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Evidence and mechanisms linking obesity to cardiovascular disease

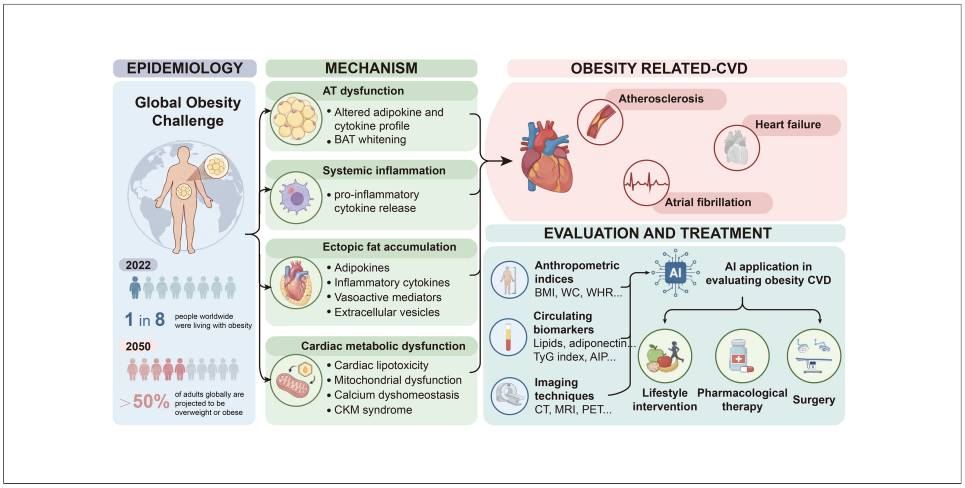
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Abstract

Obesity has emerged as a global public health crisis, with its prevalence increasing dramatically over recent decades. Accumulating evidence identifies obesity as a major independent risk factor for the development and progression of cardiovascular disease (CVD). This review comprehensively summarizes current evidence on the association between obesity and phenotype-specific CVD, and discusses the underlying pathophysiological mechanisms, including adipose tissue dysfunction, systemic inflammation, ectopic fat accumulation, and cardiac metabolic dysfunction. We also examine key indicators for assessing obesity-related cardiovascular risk and discuss emerging applications of artificial intelligence in risk prediction and personalized management. Finally, we summarize current evidence-based therapeutic approaches to provide guidance for clinicians, researchers, and public health policymakers.

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INTRODUCTION

Obesity is a chronic metabolic disorder characterized by excessive or abnormal accumulation of adipose tissue (AT), which is associated with an increased risk of various metabolic complications and chronic diseases. According to current World Health Organization (WHO) guidelines, overweight and obesity in adults are defined according to body mass index (BMI), with BMI ≥ 25 kg/m² classified as overweight and BMI ≥ 30 kg/m² classified as obesity[1]. Driven by factors including increased caloric intake and reduced physical activity, the prevalence of obesity has risen steadily in recent decades[2]. By 2022, one in eight people worldwide were living with obesity[1], with projections indicating that by 2050, more than half of adults worldwide will be overweight or obese[3]. Obesity therefore represents an escalating global public health concern. Although BMI remains the most widely used measure for obesity classification because of its simplicity and accessibility, recent studies have suggested that BMI may not fully capture body fat distribution or obesity-related health risks. Accordingly, alternative anthropometric measures, including the body roundness index (BRI), waist circumference (WC), and waist-to-hip ratio (WHR), have attracted increasing attention for the assessment of obesity and obesity-related risk[4-6].

The association between obesity and cardiovascular disease (CVD) is well established[7-9]. More than two-thirds of deaths attributable to high BMI are due to CVD[7], and obesity is associated with substantially increased risks of ischemic heart disease, heart failure (HF), and stroke[10]. Elucidating the complex interplay between obesity and CVD, together with developing targeted preventive and therapeutic strategies, is therefore essential to reducing the global burden of CVD.

This review synthesizes current evidence on obesity-related CVD across four key domains: (1) epidemiological associations between obesity and CVD; (2) the pathophysiological mechanisms underlying obesity-related CVD; (3) conventional and artificial intelligence (AI)-based approaches to cardiovascular risk assessment in obesity; and (4) current and emerging therapeutic strategies for obesity-related CVD.

EPIDEMIOLOGICAL EVIDENCE FOR OBESITY-RELATED CVD

A robust dose-response association between adiposity and CVD risk has been well established in large-scale cohorts[11-13]. In a prospective cohort study of 360,855 participants from the China Kadoorie Biobank, early-adulthood BMI showed a monotonic dose-response association with incident CVD. Compared with individuals with an early-adulthood BMI of 20.5-22.4 kg/m², those with a BMI ≥ 30 kg/m² had a 58% higher risk of incident CVD (HR = 1.58, 95%CI: 1.42-1.75)[12]. Evidence from an umbrella review and meta-analysis of more than 500 cohort studies further supported the association between adiposity and CVD risk. Across cardiovascular outcomes, each 5 kg/m² increment in BMI was associated with a 10%-49% increase in cardiovascular event risk[10]. Notably, the association between elevated BMI and CVD risk may be stronger in East and Southeast Asian populations than in Western populations. In a pooled analysis of 97 prospective cohorts involving approximately 1.8 million participants, each 5 kg/m² increase in BMI was associated with a 40% higher risk of coronary heart disease (CHD) and a 29% higher risk of stroke in Asian cohorts, compared with 24% and 14%, respectively, in Western cohorts[14]. These epidemiological findings are summarized in Table 1.

CHD is among the most extensively studied obesity-related cardiovascular conditions. Large-scale prospective studies have consistently demonstrated a positive association between excess adiposity and CHD risk. In a pooled analysis, each 5 kg/m² increase in BMI was associated with a 27% higher risk of CHD (HR = 1.27, 95%CI: 1.23-1.31)[14]. Similarly, a meta-analysis of 95 cohorts including more than 1.2 million participants found that obesity was associated with substantially increased CHD risk in both women (HR = 1.61, 95%CI: 1.42-1.82) and men (HR = 1.60, 95%CI: 1.43-1.79) compared with individuals of normal

Table 1. Epidemiological evidence for obesity-related CVDs

CVD outcome	Reference	Study design/population	Adiposity exposure	Main finding
Overall CVD	[12]	Prospective cohort; 360,855 participants, China Kadoorie Biobank	Early-adulthood BMI ≥ 30 kg/m² *vs.* 20.5-22.4 kg/m²	Incident CVD: HR 1.58 (95%CI: 1.42-1.75)
	[10]	Umbrella review/meta-analysis; > 500 cohort studies	Each 5 kg/m² increase in BMI	CVD risk increased by approximately 10%-49% across cardiovascular outcomes
CHD	[14]	Pooled analysis of 97 prospective cohorts; ~1.8 million participants	Each 5 kg/m² increase in BMI	HR 1.27 (95%CI: 1.23-1.31)
	[15]	Meta-analysis of 95 cohorts; > 1.2 million participants	Obesity *vs.* normal weight	Women: HR 1.61 (95%CI: 1.42-1.82); Men: HR 1.60 (95%CI: 1.43-1.79)
	[16]	Nurses' Health Study and Health Professionals Follow-up Study	BMI > 30 kg/m²	Women: RR 2.16 (95%CI: 1.81-2.58); Men: RR 1.81 (95%CI: 1.48-2.22)
	[17]	Global Burden of Disease analysis, 2023	High BMI	~0.94 million CHD deaths attributable to high BMI (10.6% of all CHD deaths); 24.56 million DALYs
VTE	[18]	Meta-analysis of 21 case-control and cohort studies	Obesity *vs.* non-obesity	OR 2.33 (95%CI: 1.68-3.24)
	[19]	Mendelian randomization; INVENT consortium	Each genetically predicted 1-SD increase in BMI	OR 1.59 (95%CI: 1.30-1.93)
	[20]	Tromsø Study	Abdominal obesity	HR 2.03 (95%CI: 1.49-2.75)
HF	[24]	Prospective cohort; Framingham Heart Study, 5,881 participants; mean follow-up 14 years	BMI ≥ 30 kg/m² *vs.* normal weight	Women: HR 2.12 (95%CI: 1.51-2.97); Men: HR 1.90 (95%CI: 1.30-2.79)
			Each 1 kg/m² increase in BMI	HF risk increased by 7% in women and 5% in men
	[25]	Pooled analysis of three prospective cohorts; 51,451 participants	Overweight *vs.* normal weight	HFpEF: HR 1.38 (95%CI: 1.18-1.61); HFrEF: HR 1.03 (95%CI: 0.87-1.22)
	[26]	Pooled analysis of four community-based cohorts; 22,681 participants	Each 1-SD increase in BMI	HFpEF: HR 1.34 (95%CI: 1.24-1.45); HFrEF: HR 1.18 (95%CI: 1.10-1.27)
	[27]	Framingham Heart Study	Each 1 kg/m² increase in BMI	HR 1.04 (95%CI: 1.01-1.07) in both men and women
AF	[28]	Meta-analysis of 16 observational studies	Obesity *vs.* non-obesity	RR 1.49 (95%CI: 1.36-1.64)
	[29]	Mendelian randomization	Each genetically predicted 1-SD increase in BMI	OR 1.425 (95%CI: 1.346-1.509)

Data are presented as effect estimates with 95% confidence intervals unless otherwise indicated. BMI: Body mass index; CVD: cardiovascular disease; CHD: coronary heart disease; VTE: venous thromboembolism; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; AF: atrial fibrillation; HR: hazard ratio; RR: relative risk; OR: odds ratio; SD: standard deviation; DALYs: disability-adjusted life years.

weight[15]. Moreover, findings from the Nurses' Health Study and Health Professionals Follow-up Study showed that individuals with BMI > 30 kg/m² had markedly higher risks of incident CHD, with relative risks of 2.16 (95%CI: 1.81-2.58) in women and 1.81 (95%CI: 1.48-2.22) in men[16]. According to the Global Burden of Disease analysis, high BMI accounted for approximately 0.94 million CHD-related deaths worldwide in 2023, representing 10.6% of all CHD deaths and 24.56 million disability-adjusted life years[17].

Obesity is also an important risk factor for thrombotic disorders, particularly venous thromboembolism (VTE). A meta-analysis of 21 case-control and cohort studies showed that obesity was associated with more than a twofold higher risk of VTE than non-obese individuals (OR = 2.33, 95%CI: 1.68-3.24)[18]. Mendelian randomization analysis further provided genetic evidence supporting a causal relationship between obesity and VTE. In the INVENT consortium, each genetically predicted 1-standard-deviation increase in BMI was associated with a 59% higher risk of VTE (OR = 1.59, 95%CI: 1.30-1.93)[19]. Notably, some studies have suggested that abdominal adiposity may be particularly relevant to thrombotic risk[20,21]. In the Tromsø Study,

abdominal obesity was the only component of the metabolic syndrome that remained significantly associated with VTE after multivariable adjustment (HR = 2.03, 95%CI: 1.49-2.75), suggesting that fat distribution may provide additional information beyond overall adiposity in assessing VTE risk[20].

HF represents another major cardiovascular complication associated with obesity. Based on left ventricular ejection fraction (LVEF), HF is generally classified into three phenotypes: heart failure with reduced ejection fraction (HFrEF; LVEF < 40%), HF with mildly reduced ejection fraction (HFmrEF; LVEF 40%-49%), and heart failure with preserved ejection fraction (HFpEF; LVEF ≥ 50%)[22,23]. Long-term follow-up data from the Framingham Heart Study provide compelling evidence of the association between obesity and HF. Among 5,881 participants followed for a mean of 14 years, obesity was associated with an approximately twofold higher risk of HF than normal weight, with hazard ratios of 2.12 (95%CI: 1.51-2.97) in women and 1.90 (95%CI: 1.30-2.79) in men. Moreover, each 1 kg/m² increase in BMI was associated with a 7% and 5% increase in HF risk in women and men, respectively, supporting a graded relationship between increasing adiposity and HF incidence[24]. Notably, higher BMI appears to be more consistently and more strongly associated with the development of HFpEF than with HFrEF. In a pooled analysis of 51,451 participants from three prospective cohorts, overweight was associated with a 38% higher risk of HFpEF (HR = 1.38, 95%CI: 1.18-1.61) compared with normal weight, whereas no significant increase in HFrEF risk was observed (HR = 1.03, 95%CI: 0.87-1.22)[25]. Similarly, another pooled analysis of 22,681 participants from four community-based cohorts showed that each 1-SD increase in BMI was associated with a 34% higher risk of incident HFpEF (HR = 1.34, 95%CI: 1.24-1.45), compared with an 18% increase in HFrEF risk (HR = 1.18, 95%CI: 1.10-1.27), with a significant difference between HF subtypes[26].

Atrial fibrillation (AF) is the most common obesity-related arrhythmia. In the Framingham Heart Study, obesity was identified as an independent risk factor for incident AF, with each 1 kg/m² increase in BMI associated with a 4% higher risk of AF in both men and women (HR = 1.04, 95%CI: 1.01-1.07)[27]. Consistently, a meta-analysis of 16 observational studies showed that obesity was associated with a 49% higher risk of AF (RR = 1.49, 95%CI: 1.36-1.64)[28]. More recently, Mendelian randomization analysis provided genetic support for a causal relationship between BMI and AF. A genetically predicted 1-standard-deviation increase in BMI was associated with a 42.5% higher risk of AF (OR = 1.425, 95%CI: 1.346-1.509)[29].

However, the so-called "obesity paradox" has challenged the conventional interpretation of the obesity-CVD relationship. This phenomenon refers to observations that individuals who are overweight or mildly obese and have established cardiovascular or other chronic diseases may exhibit better clinical outcomes than those with normal BMI[30]. Several methodological explanations have been proposed to account for the obesity paradox, with three major contributors receiving particular attention: reverse causation, selection bias, and the limitations of BMI as a surrogate measure of adiposity[31-33].

Reverse causation may contribute to the obesity paradox because underlying chronic diseases can cause unintentional weight loss and reduced adiposity, making individuals with lower BMI appear to have a higher risk of adverse outcomes compared with those with higher BMI. In an NHANES analysis of individuals with CVD, overweight or obesity initially appeared protective against mortality (HR = 0.89, 95%CI: 0.78-1.01); however, after accounting for reverse causation, the association was reversed (HR = 1.16, 95%CI: 0.95-1.41), with higher mortality observed among patients with overweight or obesity (HR = 1.51, 95%CI: 1.07-2.15)[31]. Mendelian randomization analyses provide additional support because they are less susceptible to reverse causation than conventional observational studies. Results showed that each genetically predicted 1 kg/m² increase in BMI was associated with a 10% higher risk of cardiovascular mortality (HR = 1.10, 95%CI: 1.01-1.19) and a 12% higher risk of CHD mortality (HR = 1.12, 95%CI: 1.00-1.25), providing little support for a true protective effect of excess adiposity[34]. Collectively, these findings suggest that the apparent obesity

paradox may largely reflect reverse causation arising from disease-related weight loss rather than a genuine survival benefit of obesity.

Selection bias may also contribute to the obesity paradox because studies restricted to patients with established disease may preferentially include individuals in whom low BMI reflects greater disease severity or frailty, thereby making higher BMI appear protective. Banack and Kaufman demonstrated through simulation analyses that selection bias alone could generate an apparent protective effect of obesity among individuals with CVD[35]. Using causal models and simulation, Sperrin *et al.* further demonstrated that conditioning on disease status can introduce collider bias and generate an apparent inverse association between obesity and mortality[36]. However, their analyses also indicated that collider bias alone is unlikely to fully explain the obesity paradox because the magnitude of bias was generally small relative to the underlying causal associations, suggesting that other factors may also contribute[36].

A more fundamental explanation for the obesity paradox may lie in the limitations of BMI as a measure of adiposity. By design, BMI is a simplified, population-level metric that cannot distinguish between fat mass and lean mass, nor capture the well-established prognostic impact of anatomical body fat distribution. Several studies have suggested that the apparent protective effect of obesity observed in patients with CVD may partly result from misclassification caused by the use of BMI alone[37,38]. Butt *et al.* compared BMI with alternative anthropometric measures, including waist-to-height ratio (WHtR), in 8,399 patients with HF enrolled in the PARADIGM-HF trial[39]. In unadjusted analyses, patients with BMI ≥ 25 kg/m^2 appeared to have a lower risk of mortality, consistent with the conventional obesity paradox. However, after comprehensive adjustment for established prognostic factors, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), this apparent survival advantage disappeared. Importantly, WHtR, which better reflects central adiposity and is less influenced by muscle mass, skeletal weight, and fluid retention, showed no obesity paradox; instead, higher WHtR was associated with a greater risk of adverse outcomes, including HF hospitalization (adjusted HR for the highest *vs.* lowest quintile: 1.39, 95%CI: 1.06-1.81)[39]. These findings suggest that the apparent protective effect of obesity observed with BMI may largely reflect the limitations of BMI in accurately characterizing adiposity rather than a true biological benefit of excess adiposity.

MECHANISMS UNDERLYING OBESITY-RELATED CVD

Obesity promotes CVD through a complex network of interconnected metabolic, inflammatory, and tissue-specific alterations. These processes can be integrated into four major mechanistic domains: (1) AT dysfunction and altered endocrine/metabolic signaling; (2) systemic inflammatory activation; (3) ectopic fat accumulation; and (4) cardiac metabolic dysfunction. Rather than acting independently, these mechanisms are interconnected through systemic and local pathways. AT dysfunction represents an important upstream disturbance, characterized by altered adipokine secretion and increased lipid availability. At the systemic level, elevated free fatty acids (FFAs) and dysregulated adipokine signaling promote macrophage activation and pro-inflammatory cytokine release, sustaining chronic low-grade inflammation. In parallel, excess lipid availability contributes to ectopic fat expansion and pathological remodeling. Ectopic fat depots, particularly epicardial and perivascular AT, further amplify cardiovascular injury through paracrine signaling. These systemic and local disturbances converge on cardiovascular tissues. In cardiomyocytes, excessive lipid accumulation and inflammatory stress disrupt mitochondrial function, cellular quality control, and Ca^{2+} homeostasis, thereby promoting cardiac metabolic dysfunction. Importantly, the interactions among these pathological mechanisms are not unidirectional. Systemic inflammation can further aggravate AT dysfunction, while cardiovascular injury may reinforce inflammatory activation and alter adipose metabolism, thereby establishing self-reinforcing feedback loops that amplify cardiovascular injury.

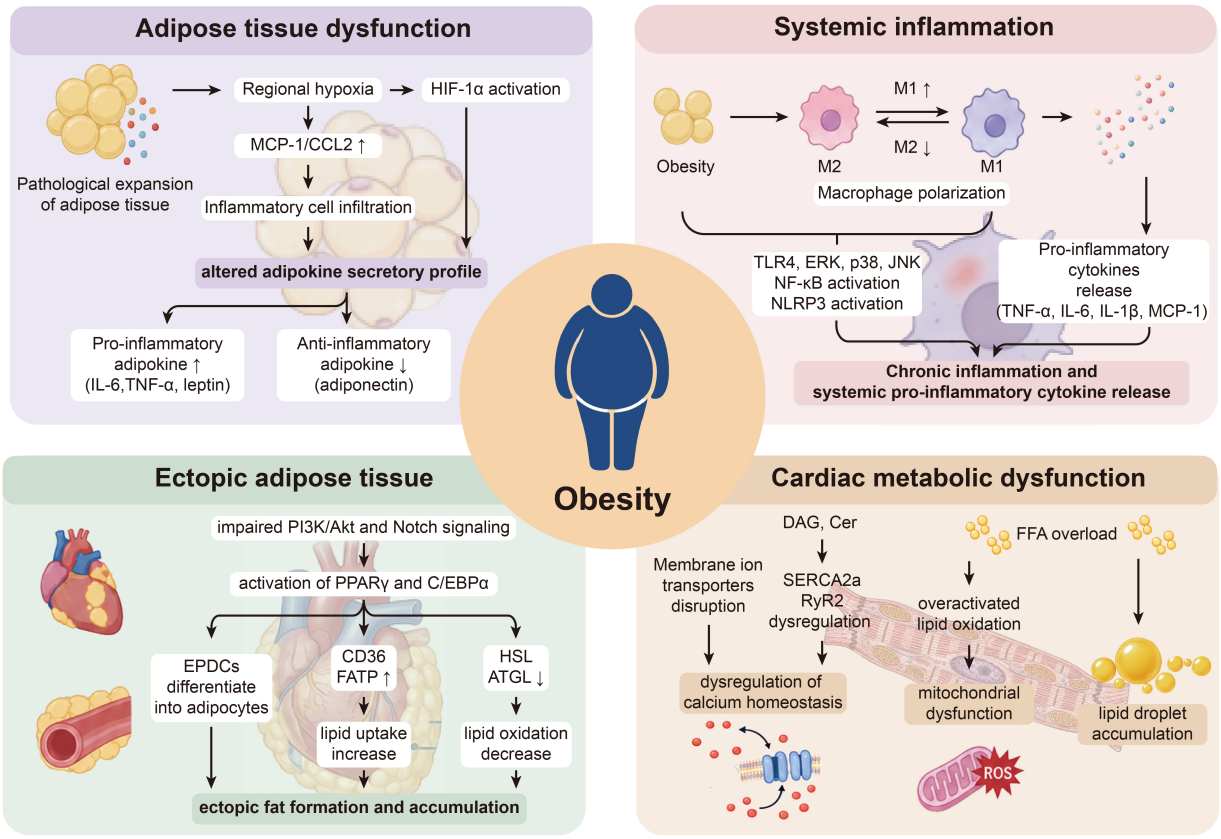


Figure 1. Molecular mechanisms linking obesity to CVD. Obesity promotes cardiovascular injury through four interconnected mechanisms: adipose tissue dysfunction, systemic inflammation, ectopic adipose tissue accumulation, and cardiac metabolic dysfunction. Pathological expansion of adipose tissue induces regional hypoxia and HIF-1α activation, accompanied by increased MCP-1/CCL2 expression and inflammatory cell infiltration, ultimately shifting the adipokine secretory profile toward increased pro-inflammatory adipokines, including IL-6, TNF-α, and leptin, and reduced anti-inflammatory adiponectin. Obesity also promotes macrophage polarization toward a pro-inflammatory M1 phenotype and suppresses the M2 phenotype. Activation of TLR4-ERK/p38/JNK, NF-κB, and NLRP3 signaling enhances the release of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and MCP-1, thereby sustaining chronic systemic inflammation. In parallel, impaired PI3K/Akt and Notch signaling activates PPARγ- and C/EBPα-dependent adipogenic programs, promotes the differentiation of epicardial progenitor-derived cells into adipocytes, increases CD36/FATP-mediated lipid uptake, and reduces HSL/ATGL-mediated lipid mobilization, collectively facilitating ectopic fat formation and accumulation. In cardiomyocytes, DAG and Cer disrupt membrane ion transport and SERCA2a/RyR2-mediated Ca^{2+} handling, whereas FFA overload promotes excessive lipid oxidation, mitochondrial dysfunction, ROS generation, and lipid droplet accumulation. Together, these processes contribute to obesity-associated cardiovascular dysfunction and remodeling. HIF-1α: Hypoxia-inducible factor-1α; MCP-1/CCL2: monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; IL: interleukin; TNF-α: tumor necrosis factor-α; TLR4: Toll-like receptor 4; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; NF-κB: nuclear factor κB; NLRP3: NOD-like receptor family pyrin domain-containing 3; PI3K/Akt: phosphoinositide 3-kinase/protein kinase B; PPARγ: peroxisome proliferator-activated receptor γ; C/EBPα: CCAAT/enhancer-binding protein α; EPDCs: epicardium-derived progenitor cells; FATP: fatty acid transport protein; HSL: hormone-sensitive lipase; ATGL: adipose triglyceride lipase; DAG: diacylglycerol; Cer: ceramide; FFA: free fatty acid; SERCA2a: sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; RyR2: ryanodine receptor 2; ROS: reactive oxygen species.

The relative contributions of these pathological mechanisms vary across cardiovascular phenotypes. In atherosclerosis, vascular inflammation, endothelial dysfunction, and macrophage lipid accumulation play central roles. In HF, myocardial metabolic dysfunction, inflammatory injury, and hemodynamic stress interact to promote adverse remodeling, with adiposity-related myocardial stiffness and microvascular dysfunction being particularly relevant to HFpEF. In AF, local epicardial fat-atrium crosstalk and systemic inflammation contribute to atrial fibrosis and electrical remodeling. Thus, different cardiovascular phenotypes may arise from distinct patterns of interaction among these shared mechanisms.

In the following sections, we first discuss the four mechanistic domains and then examine how their differential contributions are associated with atherosclerosis, HF, and AF. The major molecular pathways are summarized in Table 2 and Figures 1-4.

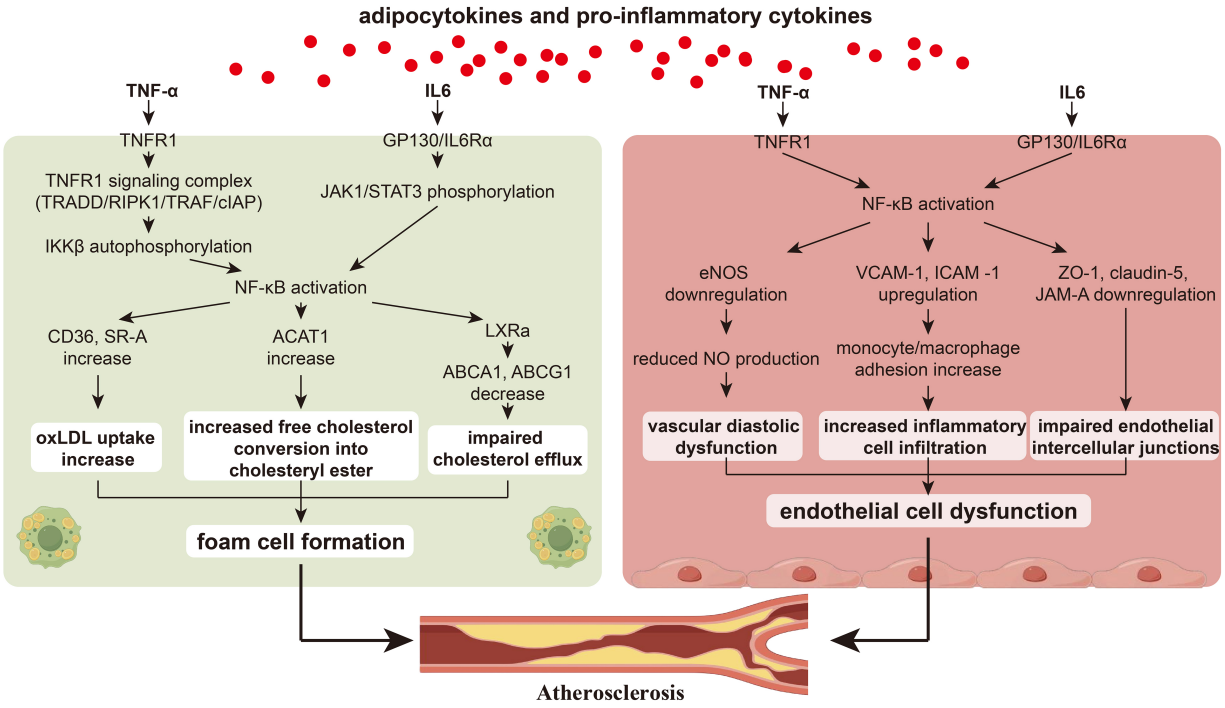


Figure 2. Mechanisms of adipocytokine- and pro-inflammatory cytokine-mediated atherosclerosis. Adipocytokines and pro-inflammatory cytokines promote atherosclerosis by enhancing macrophage lipid accumulation and impairing endothelial function. In macrophages, TNF-α binds to TNFR1 and activates the TNFR1 signaling complex, including TRADD, RIPK1, TRAFs, and cIAPs, thereby inducing IKKβ activation and subsequent NF-κB signaling. IL-6 signaling through the IL-6Rα/GP130 complex activates the JAK1/STAT3 pathway and further augments NF-κB activity. Activated NF-κB upregulates CD36 and SR-A expression, thereby increasing ox-LDL uptake, while simultaneously enhancing ACAT1 expression to promote the esterification of free cholesterol into cholesteryl esters. In parallel, suppression of LXRα-dependent ABCA1 and ABCG1 expression impairs cholesterol efflux. Together, these alterations promote intracellular cholesterol accumulation and foam-cell formation. In endothelial cells, TNF-α/TNFR1 and IL-6/IL-6Rα/GP130 signaling activate NF-κB, resulting in eNOS downregulation and reduced nitric oxide bioavailability, increased VCAM-1 and ICAM-1 expression with enhanced monocyte adhesion and transmigration, and reduced expression of endothelial junctional proteins, including ZO-1, claudin-5, and JAM-A. Collectively, these changes impair endothelium-dependent vasodilation, increase inflammatory cell recruitment and endothelial permeability, and ultimately promote endothelial dysfunction and atherosclerotic plaque development. TNF-α: Tumor necrosis factor-α; TNFR1: tumor necrosis factor receptor 1; TRADD: TNFR1-associated death domain protein; RIPK1: receptor-interacting serine/threonine-protein kinase 1; TRAF: TNF receptor-associated factor; cIAP: cellular inhibitor of apoptosis protein; IKKβ: inhibitor of nuclear factor κB kinase β; NF-κB: nuclear factor κB; IL-6: interleukin-6; IL-6Rα: interleukin-6 receptor α; GP130: glycoprotein 130; JAK1: Janus kinase 1; STAT3: signal transducer and activator of transcription 3; CD36: cluster of differentiation 36; SR-A: scavenger receptor A; ox-LDL: oxidized low-density lipoprotein; ACAT1: acyl-CoA:cholesterol acyltransferase 1; LXRα: liver X receptor α; ABCA1/ABCG1: ATP-binding cassette transporters A1/G1; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; ZO-1: zonula occludens-1; JAM-A: junctional adhesion molecule A.

Molecular mechanisms linking obesity to CVD

AT dysfunction and altered endocrine/metabolic signaling

AT is not merely an energy-storage depot but a highly active endocrine and immunometabolic tissue that regulates systemic metabolic homeostasis, immune responses, vascular function, and cardiovascular physiology[40,41]. Accordingly, pathological remodeling of AT represents an important upstream component of obesity-associated cardiovascular injury.

As obesity progresses, excessive adipocyte hypertrophy and hyperplasia drive pathological expansion of AT. When tissue growth exceeds the capacity of compensatory angiogenesis, inadequate vascularization results in local hypoxia, which represents a key initiating event in AT dysfunction[42-44]. Hypoxia stabilizes and activates hypoxia-inducible factor-1α (HIF-1α), a master transcriptional regulator of cellular adaptation to reduced oxygen availability[45,46]. Sustained activation of HIF-1α profoundly reshapes the adipokine secretory profile,

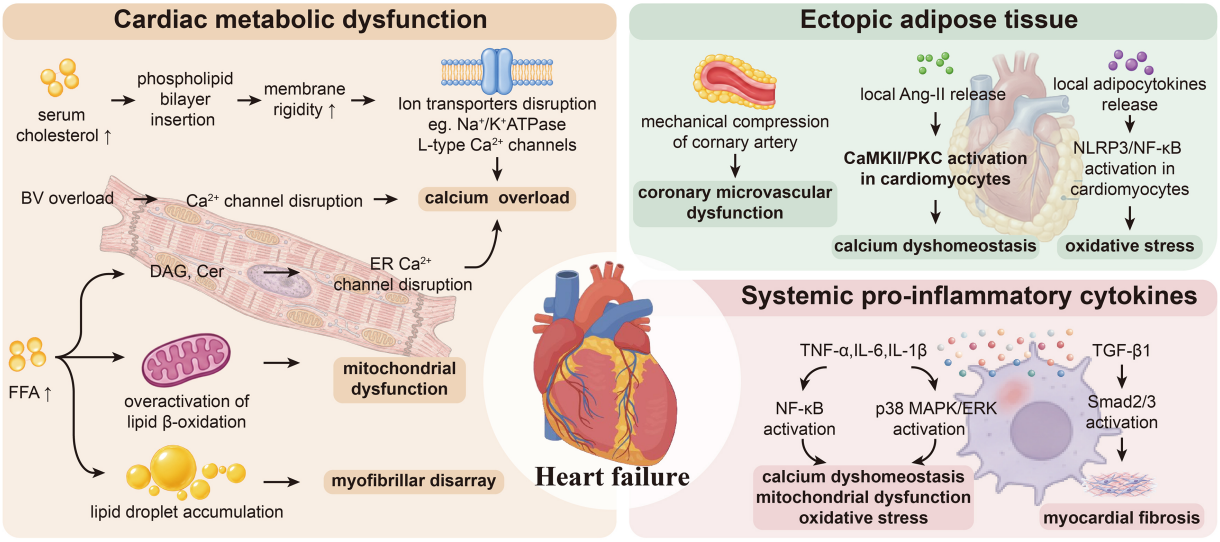


Figure 3. Mechanisms of obesity-associated HF. Obesity promotes heart failure through interconnected metabolic dysfunction and ectopic adipose tissue-mediated mechanisms. In cardiomyocytes, elevated circulating cholesterol alters membrane lipid composition and increases membrane rigidity, thereby impairing membrane transporters and ion channels, including Na^+/K^+-ATPase and L-type Ca^{2+} channels, and disrupting intracellular ionic homeostasis. Volume overload and abnormal sarcoplasmic/endoplasmic reticulum Ca^{2+} handling further aggravate Ca^{2+} dyshomeostasis. Excess free fatty acids promote lipid droplet accumulation and the generation of lipotoxic intermediates, including DAGs and Cer, while excessive fatty acid β-oxidation imposes mitochondrial metabolic stress, resulting in impaired ATP production, increased ROS generation, and myofibrillar disruption. Ectopic adipose tissue, particularly EAT, further contributes to cardiac dysfunction through mechanical compression of the coronary circulation and the local release of Ang-II and pro-inflammatory adipocytokines. These mediators activate NLRP3/NF-κB signaling, enhance oxidative stress, impair SERCA2a-dependent Ca^{2+} handling, and promote coronary microvascular dysfunction. In parallel, pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, activate NF-κB and p38 MAPK/ERK signaling, thereby exacerbating mitochondrial dysfunction, lipid accumulation, oxidative stress, and cardiomyocyte injury. TGF-β1-mediated Smad2/3 signaling further promotes the expression of collagen-associated genes, including COL1A1 and COL3A1, leading to extracellular matrix deposition, myocardial fibrosis, increased ventricular stiffness, and ultimately heart failure. FFA: Free fatty acids; DAGs: diacylglycerols; Cer: ceramide; ATP: adenosine triphosphate; ROS: reactive oxygen species; Ang-II: angiotensin II; NLRP3: NOD-like receptor family pyrin domain-containing 3; NF-κB: nuclear factor κB; SERCA2a: sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; TNF-α: tumor necrosis factor-α; IL: interleukin; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; TGF-β1: transforming growth factor-β1; COL1A1: collagen type I alpha 1 chain; COL3A1: collagen type III alpha 1 chain.

shifting it toward a pro-inflammatory and metabolically unfavorable state. Hypoxic adipocytes exhibit increased expression and secretion of inflammation-associated adipokines and cytokines, including leptin, interleukin-6 (IL-6), macrophage migration inhibitory factor, and plasminogen activator inhibitor-1, whereas the production of adiponectin, a potent insulin-sensitizing and anti-inflammatory adipokine, is markedly suppressed[44,47,48]. Mechanistically, HIF-1α can directly promote leptin transcription through a hypoxia-responsive element in the leptin promoter and suppress adiponectin expression through modulation of the SOCS3-STAT3 signaling axis[49,50].

Beyond the direct effects of HIF-1α on adipocyte function, hypoxia also promotes the recruitment and activation of immune cells within AT. Hypoxic stress enhances the expression of chemokines, particularly monocyte chemoattractant protein-1 (MCP-1/CCL2), as well as endothelial adhesion molecules, thereby facilitating the recruitment of circulating monocytes into AT[51-53]. Within the hypoxic and inflammatory microenvironment, these recruited monocytes differentiate into pro-inflammatory M1-like macrophages[54]. Activated macrophages subsequently release tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and other inflammatory mediators, establishing reciprocal signaling between adipocytes and immune cells through NF-κB, mitogen-activated protein kinase (MAPK), and STAT3 pathways[54-59]. Persistent activation of this inflammatory circuit disrupts adipose tissue endocrine and metabolic homeostasis, driving a

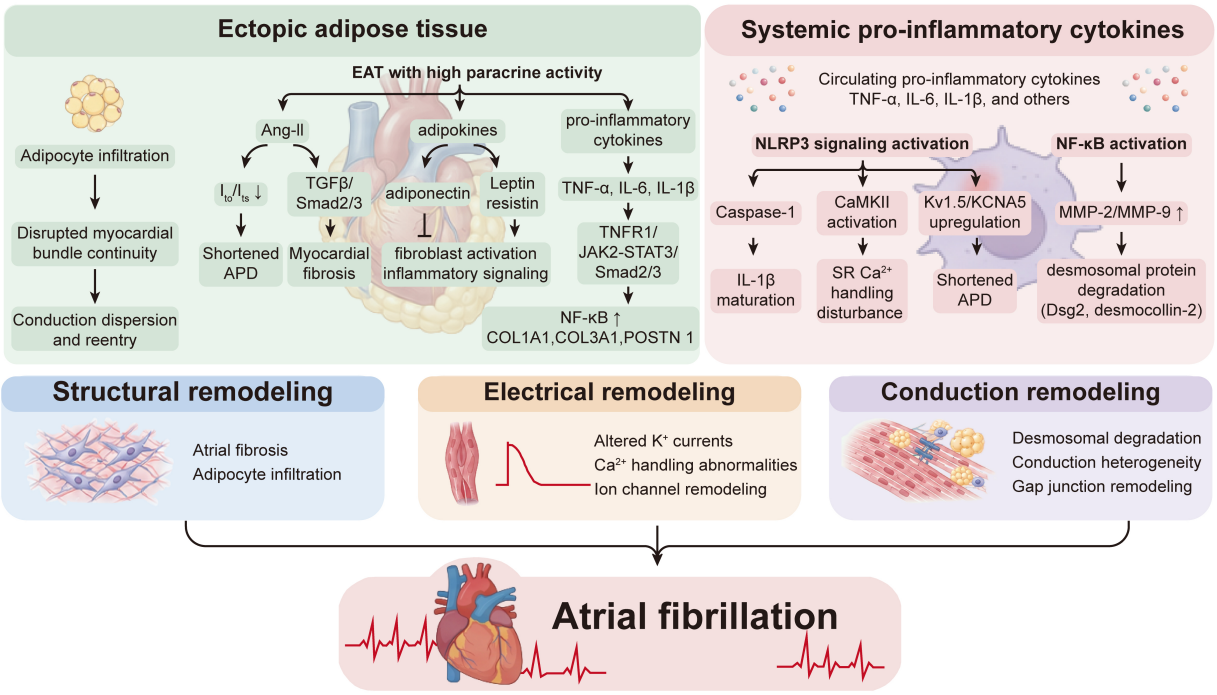


Figure 4. Mechanisms of obesity-related atrial fibrillation. Ectopic adipose tissue and systemic pro-inflammatory cytokines promote atrial fibrillation through coordinated structural, electrical, and conduction remodeling. Adipocyte infiltration disrupts the continuity of atrial myocardial bundles, thereby increasing conduction heterogeneity and susceptibility to reentry. EAT with enhanced paracrine activity further contributes to atrial remodeling through the local release of Ang-II, adipokines, and pro-inflammatory cytokines. Ang-II reduces cardiomyocyte K^+ currents, thereby shortening action potential duration, while simultaneously activating TGF-β/Smad2/3 signaling in cardiac fibroblasts to promote fibrotic remodeling. In parallel, EAT-derived TNF-α, IL-6, IL-1β, leptin, and TGF-β activate TNFR1-, JAK2/STAT3-, NF-κB-, and TGFβR/Smad2/3-dependent signaling pathways, enhancing inflammatory responses and upregulating fibrosis-associated genes, including COL1A1, COL3A1, and POSTN. Systemic pro-inflammatory cytokines further activate the NLRP3/caspase-1/IL-1β axis and CaMKII signaling, resulting in abnormal sarcoplasmic reticulum Ca^{2+} handling and electrical instability. Concurrent upregulation of Kv1.5/KCNA5-mediated IKur contributes to action potential shortening. In addition, NF-κB-dependent induction of MMP-2 and MMP-9 promotes degradation of desmosomal proteins, including Dsg2 and Dsc2, thereby impairing intercellular coupling and increasing conduction heterogeneity and effective refractory period dispersion. Collectively, these structural, electrical, and conduction abnormalities establish a pro-arrhythmic substrate that facilitates the initiation and maintenance of atrial fibrillation. EAT: Epicardial adipose tissue; Ang-II: angiotensin II; APD: action potential duration; ERP: effective refractory period; TNF-α: tumor necrosis factor-α; IL: interleukin; TNFR1: tumor necrosis factor receptor 1; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; TGF-β: transforming growth factor-β; TGFβR: transforming growth factor-β receptor; NF-κB: nuclear factor κB; COL1A1: collagen type I alpha 1 chain; COL3A1: collagen type III alpha 1 chain; POSTN: periostin; NLRP3: NOD-like receptor family pyrin domain-containing 3; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; IKur: ultra-rapid delayed rectifier potassium current; Kv1.5: voltage-gated potassium channel Kv1.5; KCNA5: potassium voltage-gated channel subfamily A member 5; MMP: matrix metalloproteinase; Dsg2: desmoglein-2; Dsc2: desmocollin-2.

pro-inflammatory adipokine imbalance that exacerbates local insulin resistance (IR) and systemic inflammation, and ultimately contributes to cardiovascular injury[60].

Elevated circulating FFAs provide an additional inflammatory stimulus that reinforces obesity-associated AT dysfunction. Excess FFAs, particularly saturated fatty acids (SFAs), can directly activate TLR4-dependent signaling in adipocytes and immune cells, resulting in activation of NF-κB and other downstream inflammatory pathways[61,62]. This, in turn, enhances the production of pro-inflammatory mediators such as IL-6 and TNF-α, thereby reinforcing adipocyte-immune cell crosstalk and perpetuating local adipose tissue inflammation[56,63].

Importantly, obesity-associated adipose tissue dysfunction is not restricted to white adipose tissue. Brown adipose tissue (BAT) also undergoes profound phenotypic and metabolic remodeling during obesity. BAT whitening refers to the pathological transition of thermogenic brown adipocytes toward a white

Table 2. Mechanisms underlying obesity-related CVD

Mechanistic category	Major molecular pathways/mediators	Major cellular consequences	Predominant CVD phenotype(s)
AT dysfunction and altered endocrine/metabolic signaling	Adipose hypoxia → HIF-1α activation → Leptin, IL-6, MIF, and PAI-1 increase; adiponectin decrease[44,47-50]	Pro-inflammatory adipokine imbalance, impaired metabolic homeostasis, insulin resistance	Shared upstream contribution to obesity-associated CVD
	Hypoxia → MCP-1/CCL2 → Monocyte recruitment/M1-like macrophage activation[51-59]	Adipocyte-macrophage inflammatory crosstalk and increased TNF-α, IL-1β, IL-6 secretion	Shared upstream contribution to obesity-associated CVD
	FFA/SFA → TLR4/NF-κB → TNF-α, IL-6[56,61-63]	Sustained adipose inflammation and systemic inflammatory signaling	Shared upstream contribution to obesity-associated CVD
	BAT whitening → UCP1 downregulation; loss of FGF21, NRG4, 12,13-diHOME; TNF-α/IL-6/MCP-1/leptin increase; adiponectin decrease[64-74]	Reduced thermogenesis, impaired glucose/lipid utilization, systemic insulin resistance and inflammation	Shared upstream contribution to obesity-associated CVD
Systemic inflammation	SFAs → PKC/MAPK signaling and enhanced inflammatory responses; SFAs → NLRP3 inflammasome activation → IL-1β release[77,78]	Macrophage pro-inflammatory activation and increased cytokine release	Shared upstream contribution to obesity-associated CVD
	Palmitate/Cer → CD11b and CD36 upregulation; DAG → PKCδ/NF-κB/p38 MAPK; Cer → NLRP3/caspase-1/IL-1β[79-81]	Enhanced macrophage lipid uptake and sustained inflammatory activation	Atherosclerosis; HF; AF
	NF-κB → CD36/SR-A increase, ACAT1 increase; LXRα-ABCA1/ABCG1 decrease[136-140]	Increased ox-LDL uptake and cholesterol esterification; impaired cholesterol efflux; foam-cell formation	Atherosclerosis
	NF-κB → eNOS/NO decrease; VCAM-1/ICAM-1 increase; ZO-1/claudin-5/JAM-A decrease[141-147]	Impaired vasodilation, monocyte adhesion/transmigration, increased endothelial permeability	Atherosclerosis
Ectopic fat accumulation	Altered PKC/JNK/IKK-NF-κB and PI3K/Akt-GSK-3β/Notch signaling→ Activation of PPARγ/C/EBPα[84,86-88]	Adipogenic differentiation and expansion/remodeling of EAT	HF; AF
	CD36/FATP-mediated lipid uptake increase; ATGL/HSL-dependent lipid mobilization decrease[89,90]	Ectopic triglyceride accumulation and adipocyte hypertrophy	HF; AF
	EAT-derived Ang-II and adipocytokines[93,94,97,157,158]	Local inflammation, mitochondrial/metabolic dysfunction, fibrosis and myocardial remodeling	HF; AF
	EAT-derived EVs carrying miR-1-3p and miR-133a-3p → Reduced Kcnj2/Kcnj12 expression[95,96]	Pro-arrhythmic signaling and impaired electrical conduction	AF
	EAT-conditioned medium → Cardiomyocyte miR-208a upregulation[97]	Impaired mitochondrial fatty acid oxidation and contractile function	HF

Cardiac metabolic dysfunction	Excess FFA → DAG/Cer/acylcarnitines → PKC activation / Akt inhibition; long-chain acylcarnitine-induced Ca^{2+} dysregulation[101-105]	Metabolic inflexibility, reduced ATP production, increased ROS and impaired contractility	HF
	Lipid overload → TFEB/LAMP-2A-associated autophagic impairment; Lipid overload → Altered DRP1- and PINK1/Parkin-dependent mitophagy[106-108]	Impaired organelle quality control, accumulation of dysfunctional mitochondria and energetic impairment	HF
	Lipotoxic stress → DRP1 acetylation → Excessive mitochondrial fission[111]	Mitochondrial fragmentation	HF
	Mitochondrial ROS → RyR2 oxidation; SERCA2a-mediated Ca^{2+} reuptake decrease; MCU-CaMKII activation[115-117]	SR Ca^{2+} leak, mitochondrial Ca^{2+} overload and excitation-contraction dysfunction	HF
	Volume expansion/mechanical stretch → Mechanosensitive signaling and MAPK activation[120,121]	Cardiomyocyte hypertrophy, extracellular matrix deposition and maladaptive remodeling	HF

AT: Adipose tissue; CVD: cardiovascular disease; HF: heart failure; AF: atrial fibrillation; BAT: brown adipose tissue; EAT: epicardial adipose tissue; FFA: free fatty acid; SFA: saturated fatty acid; HIF-1α: hypoxia-inducible factor-1α; MCP-1/CCL2: monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; IL: interleukin; TNF-α: tumor necrosis factor-α; TLR4: Toll-like receptor 4; NF-κB: nuclear factor κB; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; NLRP3: NOD-like receptor family pyrin domain-containing 3; Cer: ceramide; DAGs: diacylglycerols; ROS: reactive oxygen species; PPARγ: peroxisome proliferator-activated receptor γ; C/EBPα: CCAAT/enhancer-binding protein α; PAI-1: plasminogen activator inhibitor-1; PI3K/Akt: phosphoinositide 3-kinase/protein kinase B; PKC: protein kinase C; Ang-II: angiotensin II; EV: extracellular vesicle; miRNA: microRNA; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; MIF: migration inhibitory factor; SR-A: scavenger receptor A; ox-LDL: oxidized low-density lipoprotein; ACAT1: acyl-CoA cholesterol acyltransferase 1; LXRα: liver X receptor α; ABCA1/ABCG1: ATP-binding cassette transporters A1/G1; SERCA2a: sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; RyR2: ryanodine receptor 2; MCU: mitochondrial calcium uniporter; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; TGF-β: transforming growth factor-β; MMP: matrix metalloproteinase; APD: action potential duration; ERP: effective refractory period.

adipocyte-like phenotype, characterized by enlarged lipid droplets, reduced mitochondrial content and function, and diminished expression of thermogenic proteins such as uncoupling protein 1 (UCP1)[64]. This process is frequently observed in obesity and is accompanied by impaired thermogenesis, reduced energy expenditure, and altered lipid and glucose metabolism[65,66]. BAT whitening not only compromises the metabolic protective functions of BAT but also promotes lipid accumulation, systemic metabolic dysfunction, and inflammation, thereby contributing to the development of obesity-associated CVD[64,65,67].

BAT whitening consequently reduces energy expenditure and the utilization of circulating glucose and fatty acids, thereby promoting dyslipidemia, hyperglycemia, and systemic IR[68,69]. In addition, loss of BAT-derived protective mediators, including fibroblast growth factor 21 (FGF21), neuregulin-4 (NRG4), and 12,13-diHOME, may diminish the metabolic and cardiovascular protection normally conferred by functional BAT[70-73]. At the same time, whitened BAT increasingly exhibits a dysfunctional secretory profile characterized by increased TNF-α, IL-6, MCP-1/CCL2, and leptin and reduced adiponectin[67,74]. Thus, dysfunction of both white and brown adipose tissue constitutes an upstream endocrine and metabolic disturbance that promotes systemic inflammatory and metabolic stress and facilitates subsequent cardiovascular injury.

Systemic inflammation and macrophage-derived pro-inflammatory cytokine release

The second mechanistic domain involves the propagation of obesity-associated metabolic stress beyond adipose tissue into a state of chronic low-grade systemic inflammation. Sustained activation and metabolic reprogramming of innate immune cells, particularly macrophages, provide an important link between adipose tissue dysfunction and cardiovascular injury[75,76].

At the systemic level, elevated circulating FFAs can activate inflammatory responses in macrophages through lipid metabolism-dependent signaling. Schwartz *et al.* demonstrated that SFA pretreatment markedly enhanced lipopolysaccharide-induced IL-6 and IL-8 production in human monocytes, whereas inhibition of PKC/MAPK signaling attenuated these inflammatory responses[77]. In addition, L'Homme *et al.* showed that SFAs, including palmitate and stearate, promoted NLRP3 inflammasome activation and IL-1β release in human monocytes/macrophages, whereas unsaturated fatty acids exhibited distinct effects[78]. Chronic activation of these signaling pathways promotes macrophage pro-inflammatory reprogramming, thereby contributing to obesity-associated chronic inflammation.

In parallel, obesity-associated lipotoxic metabolites, including ceramides (Cer) and diacylglycerols (DAGs), impose substantial metabolic stress on macrophages. It is reported that palmitate increased CD11b and CD36 expression and oxidized low-density lipoprotein (LDL) uptake in macrophages, and these effects could be attenuated by inhibition of Cer synthesis but not by reactive oxygen species (ROS) scavenging[79]. Furthermore, obesity also increased DAG accumulation in mouse peritoneal macrophages, accompanied by enhanced PKCδ, NF-κB, and p38 MAPK signaling activation. Pharmacological inhibition of adipose triglyceride lipase attenuated DAG accumulation and the associated inflammatory signaling changes[80]. Moreover, Cer accumulation can promote NLRP3 inflammasome activation in macrophages, facilitating caspase-1-dependent maturation and release of IL-1β[81].

Collectively, these alterations sustain a macrophage-centered pro-inflammatory state that drives chronic systemic inflammation, ultimately contributing to obesity-related CVD.

Ectopic fat accumulation in the cardiovascular system

Ectopic fat broadly refers to the abnormal lipid deposition within or around organs and tissues not primarily specialized for lipid storage, including the liver, pancreas, skeletal muscle, heart, and vasculature[82]. Of particular relevance to CVD are adipose depots located in close anatomical proximity to cardiovascular structures, including epicardial adipose tissue (EAT), situated between the myocardium and the visceral pericardium; pericardial adipose tissue (PAT), located external to the parietal pericardium; and perivascular adipose tissue (PVAT), which surrounds large- and medium-sized blood vessels such as the aorta, coronary arteries, and carotid arteries[83].

Ectopic fat undergoes progressive expansion and pathological remodeling, partly driven by the adipogenic conversion of resident progenitor cell populations, for example, epicardial mesothelial progenitor cells (EMPCs)[84,85]. Sustained exposure to insulin, elevated FFAs, and pro-inflammatory mediators perturb protein kinase C (PKC), JNK, inhibitor of nuclear factor-κB kinase (IKK)/NF-κB, and PI3K/Akt signaling. These alterations promote glycogen synthase kinase-3β (GSK-3β) activation and suppress Notch signaling, thereby promoting the adipogenic differentiation of progenitor cells[86,87]. Concomitantly, activation of canonical adipogenic transcriptional programs, particularly peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα), promotes terminal differentiation into mature adipocytes, thereby contributing to the expansion and remodeling of the epicardial fat depot[84,88]. Once formed, EAT expands further through increased CD36/fatty acid transport protein (FATP)-mediated fatty acid uptake and reduced adipose triglyceride lipase (ATGL)/hormone-sensitive lipase (HSL)-dependent lipolysis and mitochondrial fatty acid oxidation, leading to triglyceride accumulation and adipocyte hypertrophy[89,90].

Pathologically remodeled cardiac ectopic fat exhibits a highly active secretory phenotype, releasing adipokines, inflammatory cytokines, vasoactive mediators, and extracellular vesicles (EVs) that can directly influence the adjacent coronary vasculature and myocardium[85,91,92]. Unlike conventional white AT, cardiac

ectopic fat exhibits active sympathetic and local renin-angiotensin signaling, with enhanced catecholaminergic activity and local production of vasoactive mediators such as angiotensin II (Ang-II), which contribute to its neurohumoral effects on the heart[93,94]. EAT-derived EVs, particularly exosomes carrying regulatory microRNAs (miRNAs), constitute an additional pathway of local communication. Shaihov-Teper *et al.* demonstrated that EAT-derived EVs from patients with AF exhibited pro-inflammatory, pro-fibrotic, and pro-arrhythmic properties, with AF-derived EVs inducing sustained reentrant activity in induced pluripotent stem cell-derived cardiomyocytes[95]. Further mechanistic studies identified miR-1-3p and miR-133a-3p in EAT-derived EVs and demonstrated that their overexpression in neonatal rat ventricular cardiomyocytes reduced Kcnj2 and/or Kcnj12 expression and slowed electrical conduction[96].In contrast, Blumensatt *et al.* demonstrated that conditioned medium from EAT induced cardiomyocyte miR-208a expression, impairing mitochondrial fatty acid oxidation and contractile function[97]. However, this study did not establish whether EVs were involved in this process or whether miR-208a was directly transferred from EAT to cardiomyocytes. By delivering regulatory molecules to cardiomyocytes and other cells, EAT may influence mitochondrial function, substrate metabolism, inflammatory signaling, and fibrotic responses.

Cardiac metabolic dysfunction

Under physiological conditions, the adult heart utilizes multiple substrates to meet its energetic demands, with fatty acid oxidation accounting for approximately 60%-70% of myocardial ATP production[98].In obesity, elevated circulating FFAs, IR, and dyslipidemia shift myocardial metabolism toward excessive fatty acid uptake and utilization[99,100]. When fatty acid supply exceeds myocardial oxidative capacity, excessive fatty acids and lipotoxic intermediates initiate metabolic and organelle stress responses that disrupt intracellular signaling, cellular quality control, and energetic homeostasis, ultimately driving cardiomyocyte dysfunction and injury.

Firstly, excessive fatty acids and lipotoxic intermediates could perturb key signaling pathways in cardiomyocytes. For example, DAG and ceramide interfere with myocardial insulin signaling through PKC activation and PP2A-dependent Akt dephosphorylation, respectively, thereby impairing glucose utilization and metabolic flexibility[101,102]. Palmitate can additionally activate cAMP-Epac1 signaling through palmitoylation of soluble adenylyl cyclase; activated Epac1 subsequently interacts with Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and phosphorylates other key enzymes[103]. Long-chain acylcarnitines can also directly perturb cardiomyocyte Ca^{2+} signaling. Palmitoylcarnitine has been shown to increase Ca^{2+} sparks[104], while oleoylcarnitine was reported to enhance RyR2-mediated spontaneous Ca^{2+} release[105].

Secondly, chronic lipid overload also disrupts organelle quality-control systems. In diet-induced obesity, lipotoxicity reduces the lysosomal regulator TFEB together with LAMP-2A, Hsc70, Hsp90, and cathepsin-B activity, resulting in impaired autophagic flux[106]. Mitophagy is also dynamically remodeled rather than uniformly suppressed. Using cardiac-specific Mito-Keima mice, Tong *et al.* showed that high-fat feeding initially increased DRP1-dependent mitophagy; cardiomyocyte-specific Drp1 deletion abolished these adaptive responses and aggravated cardiac dysfunction[107]. Prolonged high fat feeding has been associated with reduced PINK1/Parkin-dependent mitophagy, and pharmacological restoration of mitophagy with urolithin A improved mitochondrial integrity, diastolic function, and cardiac remodeling in obese mice[108]. In contrast to mitophagy, the role of lipophagy in obesity-associated myocardial dysfunction remains less clearly defined. Tong *et al.* found no detectable evidence of substantial lipid droplet-associated autophagy in high-fat diet-fed mouse hearts, suggesting limited activation of conventional macrolipophagy under these conditions[109]. In contrast, Ke *et al.* demonstrated that microlipophagy mediated by the Rab7-RILP axis facilitates lipid droplet degradation in diabetic cardiomyopathy. Mechanistically, Rab7 phosphorylation at Tyr183 promotes RILP recruitment, while pharmacological activation of Rab7 enhanced lipid droplet

clearance and improved cardiac function in diabetic mice[110]. These findings suggest that different forms of lipophagy may operate under distinct conditions, although their relative contributions to lipid clearance remain to be clarified.

Lipid overload additionally perturbs mitochondrial dynamics. In high-fat-fed mice, palmitate promoted DRP1 acetylation at Lys642 and activation; preventing this modification attenuated mitochondrial fission, contractile dysfunction, and cardiomyocyte death[111], supporting a pathogenic role for excessive fission under lipotoxic stress. However, Drp1-dependent fission also serves an adaptive function by segregating damaged mitochondrial components for subsequent mitophagic removal[107]. These findings suggest that obesity-related mitochondrial injury may arise when excessive fission becomes uncoupled from mitophagic clearance, resulting in the accumulation of dysfunctional mitochondria and impaired myocardial energetics.

In parallel, excessive fatty acids and lipotoxic intermediates can provoke endoplasmic reticulum stress and unfolded protein response. Palmitate increases membrane fatty acid saturation and activates IRE1- and PERK-dependent unfolded protein response, accompanied by increased GRP78 expression and ER-stress-mediated apoptosis[112,113]. PERK-ATF4 signaling pathway was also engaged in palmitate-induced ER stress[114].

These signaling and organelle abnormalities converge on energetic failure, oxidative stress, and Ca^{2+} dyshomeostasis, which are tightly interconnected. Impaired mitochondrial ATP production compromises energy-dependent Ca^{2+} handling, particularly sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a)-mediated Ca^{2+} reuptake, whereas excessive ROS can enhance ryanodine receptor 2 (RyR2)-dependent sarcoplasmic-reticulum (SR) Ca^{2+} leak[115,116]. The resulting cytosolic and mitochondrial Ca^{2+} overload further impairs ATP production and promotes additional ROS generation[117], creating a reciprocal loop.

Lipid stress may also engage cell-death programs. For example, high-fat-diet-induced cardiac injury has been associated with increased lipid peroxidation and ferroptotic signaling[118]. Moreover, dyslipidemia may alter cardiomyocyte membrane lipid composition and cholesterol content, thereby affecting membrane fluidity and the function of ion channels and transporters involved in electrical activity and Ca^{2+} handling[119].

Obesity also imposes chronic hemodynamic stress on the myocardium. Expansion of circulating blood volume and increased cardiac output elevate ventricular preload and expose cardiomyocytes to sustained mechanical stretch[120]. Activation of mechanosensitive ion channels and stress-responsive signaling pathways, including MAPK cascades, subsequently promotes cardiomyocyte hypertrophy and maladaptive remodeling and, through interactions with non-myocyte cardiac cells, contributes to extracellular matrix deposition and fibrosis[121].

Cardiovascular-kidney-metabolic (CKM) syndrome has recently been proposed to describe the interconnected pathophysiological relationships among metabolic dysfunction, chronic kidney disease, and CVD[122]. Obesity represents a major driver of CKM syndrome. In addition to IR and chronic inflammation, obesity-associated AT dysfunction simultaneously contributes to renal hyperfiltration, sodium retention, and progressive kidney injury[123,124]. The resulting volume expansion, hypertension, neurohormonal activation, and persistent metabolic disturbances further increase myocardial workload and promote cardiomyocyte hypertrophy, fibrosis, and ventricular dysfunction[125-127]. Conversely, declining cardiovascular and renal function can aggravate systemic metabolic dysregulation, establishing a multidirectional feed-forward network that accelerates the progression of obesity-associated CVD[128].

Emerging evidence suggests that gut microbiota dysbiosis represents an additional mechanism linking obesity to myocardial injury. In diet-induced obesity, alterations in microbial composition and metabolites can perturb myocardial metabolism and enhance oxidative and inflammatory stress. For example, the gut microbiota-derived metabolite trimethyl-5-aminovaleric acid aggravates cardiac hypertrophy and dysfunction in high-fat diet-fed mice by disrupting carnitine metabolism, thereby suppressing myocardial fatty acid oxidation and promoting lipid accumulation and mitochondrial dysfunction[129]. In another HFD-induced obesity model, gut dysbiosis was associated with increased left ventricular mitochondrial ROS, pathological hypertrophy, fibrosis, and cardiac dysfunction, whereas fecal microbiota transplantation from metabolically protected donors reduced myocardial ROS and preserved cardiac structure and function[130]. Together, these findings support a gut-heart axis through which obesity-associated microbial dysbiosis and altered microbial metabolites may amplify myocardial metabolic stress and remodeling.

Phenotype-specific pathogenic mechanisms of obesity-related CVD

The four mechanistic domains described above do not correspond one-to-one with individual CVDs. Instead, specific CVD phenotypes emerge from different combinations and relative contributions of these shared mechanisms. The following subsections focus on atherosclerosis, HF, and AF as representative obesity-associated CVD phenotypes and illustrate how the four upstream mechanistic domains converge into disease-specific cellular and molecular pathways.

Atherosclerosis

AT-derived adipocytokines and macrophage-derived pro-inflammatory cytokines are increasingly recognized as central drivers of obesity-associated vascular injury and atherosclerosis[131]. Among these mediators, TNF-α and IL-6 can directly disrupt vascular homeostasis by activating inflammatory signaling in vascular cells. TNF-α activates TNF receptor 1 (TNFR1)-dependent signaling, promoting the assembly of a signaling complex containing TNF receptor-associated death domain protein (TRADD), receptor-interacting serine/threonine-protein kinase 1 (RIPK1), TNF receptor-associated factors (TRAFs), and cellular inhibitors of apoptosis proteins (cIAPs)[132]. This complex subsequently activates IκB kinase β (IKKβ) and nuclear factor-κB (NF-κB) signaling[133,134]. In parallel, IL-6 binds to the IL-6 receptor α (IL-6Rα)/glycoprotein 130 (GP130) complex and activates the Janus kinase 1 (JAK1)/signal transducer and activator of transcription 3 (STAT3) pathway[135].

In macrophages within the vascular intima, which are the principal precursors of lipid-laden foam cells, TNF-α induced NF-κB activation promotes the upregulation of scavenger receptors, including CD36 and scavenger receptor A (SR-A), thereby facilitating oxidized low-density lipoprotein (ox-LDL) uptake[136,137]. Simultaneously, NF-κB signaling increases acyl-CoA cholesterol acyltransferase 1 (ACAT1) activity, enhancing the esterification of free cholesterol into cholesteryl esters[138]. Conversely, inflammatory signaling suppresses liver X receptor α (LXRα) and its downstream cholesterol efflux transporters, ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), thereby impairing reverse cholesterol transport[139,140]. The resulting imbalance between lipid influx, intracellular cholesterol esterification, and cholesterol efflux drives excessive cholesteryl ester accumulation and foam-cell formation, a hallmark event in the initiation and progression of atherosclerotic lesions.

In endothelial cells, TNF-α/TNFR1 signaling and IL-6-dependent inflammatory pathways promote a pro-inflammatory endothelial phenotype[141,142]. NF-κB activation downregulates endothelial nitric oxide synthase (eNOS) expression and nitric oxide bioavailability, thereby impairing endothelium-dependent vasodilation[143]. Moreover, increased expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) enhances monocyte adhesion and transendothelial migration, facilitating macrophage accumulation within the vascular intima[144,145]. Inflammatory signaling also disrupts

endothelial barrier integrity by reducing junctional proteins, including zonula occludens-1 (ZO-1), claudin-5, and junctional adhesion molecule A (JAM-A), thereby increasing vascular permeability[146,147].

Together, these alterations promote endothelial dysfunction, vascular inflammation, lipid deposition, and ultimately the progression of obesity-associated atherosclerosis [Figure 2].

HF

Obesity promotes the development of HF through multiple interconnected mechanisms, including direct cardiomyocyte injury, ectopic adipose tissue-heart crosstalk, coronary microvascular dysfunction, chronic inflammation, and fibrotic remodeling [Figure 3].

At the cardiomyocyte level, obesity disrupts myocardial metabolism, mitochondrial energetics, and Ca^{2+} homeostasis, ultimately impairing contractile function. Excessive fatty acid supply promotes accumulation of lipid droplets and lipotoxic intermediates, including DAG and Cer[148]. Chen *et al.* demonstrated that PAK3 promoted myocardial lipid accumulation and oxidative stress through activation of the mTOR-S6K1-SREBP1c pathway, whereas pharmacological inhibition of S6K1 or SREBP1c attenuated cardiac lipotoxicity and dysfunction in obese mice[149]. Lipid overload also disrupts mitochondrial homeostasis. Palmitate treatment increased Drp1 acetylation at Lys642, promoting excessive mitochondrial fission and cardiomyocyte injury, whereas preventing this modification attenuated mitochondrial fragmentation and contractile dysfunction[111]. Furthermore, excessive accumulation of long-chain acylcarnitines can disturb sarcoplasmic reticulum Ca^{2+} release and mitochondrial Ca^{2+} handling, leading to impaired mitochondrial energetics and cardiomyocyte injury in experimental models[104]. Obesity-associated dyslipidemia may further perturb cardiomyocyte membrane composition by promoting cholesterol accumulation within cellular membranes, thereby increasing membrane rigidity, and perturbing the function of membrane transporters and ion channels, including Na^+/K^+-ATPase and L-type Ca^{2+} channels[150-152]. Together, these metabolic, mitochondrial, and ionic disturbances impair cardiomyocyte contractility and promote HF development.

Ectopic adipose tissue, particularly expanded EAT, may serve as an important mechanistic link between obesity and HF. Owing to its anatomical proximity to the myocardium and coronary circulation, excessive EAT can influence cardiac function through both mechanical and paracrine/vasocrine effects. Excessive EAT mechanically compresses coronary arteries and impairs microvascular perfusion[153,154]. Moreover, EAT-derived vasoactive and inflammatory mediators, including Ang-II and adipocytokines, can act directly on adjacent myocardium and coronary vessels[97,154]. Local Ang-II signaling may activate Ca^{2+}/CaMKII and PKC pathways in cardiomyocytes, disrupt SERCA2a-dependent SR Ca^{2+} handling, and thereby aggravate Ca^{2+} dyshomeostasis[155,156]. Meanwhile, pro-inflammatory adipocytokines released from dysfunctional EAT may amplify NLRP3 inflammasome- and redox-sensitive inflammatory signaling within the EAT myocardium axis, thereby promoting cardiomyocyte oxidative stress, coronary endothelial dysfunction, and myocardial inflammatory injury[157,158].

Systemic inflammatory cytokines further exacerbate obesity-associated myocardial damage. Pro-inflammatory mediators such as TNF-α, IL-6, and IL-1β activate NF-κB, p38 MAPK, and ERK signaling pathways in cardiomyocytes[159]. Activation of these pathways exacerbates mitochondrial dysfunction, oxidative stress, lipid accumulation, and Ca^{2+} dyshomeostasis, thereby establishing a self-reinforcing inflammatory-metabolic feedback loop that promotes progressive myocardial dysfunction[160,161]. In addition, persistent inflammation drives maladaptive extracellular matrix remodeling. Through Smad2/3-dependent transcriptional activation, TGF-β1 upregulates collagen-associated genes, including COL1A1 and COL3A1, thereby promoting collagen deposition, interstitial fibrosis, myocardial stiffness, and impaired ventricular compliance[162].

The contribution of obesity differs substantially between HFpEF and HFrEF. The association is particularly strong for HFpEF, in which obesity, especially visceral and epicardial adiposity, is increasingly recognized as a major pathophysiological driver rather than merely a coexisting comorbidity[163,164]. Excess adiposity promotes inflammation, microvascular dysfunction, volume expansion, and adverse cardiac remodeling, leading to increased myocardial stiffness, elevated filling pressures, and impaired diastolic function, which are hallmark features of HFpEF[165,166]. Consistent with this association, an analysis of 626 patients showed that increasing obesity severity was associated with progressively greater cardiac remodeling, higher right- and left-sided filling pressures, worse functional capacity, and an increased risk of subsequent HF events[167]. In contrast, the relationship between obesity and HFrEF is more heterogeneous and is often mediated by obesity-associated cardiovascular disorders, including hypertension, diabetes, and coronary artery disease, which increase the susceptibility to myocardial ischemia and injury[168,169]. An analysis of 6,340 participants from the Framingham Heart Study showed that higher BMI preferentially predicted incident HFpEF, whereas hypertension and pre-existing CVD were more closely associated with the development of HFrEF[170]. Similarly, a prospective cohort study reported that obesity-related hypertension and diabetes predicted HFrEF[171]. In addition, chronic lipid overload, IR, mitochondrial dysfunction, oxidative stress, Ca^{2+} dyshomeostasis, and sustained activation of the sympathetic nervous system and renin-angiotensin-aldosterone system may directly impair cardiomyocyte viability and contractile function[150,172]. Collectively, although metabolic, inflammatory, neurohormonal, and hemodynamic abnormalities are shared across obesity-related HF phenotypes, obesity appears to have a particularly direct role in HFpEF, whereas the development of HFrEF more commonly reflects the combined effects of obesity-associated CVD and cumulative myocardial injury.

AF

Obesity is one of the most important modifiable risk factors for the development and progression of AF, with epidemiological evidence linking adiposity to increased AF incidence, recurrence after catheter ablation, and progression from paroxysmal to persistent AF[173-175].

EAT, particularly peri-atrial EAT, represents an important local mediator linking obesity to atrial remodeling. Excessive EAT may exert mechanical and structural effects through adipocyte infiltration into the atrial myocardium and separation of myocardial fiber bundles, thereby disrupting cardiomyocyte continuity and cell-to-cell electrical coupling[176]. This structural discontinuity increases local conduction dispersion and creates regions of slow conduction or conduction block, thereby providing an anatomical substrate for reentrant excitation and increasing susceptibility to AF[176,177]. In addition, EAT acts as a metabolically active paracrine organ that releases multiple bioactive mediators. EAT-derived Ang-II can promote both electrical and structural remodeling by altering atrial ion-channel activity and Ca^{2+} handling and by activating profibrotic TGF-β/Smad signaling[85,178]. EAT also secretes a broad range of adipokines, including adiponectin, leptin, and resistin. Leptin and resistin have been implicated in fibroblast activation, inflammatory signaling, and atrial remodeling[179,180], whereas adiponectin generally exerts anti-inflammatory and antifibrotic effects[181], although its association with AF in clinical studies appears more complex. Thus, an imbalance between protective and deleterious adipokines may contribute to the arrhythmogenic effects of EAT. Furthermore, dysfunctional EAT releases pro-inflammatory mediators, including TNF-α, IL-6, and IL-1β, which act locally on adjacent atrial cardiomyocytes and fibroblasts. These mediators enhance oxidative stress, inflammatory signaling, and extracellular matrix remodeling, thereby reinforcing atrial fibrosis and electrical instability[95,182]. Collectively, the mechanical effects and altered secretory profile of expanded EAT promote atrial structural discontinuity, fibrosis, Ca^{2+} dysregulation, and electrophysiological heterogeneity.

Obesity-induced chronic low-grade systemic inflammation further promotes AF development. Increased circulating levels of TNF-α, IL-6, and IL-1β activate inflammatory pathways in cardiomyocytes, including NF-κB-, JAK2/STAT3-, and inflammasome-dependent pathways[183]. In particular, activation of the NLRP3

inflammasome-caspase-1 axis promotes the maturation of IL-1β, which can activate Ca^{2+}/CaMKII and disturb SR Ca^{2+} handling[184,185]. NLRP3 inflammasome signaling may also enhance the ultra-rapid delayed rectifier potassium current (*IKur*) by upregulating Kv1.5/KCNA5, resulting in APD shortening and increased atrial electrical instability[184,186]. Inflammatory signaling also disrupts intercellular adhesion structures. Through NF-κB-dependent upregulation of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), inflammatory signaling promotes proteolytic degradation of desmosomal cadherins, including desmoglein-2 (Dsg2) and desmocollin-2[187,188]. Loss of desmosomal integrity weakens mechanical coupling between cardiomyocytes and impairs coordinated electrical propagation[189]. As a result, heterogeneous conduction and greater dispersion of the effective refractory period develop, creating a pro-reentrant electrophysiological environment that sustains AF.

Collectively, obesity-associated AF arises from the interaction between local EAT-mediated effects and systemic inflammatory activation. These mechanisms jointly promote progressive atrial structural and electrical remodeling, providing the substrate and triggers required for AF initiation and maintenance [Figure 4].

EVALUATION OF OBESITY-RELATED CVD

The evaluation of obesity-related CVD employs a comprehensive, multidimensional assessment framework integrating anthropometric parameters, circulating biomarkers, composite metabolic indices and advanced imaging techniques [Table 3].

Anthropometric indices

BMI remains the most widely used measure for obesity screening in public health because of its simplicity, minimal cost, and extensive validation in large-scale epidemiological studies[190]. Numerous studies have demonstrated that BMI is significantly correlated with body fat percentage, skinfold thickness, and imaging-based measurements such as dual-energy X-ray absorptiometry[191,192]. Moreover, BMI exhibits substantial predictive value for obesity-related CVD risk. In a pooled analysis of 97 prospective cohorts, each 5 kg/m^2 increase in BMI was associated with a 27% higher risk of CHD (HR 1.27, 95%CI: 1.23-1.31)[14], while an umbrella meta-analysis reported a 49% higher risk of hypertension (RR 1.49, 95%CI: 1.40-1.60)[10]. However, despite its widespread application, BMI has inherent limitations as an obesity assessment tool. Specifically, BMI cannot differentiate between fat mass and lean muscle mass, nor does it provide information regarding adipose tissue distribution, which may result in inaccurate estimation of individual metabolic and cardiovascular risks[4,193]. The utility value of BMI is more limited in athletes, the elderly, and certain ethnic populations[194,195].

Given the limitations of BMI, anthropometric indices that more directly reflect central adiposity have been increasingly developed. The use of indices such as WC, WHR, WHtR, and BRI improves cardiovascular risk stratification beyond BMI alone[6,196,197].

WC is a direct measure of abdominal girth, typically measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, and serves as a simple marker of abdominal and visceral fat accumulation[198]. Commonly used WC cutoff values for central obesity are ≥ 90 cm in men and ≥ 80 cm in women in Asian populations and ≥ 102 cm in men and ≥ 88 cm in women in non-Asian populations[199]. WC has shown robust associations with cardiovascular events. A meta-analysis involving 258,114 participants demonstrated that each 1-cm increase in WC was associated with a 2% increase in CVD risk (RR = 1.02, 95%CI: 1.01-1.03)[200].

Table 3. Summary of anthropometric, metabolic, and imaging indices for cardiovascular disease risk assessment

Category	Index/technique	Definition or measurement	Representative association with CVD	Clinical value/advantages	Limitations
Anthropometric indices	BMI	$\frac{\text{Body weight (kg)}}{\text{height}^2\ (\text{m}^2)}$	Each 5 kg/m^2 increase: CHD, HR 1.27 (95%CI: 1.23-1.31); hypertension, RR 1.49 (95%CI: 1.40-1.60)[10,14]	Simple, inexpensive, and extensively validated[190]	Cannot distinguish fat from lean mass or characterize fat distribution[4,193]
	WC	Central obesity: ≥ 90 cm in men and ≥ 80 cm in women in Asian populations; ≥ 102 and ≥ 88 cm, respectively, in non-Asian populations[199]	Each 1-cm increase: CVD, RR 1.02 (95%CI: 1.01-1.03)[200]	Simple measure of abdominal and visceral adiposity	Sensitive to measurement protocol; ethnicity-specific thresholds
	WHR	$\frac{\text{WC}}{\text{hip circumference}}$ Cutoff value: ≥ 0.90 in men and ≥ 0.85 in women[201]	Each 0.01-unit increase: CVD, RR 1.05 (95%CI: 1.04-1.07); elevated WHR: MI, OR 1.98 (95%CI: 1.75-2.24)[200,202]	Reflects abdominal relative to gluteofemoral fat distribution	Population-dependent interpretation
	WHtR	$\frac{\text{WC}}{\text{height}}$ Mean boundary value ≈ 0.50[197]	Each 5% relative increase: ischemic CVD, HR 1.23 (95%CI: 1.20-1.25); MI, HR 1.24 (1.21-1.27); ischemic stroke, HR 1.22 (1.18-1.26)[203]	Adjusts WC for body size; good discrimination across sex and ethnic groups	Measurement and population differences should be considered
	BRI	$364.2 - 365.5 * \sqrt{1 - \frac{(\text{WC}/2\pi)^2}{(0.5*\text{Height})^2}}$	Each 1-unit increase: higher 10-year ASCVD risk category, OR 1.58 (95%CI: 1.54-1.63); moderate- and high-stable trajectories: CVD, HR 1.22 and 1.55, respectively[6,204]	Low-cost; captures central adiposity and may improve risk reclassification	No universally accepted clinical cut-off; ethnic variability

	Lipid profile	TG, TC, LDL-C, HDL-C	Lower HDL-C and higher TC and LDL-C associated with increased cardiovascular mortality[206]	Widely available; characterizes obesity-associated dyslipidemia	Individual lipid levels may not fully capture obesity-related AT dysfunction
	Glucose homeostasis markers	FPG, HbA1c, fasting insulin	Prediabetic-range HbA1c associated with approximately 21%-25% higher CVD risk; impaired fasting glucose and glucose tolerance associated with composite CVD and CHD[207]	Routinely available; assesses glycemic dysregulation and IR	Individual markers reflect different aspects of glucose homeostasis
Circulating biomarkers	Adiponectin	-	Each unit increase: 10-year CVD risk, RR 0.64 (95%CI: 0.42-0.96)[208]	More directly reflects AT endocrine function; potentially protective cardiovascular marker	Clinical thresholds and routine use remain insufficiently established
	Leptin	-	Higher leptin: cardiovascular mortality in older men, HR 1.69 (95%CI: 1.06-2.70)[209]	Reflects adipose tissue expansion and endocrine dysfunction	Associations may vary according to sex, age, and adiposity phenotype
	TyG index	$\ln\left[\frac{TG*FPG}{2}\right]$	Highest *vs.* lowest TyG category: incident ASCVD, HR 1.61 (95%CI: 1.29-2.01); also associated with CAD and stroke[211]	Simple and practical surrogate marker of IR	Influenced by fasting glucose and TG levels; not a direct measure of IR
	AIP	$\log_{10}\left[\frac{TG}{HDL-C}\right]$	Each 1-unit increase: incident MACE, HR 1.453 (95%CI: 1.371-1.540)[212]	Integrates atherogenic and protective lipoprotein profiles	Clinical interpretation and thresholds require further standardization
Imaging techniques	CT	Quantification of VAT, SAT, EAT, VAT/SAT ratio, and pericoronary FAI	Each 1-SD increase in VAT: CVD, HR 1.44 (95%CI: 1.08-1.92); high FAI: MACE, adjusted HR 5.00 (95%CI: 3.30-7.58); each 1-HU increase in FAI: MACE risk +24%[215,218]	High spatial resolution; directly quantifies regional and ectopic fat	Ionizing radiation, relatively high cost; less suitable for population screening
	MRI/CMR	Fat-sensitive MRI/^{1}H-MRS for myocardial lipid; native T1 and ECV for fibrosis; T2-based techniques for edema/inflammation[220-222]	Obesity with LV hypertrophy + elevated ECV: event rate 57.1% *vs.* 17.7%; each 1-SD increase in EAT T1: composite outcome, adjusted HR 1.20 (95%CI: 1.02-1.41)[223,224]	No ionizing radiation; excellent soft-tissue characterization; simultaneous assessment of morphology, function, fat infiltration, and fibrosis	High cost and limited availability
	PET/PET-CT	^{18}F-FDG uptake quantified by SUV/TBR; assessment of myocardial metabolism and perfusion	Increased arterial ^{18}F-FDG uptake independently predicted subsequent CHD events[228]	Provides molecular and metabolic information; evaluates inflammation, myocardial metabolism, and perfusion	Radiation exposure, high cost, limited availability, potential attenuation artifacts

Associations with cardiovascular outcomes are presented as effect estimates with 95% confidence intervals where available. BMI: Body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BRI: body roundness index; CVD: cardiovascular disease; CHD: coronary heart disease; ASCVD: atherosclerotic cardiovascular disease; MI: myocardial infarction; MACE: major adverse cardiovascular events; AT: adipose tissue; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; IR: insulin resistance; TyG: triglyceride-glucose index; AIP: atherogenic index of plasma; CT: computed tomography; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; EAT: epicardial adipose tissue; FAI: fat attenuation index; MRI: magnetic resonance imaging; CMR: cardiac magnetic resonance; ^{1}H-MRS: proton magnetic resonance spectroscopy; ECV: extracellular volume fraction; LV: left ventricular; PET: positron emission tomography; ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; SUV: standardized uptake value; TBR: target-to-background ratio; HR: hazard ratio; RR: relative risk; OR: odds ratio; SD: standard deviation; HU: Hounsfield unit.

WHR, calculated as WC divided by hip circumference, reflects the relative distribution of abdominal *vs.* gluteofemoral adiposity. According to WHO criteria, a WHR ≥ 0.90 in men and ≥ 0.85 in women indicates increased obesity-related health risk[201]. Evidence indicates that each 0.01-unit increase in WHR was associated with a 5% increase in CVD risk (RR = 1.05, 95%CI: 1.04-1.07)[200]. A recent meta-analysis further found that an elevated WHR was associated with an approximately twofold higher risk of myocardial infarction (OR = 1.98, 95%CI: 1.75-2.24)[202].

WHtR, defined as WC divided by height, adjusts abdominal circumference for overall body size. A systematic review of 78 studies identified a mean WHtR boundary value of 0.50 across different sexes and ethnic populations and reported greater discrimination for cardiometabolic outcomes with WHtR than with WC or BMI[197]. In a prospective analysis of 468,333 UK Biobank participants followed for approximately 12 years, each 5% relative increase in WHtR was independently associated with a 23% higher risk of ischemic CVD (HR = 1.23, 95%CI: 1.20-1.25), a 24% higher risk of myocardial infarction (HR = 1.24, 95%CI: 1.21-1.27), and a 22% higher risk of ischemic stroke (HR = 1.22, 95%CI: 1.18-1.26)[203].

BRI was proposed by Thomas *et al.* in 2013 as a geometry-based anthropometric index designed to characterize body shape and visceral adiposity more comprehensively than BMI[5]. BRI is calculated as $364.2-365.5*\sqrt{1-\frac{(WC/2\pi)^2}{(0.5*Height)^2}}$; higher BRI values indicate a rounder body shape and greater central adiposity. Unlike WC, WHR, and WHtR, however, no universally accepted clinical cutoff value has yet been established for BRI. Nevertheless, accumulating evidence supports its utility in cardiovascular risk assessment. In a health-screening cohort of 13,086 adults, Wang *et al.* reported that each one-unit increase in BRI was associated with 58% higher odds of belonging to a higher 10-year ASCVD risk category (OR = 1.58, 95%CI: 1.54-1.63)[6]. More importantly, in the China Health and Retirement Longitudinal Study, participants with moderate-stable and high-stable BRI trajectories had 22% (HR = 1.22, 95%CI: 1.09-1.37) and 55% (HR = 1.55, 95%CI: 1.26-1.90) higher risks of incident CVD, respectively, compared with those with persistently low BRI, and incorporation of BRI trajectories further improved cardiovascular risk reclassification[204].

Collectively, these findings suggest that anthropometric measures of central adiposity and emerging indices such as BRI can provide clinically relevant cardiovascular risk information that is not fully captured by BMI. However, ethnic variability in cutoff values, differences in measurement protocols, and the lack of standardized thresholds for newer indices such as BRI remain important considerations for their broader clinical application.

Circulating biomarkers

Circulating biomarkers are also used to evaluate obesity-related cardiovascular risk and can be broadly categorized into conventional metabolic biomarkers, adipokines, and composite indices.

Among conventional metabolic biomarkers, the lipid profile and indices of glucose homeostasis are most widely used. Triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) characterize obesity-associated dyslipidemia[205]. Their prognostic relevance has been well established: higher TC and LDL-C levels were associated with increased cardiovascular mortality, whereas HDL-C showed an inverse association with cardiovascular mortality[206]. In parallel, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and fasting insulin are commonly used to assess glucose homeostasis and IR. A meta-analysis involving more than 1.6 million participants showed that impaired fasting glucose, impaired glucose tolerance, and elevated HbA1c were associated with increased risks of composite CVD and CHD; elevated HbA1c within the prediabetic range was associated with approximately 21%-25% higher CVD risk[207].

Beyond conventional metabolic markers, adipokines provide more direct information on AT dysfunction. Leptin and adiponectin are the most extensively investigated. In the ATTICA prospective cohort, higher circulating adiponectin was independently associated with a lower 10-year risk of CVD, with each unit increase corresponding to an approximately 36% reduction in risk (RR = 0.64, 95%CI: 0.42-0.96)[208]. Conversely, elevated leptin may indicate adipose tissue expansion and has been associated with adverse cardiovascular outcomes. In NHANES III, higher leptin concentrations were associated with cardiovascular mortality in older men (HR = 1.69, 95%CI: 1.06-2.70), with particularly evident associations among men with obesity defined by WC or body fat percentage[209].

More recently, composite metabolic indices derived from blood parameters have emerged. The triglyceride-glucose index (TyG), calculated as $\ln\left[\frac{TG*FPG}{2}\right]$, has been widely adopted as a simple marker of IR[210]. A meta-analysis of eight cohort studies showed that individuals in the highest TyG category had a 61% higher risk of incident ASCVD than those in the lowest category (HR = 1.61, 95%CI: 1.29-2.01), together with increased risks of coronary artery disease and stroke[211]. The atherogenic index of plasma (AIP), defined as $\log_{10}\left[\frac{TG}{HDL\text{-}C}\right]$, provides an integrated measure of the balance between atherogenic and protective lipoprotein profiles. In a UK Biobank analysis of 361,644 adults without previous major cardiovascular events, each one-unit increase in AIP was independently associated with a 45.3% higher risk of incident major adverse cardiovascular events (MACE) (HR = 1.453, 95%CI: 1.371-1.540)[212].

Imaging techniques

Imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), enable direct visualization and quantitative characterization of adipose tissue, representing powerful tools for evaluating obesity-related cardiovascular risk.

CT provides high-spatial-resolution quantification of AT distribution and is particularly useful for assessing abdominal visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and cardiovascular ectopic fat depots. CT-derived parameters, including adipose tissue area or volume, EAT volume and attenuation, and the VAT/SAT ratio, provide cardiovascular risk information beyond conventional anthropometric indices[213,214]. In the Framingham Heart Study, CT-derived VAT was independently associated with incident CVD after adjustment for conventional risk factors including BMI, with each 1-SD increase in VAT associated with a 44% higher risk of CVD (HR = 1.44, 95%CI: 1.08-1.92)[215]. Similarly, a meta-analysis involving more than 41,000 individuals demonstrated independent associations between CT-derived EAT volume and coronary stenosis, myocardial ischemia, and MACE[216]. Beyond adipose tissue quantity, pericoronary fat attenuation index (FAI) calculated from CT attenuation changes can characterize the inflammatory phenotype of pericoronary adipose tissue[217]. A recent meta-analysis found that high FAI was associated with an approximately fivefold higher risk of MACE (adjusted HR = 5.00, 95%CI: 3.30-7.58), while each 1-Hounsfield-unit increase in FAI was associated with a 24% increase in MACE risk[218].

A major advantage of MRI, particularly cardiac magnetic resonance (CMR), is the superior soft-tissue characterization and simultaneous assessment of cardiac morphology, systolic function, fat infiltration, and myocardial fibrosis[219]. Fat-sensitive MRI techniques and proton magnetic resonance spectroscopy could assess myocardial lipid accumulation[220]; native T1 mapping and extracellular volume fraction (ECV) provide quantitative measures of interstitial myocardial fibrosis[221]; and T2-based techniques are sensitive to myocardial edema and inflammatory changes[222]. These abnormalities are particularly relevant to obesity-related CVD. In a cohort of 456 patients with obesity, patients with both LV hypertrophy and elevated ECV had a substantially higher event rate than those without either abnormality (57.1% *vs.* 17.7%)[223]. Moreover, higher EAT T1 values were independently associated with a composite outcome of myocardial infarction, HF hospitalization, and all-cause mortality (adjusted HR per SD = 1.20, 95%CI: 1.02-1.41)[224].

PET further extends obesity-related cardiovascular assessment from anatomical and functional imaging to the molecular and metabolic level. When combined with CT or MRI, PET can quantify tissue-specific tracer uptake using parameters such as the standardized uptake value (SUV) and target-to-background ratio (TBR)[225]. Among commonly used tracers, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) reflects glucose utilization and has been extensively applied. In obesity, increased FDG uptake in visceral and PAT may indicate adipose tissue inflammation, whereas increased arterial FDG uptake provides a surrogate measure of vascular inflammation and atherosclerotic activity[226,227]. Studies reported that increased arterial ^{18}F-FDG uptake, quantified by TBR, independently predicted subsequent CHD events and improved risk discrimination beyond the Framingham Risk Score[228]. PET can additionally evaluate myocardial substrate metabolism and quantify myocardial perfusion, thereby offering further insight into obesity-associated coronary microvascular dysfunction and myocardial metabolic alterations[229,230].

Collectively, CT, MRI, and PET provide complementary information across different levels of obesity-related cardiovascular pathology. These imaging techniques may substantially improve phenotyping and risk stratification of obesity-related CVD.

APPLICATION OF AI IN OBESITY-RELATED CVD

Emerging applications of AI in obesity-related CVD assessment and management

AI has emerged as a powerful tool for the comprehensive evaluation of obesity-related CVD. By leveraging machine learning and deep learning algorithms, AI can analyze complex and high-dimensional data derived from electronic health records, medical imaging, electrocardiography, wearable devices, and multi-omics platforms. Its applications in obesity-related CVD can be broadly categorized into several areas, including automated image analysis, integration of multi-omics data, cardiovascular risk prediction, and personalized management [Table 4].

AI-based cardiovascular imaging analysis represents one of the most direct applications of AI in the evaluation of obesity-related CVD. Conventional image interpretation frequently requires manual delineation and measurement, which can be time-consuming and subject to interobserver variability. AI, particularly deep-learning-based image analysis, can automate image recognition, segmentation, and quantitative measurement. Commandeur *et al.* developed a convolutional neural network for fully automated EAT segmentation using multicenter cardiac CT data from 850 individuals. The algorithm showed a strong correlation with expert manual measurements ($r = 0.974$) and reduced the average analysis time from approximately 15 min for manual assessment to only 1.57 s[231]. AI can also automate the assessment of cardiac structure and function on echocardiography. Sahashi *et al.* developed EchoNet-Measurements, a deep-learning system trained using 877,983 echocardiographic measurements from 155,215 studies[232]. The model demonstrated high agreement with expert measurements across internal and external validation cohorts, and importantly, its performance remained consistent across patient characteristics, including obesity status[232]. Similar approaches have been extended to CMR. In a study including healthy individuals and patients with obesity or diabetes, deep-learning-based U-Net models were used to automatically segment EAT from standard four-chamber cine CMR images. The automated measurements showed performance comparable to interobserver variability and enabled rapid estimation of EAT burden without labor-intensive manual contouring[233]. Collectively, AI can transform qualitative or semiquantitative cardiovascular image interpretation into rapid, reproducible quantitative assessment, providing a practical foundation for more precise evaluation of obesity-related cardiac structural, functional, and adipose-tissue abnormalities.

AI also provides a powerful framework for integrating multi-omics data to achieve a more comprehensive evaluation of obesity-related CVD. Through dimensionality reduction, feature selection, unsupervised clustering, and nonlinear representation learning, AI can identify cross-omics molecular signatures that may

Table 4. Application of AI in obesity-related CVD assessment and management

Application domain	Reference	AI approach/data source	Study population/data	Key findings	Potential clinical application
AI-based cardiovascular imaging analysis	Commandeur *et al.*[231]	CNN-based automated segmentation of cardiac CT	Multicenter cardiac CT data from 850 individuals	Strong agreement with manual EAT assessment (r = 0.974); analysis time reduced to 1.57 s	Rapid EAT quantification
	EchoNet-Measurements[232]	Deep-learning analysis of echocardiography	877,983 echocardiographic measurements from 155,215 studies	High agreement with expert echocardiographic measurements	Automated cardiac assessment
	Deep-learning CMR segmentation[233]	U-Net-based automated EAT segmentation from CMR	100 participants comprising healthy individuals and patients with obesity or diabetes who underwent 3-T cardiac cine MRI	EAT measurements comparable to interobserver variability	Automated cardiac adiposity assessment
Multi-omics integration	Molecularly predicted BMI[234]	Machine learning integrating metabolomics, proteomics, genomics, gut microbiome, and other longitudinal molecular data	1,277 individuals	Multi-omic signatures distinguished metabolically favorable and unfavorable profiles despite similar anthropometric characteristics	Molecular obesity phenotyping
	CardiOmicScore[235]	Multitask deep learning integrating proteomic and metabolomic data	UK Biobank; 2,920 proteins and 168 metabolites	Multi-omic scores improved prediction of major CVDs	Molecular CVD risk stratification
Cardiovascular risk prediction and patient stratification	OBSCORE[237]	Machine-learning integration of high-dimensional clinical variables	~200,000 individuals with BMI > 27 kg/m^2; > 2,300 candidate features	20-variable model stratified 10-year cardiovascular mortality from ~ 0.1% to 5.7%	Cardiovascular risk prediction
	MetsObesity classification[238]	Random forest and recursive feature elimination	346,001 UK Biobank participants	Five-tier model stratified MACE risk from 1.4% to 8.5% and outperformed conventional obesity measures	Multidimensional risk stratification
	AI-ECG-derived BMI and delta-BMI[239]	Deep learning applied to 12-lead ECG	> 500,000 12-lead ECGs	Delta-BMI identified cardiometabolic risk beyond measured BMI	Detection of latent cardiometabolic risk
Personalized management	Personalized nutrition program[240]	Algorithm-driven integration of postprandial responses, gut microbiome, health history, and cardiovascular risk	Multidimensional metabolic and clinical data	Personalized nutrition improved cardiometabolic parameters	Personalized lifestyle intervention
	Prediction of response to GLP-1 receptor agonists[241]	Machine learning based on real-world clinical data	Real-world treatment data	High discrimination in predicting GLP-1 receptor agonist response	Personalized pharmacotherapy
	Bariatric/metabolic surgery prediction models[242,243]	AI-based prediction of longitudinal treatment response	Clinical and longitudinal surgical data	Predicted long-term weight and treatment outcomes	Personalized bariatric surgery
	Continuous digital monitoring[244]	AI analysis of wearable-device and digital-health data	Longitudinal physiological data from wearable and digital platforms	Enabled dynamic cardiometabolic risk assessment	Continuous risk monitoring

AI: Artificial intelligence; CVD: cardiovascular disease; EAT: epicardial adipose tissue; CT: computed tomography; CMR: cardiac magnetic resonance; CNN: convolutional neural network; U-Net: U-shaped convolutional neural network; ECG: electrocardiography; HF: heart failure; AF: atrial fibrillation; CAD: coronary artery disease; MACE: major adverse cardiovascular events; BMI: body mass index; EHR: electronic health record; GLP-1: glucagon-like peptide-1; UK Biobank: United Kingdom Biobank; PET: positron emission tomography. multi-omics, integration of genomic, proteomic, metabolomic, and microbiome data.

be difficult to detect using conventional analytical approaches. Watanabe *et al.* integrated longitudinal metabolomic, proteomic, genomic, gut microbiome, and other molecular data from 1,277 individuals and used machine-learning models to derive multi-omic signatures of BMI[234]. The resulting molecularly predicted BMI revealed substantial discordance with conventional BMI, distinguishing individuals with relatively favorable or unfavorable metabolic profiles despite similar anthropometric characteristics[234]. Notably, these molecular signatures were also responsive to lifestyle intervention, suggesting that multi-omics profiling can capture dynamic metabolic alterations that are not adequately represented by BMI alone[234]. More importantly, this approach extends from molecular phenotyping to cardiovascular risk prediction. Luo *et al.* recently developed CardiOmicScore, an AI-based framework using UK Biobank data to characterize cardiovascular risk from large-scale proteomic and metabolomic profiles[235]. Multitask deep-learning models analyzed 2,920 proteins and 168 metabolites to generate disease-specific molecular risk scores for six major CVDs, including coronary artery disease, HF, stroke, and AF. Proteomic and metabolomic signatures provided complementary predictive information and improved cardiovascular risk prediction when incorporated with genetic and conventional clinical risk factors[235]. Collectively, these studies demonstrate that AI enables multi-omics research to move beyond the analysis of individual biomarkers toward an integrated representation of the molecular networks underlying obesity-related cardiovascular risk. Such approaches may therefore bridge the gap between conventional obesity phenotyping and the complex biological mechanisms leading to CVD.

Cardiovascular risk prediction and patient stratification represent one of the most promising applications of AI in the evaluation of obesity-related CVD. Conventional risk assessment approaches fail to fully capture the complex interactions among adiposity, metabolic dysfunction, inflammation, comorbidities, and other determinants of cardiovascular risk. By integrating high-dimensional clinical information, including demographic characteristics, anthropometric measurements, biomarkers, imaging results, comorbidities, medication use, and potentially omics-derived features, machine-learning algorithms can identify nonlinear relationships that may not be readily detected using conventional statistical approaches[236]. Several recent studies illustrate this potential. Demircan *et al.* developed OBSCORE, a machine-learning-based risk prediction framework derived from approximately 200,000 individuals with a BMI > 27 kg/m^2[237]. From more than 2,300 candidate features, the model identified a parsimonious set of 20 clinically informative variables to predict 18 obesity-related complications. OBSCORE distinguished markedly different levels of cardiovascular mortality risk, with the 10-year incidence of cardiovascular death ranging from approximately 0.1% in the lowest-risk group to 5.7% in the highest-risk group, demonstrating that individuals with similar degrees of excess weight can have substantially different long-term cardiovascular risks[237]. Similarly, Iqbal *et al.* developed the MetsObesity classification system using data from 346,001 UK Biobank participants[238]. Random forest and recursive feature-elimination algorithms were used to select cardiovascular risk predictors, resulting in a five-tier risk classification. Over a median follow-up of 15 years, the incidence of MACE increased progressively from 1.4% in class 1 to 8.5% in class 5, and the model provided better prediction than BMI, WC, body-fat percentage, or conventional metabolic-syndrome definitions[238]. Pastika *et al.* developed a deep-learning model using more than 500,000 12-lead ECGs to estimate BMI from ECG signals and introduced "delta-BMI", defined as the difference between AI-ECG-predicted and measured BMI, as a novel cardiometabolic risk marker. Individuals in the highest delta-BMI tertile showed a significantly greater risk of subsequent cardiometabolic disease even after adjustment for measured BMI[239]. These studies highlight the potential of AI to move cardiovascular risk assessment in obesity beyond simple anthropometric classification toward more individualized, multidimensional risk stratification.

The ultimate goal of applying AI to obesity-related CVD is to translate multidimensional patient information into personalized prevention and treatment strategies. By integrating clinical characteristics, imaging-derived phenotypes, longitudinal physiological data, and molecular signatures, AI can enable individualized

decision-making and optimize therapeutic strategies. One important application of AI-based personalized management is the optimization of lifestyle and weight-loss interventions. For example, an algorithm-driven personalized nutrition program integrating postprandial metabolic responses, gut microbiome profiles, health history, and cardiovascular risk was shown to improve cardiometabolic parameters compared with conventional dietary advice[240]. AI may further facilitate personalized pharmacotherapy by predicting heterogeneous responses to anti-obesity medications. Machine-learning models based on real-world data have demonstrated high discrimination in predicting weight outcomes following GLP-1 receptor agonist initiation, suggesting a potential role for AI in identifying patients most likely to benefit from specific pharmacological therapies[241]. In metabolic and bariatric surgery, AI-based models can provide patient-specific predictions of long-term weight trajectories and treatment response, potentially informing the selection of surgical procedures and the intensity of postoperative follow-up[242,243]. AI-driven continuous monitoring represents another important component of personalized cardiovascular management. By analyzing data from wearable devices and digital health platforms, AI algorithms can detect early changes in cardiometabolic status and provide dynamic risk assessment[244,245].

Translational challenges and clinical considerations

Despite these promising advances, several important challenges remain before AI-based approaches can be applied to clinical practice.

First, the reliability and generalizability of AI models depend heavily on the quality and representativeness of their development datasets. Models trained in specific demographic cohorts may exhibit reduced performance when applied to populations with different ethnic backgrounds, and cardiometabolic risk profiles. Liu *et al.* developed neural network models for 10-year cardiovascular risk prediction using UK Biobank data and externally validated them in a Chinese cohort. Although the models maintained good discrimination in both populations (C-indices > 0.720), the predicted risks substantially underestimated the observed cardiovascular risk in the Chinese cohort by approximately 60%[246]. More broadly, differences in clinical settings, imaging acquisition systems, and data quality may further compromise model reliability. Gulati *et al.* conducted 158 independent external validations of 104 cardiovascular prediction models and found that median discrimination decreased from 0.76 during model development to 0.64 in external validation[247]. Nevertheless, encouraging evidence of model generalizability has also emerged. Demircan *et al.* externally validated OBSCORE in individuals of South Asian ancestry using a lower BMI inclusion threshold (≥ 22 kg/m^2), achieving a C-index of 0.78 for incident type 2 diabetes[237].

Second, biological interpretability remains an important consideration. For example, Pastika *et al.* demonstrated that the greater predictive value of AI-ECG-derived delta-BMI was associated with metabolic and proteomic signatures, including adiponectin, glycine, and valine. However, the selected metabolomic and proteomic markers explained only 4.6% and 9.8% of delta-BMI variability, respectively[239]. Although limited mechanistic interpretability does not necessarily invalidate a prediction model, insufficient understanding of physiological determinants of AI models may complicate the identification of confounding factors and assessment of pathophysiological processes. Recent studies have attempted to bridge this interpretability gap. Sau *et al.* developed an AI-ECG risk estimation platform and employed genome-wide association analyses to identify relationships between AI-predicted cardiovascular risk and genetic loci associated with cardiac electrophysiology, myocardial structure, and metabolism[248]. It is worth noting that mechanistic validation should be completed particularly when AI-derived models are intended to inform cardiovascular risk stratification or treatment decisions.

Perhaps most importantly, improved predictive performance does not necessarily translate into meaningful clinical benefit. Whether these improvements are sufficient to alter clinical decisions or improve patient outcomes remains uncertain. For instance, in the MARS-ED randomized controlled trial involving

1,303 patients, a machine-learning-based mortality prediction model demonstrated superior discrimination compared with conventional clinical risk scores (AUROC 0.84 *vs.* 0.65-0.75). However, its implementation did not alter clinical treatment plans (1/644 changes; 0.16%) and did not improve clinical outcomes, highlighting that superior predictive accuracy alone is insufficient to ensure meaningful clinical benefit[249]. Accordingly, the clinical translation of AI-based risk models should extend beyond conventional measures of discrimination to evaluate calibration, incremental value over established risk scores, and clinical net benefit, as emphasized in the recent American Heart Association scientific statement[250]. Prospective multicenter randomized controlled trials comparing AI-guided risk stratification and clinical management with conventional care are needed to determine whether AI-derived suggestions can meaningfully improve clinical decision-making and patient outcomes. Early randomized trials have begun to provide evidence of short-term clinical utility. Ying *et al.* conducted a multicenter randomized trial involving 149 hospitalized patients with type 2 diabetes, demonstrating that AI-assisted insulin titration achieved noninferior glycemic control compared with management by senior endocrinologists over five days (76.4% *vs.* 73.6%), without a significant increase in adverse events[251]. However, evidence regarding long-term cardiovascular benefits remains limited. Future trials evaluating hard cardiovascular endpoints, including major adverse cardiovascular events, HF hospitalization, and cardiovascular mortality, will be crucial for establishing the clinical value of AI-guided interventions and informing their broader implementation.

TREATMENT

Established guideline-recommended therapeutic strategies

Among the current therapeutic strategies for obesity-related CVD, weight reduction represents a fundamental approach supported by established clinical guideline recommendations. The main weight-management interventions include lifestyle interventions, pharmacological therapy, and metabolic and bariatric surgery [Table 5][252,253].

Lifestyle intervention represents the foundation and first-line strategy for obesity management, which mainly includes dietary modification and physical activity[253]. Current dietary strategies generally emphasize sustained energy restriction within healthy dietary patterns, such as the Mediterranean and Dietary Approaches to Stop Hypertension diets, which are characterized by greater consumption of fruits, vegetables, whole grains, legumes, and lean protein sources, together with reduced intake of saturated and trans fats, added sugars, and sodium[254]. Animal studies indicate that switching mice with obesity and HF from a high-fat to a low-fat diet can delay cardiac remodeling and improve diastolic function[255]. Consistent with these findings, Ma *et al.* reported that low-fat dietary interventions were associated with an 18% reduction in all-cause mortality (RR = 0.82, 95%CI: 0.71-0.95)[256]. In the PREDIMED study, a Mediterranean diet supplemented with extra-virgin olive oil or nuts was associated with a lower incidence of major cardiovascular events among individuals at high cardiovascular risk compared with a control diet[257].

Regular physical exercise represents another cornerstone of lifestyle intervention for obesity and exerts cardiovascular benefits through reductions in adiposity as well as direct improvements in vascular, metabolic, and myocardial function[258,259]. Different exercise types are discussed separately as they impose distinct acute hemodynamic demands on the cardiovascular system. Aerobic exercise, characterized by sustained rhythmic contraction of large muscle groups, markedly increases venous return, stroke volume, and cardiac output, predominantly imposing a sustained volume load on the ventricles with a comparatively modest pressure load[260,261]. Repeated increases in vascular shear stress also enhance endothelial nitric oxide bioavailability, contributing to improved endothelial function and lower resting blood pressure[262]. In the STRRIDE AT/RT trial, aerobic training significantly reduced visceral and hepatic fat and improved IR in sedentary adults with overweight or obesity, with greater reductions in visceral adiposity than resistance training[263]. Moreover, a meta-analysis involving 796 adults with obesity showed that aerobic exercise

Table 5. Effects of weight-management interventions on cardiovascular risk factors and clinical outcomes

Intervention category	Intervention		Population	Effect on cardiovascular outcomes
Lifestyle intervention	Dietary modification	Mediterranean diet	Individuals at high cardiovascular risk	Lower incidence of major cardiovascular events compared with the control diet[257]
		Low-fat diet	21,699 individuals with obesity	All-cause mortality: RR = 0.82 (95%CI: 0.71-0.95)[256]
	Physical activity	Aerobic exercise	796 adults with obesity	SBP: -3.4 mmHg; DBP: -2.8 mmHg[264]
		Resistance exercise	Adults with overweight or obesity	Improved body composition and cardiometabolic risk factors[266]
		HIIT	Individuals undergoing HIIT *vs.* moderate-intensity continuous training	Improved vascular function, including flow-mediated dilation[268]
Pharmacological therapy	Orlistat		36,876 patients with obesity	MACE: HR = 0.74 (95%CI: 0.66-0.83); MI: HR = 0.77 (0.66-0.88); new-onset HF: HR = 0.79 (0.67-0.94)[298]
	Liraglutide (GLP-1 RA)		Patients receiving liraglutide	MACE: HR = 0.87 (95%CI: 0.78-0.97); cardiovascular mortality: HR = 0.78 (0.66-0.93)[278]
	Semaglutide (GLP-1 RA)		17,604 adults with established CVD and BMI ≥27 kg/m^2 without diabetes	Cardiovascular death, nonfatal MI, or nonfatal stroke: HR = 0.80 (95%CI: 0.72-0.90)[280]
	Tirzepatide (dual GIP/GLP-1 RA)		731 patients with obesity and HFpEF	Cardiovascular death or worsening HF: HR = 0.62 (95%CI: 0.41-0.95)[282]
Surgery	Metabolic and bariatric surgery		Individuals with obesity	Cardiovascular mortality: HR = 0.70 (95%CI: 0.57-0.85); all-cause mortality: HR = 0.77 (0.68-0.87)[285]
			Patients with obesity and T2D	Major cardiovascular outcomes: adjusted HR = 0.61 (95%CI: 0.55-0.69); all-cause mortality: HR = 0.59 (0.48-0.72)[286]

Effects on cardiovascular outcomes are presented as effect estimates with 95% confidence intervals where available. CVD: Cardiovascular disease; MACE: major adverse cardiovascular events; MI: myocardial infarction; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; T2D: type 2 diabetes; BMI: body mass index; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; DASH: Dietary Approaches to Stop Hypertension; HIIT: high-intensity interval training; GLP-1 RA: glucagon-like peptide-1 receptor agonist; GIP: glucose-dependent insulinotropic polypeptide; SGLT2 inhibitor: sodium-glucose cotransporter 2 inhibitor; HR: hazard ratio; RR: relative risk; CI: confidence interval.

reduced systolic and diastolic blood pressure by approximately 3.4 and 2.8 mmHg, respectively[264]. Resistance exercise is characterized by brief, repetitive muscular contractions that mechanically compress the peripheral vasculature and increase sympathetic activation. These responses produce transient elevations in arterial pressure and ventricular afterload, resulting in a predominantly pressure-loading pattern and greater short-term systolic ventricular wall stress[265]. In the STRRIDE AT/RT trial, resistance training produced greater increases in lean body mass than aerobic training, whereas combined aerobic and resistance training provided benefits across both fat reduction and lean-mass preservation[266]. Long-term resistance training has also been associated with modest reductions in ambulatory blood pressure, further supporting its complementary role in cardiovascular risk management[267]. High-intensity interval training (HIIT) combines repeated short bouts of vigorous exercise with periods of active or passive recovery and therefore produces an intermittent but more intense hemodynamic stimulus, representing a time-efficient alternative to moderate-intensity continuous training. A systematic review found that HIIT improved several indices of vascular function, including flow-mediated dilation, compared with moderate-intensity continuous training[268]. However, evidence that HIIT is consistently superior for fat loss remains mixed, and its higher peak cardiovascular demand warrants individualized prescription, particularly in patients with established CVD[269,270]. Overall, aerobic exercise, resistance training, and HIIT exert cardiovascular protection through distinct but complementary hemodynamic and metabolic mechanisms.

Pharmacological therapy represents an important adjunct to lifestyle intervention in adults with obesity, particularly in individuals with obesity-related complications such as hypertension, dyslipidemia, type 2 diabetes, or CVD[271,272]. Historically, orlistat was one of the earliest pharmacotherapies approved for long-term obesity management. It inhibits gastric and pancreatic lipases, thereby reducing the hydrolysis of dietary triglycerides and subsequent intestinal fat absorption[273]. The weight-loss effect of orlistat is relatively modest: in the 4-year XENDOS trial, participants receiving orlistat in addition to lifestyle intervention lost an average of 5.8 kg, compared with 3.0 kg with lifestyle intervention alone[274]. The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) marked a major advance in pharmacological obesity treatment. GLP-1 RAs enhance satiety and reduce energy intake through central appetite-regulatory pathways, including activation of hypothalamic POMC/CART neurons and inhibition of orexigenic NPY/AgRP signaling, while also slowing gastric emptying and improving glucose homeostasis[275,276]. Liraglutide was the first GLP-1 RA widely used for chronic weight management. In the SCALE Obesity and Prediabetes trial, liraglutide produced a mean weight loss of 8.4 kg at 56 weeks compared with 2.8 kg with placebo, with 63.2% of treated participants achieving at least 5% weight loss[277]. Moreover, liraglutide reduced the incidence of major cardiovascular events by 13% (HR 0.87, 95%CI: 0.78-0.97) and cardiovascular mortality by 22% (HR 0.78, 95%CI: 0.66-0.93)[278]. The subsequent development of the longer-acting GLP-1 RA semaglutide substantially increased the magnitude of weight loss. In the STEP 1 trial, semaglutide combined with lifestyle intervention resulted in a mean body-weight reduction of 14.9% at 68 weeks compared with 2.4% with placebo[279]. Furthermore, among 17,604 participants with established CVD, semaglutide reduced the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 20% compared with placebo (HR 0.80, 95%CI: 0.72-0.90)[280]. More recently, tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, has further expanded the efficacy of incretin-based treatment. In the SURMOUNT-1 trial, mean weight reduction reached 15.0%, 19.5%, and 20.9% across increasing dose groups at 72 weeks, compared with 3.1% with placebo[281]. In the SUMMIT trial involving 731 patients with obesity and HFpEF, tirzepatide reduced the composite risk of cardiovascular death or worsening HF by 38% (HR 0.62, 95%CI: 0.41-0.95), while also improving health status and reducing body weight[282]. Collectively, pharmacological management of obesity has evolved from agents producing modest weight loss and improvements in cardiovascular risk factors toward incretin-based therapies capable of achieving substantial and sustained weight reduction together with demonstrable cardiovascular benefits. Drug selection should therefore consider not only weight-loss efficacy but also the patient's cardiovascular phenotype, metabolic comorbidities, treatment tolerability, and the strength of evidence for cardiovascular outcome improvement.

For individuals with severe obesity, particularly those with obesity-related metabolic or cardiovascular complications, metabolic and bariatric surgery (MBS) represents one of the most effective interventions for achieving substantial and sustained weight loss. According to the 2022 ASMBS/IFSO guidelines, MBS is recommended for individuals with a BMI ≥ 35 kg/m^2 regardless of the presence or severity of obesity-related comorbidities, and should also be considered in individuals with a BMI of 30-34.9 kg/m^2 who fail to achieve substantial weight loss or improvement in obesity-related complications with nonsurgical treatment; it is additionally recommended for patients with type 2 diabetes and a BMI ≥ 30 kg/m^2[283]. The most commonly performed procedures, including sleeve gastrectomy and Roux-en-Y gastric bypass, exert their effects through complex physiological mechanisms beyond gastric restriction, including altered gut-hormone signaling involving GLP-1, peptide YY, and ghrelin, as well as changes in gut microbiota and gut-brain communication[284]. Beyond weight reduction, bariatric surgery is associated with substantial cardiovascular benefits. Long-term evidence from the Swedish Obese Subjects study demonstrated that bariatric surgery was associated with lower all-cause mortality (HR = 0.77, 95%CI: 0.68-0.87) and cardiovascular mortality (HR = 0.70, 95%CI: 0.57-0.85) compared with usual obesity care, together with an approximately 3-year increase in adjusted median life expectancy[285]. Similar cardiovascular benefits have been observed in high-risk

populations. Among patients with obesity and type 2 diabetes, MBS was associated with a substantially lower incidence of major cardiovascular outcomes than nonsurgical management (adjusted HR = 0.61, 95%CI: 0.55-0.69), as well as lower all-cause mortality (HR = 0.59, 95%CI: 0.48-0.72)[286]. Nevertheless, surgery should be regarded as one component of long-term obesity management rather than an isolated intervention. Continued lifestyle modification after MBS remains important. A meta-analysis of postoperative exercise interventions demonstrated a significant improvement in cardiorespiratory fitness among patients undergoing exercise training after bariatric surgery[287]. Moreover, a randomized trial conducted three years after sleeve gastrectomy showed that supervised exercise reduced fat mass, fasting glucose, and blood cholesterol compared with usual postoperative care[288]. Therefore, combining MBS with sustained dietary modification, physical activity, and appropriate pharmacological or cardiometabolic management may provide the greatest long-term benefit for patients with obesity-related CVD.

Emerging mechanism-targeted therapeutic strategies

Beyond the established guideline-recommended interventions for weight management, increasing understanding of the molecular mechanisms linking obesity to CVD has accelerated mechanism-targeted therapeutic development. However, the clinical translation of these approaches remains at a relatively early stage.

Some agents targeting relevant signaling pathways have already been incorporated into clinical practice for other cardiovascular indications, although their efficacy specifically in obesity-related CVD remains uncertain. Among these, anti-inflammatory therapies have achieved notable clinical progress. Low-dose colchicine, which partly modulates NLRP3 inflammasome activation, has been recommended in the 2024 ESC guidelines for patients with atherosclerotic coronary artery disease[289]. In the LoDoCo2 trial, colchicine significantly reduced the risk of major cardiovascular events (HR = 0.69, 95%CI: 0.57-0.83)[290]. Similarly, IL-1 signaling inhibitors, including anakinra and rilonacept, have received guideline recommendations for patients with recurrent pericarditis[291]. In the RHAPSODY trial, rilonacept markedly reduced the risk of pericarditis recurrence compared with placebo (HR = 0.04, 95%CI: 0.01-0.18)[292]. Nevertheless, whether these therapeutic benefits extend to obesity-related cardiovascular injury remains to be established.

Several novel agents targeting pathogenic pathways have advanced to early-phase clinical trials involving individuals with obesity. For example, pegozafermin, a long-acting analog of protective adipokine FGF21, reduced triglyceride levels by 57.3%, compared with 11.9% in the placebo group, in a phase II trial involving patients with severe hypertriglyceridemia[293]. Ninerafaxstat, which partially inhibits mitochondrial 3-ketoacyl-CoA thiolase to suppress myocardial fatty acid oxidation and to promote glucose oxidation, was evaluated in the phase IIa IMPROVE-DiCE trial. In patients with obesity, type 2 diabetes, and HFpEF, ninerafaxstat treatment was associated with improved myocardial energetics and exercise capacity[294]. Similarly, pirfenidone, an antifibrotic agent that modulates TGF-β-related signaling, significantly reduced CMR-derived myocardial extracellular volume in patients with HFpEF in the phase II PIROUETTE trial[295]. Collectively, these findings highlight the therapeutic potential of targeting metabolic and fibrotic pathways in obesity-related CVD, although these approaches remain investigational and have not yet been recommended by clinical guidelines for this indication.

Other potential therapeutic strategies targeting obesity-induced myocardial lipotoxicity and mitochondrial dysfunction remain largely at the preclinical stage. For example, myriocin, an inhibitor of serine palmitoyltransferase that suppresses ceramide synthesis, reduced myocardial ceramide levels and improved glucose utilization in diet-induced obese mice[296]. Similarly, urolithin A enhanced PINK1/Parkin-dependent mitophagy, thereby alleviating mitochondrial dysfunction, improving diastolic function, and attenuating cardiac remodeling in obese mice. Mitochondrial dynamics also represent a potential therapeutic target[108].

As mentioned above, experimental inhibition of lipid-induced DRP1 acetylation attenuated excessive mitochondrial fission and cardiomyocyte injury, whereas complete DRP1 deletion impaired adaptive mitophagy and aggravated cardiac dysfunction under high-fat feeding[107,111]. Collectively, these preclinical findings support the therapeutic potential of targeting myocardial lipotoxicity and mitochondrial dysfunction, while highlighting the need to selectively modulate pathological signaling without disrupting essential adaptive mechanisms.

Taken together, these advances highlight the growing opportunities for mechanism-guided treatment of obesity-related CVD. The key challenge now lies in determining which molecular targets are pharmacologically actionable and whether their modulation translates into meaningful cardiovascular benefits in clinical trials. Such evidence will be essential for advancing these therapeutic strategies toward clinical practice and informing future guideline recommendations.

CONCLUSION

The close interplay between obesity and CVD represents a major global public health challenge. The pathogenesis of obesity-related CVD is multifactorial and involves AT dysfunction, systemic inflammation, ectopic fat deposition, cardiac metabolic dysfunction, and other interrelated mechanisms. These alterations collectively drive adverse structural remodeling and functional impairment of the cardiovascular system, ultimately contributing to the development of atherosclerosis, HF, arrhythmias, and other CVDs. Notably, many of these obesity-associated molecular and cellular abnormalities overlap with established mechanisms of cardiovascular ageing, suggesting that obesity may accelerate biological ageing of the cardiovascular system and thereby contribute to premature cardiovascular dysfunction[297].

Addressing obesity-related CVD will require coordinated efforts spanning basic research, clinical translation, and public health. Mechanistic studies should further identify the key molecular regulators and cellular switches that determine why only a subset of individuals with obesity develop cardiovascular complications. At the same time, greater emphasis is also needed on the discovery and validation of biomarkers, including circulating inflammatory mediators, imaging-derived phenotypes, and genomic or multi-omics signatures, that enable earlier and more accurate cardiovascular risk prediction. Another major priority is to translate emerging molecular targets and mechanistic insights into safe and effective therapeutic strategies. At the population level, innovative policies and long-term management strategies are also needed to prevent weight regain and sustain cardiovascular benefits after successful weight loss. Overall, research on obesity-related CVD is progressively shifting from describing broad associations to resolving biological heterogeneity, and from uniform treatment approaches to risk-adapted and precision-based preventive and therapeutic strategies.

DECLARATIONS

Authors' contributions

Designed and revised this work: Guo D
Performed the literature search and data analysis and drafted the manuscript: Liu Y, Cao Y, Qu G
Prepared tables and figures: Hu L, Li Y
Critically revised the work: Liu Y, Hu L
All authors approved the final manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the authors used ChatGPT-5.5 (OpenAI, released April 23, 2026) solely for language editing and improving readability. The authors reviewed and verified all AI-assisted revisions and take full responsibility for the accuracy, integrity, and final content of the manuscript.

ChatGPT was not used for study design, data collection or analysis, interpretation of results, or the formulation of scientific conclusions.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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