dysfunction, and cellular proliferation.<sup>24-26</sup> Endometriosis is a multifactorial disease affected by hormonal, proinflammatory, proangiogenic, immunologic, and genetic factors.<sup>26</sup> The proliferation of endometrial fragments relies on systemic oestradiol and altered hormonal signalling pathways.<sup>26,27</sup> Recruitment of macrophages and activation of cytokines and angiogenic factors promote neovascularization and ectopic lesion growth within a proinflammatory environment.<sup>26,28</sup> Endometriosis has also been associated with increased arterial stiffness and impaired flow-mediated dilation, a marker of endothelial dysfunction that may improve after surgical intervention.<sup>26,29-31</sup>



## Menopause

Menopause is characterized by an accelerated decline in oestrogen levels, which begins at the age of 35.<sup>32</sup> The role of oestrogen in the CV system is well established. It contributes to vascular reactivity, BP regulation, endothelial function, cardiac remodelling, and immune modulation. The atheroprotective effects of oestradiol have been studied.<sup>33–37</sup> The accelerated and sharp decrease in oestrogen levels during menopause causes a variety of systemic effects. It reduces basal metabolic rate and leads to a redistribution of abdominal and subcutaneous fat, with a significant increase in visceral adiposity. The menopausal transition is associated with changes in insulin and glucose metabolism, including insulin resistance and even a decrease in insulin secretion.<sup>38,39</sup> Moreover, decreased levels of sex hormone-binding globulin (SHBG) and the related increase in circulating testosterone are also associated with insulin resistance. The increase in visceral fat triggers inflammation and contributes to insulin resistance.<sup>40</sup> Additionally, lipid metabolism changes significantly during the menopausal transition, with increases in TG, total cholesterol, and LDL cholesterol, accompanied by a decrease in HDL cholesterol.<sup>41</sup> It is also noted that the increase in LDL is independent of age, BMI, and environmental factors.<sup>42</sup>

## Pregnancy

Pregnancy can exacerbate underlying CV risks, especially in women with obesity or systemic inflammation. This leads to complications, such as gestational hypertension and preeclampsia, which are linked to long-term ASCVD risk.<sup>43</sup> According to a study addressing the impact of obesity on outcomes of pregnancy in women with heart disease, with a sample size of 790 pregnancies, they found that 19% occurred in women with obesity (BMI of 30 kg/m<sup>2</sup> or higher) and 25% in overweight women (BMI of 25–29.9 kg/m<sup>2</sup>). Women with obesity had a higher incidence of CV events compared with normal-weight women (23% vs. 14%;  $P = 0.006$ ). In a multivariable analysis, both obesity (odds ratio [OR] 1.7; 95% confidence interval [CI] 1.0–2.7) and higher Cardiac Disease in Pregnancy Study II scores (OR 1.7; 95% CI 1.5–1.9) independently predicted CV events. Preeclampsia was more common in women with obesity than in those with normal weight (8% vs. 2%;  $P = 0.001$ ).<sup>43</sup> It is crucial

for women with cardiometabolic risk factors to undergo preconception CV assessment, including BP, lipid profile, BMI, insulin resistance, and inflammatory biomarkers. Early identification and management of these modifiable risks can improve maternal and foetal outcomes and reduce pregnancy complications and ASCVD risk.

## Management

Treatment of obesity has the potential to improve CV risk factors and reduce CV events. Current recommendations emphasize regular assessment of BMI, CV risk factors, established cardiovascular disease (CVD), and readiness for weight loss. For individuals with a BMI of  $\geq 30$  kg/m<sup>2</sup>, or  $\geq 27$  kg/m<sup>2</sup> in the presence of CVD or cardiometabolic risk factors, comprehensive lifestyle interventions represent the first-line therapeutic approach.<sup>44,45</sup> Bariatric surgery may be considered for individuals with a BMI of  $\geq 40$  kg/m<sup>2</sup>, or  $\geq 35$  kg/m<sup>2</sup> with CVD. Pharmacological therapies may be added to patients with an inadequate response to lifestyle interventions or in those with established CVD. Lifestyle and behavioural strategies, including nutritional counselling and structured physical activity, form the foundation of all obesity treatment approaches and are also recommended for the primary prevention of CVD. However, evidence suggests that clinically meaningful CV benefit generally requires weight loss exceeding 10% of baseline body weight.<sup>46</sup> Lifestyle interventions alone often fail to achieve or sustain this degree of weight loss and are frequently complicated by weight regain.<sup>47,48</sup>

## Nonpharmacological interventions

Obesity management involves lifestyle changes (physical health, nutritional health, emotional health), even if therapeutic or surgical treatment is considered. Obesity is a considerable burden, and the physical and mental quality of life for overweight women or women living with obesity is impaired. One way to improve their quality of life and their CV and global prognosis is to practice regular physical activity. It is recommended to practice at least 150–300 min per week of moderate endurance physical activity, spread over three to five sessions per week, or 75–150 min per week of vigorous physical activity (PA), or

a combination of both intensities. It is also recommended to practice resistance PA two to three times per week.<sup>49,50</sup>

In the middle-aged female adult population, including those suffering from obesity, there are barriers related to daily life to PA, such as the combination of family and professional life, as well as caring for children, family, and household chores, which alter the desire and motivation to engage in PA. Women also feel less justified in engaging in endurance PA. One solution is to offer a variety of physical activities, supervised by a PA instructor, combining endurance and resistance, for example, walking, running, cycling, playing tennis or team sports, gymnastics classes, and resistance training.<sup>51</sup> A weekly session of vigorous PA or high-intensity interval training (HIIT) is associated with a lower risk of hypertension and obesity and improves cardiorespiratory fitness ( $VO_2$  peak), cardiac stroke volume, BP, body composition, and lipid profile and is likely to provide similar benefits to Depot Medroxyprogesterone Acetate in terms of body fat reduction in women.<sup>52</sup>

Regarding diet, calorie reduction along with a Mediterranean-style diet is recommended. The goal is to meet the needs and preferences of women.<sup>49,50</sup> A low-calorie diet, without a prescription for PA, is sufficient for short-term weight loss, but PA is essential for changing body composition in women in situation of obesity. Fat mass is lower in women who engage in moderate exercise than in those following a low-calorie diet alone. Tailored exercise program is more effective at reducing body fat and maintaining muscle mass.<sup>53</sup> Mindful eating is associated with weight loss but is not superior to other dietary control techniques for women.<sup>54</sup> Mental and emotional health should also be addressed; outpatient counselling, cognitive-behavioural therapy, support groups, and psychosocial support should be encouraged for better weight loss, to reduce binge eating in women, who are more often affected by this phenomenon than men, and also to limit anxiety and depression associated with obesity or overweight.<sup>49,55,56</sup>

E-health interventions can increase PA and improve obesity-related outcomes by monitoring weight, food intake, and emotions. All these interventions can be encouraged by participation in long-term programmes, support groups, and psychological support, in addition to staying in CV rehabilitation centres that promote programmes for patients who are classified as overweight or obese, or centres specialized in metabolic management.<sup>49,57,58</sup>

## Pharmacological interventions

### Anti-inflammatory therapies

Obesity exacerbates the release of proinflammatory cytokines, such as leptin, IL-6, and TNF- $\alpha$ . These proinflammatory cytokines promote oxidative stress, induce a prothrombotic state, and reduce levels of anti-inflammatory adiponectin. This creates a chronic low-grade inflammatory state. This sustained inflammatory environment increases the risk of incident coronary artery disease (CAD) and major adverse cardiovascular events (MACE) in women with obesity.<sup>59</sup>

Social determinants, such as discrimination and chronic stress, have also been related to elevated inflammatory markers in women, which may further elevate their CVD risk beyond traditional factors.<sup>60</sup> Anti-inflammatory therapies, especially those targeting the central IL-6 signalling pathway, may serve as promising treatment strategies to reduce the risk of myocardial infarction (MI). Colchicine is a well-established anti-inflammatory drug. The Canakinumab Anti-inflammatory

Thrombosis Outcomes Study (CANTOS) provided the first direct evidence that targeting inflammation reduces atherosclerotic CV events independent of lipid lowering. They found that canakinumab produced a dose-dependent and significant reduction in systemic inflammation, with high-sensitivity C-reactive protein levels decreasing more than placebo by 26, 37, and 41% in the 50, 150, and 300 mg groups, respectively (all  $P < 0.001$ ). Interleukin-6 levels showed similar reductions. In contrast, canakinumab did not lower LDL or HDL cholesterol and was associated with a small (4–5%) increase in TG, indicating that its benefits are independent of lipid modification.<sup>61</sup>

Multiple large-scale clinical trials (e.g. COLCOT and LoDoCo2) have demonstrated that long-term, low-dose colchicine significantly lowers the incidence of MACE in patients with CAD.<sup>62–65</sup> A small study of colchicine also showed that colchicine resulted in favourable effects on coronary plaque stabilization at optical coherence tomography in patients with acute coronary syndrome.<sup>65</sup> Analyses from COLCOT/LoDoCo2 indicate that the hazard reduction for adverse CV events appeared statistically significant in men as colchicine trials typically have low female enrolment and are underpowered to detect real sex differences, limiting definitive conclusions on differential efficacy by sex.<sup>64,65</sup>

Ziltivekimab is a novel monoclonal antibody targeting IL-6, a key cytokine in the inflammatory cascade linked to atherosclerosis and CV risk. Early-phase clinical trials have shown that ziltivekimab significantly reduces inflammatory biomarkers (such as C-reactive protein and fibrinogen) in patients with chronic kidney disease and elevated CV risk.<sup>65–67</sup> Ongoing large-scale trials are investigating its impact on MACE, particularly in high-risk populations. While most clinical trials of anti-inflammatory drugs, such as colchicine and IL-6 inhibitors (e.g. ziltivekimab), have not been exclusively conducted in women, the pathophysiological rationale for their use is strong, given the higher inflammatory burden in obese women with CVD.<sup>65</sup>

Evidence that anti-inflammatory CV therapies differ in efficacy by sex among patients with atherosclerosis is limited. Women remain underrepresented in major trials.<sup>64,65</sup> Sex-stratified analyses are often underpowered or observational, preventing clear conclusions. Therefore, clinicians should interpret current subgroup findings and encourage future trials designed with sex-specific analyses.

## Clinical and research implications

Evidence guiding the management of atherosclerosis in women remains limited due to underrepresentation of women in CV trials and inadequate stratification by sex-specific factors. Clinically, systematic assessment of central obesity and inflammatory burden is needed, particularly during high-risk life stages, such as pregnancy and menopause. Future research should prioritize sex-disaggregated analyses, with prespecified stratification by menopausal status, hormonal exposure, and inflammatory biomarkers, to support the development of evidence-based, sex-specific strategies for atherosclerosis prevention and management in women.

### Role of hormone replacement therapy

Hormone replacement therapy (HRT) plays a significant role in modulating CV risk in postmenopausal women, particularly those with obesity. The loss of oestrogen after menopause contributes to increased visceral fat accumulation, insulin resistance, and systemic inflammation—all of which accelerate the development of atherosclerosis.<sup>68,69</sup> Oestrogen has protective

**Table 1** Current indicated pharmacological agents for the management of obesity

Pharmacological agent	Benefit	Undesirable effect	Sex-specific efficacy
Semaglutide 2.4 mg	May be preferred over other approved obesity management medication Has glucoregulatory benefit and is approved for T2DM	Causes nausea and vomiting—gradual dose titration may mitigate it GLP-1 RAs have been associated with increased risk of pancreatitis and gallbladder diseases	Women treated with semaglutide 2.4 mg lost a mean of −9.6% body weight vs. −7.2% in men <sup>84</sup>
Liraglutide 3 mg	May be preferred over other approved obesity management medication Has glucoregulatory benefit and is approved for T2DM	Causes nausea and vomiting—gradual dose titration may mitigate it Liraglutide has been associated with increased risk of pancreatitis and gallbladder diseases	Men achieved greater weight loss and BMI reduction than women <sup>85</sup>
Tirzepatide 5, 10, and 15 mg	May be preferred over other approved obesity management medication Has glucoregulatory benefit and is approved for T2DM Neoplasia syndrome type 2 Monitor for depression or suicidal thoughts	Causes nausea, vomiting, and diarrhoea—potentially severe May cause acute pancreatitis and acute gallbladder disease Use with caution in patients with a history of pancreatitis or severe gastrointestinal diseases, including gastroparesis, due to limited studies Use with caution and monitor patients with a history of diabetic retinopathy Contraindication in patients with personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia	Females have higher odds of achieving very large reductions ( $\geq 20\%$ ), while males sometimes show faster early per cent loss within responder categories <sup>86</sup>
Phentermine–topiramate	Preferred in patients with comorbid migraines	Avoided in patients with a history of CVD and uncontrolled systemic hypertension Teratogenic—women of childbearing potential should use effective contraception Monitor BP and HR periodically with phentermine	Not reported
Naltrexone–bupropion	Considered in patients who are attempting smoking cessation and in patients with depression	Avoided in patients with seizure disorders and used with caution in patients at risk of seizures Not recommended in patients with severe renal impairment ( $<30$ mL/min) Should not be used concomitantly with opiate medications Contraindicated in patients with uncontrolled systemic hypertension Monitor BP and HR periodically, especially in the first 12 weeks of treatment	Literature does not report sex-stratified outcomes for the combination; the only supplied sex-stratified result is for naltrexone alone, favouring women <sup>87</sup>

Adapted from Grunvald et al., 2022<sup>2</sup>; Garvey et al., 2016<sup>45</sup>; Zepbound PI, 2022<sup>19</sup>; and Mounjaro EPAR, 2023.<sup>20</sup>

BP, blood pressure; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HR, heart rate; T2DM, Type 2 diabetes mellitus.

vascular properties. It enhances endothelial function, promotes vasodilation through NO synthesis, improves lipid profile by lowering LDL and raising HDL, and suppresses inflammatory signalling.<sup>70,71</sup> Hormone replacement therapy, especially when initiated early in the menopausal transition, can restore many of these benefits. In obese women, it helps reduce central

adiposity, improve glucose metabolism, and lower circulating markers of inflammation.<sup>72</sup>

The KEEPS and ELITE trials showed that early HRT initiation slowed carotid intima-media thickness progression and reduced inflammatory markers.<sup>73,74</sup> These effects collectively support its potential role in reducing CV risk. The formulation and route of

**Table 2** Newer pharmacological agents under investigation for the management of obesity

Pharmacological agent	Class	Administration route	Population	Sex-specific efficacy
<i>Phase III</i>				
Orforglipron	GLP-1 RA	Oral	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM (ATTAIN-1) or with T2DM (ATTAIN-2) Adults with T2DM and obesity or overweight at increased CV risk (ACHIEVE-4)	No significant sex-based efficacy differences reported so far
CagriSema (cagrilintide + semaglutide)	Amylin analogue + GLP-1 RA	SC	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM (REDEFINE 1) Adults with BMI $\geq$ 27 kg/m <sup>2</sup> with T2DM (REDEFINE 2) and adults with established CVD (REDEFINE 3)	Not reported
Survodutide	Dual glucagon receptor agonist and GLP1-RA	SC	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM (SYNCHRONIZE-1) or with T2DM (SYNCHRONIZE-2) or with established CVD (SYNCHRONIZE-CVOT)	Females showed larger reductions in bodyweight and waist circumference than males in a prespecified Phase 2 subgroup analysis of survodutide, but exact sex-specific numeric values are not reported <sup>91</sup>
Mazdutide	GIPR agonist and glucagon receptor agonist	SC	Adults with obesity (BMI $\geq$ 28 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 24 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM (GLORY-1)	Not reported
Retatrutide	GIPR agonist, glucagon receptor agonist, and GLP1-RA	SC	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM (TRIUMPH-1)	Not reported
<i>Phase II</i>				
Danuglipron	GLP1-RA	Oral	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) without T2DM	Not reported
Cagrilintide	Amylin receptor agonist	SC	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and hypertension or dyslipidaemia without T2DM	Not reported
PYY 1875	PYY RA	SC	Adults with BMI of 25–35 kg/m <sup>2</sup> without T2DM	Not reported
Efinopegdutide	Dual glucagon receptor agonist and GLP-1 RA	SC	Adults with severe obesity (BMI $\geq$ 35 to $\leq$ 50 kg/m <sup>2</sup> ) without T2DM	Not reported
Penvidutide	Dual glucagon receptor agonist and GLP1 RA	SC	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM	Not reported
Maridebart cagraglutide (AMG-133/MarTide)	GIPR antagonist and GLP1-RA	SC	Adults with obesity (BMI $\geq$ 30 kg/m <sup>2</sup> ) or overweight (BMI $\geq$ 27 kg/m <sup>2</sup> ) and $\geq$ 1 weight-related comorbidity without T2DM	Not reported

Continued

Table 2 Continued

Pharmacological agent	Class	Administration route	Population	Sex-specific efficacy
NNC0165-1875 + semaglutide	GLP1 RA + PYY RA	SC	27 kg/m <sup>2</sup> and ≥1 weight-related comorbidity with or without T2DM Adults with BMI of 30–45 kg/m <sup>2</sup> without T2DM	Not reported
Dapiglutide	GLP1 RA + GLP-2 RA	SC	Adults with BMI ≥ 30 kg/m <sup>2</sup> without T2DM	Not reported
Semaglutide + bimagrumab	GLP1 RA + activin type II receptor blocking biologic	Semaglutide: SC Bimagrumab: IV	Adults with obesity (BMI ≥ 30 kg/m <sup>2</sup> ) or overweight (BMI ≥ 27 kg/m <sup>2</sup> ) and ≥1 weight-related comorbidity without T2DM	Not reported
S-309309	MGAT2	Oral	Adults with obesity (BMI ≥ 30 kg/m <sup>2</sup> ) without T2DM	Not reported

BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; GIPR, glucose-dependent insulinotropic peptide receptor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GLP-2, glucagon-like peptide-2 receptor agonist; IV, intravenous; MGAT2, monoacylglycerol transferase; PYY, peptide YY; SC, subcutaneous; T2DM, Type 2 diabetes mellitus.

administration matter. Transdermal oestrogen is particularly beneficial for women with higher BMI, as it avoids first-pass hepatic metabolism and is associated with a lower risk of thromboembolic events compared to oral oestrogen.<sup>75</sup> When appropriately tailored, HRT can be safely integrated into the CV risk management of postmenopausal women, particularly those with early metabolic dysfunction. Timing is also critical. Starting HRT within 10 years of menopause or before age 60 is associated with more favourable CV outcomes than initiating it later.<sup>76</sup>

Though not a universal solution, HRT offers an underused opportunity to address the intertwined roles of hormonal decline, obesity, and inflammation in the development of atherosclerosis.<sup>77</sup> It is important to note that HRT may carry potential risks, including an increased incidence of thromboembolic events, strokes, and select cancers (e.g. breast and endometrial).<sup>78,79</sup> Treatment regimens should be individually tailored, with careful monitoring of therapy duration and patient health status to minimize these complications.

## Antiobesity therapies

Individuals who are overweight or obese are at an increased risk of CV morbidity and mortality.<sup>80</sup> The concepts of 'obesity paradox' and 'metabolically healthy obesity', which have suggested a more favourable prognosis in certain subgroups, have been increasingly questioned considering recent evidence.<sup>81</sup> Large epidemiological studies have demonstrated a nonlinear relationship between BMI and total mortality.<sup>82</sup> For example, the HUNT study and the UK Biobank reported that every 1 unit increase in BMI above 25 kg/m<sup>2</sup> was associated with a 5 and 9% increase in total mortality, respectively.<sup>82</sup> This excess risk is primarily driven by CVD death, particularly due to MI and stroke.<sup>81,82</sup>

Several pharmacological options are currently approved for the long-term management of obesity (Figure 3).<sup>83</sup> Earlier agents, such as phentermine-topiramate, naltrexone-bupropion, and orlistat, achieved only modest weight loss and showed no consistent CV benefits. More recently, newer therapies, including liraglutide (3 mg), semaglutide (2.4 mg), and tirzepatide (5, 10, or 15 mg), have demonstrated a substantially higher weight loss along with evidence of CV benefit.<sup>83</sup> Selection among these agents should be based on costs and availability as primary determinants while also considering patients' clinical profile, individual needs, and risk factors (Table 1).

These three newer agents, liraglutide, semaglutide, and tirzepatide, have demonstrated sustained and superior weight reduction in randomized clinical trials (RCTs). A recent meta-analysis on liraglutide 3 mg reported significant weight loss compared to placebo, with a higher likelihood of achieving at least 5 and 10% weight loss. In the Semaglutide Treatment Effect in People with Obesity (STEP) programme, semaglutide 2.4 mg plus lifestyle intervention achieved greater weight reduction as well as weight-loss targets compared with lifestyle intervention alone. In the STEP 1 trial, nondiabetic individuals receiving semaglutide 2.4 mg plus lifestyle intervention achieved a 14.9% body weight reduction from baseline, vs.2.4% in the lifestyle intervention arm, over 68 weeks.

Tirzepatide, a novel first-in-class dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), has been evaluated at doses of 5, 10, and 15 mg, respectively in the SURMOUNT-1 trial. This trial included patients with obesity or overweight and at least one weight-related complication, excluding diabetes. Participants achieved mean weight reductions of 11.9, 16.4, and 17.8% for 5, 10, and 15 mg doses, respectively, at 72 weeks.<sup>88</sup>

Ongoing RCTs are evaluating the potential CV benefits and the safety of this dual agonist. Several studies have shown that weight loss can reduce MACE. The Look AHEAD trial highlighted the role of lifestyle interventions in improving CV outcomes.<sup>46</sup> Notably, clinical benefits of semaglutide appeared early during follow-up and are only partly attributable to weight loss with GLP-1 RA modulation. Concerning tirzepatide, the ongoing RCT SURMOUNT-MMO trial investigates its potential and the magnitude of CV benefit in adults with obesity and CVD.<sup>89</sup> Retrospective data from a large US Medicare database (>85 000 obese individuals) suggested that semaglutide and tirzepatide may lead to a reduction in CVD outcomes, particularly heart failure (HF), atrial fibrillation (AF), arrhythmia, and peripheral vascular disease—findings that warrant confirmation in prospective studies.<sup>90</sup> In this way, in a meta-analysis of 10 trials, including patients with AF undergoing catheter ablation, weight loss was associated with a greater reduction in recurrent AF after ablation. Newer pharmacological agents are under investigation and will add to the current body of evidence (Table 2). Evidence on sex-specific differences in the efficacy of anti-inflammatory CV therapies in patients with atherosclerosis is summarized in Tables 1 and 2.

## Surgical interventions

When lifestyle changes and pharmacological treatments fail to provide adequate results, bariatric surgery should be considered. According to current guidelines<sup>92</sup> and recent review of global practices,<sup>93</sup> the benefits of metabolic and bariatric surgery (MBS), especially when combined with multidisciplinary team (MDT) management, are quantified. However, there remains a need for additional RCTs, particularly in<sup>68–70</sup> patients who are borderline candidates for MBS.<sup>94</sup> Although MBS has been associated with reversal of cardiac remodelling—as soon as 12 months postsurgery and independent of BMI reduction<sup>95</sup>—long-term benefits appear limited by suboptimal control of BMI and BP at 5-year follow-up.<sup>96</sup> Metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatohepatitis (MASH) are also highly prevalent in individuals with severe obesity. Unfortunately, no anthropometric measurements or laboratory tests have proven reliable in predicting the presence or severity of either condition. Once MAFLD is diagnosed, research from Canadian investigators has shown that women may be at higher risk of progressing to advanced stages of liver fibrosis.<sup>97</sup>

Metabolic and bariatric surgery is associated with significant decreases in the risk of Type 2 diabetes mellitus (T2DM) and CVD,<sup>98</sup> MACE,<sup>99,100</sup> new-onset HF, and MI,<sup>101</sup> as well as all-cause mortality<sup>101,102</sup>—particularly in patients with T2DM.<sup>103</sup> A recent 15-year follow-up study showed a substantial reduction in the progression from prediabetes to T2DM, particularly in women. The study included a cohort composed of 83% women and demonstrated that Roux-en-Y gastric bypass (RYGB) was more effective than sleeve gastrectomy (SG) in preventing diabetes progression.<sup>104</sup> Importantly, women constituted at least 60% of the populations in most of the referenced MBS studies. Even among paediatric patients—43% of whom were female—MBS has been shown to significantly reduce morbidity in young adulthood.<sup>105</sup>

Two additional aspects of women's CV health that have been positively influenced by MBS are reproductive and mental health. Nearly half of women with PCOS experience clinically significant anxiety. Although the prevalence of PCOS was low during the 4-year follow-up period after MBS, women with PCOS were more likely to report migraines, disinhibited eating

behaviours, and anxiety, despite achieving comparable BMI outcomes to those without PCOS.<sup>106</sup> Moreover, in a predominantly female cohort, a history of anxiety among patients undergoing MBS was associated with nearly a three-fold increase in the odds of developing hypertension<sup>107</sup>—a key contributor to adverse long-term CV outcomes.

## Conclusion and recommendations

Obesity and chronic inflammation play an important role and effect in the development of atherosclerosis in women. These effects are exaggerated by female-specific factors across different stages of life, yet current management strategies are still largely based on men-dominant evidence. Greater attention to body fat distribution, inflammatory burden, and women-specific risk factors is needed in everyday clinical practice. Improving research design and clinical care with a stronger focus on women is essential to achieve better CV outcomes.

## Recommendations:

### (1) Screening and risk assessment

- Reproductive history documentation, including age at menarche/menopause, parity, pregnancy complications (pre-eclampsia, gestational diabetes, preterm delivery), PCOS, and infertility
- Measurement of BMI and waist circumference or waist-to-hip ratio at baseline and annually
- Measurement of cardiometabolic panels, including BP, fasting lipids, fasting glucose or glycosylated hemoglobin A1c, and smoking status
- Screening for autoimmune and inflammatory conditions, such as CV risk enhancers

### (2) Weight management intervention

- Setting individualized, measurable short-term goals that improve cardiometabolic markers and functions, such as dietary counselling and calorie awareness
- Integration of social support and multidisciplinary teams
- Reservation of pharmacotherapy or bariatric referral for women who do not achieve meaningful improvement with lifestyle measures
- Coordination with obesity specialists and considering impacts on reproductive plans
- Documentation of weight management goals and tracking progress at each visit

### (3) Structured PA programmes

- Prescribe combined aerobic and resistance training tailored to baseline fitness and comorbidities.
- Emphasize progressive increases with moderate-to-vigorous activity adapted to individual capacity.
- Set concrete weekly activity goals and review barriers at follow-up visits.

#### Women-specific considerations

- Account for life stage factors: pregnancy, postpartum recovery, menopausal symptoms, and musculoskeletal issues.
- Address caregiving constraints and time barriers in programme design.

### (4) Pregnancy-specific considerations

#### Prepregnancy screening

- Evaluate traditional risk factors plus prior pregnancy complications.
- Optimize hypertension, lipids, diabetes, and weight before conception.

- Refer to cardio-obstetrics for women with high baseline risk or prior adverse pregnancy outcomes.

#### **During pregnancy**

- Emphasize healthy gestational weight gain tailored to pre-pregnancy BMI.
- Prioritize nutrition, PA, and glycaemic control rather than weight loss.
- Avoid weight-loss pharmacotherapies during pregnancy.

#### **Postpartum follow-up**

- Arrange early cardiometabolic reassessment for women with hypertensive disorders, gestational diabetes, or substantial gestational weight gain.
- Ensure secure handoff from obstetric to primary/cardiology care with documented CV risk reduction plan.
- Continue surveillance into midlife with regular monitoring.

#### **(5) Menopause management**

- Perform CV risk assessment at menopause onset.
- Document menopausal status and associated symptoms in CV risk profile.

#### **(6) Inflammation management**

- Recommend eating vegetables, whole grains, healthy fats, and lean proteins.
- Manage autoimmune and systemic inflammatory disorders to reduce vascular risk.
- Coordinate with rheumatology or specialty care for complex inflammatory conditions.

#### **(7) Follow-up and monitoring**

- Baseline and annual reassessment for women with risk factors
- More frequent visits following acute events or medication changes

**Conflict of interest:** None declared.

## **Funding**

This manuscript did not receive any funding.

## **References**

1. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;**140**: e596-e646.
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Böck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglul L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wannier C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227-3337.
3. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;**377**:13-27.
4. Yao Z, Dardari ZA, Razavi AC, Silver N, Jelwan Y, Erhabor J, Burka S, Blaha MJ. Prevalence of clinical obesity versus BMI-defined obesity among US adults: a cohort study. *Lancet Diabetes Endocrinol* 2025;**13**:647-649.
5. Battineni G, Sagaro GG, Chintalapudi N, Amenta F, Tomassoni D, Tayebati SK. Impact of obesity-induced inflammation on cardiovascular diseases (CVD). *Int J Mol Sci* 2021;**22**:4798.
6. Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: role of vascular injury and smooth muscle cell proliferation. *J Am Coll Cardiol* 1990;**15**:1667-1687.
7. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res* 2016;**118**:535-546.
8. Gimbrone MA, García-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* 2016;**118**:620-636.
9. Koskinas KC, Van Craenenbroeck EM, Antoniadou C, Blüher M, Gorter TM, Hanssen H, Marx N, McDonagh TA, Mingrone G, Rosengren A, Prescott EB; ESC Scientific Document Group. Obesity and cardiovascular disease: an ESC clinical consensus statement. *Eur Heart J* 2024;**45**:4063-4098.
10. Bays H. Central obesity as a clinical marker of adiposopathy; increased visceral adiposity as a surrogate marker for global fat dysfunction. *Curr Opin Endocrinol Diabetes Obes* 2014;**21**:345-351.
11. Ruggiero AD, Key CCC, Kavanagh K. Adipose tissue macrophage polarization in healthy and unhealthy obesity. *Front Nutr* 2021;**8**:625331.
12. Lee H, Rhee TM, Choi JM, Choi SY, Kim DW. The close link between obesity and cardiovascular disease. *Endocrinol Metab Clin North Am* 2025;**54**: 175-192.
13. Lamers D, Famulla S, Wronkowitz N, Hartwig S, Lehr S, Ouwens DM, Eckardt K, Kaufman JM, Ryden M, Müller S, Hanisch FG, Ruige J, Arner P, Sell H, Eckel J. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes* 2011;**60**:1917-1925.
14. Unamuno X, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest* 2018;**48**:e12997.
15. Manrique-Acevedo C, Chinnakotla B, Padilla J, Martinez-Lemus LA, Gozal D. Obesity and cardiovascular disease in women. *Int J Obes* 2020;**44**: 1210-1226.
16. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, Wians FH Jr, Grundy SM, de Lemos JA. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol* 2005;**46**:464-469.
17. Lew J, Sanghavi M, Ayers CR, McGuire DK, Omland T, Atzler D, Gore MO, Neeland I, Berry JD, Khera A, Rohatgi A, de Lemos JA. Sex-based differences in cardiometabolic biomarkers. *Circulation* 2017;**135**:544-555.
18. Yanes LL, Romero DG, Moulana M, Lima R, Davis DD, Zhang H, Lockhart R, Racusen LC, Reckelhoff JF. Cardiovascular-renal and metabolic characterization of a rat model of polycystic ovary syndrome. *Gen Med* 2011;**8**:103-115.
19. Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, Chandler WL, Boyko EJ, Brunzell JD. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. *J Clin Endocrinol Metab* 2009;**94**:1104-1110.
20. Yanes Cardozo LL, Romero DG, Reckelhoff JF. Cardiometabolic features of polycystic ovary syndrome: role of androgens. *Physiology* 2017;**32**:357-366.
21. Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos GP. Pathophysiology and types of dyslipidemia in PCOS. *Trends Endocrinol Metab* 2007;**18**:280-285.
22. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. *Fertil Steril* 2011;**95**: 1073-1079.e11.
23. Diamanti-Kandarakis E, Mitrakou A, Raptis S, Tolis G, Duleba AJ. The effect of a pure antiandrogen receptor blocker, flutamide, on the lipid profile in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998;**83**:2699-2705.
24. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012; **32**:2045-2051.
25. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L, Lewis EF. Atherosclerosis. *Nat Rev Dis Primers* 2019;**5**:56.
26. Marchandot B, Curtiaud A, Matsushita K, Trimaille A, Host A, Faller E, Garbin O, Akladios C, Jesel L, Morel O. Endometriosis and cardiovascular disease. *Eur Heart J Open* 2022;**2**:oeac001.
27. Marquardt RM, Kim TH, Shin JH, Jeong JW. Progesterone and estrogen signaling in the endometrium: what goes wrong in endometriosis? *Int J Mol Sci* 2019;**20**:3822.
28. Capobianco A. Endometriosis, a disease of the macrophage. *Front Immunol* 2013;**4**:9.
29. Santoro L, D'Onofrio F, Campo S, Ferraro PM, Tondi P, Campo V, Flex A, Gasbarrini A, Santoliquido A. Endothelial dysfunction but not increased carotid intima-media thickness in young European women with endometriosis. *Hum Reprod* 2012;**27**:1320-1326.
30. Kinugasa S, Shinohara K, Wakatsuki A. Increased asymmetric dimethylarginine and enhanced inflammation are associated with impaired vascular reactivity in women with endometriosis. *Atherosclerosis* 2011;**219**:784-788.
31. Tani A, Yamamoto S, Maegawa M, Kunimi K, Matsui S, Keyama K, Kato T, Uemura H, Kuwahara A, Matsuzaki T, Yasui T, Kamada M, Soeki T, Sata M, Irahara M. Arterial stiffness is increased in young women with endometriosis. *J Obstet Gynaecol (Lahore)* 2015;**35**:711-715.
32. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev* 2012;**33**:981-1030.

33. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2012;**18**:618–637.
34. Lephart ED, Naftolin F. Menopause and the skin: old favorites and new innovations in cosmeceuticals for estrogen-deficient skin. *Dermatol Ther (Heidelb)* 2021;**11**:53–69.
35. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. *Pharmacol Rev* 2008;**60**:210–241.
36. Menazza S, Murphy E. The expanding complexity of estrogen receptor signaling in the cardiovascular system. *Circ Res* 2016;**118**:994–1007.
37. Turgeon JL, Carr MC, Maki PM, Mendelsohn ME, Wise PM. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: insights from basic science and clinical studies. *Endocr Rev* 2006;**27**:575–605.
38. Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. *Cell Immunol* 2015;**294**:63–69.
39. Arnal JF, Douin-Echinard V, Brouchet L, Tremollières F, Laurell H, Lenfant F, Gadeau AP, Guery JC, Gourdy P. Understanding the oestrogen action in experimental and clinical atherosclerosis. *Fundam Clin Pharmacol* 2006;**20**:539–548.
40. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol* 2009;**54**:2366–2373.
41. Thurston RC, Karvonen-Gutierrez CA, Derby CA, El Khoudary SR, Kravitz HM, Manson JE. Menopause versus chronologic aging: their roles in women's health. *Menopause* 2018;**25**:849–854.
42. Chedraui P, Pérez-López FR. Metabolic syndrome during female midlife: what are the risks? *Climacteric* 2019;**22**:127–132.
43. Pfaller B, Siu SC, D'Souza R, Wichert-Schmitt B, Kumar Nair GK, Haberer K, Maxwell C, Silversides CK. Impact of obesity on outcomes of pregnancy in women with heart disease. *J Am Coll Cardiol* 2021;**77**:1317–1326.
44. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;**143**:e984–e1010.
45. Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *Circulation* 2014;**129**:S102–S138.
46. Look AHEAD Research Group; Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, Foreyt J, Foster G, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jeffery RW, Johnson KC, Kitabchi AE, Knowler WC, Kriska A, Lang W, Lewis CE, Montez MG, Nathan DM, Neiberg RH, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Redmon B, Regensteiner J, Rejeski J, Ribisl PM, Safford M, Stewart K, Trencle D, Wadden TA, Wing RR, Yanovski SZ. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;**4**:913–921.
47. Look AHEAD Research Group; Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;**369**:145–154.
48. Behrooz L, Lenneman CG, Hamburg NM. Emerging medical therapies for the treatment of obesity in women with cardiovascular diseases. *Curr Cardiol Rep* 2023;**25**:1475–1488.
49. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, Nadolsky K, Pessah-Pollack R, Plodkowski R; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American association of clinical endocrinologists and American college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract* 2016;**22**:1–203.
50. Muscogiuri G, El Ghoch M, Colao A, Hassapidou M, Yumuk V, Busetto L. European guidelines for obesity management in adults with a very low-calorie ketogenic diet: a systematic review and meta-analysis. *Obes Facts* 2021;**14**:222–245.
51. Mielke GI, Bailey TG, Burton NW, Brown WJ. Participation in sports/recreational activities and incidence of hypertension, diabetes, and obesity in adults. *Scand J Med Sci Sports* 2020;**30**:2390–2398.
52. Mielke GI, Ding D, Keating SE, Nunes BP, Brady R, Brown WJ. Physical activity volume, frequency, and intensity: associations with hypertension and obesity over 21 years in Australian women. *J Sport Health Sci* 2024;**13**:631–641.
53. Hernández-Reyes A, Cámara-Martos F, Molina-Luque R, Romero-Saldaña M, Molina-Recio G, Moreno-Rojas R. Changes in body composition with a hypocaloric diet combined with sedentary, moderate and high-intense physical activity: a randomized controlled trial. *BMC Womens Health* 2019;**19**:167.
54. Pepe RB, Coelho GSMA, Miguel FDS, Gualassi AC, Sarvas MM, Cercato C, Mancini MC, de Melo ME. Mindful eating for weight loss in women with obesity: a randomised controlled trial. *Br J Nutr* 2023;**130**:911–920.
55. van Dammen L, Wekker V, de Rooij SR, Groen H, Hoek A, Roseboom TJ. A systematic review and meta-analysis of lifestyle interventions in women of reproductive age with overweight or obesity: the effects on symptoms of depression and anxiety. *Obes Rev* 2018;**19**:1679–1687.
56. Giel KE, Bulik CM, Fernandez-Aranda F, Hay P, Keski-Rahkonen A, Schag K, Schmidt U, Zipfel S. Binge eating disorder. *Nat Rev Dis Primers* 2022;**8**:16.
57. Hansel B, Giral P, Gambotti L, Lafourcade A, Peres G, Filipecki C, Kadouch D, Hartemann A, Oppert JM, Bruckert E, Marre M, Bruneel A, Duchene E, Roussel R. A fully automated web-based program improves lifestyle habits and HbA1c in patients with type 2 diabetes and abdominal obesity: randomized trial of patient E-coaching nutritional support (the ANODE study). *J Med Internet Res* 2017;**19**:e360.
58. Cotie LM, Prince SA, Elliott CG, Ziss MC, McDonnell LA, Mullen KA, Hiremath S, Pipe AL, Reid RD, Reed JL. The effectiveness of eHealth interventions on physical activity and measures of obesity among working-age women: a systematic review and meta-analysis. *Obes Rev* 2018;**19**:1340–1358.
59. Ellulu MS, Patimah I, Khaza'i H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017;**4**:851–863.
60. Paixão de Gois B, Figueiredo N, Soares Lopes KL, Esselin de Melo PR, Horst MA, Molin Netto BD, Oyama LM, Lima GC, Dâmaso AR, Mota JF, Corgosinho FC. The impact of the obesity onset on the inflammatory and glycemic profile of women with severe obesity. *Surg Obes Relat Dis* 2024;**20**:976–983.
61. Baylis RA, Gomez D, Mallat Z, Pasterkamp G, Owens GK. The CANTOS trial. *Arterioscler Thromb Vasc Biol* 2017;**37**:e174–e177.
62. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, Guerrero M, Kunadian V, Lam CSP, Maas AHEM, Mihailidou AS, Olczanecka A, Poole JE, Saldarriaga C, Saw J, Zühlke L, Mehran R. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *The Lancet* 2021;**397**:2385–2438.
63. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koeng W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhoads D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;**381**:2497–2505.
64. Nidorf SM, Fiolet ATL, Eikelboom JW, Schut A, Opstal TSJ, Bax WA, Budgeon CA, Tijssen JGP, Mosterd A, Cornel JH, Thompson PL; LoDoCo2 Investigators. The effect of low-dose colchicine in patients with stable coronary artery disease: the LoDoCo2 trial rationale, design, and baseline characteristics. *Am Heart J* 2019;**218**:46–56.
65. Yu M, Yang Y, Dong SL, Zhao C, Yang F, Yuan YF, Liao YH, He SL, Liu K, Wei F, Jia HB, Yu B, Cheng X. Effect of colchicine on coronary plaque stability in acute coronary syndrome as assessed by optical coherence tomography: the COLOCT randomized clinical trial. *Circulation* 2024;**150**:981–993.
66. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, Lo L, Kling D, Pergola P, Raj D, Libby P, Davidson M; RESCUE Investigators. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *The Lancet* 2021;**397**:2060–2069.
67. Wada Y, Jensen C, Meyer ASP, Zonoozi AAM, Honda H. Efficacy and safety of interleukin-6 inhibition with ziltivekimab in patients at high risk of atherosclerotic events in Japan (RESCUE-2): a randomized, double-blind, placebo-controlled, phase 2 trial. *J Cardiol* 2023;**82**:279–285.
68. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;**88**:2404–2411.
69. Lizzano F, Guzmán G. Estrogen deficiency and the origin of obesity during menopause. *Biomed Res Int* 2014;**2014**:1–11.

70. Sudhir K, Chou TM, Mullen WL, Hausmann D, Collins P, Yock PG, Chatterjee K. Mechanisms of estrogen-induced vasodilation: in vivo studies in canine coronary conductance and resistance arteries. *J Am Coll Cardiol* 1995;**26**: 807–814.
71. Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis* 1993;**98**:83–90.
72. Salpeter SR, Walsh JME, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab* 2006;**8**:538–554.
73. Harman SM, Brinton EA, Cedars M, Lobo R, Manson JE, Merriam GR, Miller VM, Naftolin F, Santoro N. KEEPS: the Kronos Early Estrogen Prevention Study. *Climacteric* 2005;**8**:3–12.
74. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M, Dustin L, Kono N, Stanczyk FZ, Selzer RH, Azen SP; ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;**374**:1221–1231.
75. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women. *Circulation* 2007;**115**:840–845.
76. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. *JAMA* 2013;**310**:1353.
77. Maas AHEM, Rosano G, Cifkova R, Chieffo A, van Dijken D, Hamoda H, Kunadian V, Laan E, Lambrinouadaki I, Maclaran K, Panay N, Stevenson JC, van Trotsenburg M, Collins P. Cardiovascular health after menopause: transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. *Eur Heart J* 2021;**42**:967–984.
78. Sare GM, Gray LJ, Bath PMW. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. *Eur Heart J* 2008;**29**:2031–2041.
79. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002;**288**:321–333.
80. Burki T. European commission classifies obesity as a chronic disease. *Lancet Diabetes Endocrinol* 2021;**9**:418.
81. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, Sattar N, Sun MC, Wittert G, Pinto FJ, Wilding JPH. Obesity and cardiovascular disease: mechanistic insights and management strategies. A joint position paper by the World Heart Federation and World Obesity Federation. *Eur J Prev Cardiol* 2022;**29**:2218–2237.
82. Sun YQ, Burgess S, Staley JR, Wood AM, Bell S, Kaptoge SK, Guo Q, Bolton TR, Mason AM, Butterworth AS, Di Angelantonio E, Vie GÅ, Bjørngaard JH, Kinge JM, Chen Y, Mai XM. Body mass index and all cause mortality in HUNT and UK Biobank studies: linear and non-linear Mendelian randomisation analyses. *BMJ* 2019;**1042**.
83. Gjermani E, Kirstein AS, Kolbig F, Kirchhof M, Bundalian L, Katzmann JL, Laufs U, Blüher M, Garten A, Le Duc D. Obesity—an update on the basic pathophysiology and review of recent therapeutic advances. *Biomolecules* 2021;**11**:1426.
84. Levy M, Telis N, McEwen L, Schiabor Barrett K, Bolze A, White S, Stoller D, Chapman C, Chahal CA, Judge D, Olson D. Abstract 4142226: quantifying the influence of baseline body weight on sex differences in semaglutide-associated weight loss. *Circulation* 2024;**150**:A4142226.
85. Milani I, Guarisco G, Chinucci M, Gaita C, Leonetti F, Capoccia D. Sex-differences in response to treatment with liraglutide 3.0 mg. *J Clin Med* 2024;**13**: 3369. doi: 10.3390/jcm13123369.
86. Look M, Dunn JP, Kushner RF, Cao D, Harris C, Gibble TH, Stefanski A, Griffin R. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight. *Diabetes Obes Metab* 2025;**27**:2720–2729.
87. Vangoitsenhoven R, Yskout M, Hoste J, Steenackers N, Simoens C, Mattelaer N, Deleus E, Lannoo M, Mertens A, Vanderschueren B. Real world efficacy of naltrexone/bupropion for weight management in obesity and after bariatric surgery. *Int J Obes* 2025;**49**:2102–2109.
88. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;**387**:205–216.
89. Lam CSP, Rodriguez A, Aminian A, Ferrannini E, Heerspink HJL, Jastreboff AM, Laffin LJ, Pandey A, Ray KK, Ridker PM, Sanyal AJ, Yki-Jarvinen H, Mason D, Strzelecki M, Bartee AK, Cui C, Hurt K, Linetzky B, Bunck MC, Nissen SE. Tirzepatide for reduction of morbidity and mortality in adults with obesity: rationale and design of the SURMOUNT-MMO trial. *Obesity (Silver Spring)* 2025;**33**:1645–1656.
90. Baser O, Samayoa G, Rodchenko K, Isenman L, Baser E, Yapar N. The association between weight loss medications and cardiovascular complications. *Obesity* 2024;**32**:1401–1409.
91. le Roux CW, Steen O, Lucas KJ, Startseva E, Unsel A, Hussain SA, Hennige AM. Subgroup analysis by sex and baseline BMI in people with a BMI  $\geq 27$  kg/m<sup>2</sup> in the phase 2 trial of survodutide, a glucagon/GLP-1 receptor dual agonist. *Diabetes Obes Metab* 2025;**27**:1773–1782.
92. Eisenberg D, Shikora SA, Aarts E, Aminian A, Angrisani L, Cohen RV, de Luca M, Faria SL, Goodpaster KPS, Haddad A, Himpens JM, Kow L, Kurian M, Loi K, Mahawar K, Nimeri A, O'Kane M, Papasavas PK, Ponce J, Pratt JSA, Rogers AM, Steele KE, Suter M, Kothari SN. 2022 American Society of Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) indications for metabolic and bariatric surgery. *Obes Surg* 2023;**33**:3–14.
93. De Luca M, Shikora S, Eisenberg D, Angrisani L, Parmar C, Alqahtani A, Aminian A, Aarts E, Brown W, Cohen RV, Di Lorenzo N, Faria SL, Goodpaster KPS, Haddad A, Herrera M, Rosenthal R, Himpens J, Iossa A, Kermansaravi M, Kow L, Kurian M, Chiappetta S, LaMasters T, Mahawar K, Merola G, Nimeri A, O'Kane M, Papasavas P, Piatto G, Ponce J, Prager G, Pratt JSA, Rogers AM, Salminen P, Steele KE, Suter M, Tolone S, Vitiello A, Zappa M, Kothari SN. Scientific evidence for the updated guidelines on indications for metabolic and bariatric surgery (IFSO/ASMBS). *Obes Surg* 2024;**34**:3963–4096.
94. Ayesh H, Nasser SA, Ferdinand KC, Carranza Leon BG. Sex-specific factors influencing obesity in women: bridging the gap between science and clinical practice. *Circ Res* 2025;**136**:594–605.
95. Rozandal V, Mishima R, Garcia M, Berdeja N, Vambakianos PNM, Valdez M, Catellanos V, Lascano FM, Esquivel CM. Cardiac remodeling after bariatric surgery beyond weight loss: a dose-response analysis. *Obes Surg* 2025;**35**: 1638–1648.
96. Grymyr LMD, Nadirpour S, Gerdtz E, Nedrebø BG, Matre K, Cramariuc D. Long-term trajectories of left heart geometry, mechanics, and oxygen demand after bariatric surgery. *Circ Heart Fail* 2025;**18**:e012367.
97. Lajeunesse-Trempe F, Dugas S, Maltais-Payette I, Tremblay ÈJ, Piché ME, Dimitriadis GK, Lafortune A, Marceau S, Biertho L, Tchernof A. Anthropometric indices and metabolic dysfunction-associated fatty liver disease in males and females living with severe obesity. *Can J Gastroenterol Hepatol* 2025;**2025**:5545227.
98. Rubio-Almanza M, Cámara-Gómez R, Hervás-Marín D, Ponce-Marco JL, Merino-Torres JF. Cardiovascular risk reduction over time in patients with diabetes or pre-diabetes undergoing bariatric surgery: data from a single-center retrospective observational study. *BMC Endocr Disord* 2018;**18**:90.
99. Aminian A, Zajichek A, Arterburn DE, Wolski KE, Brethauer SA, Schauer PR, Kattan MW, Nissen SE. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. *JAMA* 2019;**322**:1271.
100. Doumouras AG, Wong JA, Paterson JM, Lee Y, Sivapathasundaram B, Tarride JE, Thabane L, Hong D, Yusuf S, Anvari M. Bariatric surgery and cardiovascular outcomes in patients with obesity and cardiovascular disease. *Circulation* 2021;**143**:1468–1480.
101. Mentias A, Aminian A, Youssef D, Pandey A, Menon V, Cho L, Nissen SE, Desai MY. Long-term cardiovascular outcomes after bariatric surgery in the Medicare population. *J Am Coll Cardiol* 2022;**79**:1429–1437.
102. Sonaiya S, Zevallos A, Adrales G. Long-term cardiovascular disease outcomes following bariatric surgery. *J Surg Res* 2024;**304**:225–231.
103. Syn NL, Cummings DE, Wang LZ, Lin DJ, Zhao JJ, Loh M, Koh ZJ, Chew CA, Loo YE, Tai BC, Kim G, So JB, Kaplan LM, Dixon JB, Shabbir A. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174772 participants. *The Lancet* 2021;**397**: 1830–1841.

104. Pina L, Nguyen-Lee J, Wood GC, Furey MJ, Petrick AT, Parker DM. Bariatric surgery significantly reduces progression from prediabetes to diabetes compared with the general population: 15-year single-institution data. *Surg Obes Relat Dis* 2025;21:689–694.
105. Putri RR, Danielsson P, Ekström N, Ericsson Å, Lindberg L, Marcus C, Hagman E. Effect of pediatric obesity treatment on long-term health. *JAMA Pediatr* 2025;179:302.
106. Haley E, Coyne P, Carlin A, Santarossa S, Loree A, Braciszewski J, Brescacin C, Matero L. Characteristics and clinical outcomes of women with polycystic ovary syndrome after bariatric surgery. *Obes Surg* 2025;35:419–425.
107. Tajeu GS, Wu J, Tewksbury C, Spitzer JC, Rubin DJ, Gadegbeku CA, Soans R, Allison KC, Sarwer DB. Association of psychiatric history with hypertension among adults who present for metabolic and bariatric surgery. *Surg Obes Relat Dis* 2025;21:279–287.