

Obesity and Cardiovascular Disease: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2026

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ABSTRACT

Background: Obesity is a chronic disease that directly contributes to cardiovascular disease (CVD) through biomechanical “fat mass disease” and dysfunction of epicardial adipose tissue, or “sick fat disease.” It also indirectly promotes CVD through adiposopathic immune and endocrine abnormalities that drive type 2 diabetes mellitus, hypertension, dyslipidemia, and thrombosis – all major CVD risk factors. This Clinical Practice Statement (CPS) reviews obesity-related cardiovascular disease pathology and outlines evidence-based strategies for clinical management.

Methods: This CPS is based on a review of relevant medical literature, interpreted through the clinical expertise of authors specializing in obesity medicine, all members of the Obesity Medicine Association (OMA). Organized into 26 sections, each includes an introduction, essential principles, a “top ten” list of key points, and a summary figure.

Results: The CPS reviews how obesity intersects with major cardiovascular risk factors, including type 2 diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, and thrombosis. Additional metabolic complications such as metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic kidney disease further elevate CVD risk. The CPS details obesity's impact on cardiac structure and function, including its role in heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, and CVD considerations in patients with obstructive sleep apnea, cancer, and psychiatric disease. It also addresses the “obesity paradox,” social determinants of health, pediatric considerations, and disparities by age, sex, and race. Also included are CVD diagnostic challenges and comprehensive management strategies, including medical nutrition therapy, physical activity, behavioral intervention, cardiometabolic medications, glucagon-like peptide-1 receptor agonists, and bariatric procedures.

Conclusion: Effective reduction of obesity-related CVD risk requires shifting from treating downstream risk factors to addressing excessive adipose tissue itself, along with improving adipose tissue function. Clinically, this approach is often manifest by a “treat obesity first” approach. Precision diagnostics, lifestyle therapy, obesity medications, and bariatric procedures can modify both adiposopathy (“sick fat disease”) and fat mass disease, improving long-term cardiovascular outcomes.

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Table 1
Ten things to know about obesity, epidemiology, and cardiovascular disease (CVD) [1].

Key Points	References
1. In the past 4 decades, the prevalence of obesity has doubled in more than 70 countries and tripled in the United States (US). In the US (NHANES August 2021–August 2023), obesity prevalence is 40.3% and severe obesity is 9.4%, with severe obesity higher in women than men in each age group. While overall obesity prevalence has plateaued, severe obesity continues to rise. Cardiovascular disease (CVD) accounts for two thirds of deaths attributable to obesity.	[1,2,14]
2. At a population level, increased body mass index (BMI) is associated with CVD risk. Compared to body mass index (BMI), percent body fat is a better diagnostic assessment of the relative amount of adipose tissue. Visceral adipose tissue accumulation is a better prognostic assessment for CVD risk.	[1,38]
3. Obesity is both a direct and indirect contributor to CVD. Obesity is a direct contributor to CVD via biomechanical mechanisms (e.g., increased blood volume and cardiac output, left ventricular hypertrophy from pressure/volume overload, impaired diastolic filling due to pericardial fat, and facilitation of sleep apnea).	[1,3]
4. Obesity is also an indirect contributor to CVD and adiposopathic immunopathies and endocrinopathies that lead to the promotion of major CVD risk factors such as type 2 diabetes mellitus, hypertension, dyslipidemia, and thrombosis, via chronic low-grade inflammation, contribution to insulin resistance, activation of the renin–angiotensin–aldosterone system, lipotoxicity, and generation of a procoagulant state.	[1,4,5,7,9]
5. Regarding types of CVD, increasing body fat contributes to increased risk of CVD such as coronary heart disease, heart failure, cardiac dysrhythmias (e.g., atrial fibrillation), and stroke.	[1,3]
6. Obesity and CVD risk is influenced by age, sex, race, income, education, as well as urban versus rural settings.	[1,39]
7. Other major contributors to both obesity and CVD are physical inactivity, commercial and environmental factors including ultra-processed foods, food systems, marketing, urbanization, and social determinants of health.	[1,40]
8. Childhood obesity increases the risk of adult obesity and CVD. The degree to which obesity contributes to CVD is dependent on lifetime exposure to obesity.	[1,41]
9. Sustained weight reduction among individuals with obesity at risk for CVD often improves CVD risk factors and reduces CVD risk.	[1,42]
10. Management of obesity and the reduction of cardiovascular disease risk are most effective when delivered through integrated team-based care with equity-focused health strategies, supported by public health interventions that drive population-level change. The World Heart Federation highlights pillars essential to this effort, including strong nutrition and food policy, promotion of physical activity, health-supportive urban design, education and behavioral initiatives, as well as coordinated action across sectors to create environments that enable healthful choices and sustained risk reduction.	[1,12]

1. Obesity, epidemiology, and cardiovascular disease (CVD) [1]
(See Table 1 and Fig. 1)

Between 1980 and 2015, the prevalence of obesity doubled in more than 70 countries and continued to increase in most other countries. In 2015, an estimated 603.7 million adults and 107.7 million children worldwide were living with obesity. This surge in increased adiposity is linked to 4.0 million deaths annually, over two-thirds being the result of cardiovascular disease (CVD). In the United States (August 2021–August 2023), the prevalence of obesity was above 40%, with severe obesity in adults at 9.4% (higher in women than men in each age group); overall obesity prevalence has plateaued while severe obesity continues to rise

[2]. Beyond its contribution to risk factors like type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia (as well as thrombosis, sleep apnea, and fatty infiltration of body organs – including fat infiltration of the heart) obesity is an independent driver of CVD development and mortality. Childhood and adolescent obesity trends suggest a continued rise in future global CVD risk. Essential principles include:

- Obesity increases CVD morbidity and mortality.
- Increased visceral adiposity is a body composition pattern associated with increased CVD risk.
- Treating obesity and CVD risk requires a comprehensive, equity-focused, system-level, team-based approach.

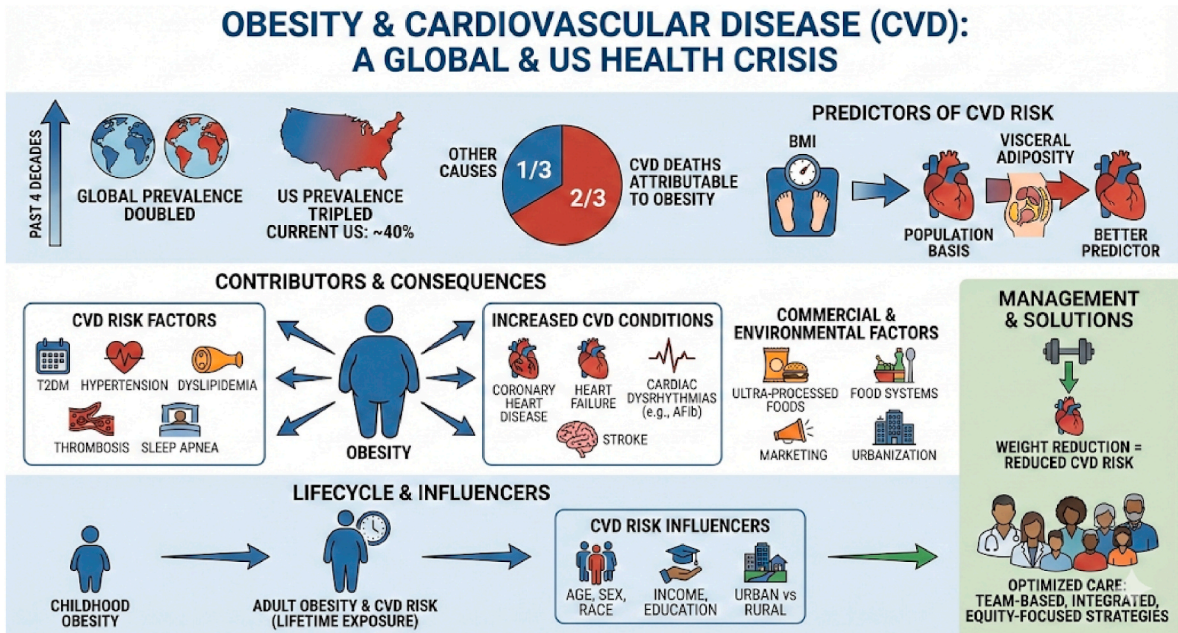


Fig. 1. Obesity, Epidemiology, and Cardiovascular Disease (CVD). Global obesity rates have climbed sharply, doubling in 73 countries since 1980 and contributing to millions of deaths each year—most from cardiovascular disease. In the United States, over 40% of adults have obesity, independently accelerating cardiovascular risk beyond traditional metabolic complications. Commercial, social, and environmental forces are major drivers of this epidemic and its downstream CVD burden. Meaningful reductions in obesity-related cardiovascular disease require a comprehensive, equity-focused, system-level, team-based approach. Sustained weight reduction lowers CVD risk, and the most effective and equitable outcomes arise from coordinated, optimized, multidisciplinary care. Although a higher body mass index (BMI) correlates with cardiovascular risk at the population level, increased visceral adipose tissue accumulation is a more accurate indicator of pathogenic adipose tissue distribution and a stronger predictor of individual cardiometabolic complications and cardiovascular disease risk.

2. Obesity, sick fat disease (adiposopathy), fat mass disease, and cardiovascular disease (CVD) [3] (See Table 2 and Fig. 2)

Obesity can contribute to CVD via “fat mass disease.” Obesity can also contribute to CVD via adiposopathy or “sick fat disease.” Regarding

“fat mass disease,” the biomechanical accumulation of adipose tissue may increase blood volume and cardiac contraction (due to increased adipose tissue blood supply), resulting in increase in heart size (i.e., left ventricular hypertrophy), cardiac dilation, and limitations on post contraction refill (i.e., “diastolic heart failure”), all contributing to heart

Table 2
Ten things to know about obesity, sick fat disease (adiposopathy), fat mass disease, and cardiovascular disease (CVD) [3].

Key Points	References
1. While the main function of body fat is to store excess energy, adipocytes and adipose tissue are active endocrine and immune tissues whose function and dysfunction have implications regarding cardiovascular disease (CVD).	[3,43]
2. Increased adipocyte hypertrophy and visceral adipose tissue accumulation can cause adipose tissue to become “sick” or become diseased or dysfunctional. Adiposopathy is analogous to the “pathies” of other body organs (e.g., myopathy, encephalopathy, ophthalmopathy, retinopathy, enteropathy, nephropathy, neuropathy, and dermopathy).	[3,8]
3. Cardiomyopathy describes a “disease” wherein pathologic enlargement of heart cells and the heart organ results in anatomic/functional abnormalities leading to adverse clinical consequences. Similarly, adiposopathy describes a “disease” wherein pathogenic enlargement of fat cells and the adipose tissue organ result in anatomic/functional abnormalities leading to adverse clinical consequences.	[3,8]
4. “Fat Mass Disease” reflects the biomechanical and structural burden of excess adiposity, driving conditions such as obstructive sleep apnea, diastolic dysfunction, heart failure with preserved ejection fraction (HFpEF), and venous thrombosis through direct mechanical compromise of airway, cardiac, and vascular function. These complications are further amplified by obesity-related physical inactivity, which worsens cardiopulmonary loading, impairs venous return, and accelerates the adverse downstream consequences of excess fat mass.	[3,8]
5. The adverse “sick fat” adiposopathic consequences of obesity often contribute to endocrine and immune dysfunction leading to insulin resistance and development of major cardiovascular risk factors including type 2 diabetes mellitus, hypertension, and dyslipidemia. These pathologic adipose-tissue signals also promote a pro-thrombotic state, further amplifying cardiometabolic risk.	[3,8]
6. Illustrative adiposopathic endocrine abnormalities include hypoadiponectinemia, hyperleptinemia, excess circulating free-fatty-acids, and dysregulated adipose-derived renin-angiotensin-aldosterone system (RAAS) activity, which collectively, can drive insulin resistance and major cardiometabolic risk factors (e.g., type 2 diabetes mellitus, hypertension, and dyslipidemia). These maladaptive hormonal signals may contribute to “ectopic fat deposition,” endothelial dysfunction, and pro-thrombotic adipokine patterns, thereby increasing the risk of CVD.	[3,8]
7. Illustrative adiposopathy immune abnormalities include macrophage infiltration of adipose tissue, increased production of pro-inflammatory cytokines, and impaired resolution of inflammation. The increased proinflammatory response coupled with reduced anti-inflammatory response promotes insulin resistance and cardiometabolic dysfunction (e.g., type 2 diabetes mellitus, hypertension, and dyslipidemia). These immune-mediated disturbances also contribute to endothelial injury and a pro-thrombotic state, accelerating the development of CVD.	[1,3,44]
8. Treatment of the consequences of obesity must not only reduce adiposity but also improve adiposopathy.	[3,8]
9. Obesity-related adiposopathy and the accumulation of adipose tissue in the visceral region, as well as ectopic fat accumulation in organs such as liver, skeletal muscle, pancreas, and kidneys drive insulin resistance, inflammation, lipotoxicity, and metabolic dysfunction, key mechanisms that accelerate the development of cardiovascular disease. These dysfunctional fat depots act not merely as markers of disease but as active contributors to atherogenesis, cardiomyopathy, and vascular injury.	[3,45]
10. Adiposopathy can drive inflammation, insulin resistance, and ectopic lipid spillover to other body areas. Epicardial adipose tissue (EAT) is the fat depot in contact with the myocardium. EAT is a potential local mediator of cardiovascular injury. Dysfunctional epicardial adipose tissue releases pro-inflammatory and pro-atherogenic factors that accelerate coronary heart disease and other CVD, making it a mechanistic etiological bridge between systemic and local CVD progression.	[3,46]

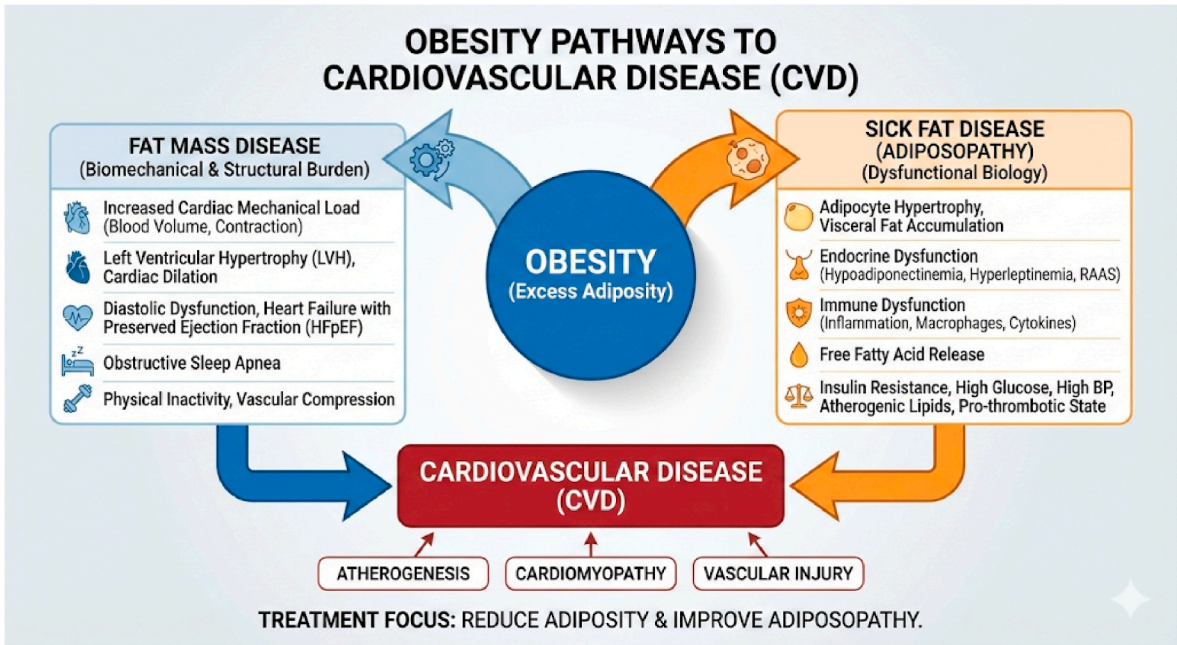


Fig. 2. Obesity, Sick Fat Disease (Adiposopathy), Fat Mass Disease, and Cardiovascular Disease (CVD). Obesity promotes CVD through two complementary mechanisms: the mechanical effects of excess fat mass (“fat mass disease”) and the metabolic–inflammatory dysfunction of adipose tissue (“sick fat disease”). Fat mass disease increases cardiac workload and impairs cardiopulmonary function, contributing to left-ventricular hypertrophy, diastolic dysfunction, sleep apnea, and reduced physical activity. Adiposopathy (“sick fat disease”) arises when hypertrophic, dysfunctional adipocytes trigger hormonal and immune disturbances that elevate glucose, blood pressure, atherogenic lipids, and thrombosis risk, collectively accelerating the risk of CVD.

Table 3
Ten things to know about obesity, “ectopic fat” (e.g., visceral fat, heart, muscle, liver, pancreas, kidney) and cardiovascular disease (CVD) [3,4].

Key Points	References
1. Non-adipose tissues help to determine the degree that obesity leads to glucose dysregulation and cardiometabolic disease, including CVD. Ectopic fat delivery to non-adipose tissue can result in either physiological or pathophysiological responses that can either help mitigate or facilitate vascular injury and cardiac dysfunction.	[3,4,45]
2. Healthy expansion of peripheral subcutaneous adipose tissue can buffer excess energy and prevent harmful ectopic fat deposition. By limiting lipid overflow into the heart, vessels, and liver, this protective mechanism reduces cardiovascular disease risk despite increased fat mass.	[3,4,45]
3. When adipocyte proliferation or differentiation in peripheral subcutaneous adipose tissue is impaired, then adipocytes may become enlarged (i.e., hypertrophied) and dysfunctional with limitations in further energy storage. The ensuing energy spillover drives ectopic fat deposition in cardiovascular-relevant organs, promoting inflammation, endothelial injury, and atherosclerosis.	[3,4,45]
4. Ectopic fat accumulation in the liver and muscle can cause “lipotoxicity,” which can directly impair organ function, resulting in insulin resistance. One illustrative adverse consequence is the accumulation of ceramides, which are sphingolipids that accumulate when tissues are exposed to excess fatty acids. Ceramides can act as key mediators of lipotoxicity by blocking insulin signaling, damaging mitochondria, and promoting inflammation. The end result of lipotoxicity is disruption of the function of the liver, muscle, pancreas, and heart, contributing to insulin resistance and CVD risk factors and CVD. For example, in the cardiovascular system, ectopic fat in epicardial adipose tissue (EAT) can contribute to lipotoxicity, myocardial steatosis, diastolic dysfunction, dysrhythmic remodeling, and accelerated atherosclerotic disease. Pancreatic fat can contribute to beta cell dysfunction and diminished insulin secretion, increasing the risk of onset of diabetes mellitus, a major CVD risk factor. Renal fat may activate the renin-angiotensin-aldosterone system (RAAS), increasing the risk of onset of hypertension, a major CVD risk factor.	[3,4,47]
5. Prediabetes, type 2 diabetes, hypertension, and dyslipidemia arise from multi-organ insulin resistance, which is worsened when ectopic fat infiltrates organs such as the liver, muscle and pancreas. Insulin resistance, type 2 diabetes mellitus, and dyslipidemia are CVD risk factors.	[3,4,48]
6. Age, sex, race, genetics, medications, and comorbidities may potentially influence whether excess energy (caloric intake beyond energy absorbed and expended) is stored safely in adipose tissue or diverted into ectopic depots. These same factors therefore shape susceptibility to CVD driven by ectopic fat. For example, aging compromises the storage capacity of peripheral adipose tissue, contributing to a ‘lipid spillover’ effect that shifts fat accumulation toward visceral and ectopic sites. Compared to White individuals and males, Black individuals and females tend to sequester excess energy in subcutaneous adipose tissue, resulting in lower visceral fat mass for any given body mass index. Individuals of Asian descent typically exhibit a limited capacity for subcutaneous adipose tissue expansion, causing excess lipid to overflow into visceral adipose tissue depots at a lower Body Mass Index (BMI) compared to other populations. Thiazolidinediones (TZDs) activate PPAR-gamma which promotes the creation of a “metabolic sink” where energy storage is enhanced via the proliferation and differentiation of more healthy, insulin-sensitive subcutaneous adipose tissue - which in turn - helps mitigate the otherwise harmful ectopic fat deposition such as energy spillover into visceral adipose tissue depots.	[3,4,45]
7. During weight-reduction interventions, peripheral subcutaneous adipose tissue (by far the largest fat depot) typically shows the greatest absolute reduction, increasing the potential for energy storage, which helps reduce lipid spillover. The greater capacity for energy storage via weight reduction reduces the substrate available for ectopic fat deposition, thereby lowering CVD risk.	[3,4,40]
8. Weight reduction improves the function of multiple organs, but the degree of improvement varies widely among individuals. These variable responses influence how effectively ectopic fat is cleared from organs, thereby modifying CVD risk.	[3,4,49]
9. Adipose-tissue and hepatic insulin sensitivity often improve with modest weight reduction, reducing systemic lipid spillover to other body organs and reducing hepatic secretion of atherogenic triglyceride-rich lipoproteins, both which may slow progression of CVD.	[3,4,48]
10. Obesity promotes ectopic fat deposition within epicardial adipose tissue (EAT), creating a metabolically active reservoir that releases pro-inflammatory cytokines, free fatty acids, and oxidative stress mediators that directly injure adjacent coronary vessels and myocardium. This inflammatory and lipotoxic microenvironment accelerates atherosclerosis, impairs vascular function, and increases the overall risk of CVD.	[3,4,46]

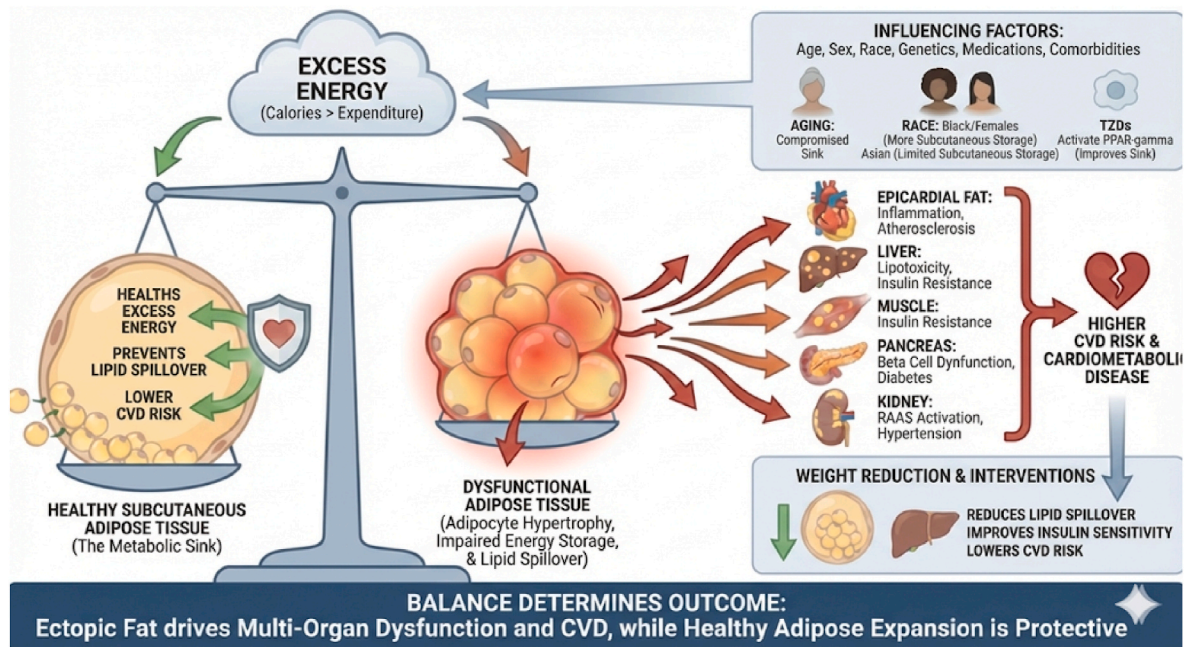


Fig. 3. Obesity, “Ectopic Fat” (e.g., Visceral, Cardiac, Hepatic, Muscle, Pancreas, Kidney) and Cardiovascular Disease (CVD). Obesity leads to CVD not simply through excess body weight, but through limits in adipose tissue expandability in peripheral subcutaneous adipose tissue (SAT), triggering both adiposopathy (i.e., resulting in adipocyte and adipose tissue endocrinopathies and immunopathies/inflammation) and energy overflow. During limitations in SAT energy storage, free fatty acids spill into the circulation and deposit as ectopic fat in visceral adipose tissue depots and within organs such as the liver, muscle, heart, and pancreas. In addition to adiposopathic immunopathies and endocrinopathies, the “ectopic fat” infiltrations of non-adipose tissue organs may result in lipotoxicity, insulin resistance, worsening cardiometabolic risk factors, and ultimately, CVD (i.e., atherosclerosis and myocardial damage).

Table 4
Ten things to know about obesity, diabetes mellitus, and cardiovascular disease (CVD) [4].

Key Points	References
1. Excess adiposity is a dose-dependent risk factor for type 2 diabetes mellitus (T2DM), raising the risk roughly three-fold for those who are overweight and sevenfold or more among those with obesity. T2DM is a major cardiovascular disease (CVD) risk factor. Higher body weight further increases both these risks. For most non-pregnant adults with T2DM, a hemoglobin A1c goal is <7.0%, with an even lower goal of <6.5% among select patients with diabetes mellitus and obesity who can achieve it safely through evidence-based weight reduction interventions (e.g., healthful nutrition, physical activity, behavior modification, obesity medications, and/or bariatric procedures).	[4,50,51]
2. About 40% of US adults have obesity; over 70% of US adults have overweight or obesity; about 25% of patients with obesity have T2DM; about 80–90% of adults with T2DM have overweight or obesity.	[4,52]
3. The adiposopathic effects of increased body fat are not the only causes of hyperglycemia. Other potential causes of hyperglycemia include hemochromatosis, hypercortisolism, excessive growth hormone, pancreatic insufficiency due to pancreatitis or surgical excision, side effects of concomitant therapies, genetic syndromes of insulin resistance, and genetic syndromes of limited pancreatic insulin secretion.	[3,4]
4. Adipocyte hypertrophy and visceral adipose tissue accumulation is reflective of an anatomic body composition pattern that results in endocrinopathies and immunopathies that directly contribute to glycemic-related CVD and indirectly contribute to CVD risk factors such as insulin resistance, hyperinsulinemia, and hyperglycemia.	[3,4]
5. Both obesity and T2DM are CVD risk factors that contribute to atherosclerotic coronary heart disease, endothelial dysfunction, microvascular disease, and left ventricular dysfunction (i.e., heart failure with preserved ejection fraction). An important unifying pathogenic mechanism among many patients with overweight or obesity is insulin resistance, which often leads to compensatory hyperinsulinemia. In addition to being a metabolic hormone, insulin has growth factor activities such that hyperinsulinemia promotes cardiovascular disease through pathway-selective resistance. While the metabolic signaling pathway (Phosphoinositide 3-Kinase or PI3K) is impaired with hyperinsulinemia - causing endothelial dysfunction and reduced nitric oxide - the growth-promoting pathway (Mitogen-Activated Protein Kinase or MAPK) remains sensitive to the high insulin levels. Consequently, hyperinsulinemia drives excessive anabolic signaling via MAPK, triggering inflammation and pathological cardiac hypertrophy, effectively acting as a potent, independent risk factor for heart and vascular disease.	[4,53]
6. Hyperglycemia develops when pancreatic beta-cell hyperinsulinemia can no longer compensate for insulin resistance. Hyperglycemia itself can drive cardiovascular disease through mitochondrial superoxide overproduction that activates four major injurious pathways: increased flux through the polyol pathway with depletion of antioxidant defenses, heightened hexosamine pathway activity, accelerated formation of advanced glycation end-products (AGEs), and activation of protein kinase C (PKC). Together, these mechanisms produce endothelial dysfunction, vascular inflammation, vasoconstriction, impaired nitric oxide signaling, and a pro-thrombotic state that promotes adverse CVD consequences such as atherosclerosis, cardiomyopathy, microvascular dysfunction, and even autonomic cardiac dysregulation potentially resulting in resting tachycardia, silent ischemia, orthostatic hypotension, and cardiac dysrhythmias.	[4,54]
7. While from a population standpoint, central obesity (increased waist circumference) is associated with both increased risk of T2DM and CVD, from an individual standpoint, an increase in waist circumference has variable correlation to an increase in visceral adiposity, especially upon consideration of age (i.e., older individuals have increased visceral adiposity), sex (i.e., females have less visceral adiposity than males), and race (i.e., Black individuals generally have decreased visceral adiposity while those of Asian descent may have increased visceral adiposity).	[4,55]
8. Hyperglycemia is one component of the metabolic syndrome (MetSyn), with MetSyn being a constellation of CVD risk factors. MetSyn includes central adiposity (as the only anatomic physical exam component), as well as high blood sugar, high blood pressure, and abnormal blood lipids.	[4,8]
9. In individuals with obesity and T2DM, weight reduction not only lowers CVD risk but is also the most reliable predictor of diabetes remission, whether achieved through dietary intervention, obesity medications, or bariatric procedures.	[4,56]
10. While some diabetes medications potentially worsen obesity (e.g., sulfonylureas, insulin), medications whose mechanisms reduce both blood glucose and body weight have among the strongest degree of evidence of reducing the risk of CVD (e.g., incretin mimetics such as glucagon-like peptide – 1 receptor agonist based therapies and sodium glucose transporter - 2 inhibitors).	[4,57]

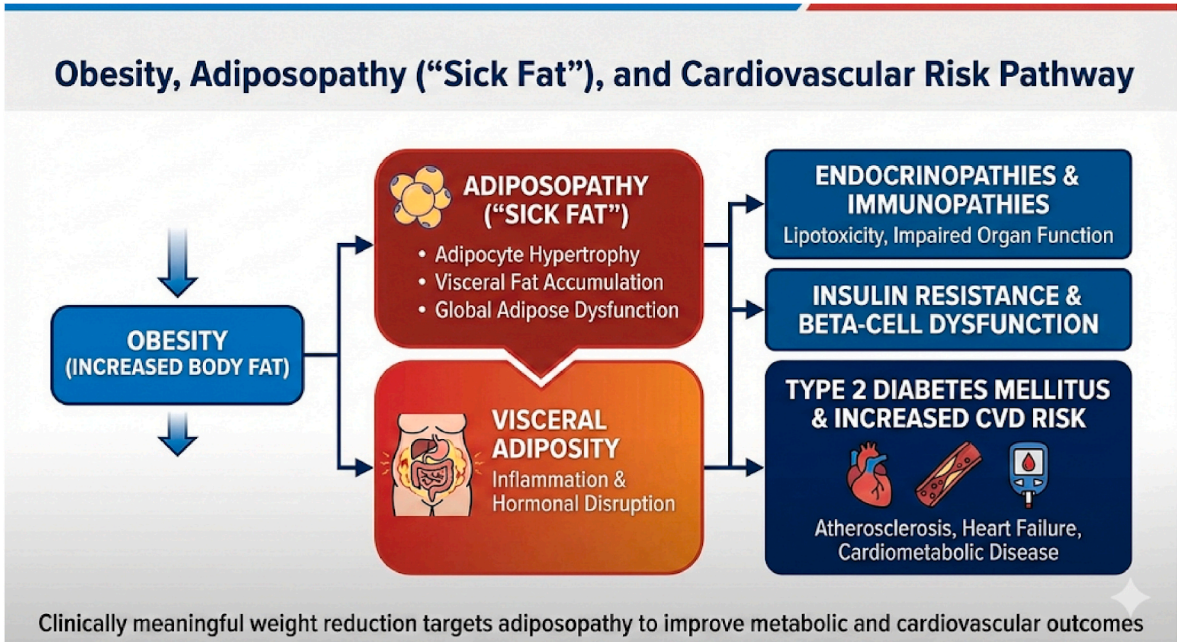


Fig. 4. Obesity, Diabetes Mellitus, and Cardiovascular Disease (CVD). “Sick fat” (adiposopathy) is anatomically manifest by adipocyte hypertrophy and visceral adipose tissue accumulation. The accumulation of visceral adiposity can be considered a marker of global fat dysfunction and immune/endocrine dysregulation. The resultant insulin resistance and beta cell dysfunction can lead to hyperglycemia, with type 2 diabetes mellitus being a major CVD risk factor. Clinically meaningful weight reduction can reverse aspects of adiposopathy, improve conditions like obstructive sleep apnea that worsen glycemic control, and in some cases even facilitate diabetes remission. Effective treatment of patients with obesity and type 2 diabetes mellitus combines healthful nutrition, regular physical activity, behavioral strategies, and evidence-based therapies (e.g., obesity medications and bariatric procedures) to reduce excess body fat and lower cardiometabolic risk.

Table 5
Ten things to know about obesity, hypertension, and cardiovascular disease (CVD) [5].

Key Points	References
1. Hypertension increases the risk of cardiovascular disease (CVD) such as coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, and aortic aneurysm. The 2025 American College of Cardiology/American Heart Association blood pressure goal for nonpregnant adults is <130/80 mmHg, with encouragement to achieve a systolic blood pressure <120 mmHg (when it can be safely attained) for potential additional health benefits. The lower optimal blood pressure goal is relevant for patients with obesity who can achieve it safely through evidence-based weight reduction interventions (e.g., healthful nutrition, physical activity, behavior modification, obesity medications, and/or bariatric procedures).	[5,58]
2. The adiposopathic effects of increased body fat are not the only causes of hypertension. Other potential causes of high blood pressure include pheochromocytoma, primary hyperaldosteronism, hypercortisolism, hyperthyroidism, renal artery stenosis, kidney diseases, side effects of concomitant therapies, and familial or genetic syndromes.	[5,58]
3. The relationship between body fat and blood pressure is approximately linear on a population level. Obesity-related hypertension arises partly from “fat mass disease,” in which visceral adipose tissue mechanically compresses the kidneys - activating the renin-angiotensin-aldosterone system (RAAS). Expanded adipose tissue increases total blood volume, cardiac output, and results in venous compression. Unlike the kidney, arteries are not confined within a rigid capsule, so perivascular adipose tissue (PVAT) does not raise blood pressure by physically squeezing them; arterial pressure far exceeds the pressure of surrounding soft fat, and healthy PVAT even acts as a buttress that stabilizes the vessel. Instead, dysfunctional, obesity-associated PVAT drives hypertension through an “outside-in” process: inflammation and fibrosis stiffen the adipose tissue into a rigid scaffold that limits arterial expansion, loss of normal PVAT stress-relaxation keeps vessels under higher tension, and paracrine signaling promotes collagen deposition within the arterial wall, collectively increasing arterial stiffness and promoting hypertension.	[5,59]
4. Increased fat mass contributes to obstructive sleep apnea (OSA), which promotes hypertension through activation of the sympathetic pathways and the RAAS, leading to increased blood pressure. Treating obesity and OSA - through weight reduction (e.g., including the use of tirzepatide) or continuous positive airway pressure (CPAP) - reduces blood pressure and improves other CVD risk factors.	[5,58]
5. Adiposopathic “sick fat” contributors to hypertension include hyperinsulinemia and hyperleptinemia, which increase sympathetic nervous system activity; increase angiotensinogen, mineralocorticoids, RAAS activity, and sodium reabsorption; increase the adiposopathic release of pro-inflammatory cytokines (e.g., tumor necrosis factor and interleukin-6) that impair endothelial function; and reduce anti-inflammatory adiponectin release.	[3,5]
6. Ensuring an accurate diagnosis of hypertension requires consistent measurement techniques tailored for patients with obesity. Improper cuff size can significantly distort readings, sometimes (depending on the cited reference) by as much as ~5–20 mmHg. Given the bias and discrimination against those with obesity, and/or fear of potential bias and discrimination (even within the healthcare setting), standardized measurements are necessary to control for “white coat syndrome,” which better allows for clinicians to distinguish true hypertension from stress-related elevations and avoid misdiagnosis.	[5,58,60,61]
7. Medical nutrition therapy (MNT) uses individualized nutrition assessment, education, and behavioral counseling to help patients modify dietary patterns in ways that improve obesity and hypertension. MNT emphasizes calorie-appropriate, nutrient-dense eating patterns such as reducing sodium and saturated fat while increasing fruits, vegetables, and whole grains to support weight reduction and improve blood pressure control. Illustrative examples of recommended, healthful eating pattern to help manage obesity and hypertension include the “Dietary Approaches to Stop Hypertension” or DASH diet or Mediterranean Diet.	[5,62]
8. Among patients with obesity and hypertension, regular physical activity includes routine non-exercise activity thermogenesis (i.e., NEAT), dynamic training, beginning at a minimum of 5000 steps per day and potentially progressing toward 10,000 steps per day or more and resistance training, all which may help support weight reduction management, improve blood pressure, enhance functional capacity, and reduce cardiometabolic risk. Health risks of physical exercise are generally low but may include musculoskeletal strain, overexertion, or transient blood-pressure elevations, underscoring the importance of medical supervision, gradual progression, and individualized guidance (such as through an exercise prescription), especially in those with obesity-related complications, such as CVD.	[5,63]
9. Optimal choice of antihypertensive agent is essential because different drug classes have different side-effect profiles [e.g., edema with some calcium-channel blockers, electrolyte disturbances with thiazide diuretics, weight gain with some older beta-blockers (e.g., atenolol and metoprolol) and risks like hypotension or syncope]. Patient-centered antihypertensive therapy better allows clinicians to balance efficacy with safety by anticipating these potential complications and tailoring treatment to each patient's comorbidities, risk factors, and physiological vulnerabilities. For example, in patients with obesity who have increased RAAS activity, a mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone, finerenone) may be effective.	[5,64]
10. Among patients with obesity and hypertension, weight reduction through healthful nutrition, physical activity, behavior modification, obesity medications, or bariatric procedures, may all lower blood pressure - depending on the degree the evidence-based interventions are implemented. Substantial weight reduction can even lead to hypertension “remission” or a reduced need for antihypertensive medications, highlighting the importance of weight-focused and blood pressure treatments as adjunct to traditional blood-pressure management. While obesity medications such as orlistat do not generally alter heart rate, and while weight reduction among patients with obesity generally decreases blood pressure, glucagon-like peptide-1 receptor agonists may mildly increase heart rate by 2–3 beats per minute. Phentermine/topiramate, phentermine monotherapy, and naltrexone/bupropion may have a higher heart rate at the end of studies compared to placebo, but many have the same heart rate or lower than baseline.	[5,63]

failure with preserved ejection fraction. Fat mass disease can also contribute to obstructive sleep apnea, physical inactivity, and arterial vascular compression. Adiposopathy or “sick fat” arises when, unlike healthy adipose tissue that serves as a safe energy reservoir and endocrine/immune regulator, fat cells (adipocytes) undergo excessive enlargement (hypertrophy) with subsequent limitations on further energy storage in peripheral subcutaneous adipose tissue, thus resulting in visceral adipose tissue accumulation. The ensuing endocrinopathies, immunopathies, and free fatty acid release promote insulin resistance, high blood glucose, high blood pressure, and elevated atherogenic blood lipids, as well as increased risk of thrombosis. Ultimately, the adiposopathic consequences of obesity may lead to an array of CVD. Essential principles include:

- Obesity contributes to CVD in two main ways: through excess fat mass (“fat mass disease”) and through dysfunctional fat biology (“sick fat disease”).
- Fat mass disease increases the mechanical burden on the heart and lungs, contributing to conditions like left-ventricular hypertrophy, diastolic dysfunction, sleep apnea, and reduced physical activity.
- Sick fat disease occurs when enlarged, dysfunctional fat cells drive hormonal and inflammatory disturbances that raise blood sugar,

blood pressure, atherogenic lipids, and clotting risk, ultimately promoting CVD.

3. Obesity, “ectopic fat” (e.g., visceral, cardiac, hepatic, muscle, pancreas, kidney) and cardiovascular disease (CVD) (See Table 3 and Fig. 3)

The progression from obesity to adverse health outcomes is best understood not just by an assessment of body weight, but by body composition and the concept of energy overflow and adiposopathy (dysfunctional “sick” adipose tissue). When peripheral subcutaneous adipose tissue stores reach their expansion limit or become inflamed, then they fail to safely sequester additional or excess energy. This failure forces an energy metabolic “spillover,” resulting in increased circulating free fatty acids and the pathogenic accumulation of “ectopic fat” in areas other than peripheral subcutaneous adipose tissue, such as visceral depots (abdominal and cardiac), the liver, skeletal muscle, pancreas, and kidneys. This ectopic deposition induces organ-specific toxicity (lipotoxicity) and systemic insulin resistance, serving as a driver of atherosclerosis and structural heart changes that increase the risk of CVD. Essential principles include:

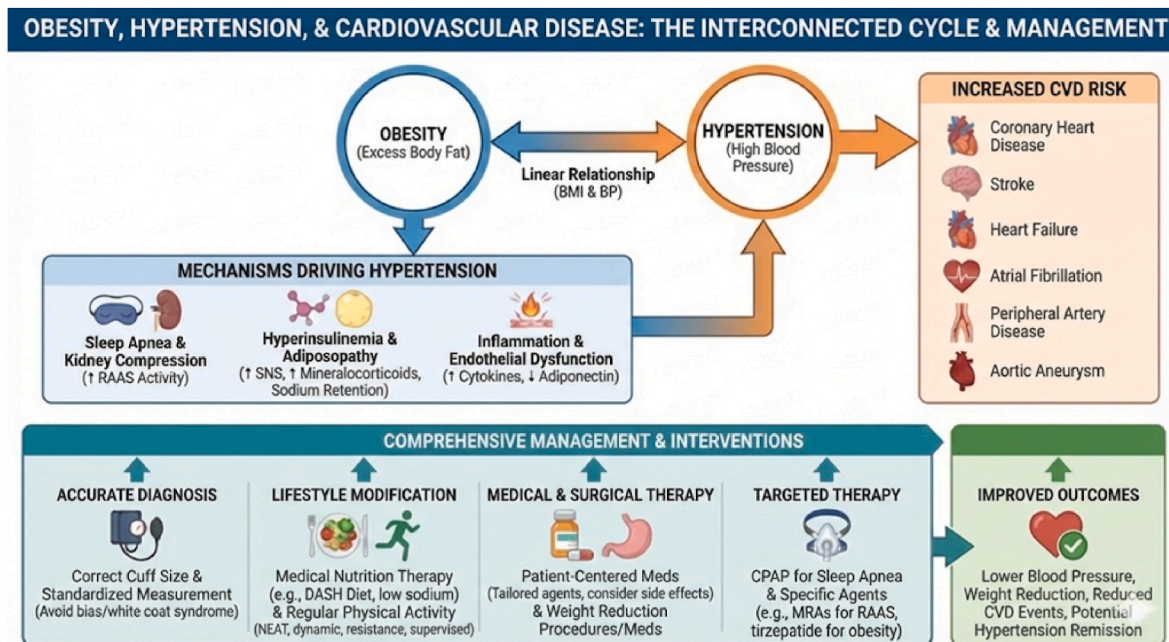


Fig. 5. Obesity, Hypertension, and Cardiovascular Disease (CVD). Increased body fat is the leading contributor to high blood pressure, driven both by the physical effects of excess body fat (e.g., compression of the kidneys and sleep apnea) which activate the renin–angiotensin–aldosterone system, and by dysfunctional adipose tissue that increases hormone and immune activity. Among the adiposopathic consequences of obesity leading to hypertension include increased sympathetic nervous system activity because of insulin resistance, hyperinsulinemia, and hyperleptinemia. Accurate measurement of blood pressure requires consistent technique, including proper cuff size and awareness of “white-coat syndrome” elevation. Treatment of obesity and hypertension is best focused on weight reduction through healthful nutrition such as the Dietary Approaches to Stop Hypertension and Mediterranean eating patterns, regular physical activity, behavior modification, obesity medications, and bariatric procedures, with improvements in blood pressure generally proportional to the degree of weight reduction.

- Obesity-related increase in CVD risk stems less from body weight alone and more from the functionality or dysfunctionality of adipose tissue, which can be reflected by body composition (i.e., increase in visceral adiposity).
- When subcutaneous adipose tissue can no longer expand or becomes resistant to further energy storage (e.g., as might occur with inflammation), then excess energy spills over into the bloodstream in the form of free fatty acids and deposits as “ectopic fat” in the visceral area of the abdomen, and organs like the liver, muscle, heart, pancreas, and kidneys.
- Non-adipose organ accumulation of fat can result in “lipotoxicity” leading to insulin resistance, and driving the onset of CVD risk factors, atherosclerosis, and structural heart changes that increase the risk of CVD.

4. Obesity, diabetes mellitus, and cardiovascular disease (CVD) [4] (See Table 4 and Fig. 4)

“Sick fat” (i.e., adiposopathy) is a common pathophysiological link between obesity, T2DM, and CVD. Adipocyte hypertrophy and visceral adipose tissue accumulation reflect an anatomic manifestation of global adipose tissue dysfunction leading to immunopathies, endocrinopathies, and lipotoxicity that impair the function of non-adipose organs (such as the liver, muscle, and pancreas), ultimately driving insulin resistance and beta-cell dysfunction. Addressing the adiposopathic consequences of increased body fat is one of the rationales for the “treating obesity first” paradigm, where clinically meaningful weight reduction can potentially lead to T2DM remission and improved cardiometabolic outcomes. Weight reduction can also improve fat mass disease, which has implications regarding glycemic control. Among patients with overweight or obesity, alleviating conditions such as obstructive sleep apnea through weight reduction may help improve hyperglycemia otherwise driven by hypoxia, sympathetic activation, and insulin resistance. Weight reduction strategies include evidence-based healthful

nutrition, routine physical activity, behavior modification, and the use of pharmacotherapy [specifically incretin mimetics such as glucagon-like peptide-1 receptor agonists (GLP-1 RA), as well as sodium-glucose linked co-transporter 2 (SGLT2) inhibitors] or bariatric procedures - that all collectively treat excessive body weight, type 2 diabetes mellitus, CVD risk and CVD. Essential principles include:

- “Sick fat” (adiposopathy) links obesity, type 2 diabetes, and cardiovascular disease through dysfunctional adipose tissue that drives inflammation, hormonal disruption, and lipotoxicity leading to insulin resistance and beta-cell stress.
- Clinically meaningful weight reduction can help treat adiposopathic consequences, improve obstructive sleep apnea-related metabolic stress, and even enable diabetes remission with better cardiometabolic outcomes.
- Effective management of obesity and type 2 diabetes includes healthful nutrition, regular physical activity, and evidence-based therapies such as GLP-1 RA, SGLT2 inhibitors, or bariatric procedures to reduce adiposity and cardiometabolic risk.

5. Obesity, hypertension, and cardiovascular disease (CVD) [5] (See Table 5 and Fig. 5)

Increased body fat is the leading modifiable contributor to hypertension, with population-attributable estimates of approximately 78% in men and 65% in women. This strong correlation is driven by “fat mass disease,” where pathogenic physical forces - such as the compression of kidneys by visceral adipose tissue - increase intrarenal pressure and stimulate the renin-angiotensin-aldosterone system (RAAS), leading to sodium retention and volume expansion. Additionally, “sick fat disease” (adiposopathy) contributes to hypertension through metabolic dysfunctions, including the secretion of angiotensinogen by adipose tissue which upregulates RAAS, as well as hyperleptinemia and insulin resistance which increase sympathetic nervous system activity. Ensuring an

accurate assessment of blood pressure requires consistent measurement techniques to control for variables such as cuff size and white-coat hypertension. Clinical management of obesity-related hypertension prioritizes weight reduction through healthful nutrition (e.g., the “Dietary Approaches to Stop Hypertension” or DASH diet), other healthful eating plans that reduce blood pressure (e.g., low carbohydrate dietary intake) [6], routine physical activity, bariatric procedures, and obesity medications like GLP-1 RA. Among patients with obesity-related hypertension, the degree of blood pressure reduction generally correlates with the magnitude of weight reduction. Essential principles include:

- Increased body fat is the leading contributor to hypertension.
- Accurate blood pressure assessment requires consistent technique, including proper cuff size and attention to white-coat effects.
- Treatment of high blood pressure in patients with obesity focuses on weight reduction through evidence-based healthful nutrition, physical activity, obesity medications, and bariatric procedures, with blood pressure improvements generally proportional to the amount of weight lost.

6. Obesity, dyslipidemia, and cardiovascular disease (CVD) [7] (See Table 6 and Fig. 6)

Obesity is defined as a chronic, relapsing disease characterized by “adiposopathy” (adipose tissue dysfunction), wherein excess adiposity both directly and indirectly contributes to increased risk of CVD. “Adiposopathic dyslipidemia” is a lipid pattern often found in patients with obesity, distinguished by elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), and increased atherogenic particles such as increased small dense LDL concentration and increased apolipoprotein B (apoB) levels, even when LDL cholesterol levels are only modestly elevated. Pathophysiologically, this state is driven by adipocyte hypertrophy, inflammation, and impaired lipolysis, which increase circulating free fatty acids. Weight reduction therapies such as healthful nutrition, physical activity, behavior modification, obesity medications, and bariatric procedures can often improve the patient's lipid profile (particularly triglycerides and HDL-C) and reduce adverse CVD outcomes. This underscores the benefits of an “all of the above” approach when treating excess adiposity and atherogenic cholesterol levels. Essential principles include:

- Obesity is a chronic, relapsing disease marked by adipose-tissue dysfunction that increases cardiometabolic risk, at least partially through generation of “adiposopathic dyslipidemia.”
- “Adiposopathic dyslipidemia” is characterized by high triglycerides, low HDL cholesterol, and often, an increase in non-HDL cholesterol and apoB-containing particles.
- While weight-reduction strategies can often improve triglyceride and HDL cholesterol levels, optimal control of LDL cholesterol often requires specific cholesterol lowering therapies such as statins.

7. Obesity, metabolic syndrome, and cardiovascular disease (CVD) [8] (See Table 7 and Fig. 7)

The relationship between obesity, metabolic syndrome, and CVD can be attributable to “adiposopathy” or “sick fat,” which can be defined as adipose tissue dysfunction resulting from positive caloric balance and sedentary lifestyle in susceptible individuals. Rather than obesity being merely an accumulation of inert mass, this “sick fat” acts as an active endocrine and immune organ that drives the cluster of CVD risk factors associated with metabolic syndrome - such as high glucose, high blood pressure, and high atherogenic lipids. Beyond genetic influences, in many patients, adiposopathy represents the single, primary cause of this constellation of CVD risk factors. Essential principles include:

Metabolic syndrome diagnosis includes the presence of **3 or more of the following 5 risk factors:**

1. **Abdominal Obesity:** Waist circumference ≥ 102 cm (40 in) for men, ≥ 88 cm (35 in) for women.
2. **Elevated Fasting Glucose:** ≥ 100 mg/dL (or on drug therapy for hyperglycemia).
3. **Elevated Blood Pressure:** Systolic ≥ 130 mmHg and/or Diastolic ≥ 85 mmHg (or on antihypertensive drug therapy).
4. **Elevated Triglycerides:** ≥ 150 mg/dL (or on drug therapy for hypertriglyceridemia).
5. **Reduced HDL Cholesterol:** < 40 mg/dL in men, < 50 mg/dL in women (or on drug therapy for reduced HDL cholesterol).

8. Obesity, thrombosis, and cardiovascular disease (CVD) [9] (See Table 8 and Fig. 8)

Obesity contributes to a prothrombotic state through “fat mass disease,” where adipose tissue exerts pathogenic physical forces causing vascular compression and venous stasis. Obesity can also promote thrombosis through “sick fat disease” (adiposopathy), which promotes inflammation, endothelial dysfunction, and hypercoagulability. In addition to managing deep vein thrombosis, pulmonary embolism, and chronic venous insufficiency, clinicians sometimes encounter obesity-related lymphedema and the distinct familial disorder of lipedema (i.e., chronic accumulation of adipose tissue, primarily in the legs, that often causes pain, tenderness, easy bruising) [10]. Regarding treatment of thrombosis, some anti-thrombotic medications are weight based. This is important because while weight reduction strategies such as healthful nutrition, physical activity, behavior modification, and bariatric procedures have their role, weight reduction alone among patients with obesity is often not sufficient for all venous, lymphatic, or lipedemic disorders. Essential principles include:

- Obesity contributes to venous and lymphatic disorders through both “fat mass disease,” which causes mechanical compression and stasis, and “sick fat disease,” which drives inflammation, endothelial dysfunction, and hypercoagulability.
- In addition to deep vein thrombosis, pulmonary embolism, and chronic venous insufficiency, clinicians may also encounter obesity-related lymphedema and the distinct familial condition of lipedema.
- Although weight-reduction strategies are valuable, they are often insufficient on their own to fully address venous, lymphatic, or lipedemic disorders in patients with obesity.

9. Obesity, obstructive sleep apnea (OSA), and cardiovascular disease (CVD) [11] (See Table 9, Figs. 9a and 9b)

Obesity is a primary contributor to sleep-disordered breathing. An example would be adverse anatomical changes such as pharyngeal airway narrowing and increased tongue fat deposition which play mechanistic roles in obstructive sleep apnea (OSA). OSA may occur in up to 70% of patients with obesity. The relationship is bidirectional: pharyngeal fat narrows the airway contributing to OSA, while sleep fragmentation from OSA increases ghrelin and decreases leptin, resulting in increased appetite and a vicious cycle of weight gain and worsening sleep dysfunction. Untreated OSA leads to sympathetic overactivity, resistant hypertension, and dysrhythmias like atrial fibrillation, as well as increased risks for T2DM and hypertension (two major CVD risk factors), as well as stroke, heart failure, and sudden death. Treatment includes weight reduction through healthful nutrition, physical activity, and behavior modification. Obesity medications (e.g., tirzepatide) and bariatric procedures can also improve OSA. Essential principles include:

- Obesity contributes to obstructive sleep apnea (OSA) through anatomical changes such as pharyngeal airway narrowing and increased tongue fat, and up to 70% of people with obesity may develop OSA.

Table 6
Ten things to know about obesity, dyslipidemia, and cardiovascular disease (CVD) [7].

Key Points	References
1. Obesity is often associated with an “adiposopathic dyslipidemia” which includes increased triglycerides and reduced high density lipoprotein cholesterol. Most medical organizations recommend the following goals among patients at high CVD risk, which may include many patients with obesity having other CVD risk factors: Low density lipoprotein (LDL) cholesterol <70 mg/dL, non-high density lipoprotein (non-HDL) cholesterol goal <100 mg/dL, and apolipoprotein B goal <80 mg/dL. Patients with obesity at higher CVD risk have even lower, more aggressive lipid goals.	[7,65]
2. Particularly when accompanied by insulin resistance and type 2 diabetes mellitus, the obesity-driven “adiposopathic dyslipidemia” may include increased atherogenic particles such as increased number of circulating small dense low density lipoproteins (LDL) and increased apolipoprotein B, even when LDL cholesterol levels are only modestly elevated. Small, dense LDL particles are more likely to penetrate arterial walls and contribute to atherosclerosis.	[7,66]
3. The adiposopathic effects of increased body fat are not the only causes of dyslipidemia. Other potential causes of increased circulating atherogenic lipids include inadequately controlled hypothyroidism or diabetes mellitus, liver disease, kidney disease, side effects of concomitant therapies, and genetic dyslipidemias.	[7,65]
4. Impaired storage of triglycerides in adipose tissue may lead to increased circulating free fatty acids, increased delivery of fatty acids to the liver, increased hepatic very low density lipoprotein (VLDL) cholesterol secretion (which carry triglycerides) and thus increased circulating triglyceride levels.	[7,45]
5. Increased triglyceride rich lipoprotein production may contribute to enzymatic exchanges of lipoprotein cholesterol and triglycerides, resulting in reduced levels of high density lipoprotein cholesterol, which is a hallmark of “adiposopathic dyslipidemia.”	[7,66]
6. Typically, obesity only results in modest increases in LDL cholesterol levels. However, an LDL cholesterol level alone may underestimate the number of atherogenic lipoprotein particles. Better lipid measures include non-HDL-cholesterol, which is a measure of cholesterol carried by all atherogenic lipoproteins (i.e., inclusive of atherogenic triglyceride rich lipoproteins, and not just LDL). A perhaps even better measure is apoB, which is a direct measure of atherogenic particles number and a proven CVD risk factor.	[7,65]
7. Increased visceral adiposity strongly correlates with elevated apolipoprotein B (apoB) levels, which is a structural protein found on the surface of all atherogenic (plaque-forming) lipoproteins. ApoB is thus a measure of the number of all circulating atherogenic lipoproteins.	[7,40]
8. Lipoprotein(a) [Lp(a)] is a genetically determined CVD risk factor not meaningfully affected by nutrition, physical activity or weight reduction in patients with obesity. Especially in patients at high CVD risk, it is often recommended that Lp(a) be measured at least once in a lifetime.	[7,67]
9. Among patients with obesity, healthful nutrition, physical activity, behavior modification, and obesity medications may somewhat improve dyslipidemia, mainly via lowering triglycerides and raising HDL-cholesterol. Unless substantial weight reduction is achieved via highly effective obesity medication and bariatric procedures, LDL cholesterol is often only marginally improved. That said, especially with lower dietary fat intake, HDL cholesterol may transiently decrease during weight reduction.	[7,68,69]
10. Statin therapy remains a cornerstone treatment for patients with obesity at increased risk for CVD – a recommended treatment unlikely to change with the modest improvement in LDL cholesterol most often found in most clinical treatments of obesity.	[7,65]

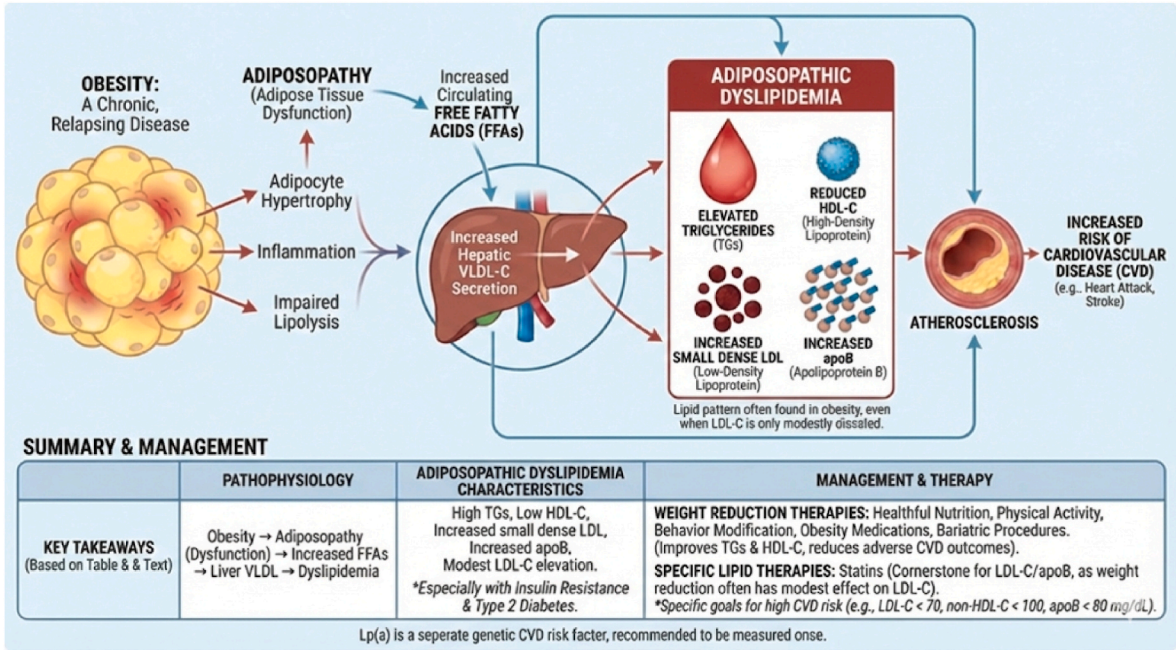


Fig. 6. Obesity, Dyslipidemia, and Cardiovascular Disease (CVD). Obesity is a chronic, relapsing disease that in addition to adverse fat mass consequences, may result in dysfunctional adipose tissue, which in turn, promotes a harmful lipid pattern known as “adiposopathic dyslipidemia.” This pattern features high triglycerides, low high-density lipoprotein cholesterol (HDL-C), and increased atherogenic particles such as small dense low-density lipoprotein (LDL) and apolipoprotein B. While weight-reduction strategies improve triglycerides and high-density lipoprotein cholesterol, achieving optimal low-density lipoprotein cholesterol (LDL-C) control often requires substantial weight reduction coupled with evidence-based cholesterol-lowering therapies such as statins.

- The relationship is bidirectional, as OSA worsens appetite-regulating hormones and promotes weight gain, creating a cycle of worsening sleep and metabolic dysfunction.
 - Untreated OSA increases cardiovascular and metabolic risks, while weight-related treatments such as weight reduction, lifestyle changes, obesity medications (e.g., tirzepatide), and bariatric procedures can improve OSA
- 10. Obesity and cardiovascular structural changes [12]** (See Table 10 and Fig. 10)

With obesity, cardiovascular pathology is driven by the specific anatomical location of adipose tissue and its subsequent structural impact on the heart and vasculature. Epicardial Adipose Tissue (EAT) lies within the pericardial sac directly contacting the myocardium, and

Table 7
Ten things to know about obesity, metabolic syndrome, and cardiovascular disease (CVD) [8].

Key Points	References
1. Those of Asian descent may have different metabolic syndrome cutoff points regarding waist circumference: men ≥ 35.4 inches or ≥ 90 cm and women ≥ 31.5 inches or ≥ 80 cm.	[8,19,20]
2. The presence of metabolic syndrome is associated with a 2–3 $\times$ higher risk of cardiovascular events (myocardial infarction, stroke). The presence of metabolic syndrome is associated with a 2 $\times$ higher risk of cardiovascular mortality.	[8,70]
3. Metabolic syndrome (utilizing Adult Treatment Panel III criteria) has a $>90\%$ specificity for insulin resistance (albeit $<50\%$ sensitivity).	[8,71–73]
4. The presence of metabolic syndrome is associated with 5 $\times$ higher risk of developing T2DM, which is a major CVD risk factor.	[8,74]
5. Increased waist circumference (abdominal obesity) is the only anthropometric physical exam/phenotypic component of the metabolic syndrome.	[8,75–77]
6. Body mass index (BMI) is sometimes substituted for waist circumference in some definitions of metabolic syndrome. BMI definition for overweight is commonly 25–29.9 kg/m ² and for obesity is commonly ≥ 30 kg/m ² . In the case of those of Asian descent, the cutoff points are more commonly BMI 23–24.9 kg/m ² for overweight and ≥ 25 kg/m ² for obesity.	[8,78]
7. Increased low density lipoprotein (LDL) cholesterol is not a component of the metabolic syndrome; however, those with metabolic syndrome (especially those with obesity, T2DM, and increased triglyceride levels) may have an increased number of atherogenic lipoproteins, including an increase in small, dense LDL particles.	[8,69]
8. In addition to the defined diagnostic components, metabolic syndrome is also often a state of insulin resistance and chronic low grade inflammation, as can be measured by high-sensitivity C-Reactive Protein. Adiposopathic increases in circulating insulin levels are often considered a contributor to metabolic syndrome; other contributors may be genetic predisposition, physical inactivity, and aging.	[8,76]
9. The presence of the metabolic syndrome may be associated with other systemic disorders, such as metabolic dysfunction-associated steatotic liver disease (MASLD), polycystic ovarian syndrome (PMOS; formerly polycystic ovary syndrome or PCOS), gout, and acanthosis nigricans.	[8,79]
10. Among patients with obesity and metabolic syndrome, treatment includes evidence-based weight reduction interventions as well as treatment of individual components (e.g., treatment of T2DM, hypertriglyceridemia).	[8,80]

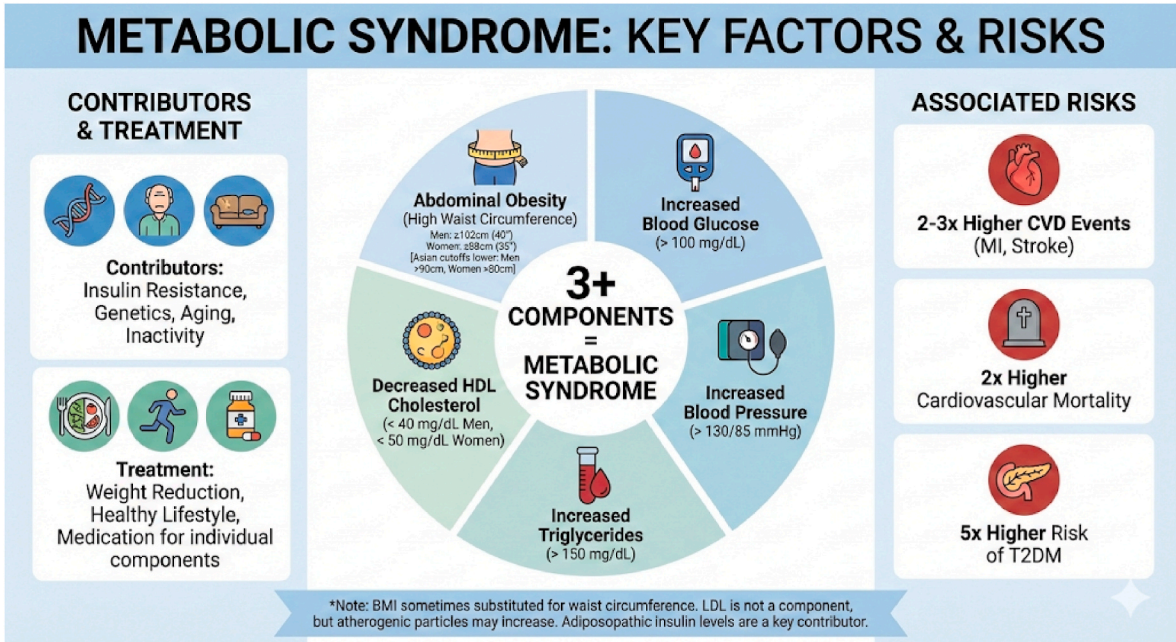


Fig. 7. Obesity, Metabolic Syndrome, and Cardiovascular Disease (CVD). Adiposopathy, or “sick fat,” explains how obesity leads to metabolic syndrome and CVD by transforming adipose tissue into a dysfunctional endocrine and immune organ that drives high glucose, high blood pressure, and atherogenic lipid abnormalities. In many individuals, this adipose-tissue dysfunction—not genetics alone—is the primary cause of the clustered risk factors that define metabolic syndrome. Metabolic syndrome is diagnosed when three or more are present: abdominal obesity, elevated fasting glucose, elevated blood pressure, high triglycerides, or reduced high-density lipoprotein cholesterol. Increased low density lipoprotein cholesterol is not a diagnostic component of the metabolic syndrome.

without a separating fascia, can direct “outside-to-inside” diffusion of inflammatory cytokines, fatty acids, and lipotoxic intermediates (e.g., ceramides, diacylglycerols) into coronary arteries and heart muscle. This local toxicity, combined with systemic volume overload, systemic inflammation, RAAS activation, and metabolic dysregulation, can contribute to left ventricular hypertrophy, myocardial steatosis (intracellular lipotoxicity), and interstitial fibrosis that stiffens the heart and disrupts electrical pathways. In addition to “outside-to-inside” damage that stimulates vascular smooth muscle hypertrophy, resulting in generalized arterial stiffness and accelerated atherosclerosis, coronary arteries may suffer a dual assault via “inside-to-outside” damage from intraluminal proinflammatory factors and atherogenic lipids that generate inflammation and plaque and result in adverse metabolic consequences such as the uncoupling of endothelial nitric oxide synthase. Thus, both the “outside-to-inside” pathogenic effects from EAT

and “inside-to-outside” from atherogenic promoting circulating factors within the vascular lumen to vessel wall increase the risk for CVD. Essential principles include:

- Obesity affects the heart and blood vessels not just by excess weight, but by where adipose tissue is located and how it interacts with nearby tissues.
- Epicardial and perivascular adipose tissue release inflammatory signals and toxic lipids directly into the heart and coronary arteries (“outside-to-inside”), promoting cardiac hypertrophy, steatosis, and fibrosis.
- In addition to potential adiposopathic effects on all arteries in patients with obesity, coronary arteries can also be damaged from the systemic complications of obesity, resulting in “inside-to-outside” pathogenic effects where inflammatory factors and atherogenic

Table 8
Ten things to know about obesity, thrombosis, and cardiovascular disease (CVD) [9].

Key Points	References
1. Obesity creates a chronic pro-thrombotic state, through mechanical, metabolic, and inflammatory pathways.	[9,81]
2. Adiposopathic pathways that increase the risk of thrombosis among patients with obesity include increased coagulation factors, platelet activation, thrombin generation, and inflammation via inflammatory cytokines that contribute to plaque instability (i.e., vulnerable atherosclerotic plaques have a thin fibrous cap that are prone to rupture).	[9,81]
3. Among patients with obesity and adiposopathy, fibrinolytic activity is downregulated.	[9,82]
4. Obesity contributes to endothelial dysfunction which may promote platelet adhesion.	[9,83]
5. Obesity leading to adiposopathic “sick fat disease” and biomechanical “fat mass disease” may create a pathogenic environment with all components of Virchow’s Triad (i.e., endothelial dysfunction, hypercoagulability, and venous stasis).	[9,84]
6. Venous stasis in obesity increases the risk of deep vein thrombosis (DVT) and pulmonary emboli. Specifically regarding DVT, patients with obesity are at increased risk for post-thrombotic syndrome (PTS), with greater challenges in recanalizing (clearing) the vein after a clot, and thus potentially leading to chronic venous insufficiency, ulcers, and permanent swelling that is distinct from lymphedema (see below).	[9,85]
7. The risk of thrombosis varies among patients with obesity, and is dependent on other risk factors such as age, sex, comorbidities, concomitant medications, socioeconomic status, and mobility status. In many, if not most cases, thrombosis among patients with obesity represents a “two-hit” phenomenon, such as obesity and prothrombotic states such as pregnancy, estrogen therapy, or cancer. Obesity itself can complicate diagnosis of thrombosis in limbs, resulting in under-recognition; similarly, obesity stigma can obscure clinical risk, reduce patient engagement, and lead to underdiagnosis of thrombotic conditions.	[9,84]
8. Anticoagulation management is more complex in patients with obesity, sometimes presenting challenges regarding optimal dosing, monitoring, and drug selection, especially for direct oral anticoagulants or DOACs (e.g., direct thrombin inhibitors like dabigatran and factor Xa inhibitors like apixaban, rivaroxaban, edoxaban). Optimal treatment is patient centered.	[9,86]
9. Lymphedema (i.e., lymphatic accumulation causing persistent swelling of the arms or legs) is typically asymmetrical and can sometimes present diagnostic challenges in patients with obesity; delayed recognition can potentially lead to irreversible lymphatic damage and more severe swelling. Early diagnosis of lymphedema enables more timely therapeutic interventions, such as compression therapy, weight management, and infection prevention, which can reduce complications and improve long-term outcomes.	[9,87]
10. Lipedema (i.e., abnormal, painful fat accumulation in the hips, thighs, legs, and sometimes the arms) is typically symmetrical and can sometimes present diagnostic challenges in patients with obesity, with physical findings sometimes perceived as due to simple weight gain. Treatments such as compression therapy, lymphatic support, and when appropriate, surgical intervention can reduce pain, improve mobility, and limit additional fat accumulation.	[9,88]

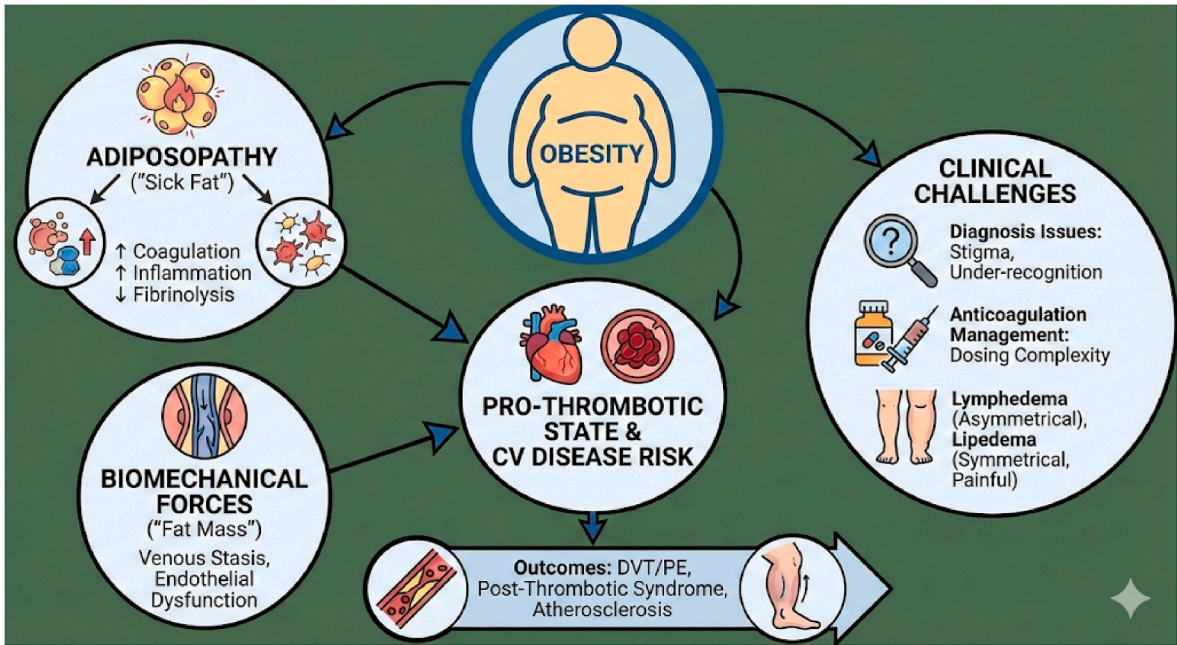


Fig. 8. Obesity, Thrombosis, and Cardiovascular Disease (CVD). Obesity promotes a prothrombotic state through the mechanical effects of excess fat (“fat mass disease”), which cause vascular compression and venous stasis. Obesity may also facilitate thrombosis through the metabolic–inflammatory effects of dysfunctional adipose tissue (“sick fat disease”), which may lead to increased inflammation, endothelial injury, and increased tendency for blood clotting. In addition to deep vein thrombosis, pulmonary embolism, and chronic venous insufficiency, clinicians may also encounter obesity-related lymphedema and the distinct familial condition of lipedema. Although weight-reduction strategies are beneficial, they are often not sufficient to fully address venous, lymphatic, or lipedemic disorders.

lipoproteins within the lumen of coronary arteries cross from inside the arterial lumen into the respective endothelia, leading to stiffness and accelerated atherosclerosis.

11. Obesity and heart failure [13] (See Table 11 and Fig. 11)

Obesity increases cardiac output because expanded adipose mass increases whole-body metabolic demand, prompting the cardiovascular system to enlarge blood volume, boost preload and stroke volume, and activate sympathetic pathways. Although individual adipose tissue

depots develop microvascular rarefaction and higher local resistance, the early systemic cardiovascular phenotype is a high-output, low-resistance state driven by metabolic demand, vasodilatory adipokines, hyperinsulinemia, and compensatory vasodilation in non-adipose vascular beds. However, over time, progressive sympathetic activation and arterial stiffening elevate systemic vascular resistance, creating a combined pressure-and-volume load that drives left ventricular hypertrophy and forms a central mechanistic link to HFpEF – with these systemic hemodynamic burdens representing a first “hit.” Excess epicardial adipose tissue (EAT) then delivers the second “hit” by

Table 9
Ten things to know about obesity, obstructive sleep apnea (OSA), and cardiovascular disease (CVD) [11].

Key Points	References
1. Approximately 70% of patients with obesity may have OSA. In community-based cohorts, roughly 30–40% of adults with OSA have obesity, rising to ~50% among those with severe OSA; clinic-referred populations report substantially higher proportions.	[11,89]
2. Obesity contributes to airway obstruction, leading to hypoxia, sympathetic surges, physiological vascular stress, and hypertension. Intermittent hypoxemia and sleep fragmentation trigger sympathetic activation, oxidative stress, endothelial dysfunction, and insulin resistance – all potentially contributing to increase CVD risk.	[11,90]
3. The relationship between obesity and OSA is bidirectional. Excess body weight increases the likelihood of obstructive sleep apnea because adipose tissue deposition around the neck and upper airway makes the airway more prone to collapse during sleep. In turn, poor-quality sleep from untreated obstructive sleep apnea can disrupt hormones that regulate appetite and metabolism, making weight gain and obesity more likely over time.	[11,91]
4. OSA contributes to T2DM and hypertension (two major CVD risk factors), as well as stroke, heart failure (e.g., left ventricular dysfunction and pulmonary hypertension/right sided heart failure), cardiac dysrhythmias (e.g., bradycardia, atrial fibrillation, and ventricular tachycardia), and sudden death. OSA is a leading cause of “resistant hypertension”, defined as blood pressure above goal despite three or more antihypertensive medications of different classes at maximally tolerated doses, one of which is a diuretic.	[11,92]
5. Estimates suggest that up to 70% of patients hospitalized with coronary artery disease have OSA. Severe untreated OSA doubles the risk of future myocardial infarction.	[11,92]
6. OSA is diagnosed by objective sleep testing, most commonly an overnight polysomnogram that measures breathing, oxygen levels, and sleep stages. In selected patients, a simplified home sleep apnea test may be used to detect breathing pauses and oxygen drops during sleep. During these sleep studies, the apnea–hypopnea index (AHI) is the average number of apneas (complete breathing pauses) and hypopneas (partial obstructions with reduced airflow and oxygen drops) that occur per hour of sleep, measured during a sleep study. Mild OSA is defined as 5–14 events per hour, moderate OSA as 15–29, and severe OSA as 30 or more events per hour.	[11,93]
7. The STOP-Bang questionnaire is an eight-item screening tool for obstructive sleep apnea that combines four symptom questions (snoring, tiredness, observed apneas, and high blood pressure) with four objective measures: body mass index (BMI), age, neck circumference, and gender. Its cutoff points assign one risk point each for BMI >35 kg/m ² , age >50 years, neck circumference >40 cm, and male sex, helping stratify patients into low-, intermediate-, or high-risk categories for OSA.	[11,94]
8. Continuous positive airway pressure (CPAP) therapy delivers a stream of pressurized air through a mask to keep the upper airway open during sleep, preventing the repeated oxygen delivery pauses that characterize obstructive sleep apnea. This form of positive airway pressure (PAP) treatment is the most effective non-invasive option for reducing nighttime oxygen drops of OSA, improving daytime alertness, and lowering long-term health risks associated with untreated sleep apnea. Other treatments include mandibular advancement devices, hypoglossal nerve stimulation, and positional therapy. Finally, other interventions include avoidance of alcohol and sedative-hypnotics (like benzodiazepines), which relax the upper airway muscles and worsen OSA and nighttime hypoxia.	[11,93]
9. Some obesity medications can improve OSA because even modest reductions in body weight decrease upper-airway collapsibility and reduce the frequency of oxygen delivery interruptions during sleep. More effective obesity medications have shown the ability to lower apnea severity and enhance overall sleep quality when used alongside standard sleep apnea treatments. Tirzepatide is illustrative of an obesity medication that has an FDA indication to treat moderate-to-severe OSA in adults with obesity. Weight reduction via bariatric procedures can improve obstructive sleep apnea via reduced upper-airway collapse and decreased number of breathing interruptions during sleep. While many patients experience meaningful reductions in apnea severity after bariatric surgery, some may still require ongoing sleep-focused evaluation and treatment to achieve full symptom control.	[11, 95–97]
10. Addressing the dual burden of obesity and OSA significantly reduces cardiovascular strain by lowering chronic systemic inflammation and decreasing sympathetic nervous system overactivity. Effective treatment of OSA leads to clinically meaningful improvements in blood pressure control, often resolving resistant hypertension, and significantly reduces the risk of dysrhythmias such as atrial fibrillation. Ultimately, managing these interconnected conditions improves heart structure and metabolic health, providing a robust defense against long-term complications such as heart failure, myocardial infarction, and stroke.	[11,92]

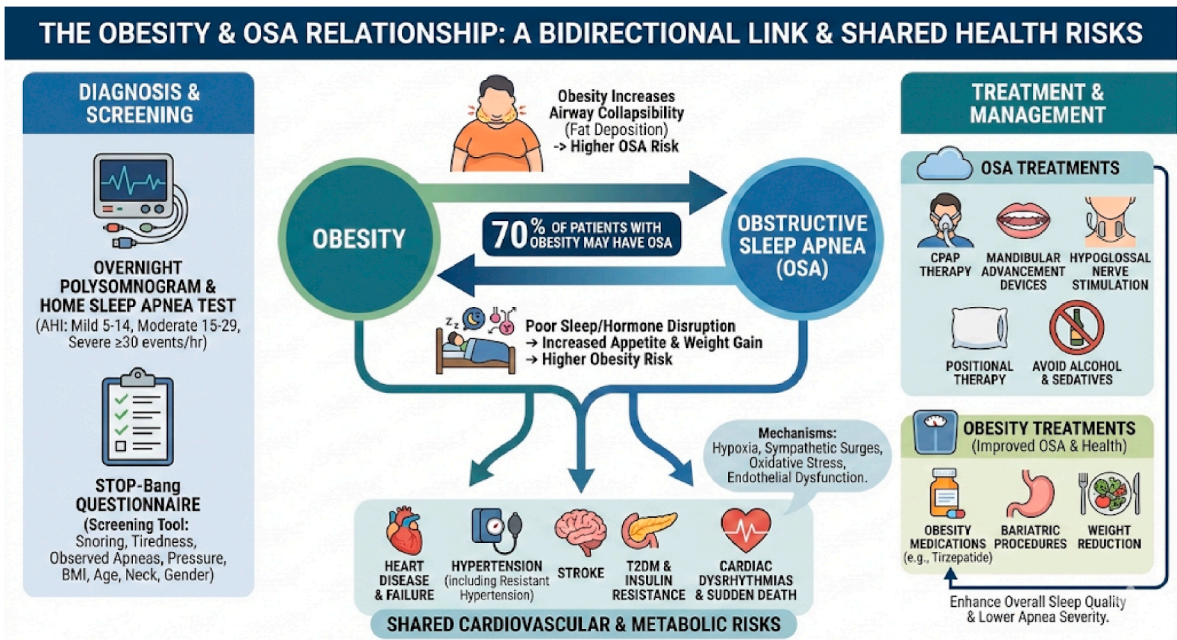


Fig. 9a. Obesity, Obstructive Sleep Apnea (OSA), and Cardiovascular Disease (CVD). Obesity drives obstructive sleep apnea (OSA) through anatomical airway narrowing and excess pharyngeal and tongue fat. As many as 70% of individuals with obesity may develop OSA. The relationship is bidirectional: OSA disrupts sleep and alters appetite-regulating hormones, promoting weight gain and further worsening airway obstruction. Untreated OSA increases cardiovascular and metabolic risks, while weight reduction, lifestyle changes, obesity medications, and bariatric procedures can reduce OSA severity.

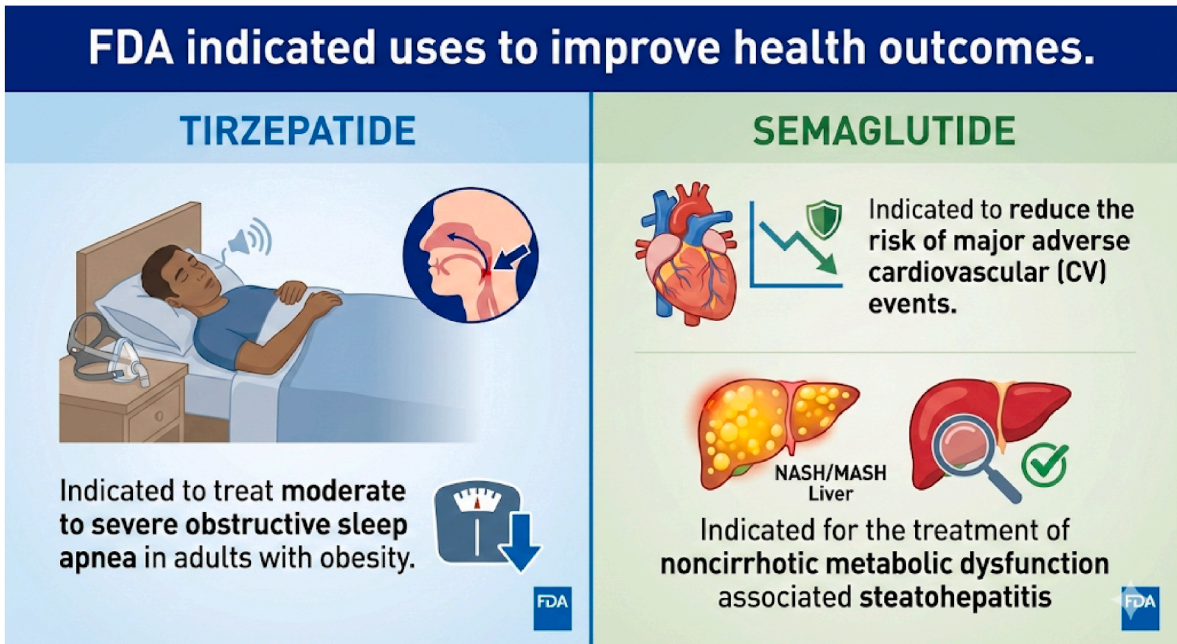


Fig. 9b. Some obesity medications have approved Food and Drug Administration (FDA) indicated uses to treat adverse health outcomes that go beyond improvement in obesity alone. Optimal medical management acknowledges that the priority is not to just treat the weight of the patient, but to also improve the health outcomes of the patient. Not only is tirzepatide indicated to treat overweight and/or obesity, but tirzepatide also has an explicit FDA indication to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity. Similarly, in addition to an indicated use to treat overweight and/or obesity, semaglutide has FDA indicated uses to reduce the risk of major adverse cardiovascular events and as a treatment for noncirrhotic metabolic dysfunction associated steatohepatitis.

Table 10
Ten things to know about obesity and cardiovascular structural changes [12].

Key Points	References
1. Epicardial adipose tissue (EAT) lies directly between the myocardium and visceral pericardium, with no fascial barrier. Its shared microcirculation with the coronary arteries places it in intimate structural continuity with the heart. EAT thickness is often measured via echocardiography (parasternal long axis), while volumetric quantification is done via cardiac computed tomography or magnetic resonance imaging. This is relevant because EAT volume is an independent predictor of coronary events, separate from body mass index.	[12,98]
2. Paracardial adipose tissue resides outside the parietal pericardium, is supplied by non-coronary vessels, and is anatomically separated from the myocardium, preventing the direct paracrine diffusion of inflammatory or lipotoxic mediators that characterizes EAT. Both depots expand in obesity and are often grouped under the umbrella term “pericardial fat,” and their structural differences determine their distinct cardiovascular effects. EAT drives injury through two separate tracks — direct paracrine/vasocrine vascular toxicity (via shared microcirculation) and mechanical restraint on diastolic filling (via its location inside the pericardial sac). Paracardial fat, lacking shared circulation and lying outside the sac, contributes mainly as a systemic visceral-adiposity marker rather than through either of those local mechanisms.	[12,99, 100]
3. EAT and visceral abdominal adipose tissue arise from the same mesodermal embryonic origin, with EAT representing the visceral adipose tissue depot of the heart. These two adipose tissue depots expand in parallel, and both correlate to a higher risk of CVD. Both EAT and visceral abdominal adipose tissue are also associated with greater coronary artery calcification, underscoring their shared contribution to adverse cardiometabolic outcomes. Thus, during an evaluation of body composition, an increase in visceral adipose tissue may suggest an increase in EAT. That said, unlike the white adipose tissue found in the abdomen, EAT expresses Uncoupling Protein-1 (UCP-1), giving it characteristics of brown or “beige” adipose tissue making it more metabolically active than paracardial or subcutaneous adipose tissue. The loss of this “brown” phenotype during obesity (whitening of fat cells) is a key driver of dysfunction.	[12,100]
4. In obesity, EAT undergoes hypertrophy and becomes metabolically inflamed which may result in structurally disruptive, pro-inflammatory tissue.	[12,46]
5. EAT can serve as the origin of inflammatory cytokines and free fatty acids that can diffuse directly into the coronary adventitia. This structural pathway accelerates atherosclerosis, endothelial dysfunction, and dysrhythmogenic remodeling.	[12,100]
6. Obesity increases total adipose mass requiring perfusion, creating chronic volume overload. This drives left ventricular dilation and eccentric hypertrophy as the heart adapts to increased circulatory demand.	[12,101]
7. When obesity causes hypertension, the cardiac left ventricular remodeling pattern shifts toward concentric hypertrophy. This structural change of the heart reflects the combined effects of increased pressure and volume overload.	[12,102]
8. Excess circulating free fatty acids in obesity accumulate within cardiomyocytes, producing myocardial steatosis. This lipid infiltration and accumulation of pathogenic lipids such as ceramides (“lipotoxicity”) impairs contractile architecture and contributes to diastolic dysfunction.	[12,103]
9. Adiposopathy is characterized by a shift toward a pro-inflammatory local and systemic immune environment, with increased inflammatory macrophages, T-lymphocytes, and mast cells. Increased adiposopathic adipokines and fewer vasculoprotective adipokines create an imbalance that promotes cardiovascular injury and increases the risk of CVD.	[3,12]
10. Obesity cardiomyopathy reflects the combined impact of EAT, lipotoxicity, inflammatory signaling, and chronic hemodynamic load. These processes drive structural and functional myocardial changes that manifest as impaired cardiac performance, heart failure with preserved ejection fraction (HFpEF), atherosclerotic coronary disease, cardiac dysrhythmias, and increased coronary calcium. In the development of dysrhythmias specifically, EAT can infiltrate the myocardium, separate cardiomyocytes, and create fibro-fatty disruption that interferes with electrical conduction and promotes micro-reentry circuits. Additionally, because EAT houses cardiac autonomic ganglia, local inflammation can heighten autonomic activity, further predisposing the heart to dysrhythmogenesis.	[12,46]

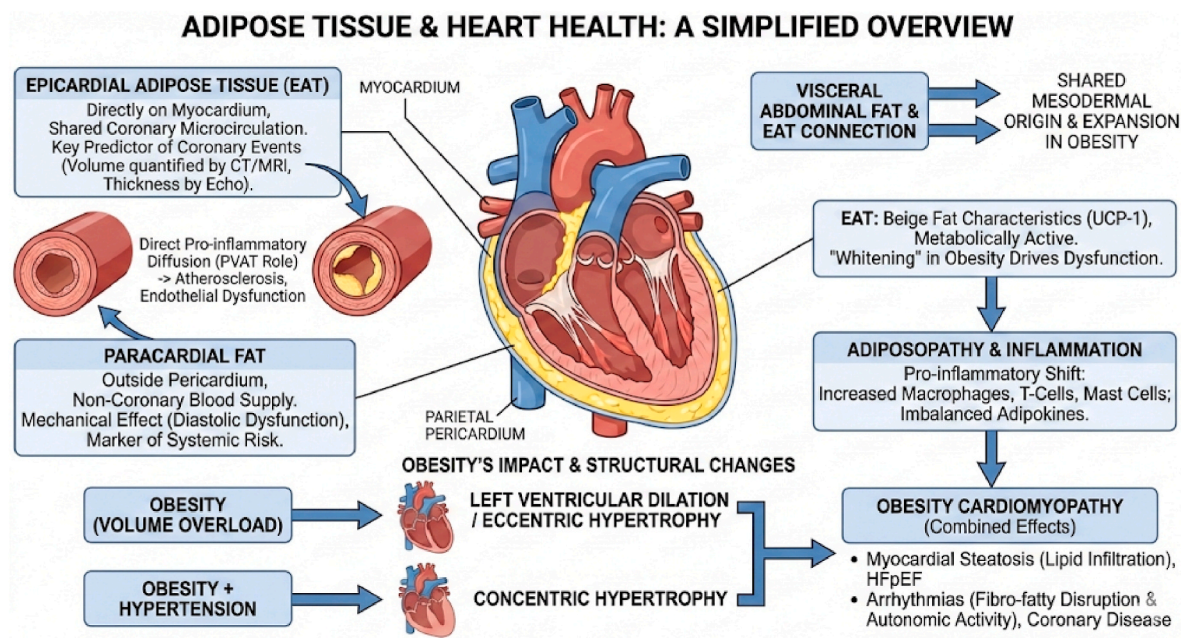


Fig. 10. Obesity and Cardiovascular Structural Changes. Obesity contributes to CVD not only through excess body fat but also through the specific location of adipose tissue and its direct structural effects on the heart and blood vessels. Epicardial and perivascular adipose tissue can release inflammatory signals and toxic lipids directly into the heart and coronary arteries, promoting hypertrophy, steatosis, and fibrosis through an “outside-to-inside” mechanism. At the same time, circulating inflammatory factors and atherogenic lipoproteins can injure coronary arteries from the lumen outward, creating an “inside-to-outside” assault that accelerates arterial stiffness and atherosclerosis.

Table 11
Ten things to know about obesity and heart failure [13,104–106].

Key Points	References
1. Obesity raises cardiac output because the enlarged mass of adipose tissue increases the body's metabolic needs. Meeting these needs requires a greater volume of circulating blood.	[13,101,104–106]
2. In heart failure, expanded total blood volume increases the amount of blood returning to the heart, boosts the amount of blood ejected with each heartbeat, and heightens sympathetic nervous system activity.	[13,104–107]
3. A sustained increase in cardiac output creates structural strain on the heart, even at rest, to maintain adequate tissue perfusion.	[13,104–106,108]
4. The “first hit” in obesity-related hemodynamic change is a high-output state: expansion of both fat and lean mass increases metabolic demand and plasma volume, so cardiac output rises - largely via increased stroke volume - while systemic vascular resistance falls to normal or subnormal levels. Superimposed early is neurohormonal volume retention, with sympathetic activation and renal sodium retention driven by leptin signaling, hyperinsulinemia, obstructive sleep apnea, physical compression of the kidney by visceral and perirenal fat, and RAAS/mineralocorticoid activation. Sustained preload elevation from this chronic volume overload produces ventricular dilation with eccentric remodeling and left atrial enlargement.	[13,104–106,109]
5. A “second hit” arises when adipose tissue expands faster than its vascular supply, producing local hypoxia, capillary rarefaction, and a shift in secretory profile toward pro-inflammatory adipokines and away from protective ones such as adiponectin. Analogous capillary rarefaction and endothelial dysfunction are described in skeletal muscle, kidney, and myocardium, contributing to coronary microvascular dysfunction, while arterial stiffening progresses in parallel. Superimposed on pre-existing volume overload, these afterload- and fibrosis-promoting influences can shift remodeling away from a purely eccentric pattern toward a mixed or concentric geometry. The net effect is accelerated progression to diastolic dysfunction and heart failure over years to decades.	[13,104–106,110]
6. The persistent elevation in cardiac output often leads to thickening of the left ventricular wall. This structural change reflects the chronic hemodynamic burden placed on the heart.	[13,104–106,111]
7. An increase in hemodynamic burden on the heart helps explain the strong association between obesity and Heart Failure with Preserved Ejection Fraction (HFpEF). Additionally, accumulation of EAT around the heart restricts cardiac motion and promotes fatty infiltration of the heart muscle, impairing its ability to relax and fill properly.	[13,104–106,112]
8. In a ~2 year randomized, placebo-controlled trial of 731 adults with heart failure with preserved ejection fraction and obesity (SUMMIT), tirzepatide significantly reduced the combined risk of cardiovascular death or worsening heart failure and substantially lowered the rate of heart-failure-related events. Although cardiovascular death alone did not differ meaningfully between groups, tirzepatide overall improved clinical outcomes and patient-reported health status compared with placebo.	[13,104–106,113]
9. In a 52-week, randomized, placebo-controlled trial of 529 adults with heart failure with preserved ejection fraction and obesity (STEP-HFpEF), once-weekly semaglutide produced greater improvements in symptoms, physical function, and inflammation, including larger gains in Kansas City Cardiomyopathy Questionnaire scores, 6-min walk distance, and reductions in C-reactive protein. It also led to substantially greater weight reduction than placebo, with a mean reduction of 13.3% compared with 2.6%.	[13,104–106,114, 115]
10. While evaluations of the health effects among patients with heart failure with reduced ejection fraction have reported variable results, glucagon-like peptide-1 receptor agonists in patients with heart failure and preserved ejection fraction may reduce CVD events when used in a patient-centric manner.	

mechanically constraining the heart within the pericardial space and infiltrating the myocardium with fat, impairing diastolic relaxation and amplifying the hemodynamic injury initiated by obesity. Essential principles include:

- Obesity initially creates a high-output, low-resistance circulatory state because increased adipose mass raises metabolic demand, prompting expanded blood volume, greater preload, and sympathetic activation.

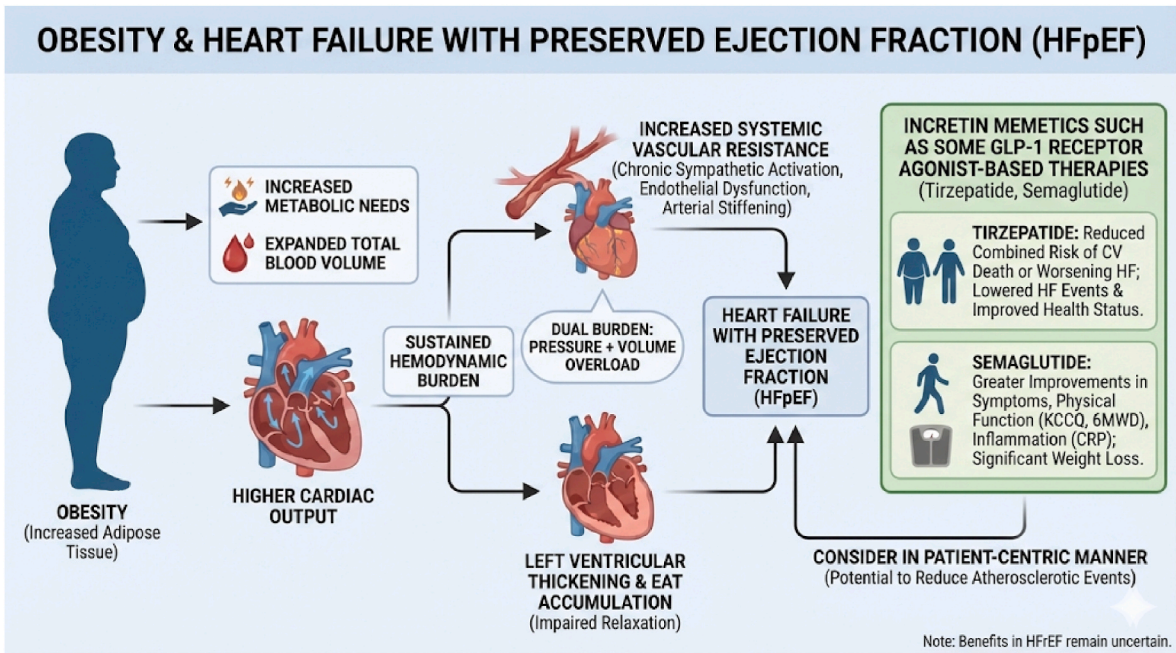


Fig. 11. Obesity and Heart Failure. Obesity initially creates a high-output state with normal-to-low vascular resistance: the expanded fat mass raises metabolic demand, which increases blood volume, preload, and sympathetic activity. Over time, sustained sympathetic tone and arterial stiffening raise afterload, so the combined volume and pressure load produces left-ventricular hypertrophy and a central pathway to heart failure with preserved ejection fraction (HFpEF). Excess epicardial adipose tissue adds a second injury by restraining the heart within the pericardium and infiltrating the myocardium with inflammatory and fibrotic signaling, further impairing diastolic filling and worsening HFpEF.

- Chronically elevated cardiac output drives left ventricular hypertrophy and establishes a key hemodynamic link to HFpEF.
- Excess epicardial adipose tissue further worsens HFpEF by mechanically constraining the heart and promoting myocardial fatty infiltration, both of which impair diastolic filling.

12. Obesity and cardiac dysrhythmias [1,14,15] (See Table 12 and Fig. 12)

Obesity contributes to a wide spectrum of cardiac rhythm disturbances through its effects on cardiac structure, electrical signaling, and systemic metabolic stress. Structural and electrical remodeling in

Table 12
Ten things to know about obesity and cardiac dysrhythmias [1,14,15].

Key Points	References
1. Increasing adiposity alters cardiac structure, autonomic tone, and metabolic milieu in ways that collectively favor the development and maintenance of cardiac dysrhythmias. Beyond its association with hypertension, diabetes, and sleep apnea, obesity is an independent risk factor for both atrial and ventricular dysrhythmias, as well as sudden cardiac death.	[1,14,15]
2. Excess adiposity leads to left atrial enlargement, increased wall stress, and cellular changes that create a vulnerable substrate for atrial fibrillation. Structural and electrical remodeling in obesity creates a substrate for atrial fibrillation, with atrial dilation, myocyte hypertrophy, and altered ion channel expression all contributing to dysrhythmia susceptibility.	[1,14,15]
3. Fatty infiltration of the atrial myocardium and fibrosis disrupt conduction pathways, creating regions of slow and heterogeneous conduction that promote reentry. Expansion of epicardial adipose tissue adjacent to atrial tissue is strongly linked to atrial fibrillation burden, likely through local inflammatory and fibrotic signaling.	[1,14,15]
4. Atrial fibrillation risk increases progressively with body mass index, with higher classes of obesity associated with a markedly greater incidence of atrial fibrillation. This gradient suggests that both total adiposity and central adipose tissue distribution contribute to atrial electrical instability, making weight management a key upstream prevention strategy.	[1,14,15]
5. Obesity is also associated with increased risk of ventricular dysrhythmias and sudden cardiac death, potentially mediated by left ventricular hypertrophy, fibrosis, and ischemia. Prolongation of repolarization, altered autonomic balance, and sleep apnea-related hypoxia may further destabilize ventricular electrophysiology in people with obesity.	[1,14,15]
6. Weight reduction reduces the incidence and burden of atrial fibrillation, partly by reversing atrial enlargement and improving hemodynamics. Sustained reductions in adiposity also improve blood pressure, glycemic control, and sleep apnea, which collectively lower the overall pro-dysrhythmic load.	[1,14,15]
7. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) increase heart rate primarily by enhancing sympathetic activity and reducing parasympathetic (vagal) tone at the sinus node, leading to modest sinus tachycardia in many patients. Despite this chronotropic effect, emerging data suggest that GLP-1 RAs may lower atrial fibrillation-related events in people with obesity, likely through weight reduction, reduced inflammation, and favorable atrial remodeling.	[1,14,15]
8. Real-world and observational data in populations with obesity and atrial fibrillation indicate fewer atrial fibrillation-related hospitalizations, cardioversions, and ablation procedures among GLP-1 RA users, supporting a net antidysrhythmic effect despite a small increase in resting heart rate.	[1,14,15]
9. Sympathomimetic agents such as phentermine can raise heart rate and blood pressure, and they may increase the risk of palpitations, sinus tachycardia, and, in susceptible patients, atrial or ventricular dysrhythmias. In contrast, agents without direct sympathomimetic effects, such as orlistat, are generally considered to have a neutral or favorable profile regarding cardiac rhythm, with dysrhythmia risk largely mediated indirectly through weight reduction and metabolic improvement.	[1,14,15]
10. As previously noted above, GLP-1 RA can modestly increase heart rate, but generally decrease blood pressure. Similarly, naltrexone/bupropion and phentermine/topiramate may also modestly increase heart rate. Because weight reduction typically lowers blood pressure and heart rate compared to baseline in both treatment and placebo groups, the net, placebo-adjusted signal is the meaningful metric when interpreting cardiovascular effects of obesity medications. Thus, in patients with atrial fibrillation or elevated dysrhythmia risk, obesity medication choice should balance the data on the potential for dysrhythmia and prescribing information cautions, balanced against the potential cardiometabolic benefits of sustained weight reduction, improved hemodynamics, and better control of cardiometabolic disease.	[1,14,15]

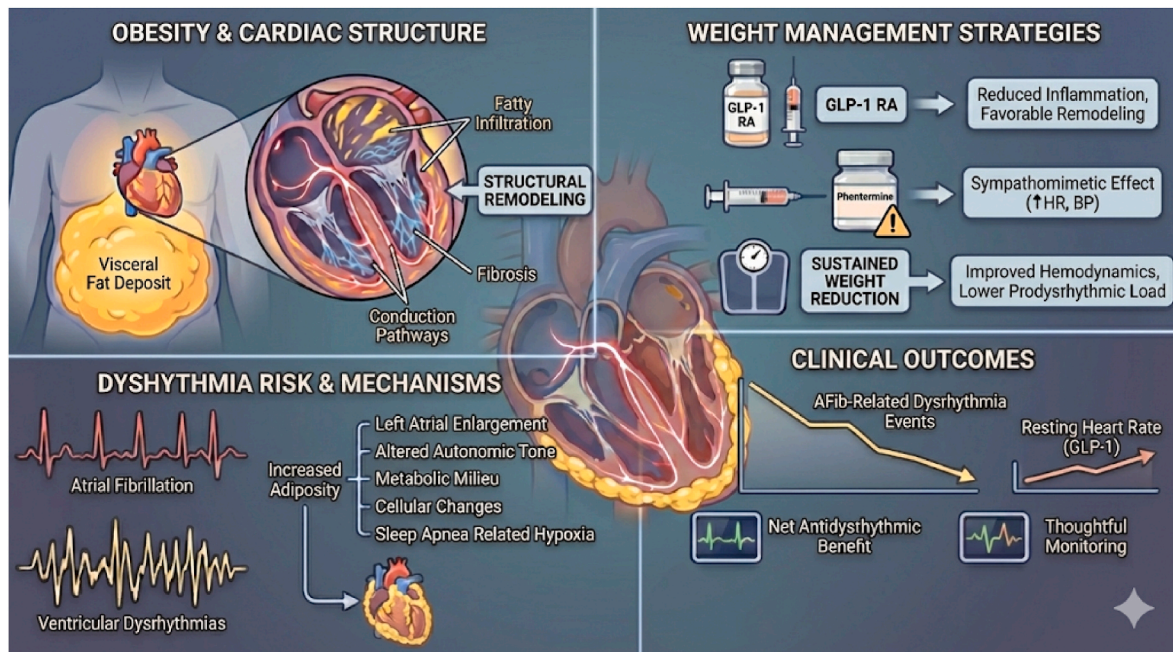


Fig. 12. Obesity and Cardiac Dysrhythmias. Obesity increases the risk of cardiac rhythm disturbances by altering heart structure, disrupting electrical signaling, and creating metabolic stress that destabilizes normal conduction. These changes—including atrial enlargement, fatty infiltration, and fibrosis—form a potent substrate for atrial fibrillation, with risk rising steadily as body mass increases. Weight reduction and therapies such as glucagon-like peptide-1 receptor agonists can reverse aspects of atrial remodeling and reduce atrial fibrillation burden, emphasizing the importance of comprehensive metabolic management.

obesity creates a substrate for atrial fibrillation. Fatty infiltration of the atrial myocardium and fibrosis disrupt conduction pathways, promoting erratic electrical activity and increasing the likelihood of sustained rhythm disturbances. Atrial fibrillation risk increases progressively with increasing body mass index, reflecting the cumulative impact of excess adiposity on atrial size, pressure, inflammation, and cellular architecture. Weight reduction and incretin mimetics (e.g., GLP-1 RA based therapies) have shown promise in reversing atrial remodeling and reducing the incidence and burden of atrial fibrillation, underscoring the importance of comprehensive metabolic management in preventing obesity-related cardiac dysrhythmias. Essential principles include:

- Obesity promotes a range of cardiac rhythm disturbances by altering cardiac structure, electrical signaling, and metabolic homeostasis.
- Obesity-related pathogenic changes such as atrial enlargement, fatty infiltration, and fibrosis, create a potent substrate for atrial fibrillation, with risk rising steadily as BMI increases.
- Among patients with obesity, weight reduction and GLP-1 RA can improve atrial remodeling and reduce atrial fibrillation burden, highlighting the value of comprehensive metabolic management in preventing obesity-related dysrhythmias.

13. Obesity paradox and cardiovascular disease (CVD) [8] (See Table 13 and Fig. 13)

An apparent “obesity paradox” arises when individuals with higher body weight appear to experience better health outcomes than those with lower body weight. However, this pattern becomes less paradoxical when the clinical context and physiological role of body fat are considered. Many people at low body weight have serious underlying conditions (e.g., cancer, chronic infections, advanced pulmonary disease, malnutrition, or severe cardiovascular disease) that drive unintentional weight reduction. Behaviors like cigarette smoking can also reduce body weight. It is expected, and not “paradoxical,” that individuals who are underweight due to life-threatening illness or cigarette smoking have poorer outcomes than individuals with overweight

or obesity who do not have these chronic illnesses. Even in the absence of chronic disease, elevated mortality among the lowest-weight individuals may stem from frailty, sarcopenia, and reduced metabolic reserves. Higher-weight individuals may possess greater nutritional and energy stores, which can be beneficial during episodes of acute severe illness. Because body mass index (BMI) cannot distinguish between fat mass and lean mass, those classified as having “normal” weight may actually have sarcopenia, which is a high health-risk state marked by a substantial loss of muscle mass, potentially accompanied by loss of muscle function. In this case, any apparent survival advantage attributed to obesity may better reflect the increased mortality associated with low muscle mass in leaner patients, rather than a true protective effect of excess adiposity. Essential principles include:

- The so called “obesity paradox” largely reflects the poor health outcomes in individuals with low body weight due to underlying illness, smoking, frailty, or sarcopenia rather than any true protective effect of excess adiposity. This creates selection bias leading to the illusion of an effect if not appropriately accounted for in the statistical methods [16–18].
- Higher-weight individuals often have greater metabolic and nutritional reserves, which can be advantageous during acute illness, while BMI fails to distinguish between healthy lean mass and high-risk muscle loss in people labeled as “normal weight.”
- Individuals with obesity who are physically fit generally have better prognoses than unfit individuals of normal weight, indicating that degree of physical fitness, rather than the amount of body fat, is the primary driver of survival.

14. Obesity, age, sex, race, and cardiovascular disease (CVD) [19–23] (See Table 14 and Fig. 14)

Across the lifespan, cardiometabolic and cardiovascular disease (CVD) risk is shaped by how excess adiposity interacts with biology, sex-specific physiology, and social determinants of health: older adults face sarcopenic obesity and the cumulative effects of long-standing

Table 13

Ten things to know about the obesity paradox and cardiovascular disease (CVD) [8].

Key Points	References
1. Anatomic Obesity Paradox: Peripheral subcutaneous adipose tissue (SAT) can be metabolically “protective” via healthy adipocyte proliferation during times of excess energy (i.e., when caloric gastrointestinal absorption from food exceeds energy expenditure). SAT can become pathogenic when the ability to expand is limited (i.e., via genetics or concomitant medications), resulting in adipocyte hypertrophy, energy overflow, and ectopic fat deposition, as reflected by the increase in visceral adiposity and epicardial adipose tissue and fatty infiltration of other body organs.	[8,45]
2. Physiologic Obesity Paradox: Individuals with obesity vary in their susceptibility to the development of cardiometabolic disease and CVD risk factors, giving rise to phenotypes such as “obesity without complications,” which has many other analogous terms. The prevalence of obesity without complication is directly dependent on the intensity of the diagnosis of complications and whether diagnoses are inclusive of all “sick fat disease” (adiposopathic) and “fat mass disease” complications. Conversely, individuals without obesity or overweight may exhibit cardiometabolic disease due to adiposopathy or dysfunction in other organ systems.	[8,116]
3. Demographic Paradox (Age, Sex, and Race): Age, sex, and race influence body fat distribution and cardiometabolic risk, creating paradoxical patterns where similar BMI values do not translate to similar cardiometabolic outcomes. For example, among those with overweight or obesity, women, and Black individuals may have lower visceral adipose tissue, while older individuals and those of Asian descent may have higher visceral adipose tissue for comparable body weight.	[8,55]
4. Therapeutic Obesity Paradox: Although increase in body fat generally promotes type 2 diabetes mellitus (T2DM), thiazolidinediones represent a drug treatment for T2DM that increases the proliferation and differentiation of functional fat cells. This “paradoxically” increases adipocyte number and increases fat mass despite better achieving improved glucose control. Conversely, some drugs associated with reduced fat mass, such as some human immunodeficiency virus (HIV) antiretroviral regimens (e.g., older protease inhibitors including indinavir, lopinavir, ritonavir), may worsen metabolic disease by impairing adipocyte function, generating relative loss of subcutaneous adipose tissue, and increasing the relative proportion of visceral adipose tissue.	[8,117, 118]
5. Cardiovascular Disease (CVD) Outcomes Obesity Paradox: Patients with overweight or obesity may demonstrate better survival after cardiovascular events, potentially due to greater metabolic reserve, earlier diagnosis due to management of cardiovascular disease risk factors, or more aggressive preventive therapy. Additionally, evidence suggests that the CVD outcome paradox is largely explained by cardiorespiratory fitness, as the apparent survival advantage of higher body mass index often disappears when studies adjust for aerobic capacity. This suggests that individuals with obesity who are physically fit generally have better prognoses than unfit individuals of normal weight, indicating that degree of fitness, rather than the amount of body fat, is the primary driver of survival.	[8,119]
6. Stroke Obesity Paradox: Although obesity increases stroke risk, individuals with higher body weight may experience better post-stroke outcomes due to greater nutritional reserve and fewer catabolic comorbidities. Patients who are at low weight may have poorer outcomes because of frailty, chronic illness, or smoking-related diseases, with cigarette smoking contributing to both reduced body weight and poorer outcomes from stroke.	[8,120]
7. Acute Respiratory Distress and Critical Illness Obesity Paradox: Patients with obesity may have improved survival in acute respiratory distress syndromes and critical illness, possibly due to enhanced energy reserves. In contrast, underweight individuals often have chronic lung disease, malnutrition, or other chronic conditions that worsen respiratory and health outcomes after an acute illness.	[8,121]
8. Kidney Disease Obesity Paradox: In chronic kidney disease, higher BMI is associated with lower mortality. This may reflect better nutritional status, improved hemodynamic stability, or sequestration of uremic toxins within adipose tissue.	[8,122]
9. Therapeutic Approach Obesity Paradox: It is usually not productive, and may be counterproductive, to assign “blame” to patients with adverse health outcomes as the result of obesity. As such, some might believe it “paradoxical” that accountability is a mainstay component of most behavior modification interventions. However, blame focuses on fault and shame, while accountability focuses on metrics to achieve better health and without judgment. Effective obesity management requires balancing accountability with empathy, avoiding blame while encouraging shared decision-making and behavior tracking. Overemphasizing guilt undermines engagement, whereas structured accountability supports sustainable change.	[8,123]
10. Cardiovascular Frequency and Severity Obesity Paradox: Cigarette smoking is disproportionately represented among ST-elevation myocardial infarction (STEMI) relative to non-STEMI presentations, reflecting acute thrombotic occlusion of a coronary artery. Smoking is also associated with worse risk-adjusted long-term mortality after myocardial infarction (MI). Smokers tend to have lower BMI than non-smokers and leaner MI cohorts are therefore enriched for smoking-driven STEMI with intrinsically worse prognosis. Thus, while obesity may increase the risk of both STEMI and NSTEMI, the confounding of infarct type and etiology by adiposity means the apparently more favorable outcomes in patients with obesity cannot be attributed to increased body fat itself.	[8,124]

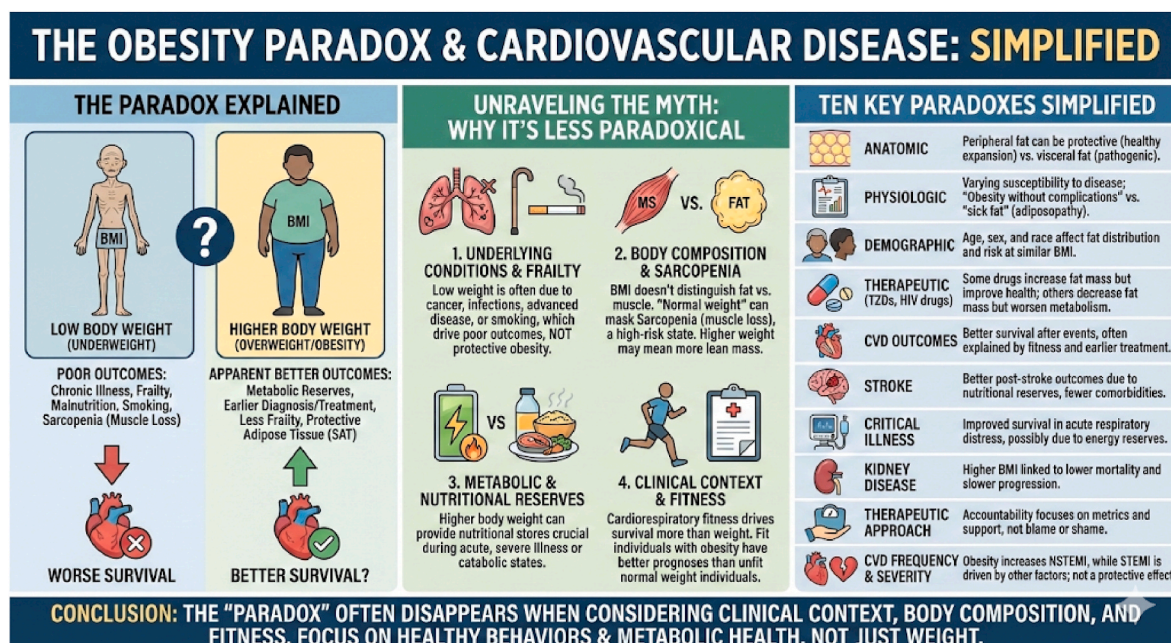


Fig. 13. Obesity, “Obesity Paradox,” and Cardiovascular Disease. The so-called “obesity paradox” is largely explained by the poor outcomes seen in people with low body weight due to underlying illness, smoking, frailty, or loss of muscle mass, rather than any true protective effect of excess body fat. Higher-weight individuals may fare better during acute illness because they often have greater metabolic and nutritional reserves, while body mass index cannot distinguish between healthy lean mass and high-risk sarcopenia in those labeled as “normal weight.” Overall, physical fitness—not body fat—is the strongest predictor of survival, with fit individuals who have obesity generally experiencing better outcomes than unfit individuals of lower weight.

Table 14
Ten things to know about obesity, age, sex, race, and cardiovascular disease (CVD) [19–23].

Key Points	References
1. Older individuals are at risk for sarcopenic obesity, which is characterized by excess adiposity combined with age-related loss of skeletal muscle mass and function. Sarcopenic obesity may amplify cardiometabolic risk by contributing to insulin resistance, worsening endothelial function and physical inactivity; it is a phenotype associated with frailty, reduced cardiorespiratory fitness, and increased cardiovascular disease (CVD) events.	[19–23]
2. Among older individuals, the longer the duration of the chronic disease of obesity, the longer the cumulative exposure to obesity-related adiposopathic endocrine and immune dysfunction, thus accelerating atherosclerotic processes. Early-onset obesity leads to earlier and more severe CVD.	[19–23]
3. Individuals with central adiposity (i.e., more common in males) may be associated with accumulation of visceral and deep abdominal subcutaneous adipose tissue that drives insulin resistance, type 2 diabetes mellitus, hypertension, and dyslipidemia, all CVD risk factors. Lower-body adiposity (i.e., more common in females) is associated with the accumulation of gluteofemoral fat, which reflects a more favorable adipose tissue distribution pattern, and thus less likely to promote cardiometabolic disease and less likely to increase CVD risk.	[19–23]
4. Polyendocrine metabolic ovarian syndrome (PMOS) can be worsened by obesity and is characterized by hyperandrogenism, anovulation, and insulin resistance, all of which increase lifetime cardiometabolic risk. Women with PMOS have higher rates of type 2 diabetes mellitus, hypertension, and dyslipidemia, contributing to elevated CVD risk, even at younger ages.	[19–23]
5. Pregnancy related disorders that can be worsened by obesity include gestational diabetes mellitus (GDM) and pre-eclampsia. GDM reflects underlying beta-cell vulnerability and insulin resistance that often persist after pregnancy. Women with a history of GDM face increased risk of type 2 diabetes and CVD later in life, independent of postpartum body weight. Similarly, obesity is one of the strongest predictors for developing pre-eclampsia, with the higher the body mass index, the higher the risk of pre-eclampsia. A history of pre-eclampsia increases the risk of CVD even upon a return to normal weight after pregnancy.	[19–23]
6. The transition to menopause and declining estrogen levels may increase hunger, increase visceral adipose tissue accumulation, increase insulin resistance, increase blood glucose, increase blood pressure, increase atherogenic blood lipids, and contribute to deterioration of vascular health (resulting in endothelial dysfunction and arterial stiffness). This shift contributes to a rise in CVD risk factors and CVD risk for menopausal women.	[19–23]
7. Heart failure with preserved ejection fraction (HFpEF) disproportionately affects females, particularly those with obesity-related systemic inflammation and diastolic dysfunction. Adiposopathy, endothelial impairment, and increased arterial stiffness create a pathophysiologic environment that is significantly more prevalent in females, particularly postmenopausal females.	[19–23]
8. Black individuals experience higher rates of hypertension, arterial stiffness, and chronic stress-related neurohormonal activation that elevate CVD risk, which persist after accounting for differences in adiposity. These factors interact with social determinants of health to produce a disproportionate increase in CVD morbidity and mortality.	[19–23]
9. Those of Asian descent (especially South Asians) often develop increased visceral adiposity and adiposopathic metabolic complications at lower BMI thresholds due to differences in adipose tissue distribution and adipocyte biology. This predisposition increases risk for insulin resistance, type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and CVD even when body weight appears “normal” by standard BMI criteria.	[19–23]
10. Racial and ethnic minority groups are more likely to face socioeconomic disadvantages, limited access to preventive healthcare, limited access to healthful foods, and greater exposure to environmental stressors. These systemic inequities drive higher rates of CVD risk factors such as obesity, type 2 diabetes mellitus, hypertension, and dyslipidemia, leading to increased CVD event rates.	[19–23]

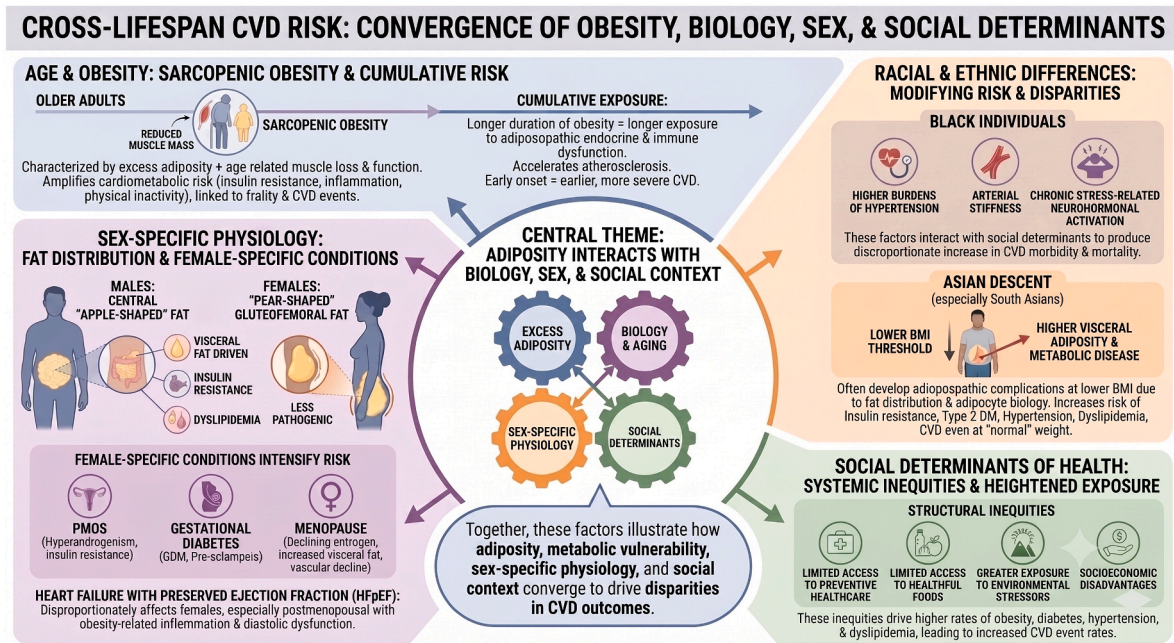


Fig. 14. Obesity, Age, Sex, Race, and Cardiovascular Disease (CVD). Excess body fat influences cardiometabolic and cardiovascular risk differently across the lifespan, shaped by age-related changes such as sarcopenic obesity, sex-specific physiology, and adipose tissue distribution patterns that vary in metabolic harm. Women face additional vulnerability due to conditions like polyendocrine metabolic ovarian syndrome (PMOS), gestational diabetes, and menopause-related estrogen decline, while racial and ethnic groups experience distinct risks—including higher hypertension and arterial stiffness in Black individuals and increased visceral adiposity at lower body-mass thresholds in many Asian populations. Structural inequities further magnify these biological and metabolic differences, illustrating how adiposity, sex, and social context converge to drive disparities in cardiovascular outcomes.

Table 15
Ten things to know about obesity and cardiovascular diagnostic procedures [125].

Key Points	References
1. Most standard cardiovascular risk calculators do not incorporate body mass index (BMI) or body composition, despite the well-established cardiometabolic impact of excess adiposity. The non-laboratory version of Predicting Risk of Cardiovascular disease EVENTS (PREVENT), QRResearch (QRISK2, QRISK3, and QRISK-lifetime calculator), and the non-lipid version of the Framingham Risk Score (where BMI is used instead of total cholesterol and high density lipoprotein cholesterol) are exceptions that include BMI to better reflect obesity-related CVD risk.	[125–127]
2. Incorrect cuff selection is the most frequent blood pressure-related diagnostic error in people with obesity. Using a standard-sized cuff on a large arm produces cuff size error, which depending on the cited reference/source, may result in spuriously high readings that can exceed the true value by (depending on the reference) as much as ~5–20 mmHg. This can lead to false diagnoses of hypertension and unnecessary treatment. Additionally, the conical arm shape common in severe obesity can prevent oscillometric devices from obtaining reliable measurements. These challenges underscore the importance of proper cuff sizing and, when non-invasive methods remain inaccurate, consideration of invasive arterial monitoring.	[58,60,61,125,128]
3. Obesity can alter electrocardiographic electrical signals through increased chest wall mass, axis shifts, and low-voltage patterns (e.g., left axis deviation, T-wave flattening, low QRS voltage, prolonged QTc interval, ST depression, and false-positive criteria for inferior myocardial infarction). Obesity most commonly causes false-negative ECG detection of left ventricular hypertrophy via voltage attenuation (worsened, not offset, by an accompanying leftward axis shift), and separately reduces the accuracy of ECG-based coronary artery disease testing through mechanisms like limited exercise tolerance and baseline ST-T abnormalities rather than the same voltage/axis effect.	[1,125,129]
4. Excessive body weight often limits a patient's ability to perform exercise stress testing due to early fatigue, breathlessness, and mechanical constraints, requiring pharmacologic stress testing instead. Common pharmacologic stress testing agents include regadenoson, adenosine, dipyridamole, or dobutamine, which are typically paired with nuclear myocardial perfusion imaging (MPI) or cardiac magnetic resonance (CMR). However, Single Photon Emission Computed Tomography (SPECT) myocardial perfusion imaging (MPI) often performs poorly in obesity because soft-tissue attenuation - particularly from breast or diaphragmatic fat - can obscure the signal. This artifact often produces apparent 'fixed defects' that mimic prior infarction or ischemia, prompting avoidable invasive angiography. For this reason, many diagnostic pathways favor PET or coronary CT angiography (CCTA) in individuals with obesity, as these modalities offer superior attenuation correction and more reliable image quality.	[1,86,125]
5. Excess body weight can exceed the table or gantry limits of common imaging modalities, including dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI), which often cap at 350–450 pounds, depending on the scanner. Although newer systems may accommodate higher weights, image quality can still be compromised by increased tissue thickness. Obesity is also closely associated with atrial fibrillation and elevated resting heart rates. Because coronary CT angiography (CCTA) and cardiac MRI rely on electrocardiographic (ECG) gating to capture motion-free images, dysrhythmias such as atrial fibrillation or tachycardia significantly hinder image acquisition. Achieving adequate image quality may require aggressive beta-blockade for rate control, which introduces additional risk in patients with reactive airway disease - a condition frequently seen alongside obesity.	[86,125]
6. Increased soft-tissue mass in obesity attenuates ultrasound waves, making cardiac structures harder to visualize and reducing the reliability of echocardiographic evaluation, especially for valvular assessment and diastolic function. Ultrasound Enhancing Agents (UEAs), such as perflutren lipid microspheres or sulfur hexafluoride lipid-type A microspheres, are guideline-recommended for patients with obesity who have suboptimal acoustic windows to improve endocardial border definition. The threshold for using UEAs should be low, as they are often essential for rescuing non-diagnostic studies and ensuring accurate measurement of left ventricular ejection fraction.	[125,130]
7. Perivascular Fat Attenuation Index (FAI) provides a noninvasive CT-based biomarker of coronary inflammation. In many clinical practices, Coronary Artery Calcium (CAC) scoring is a more common CT-based assessment that correlates not only with coronary plaque burden but also is associated with epicardial adipose tissue volume. Increased abdominal visceral adiposity similarly tracks with higher CAC scores, reflecting shared pathophysiologic pathways (e.g., adiposopathy, insulin resistance, hypertension, dyslipidemia, as well as immunopathies and endocrinopathies such as systemic inflammation and oxidative stress). CAC is reported in Agatston scores that quantify calcified plaque in heart arteries:	[125,131,132]
• 0: No calcified plaque, unless accompanied by diabetes mellitus, cigarette smoking, or strong family history of cardiovascular disease, suggests very low risk for major adverse cardiovascular event (MACE) for the subsequent 5 or more years • 1–10: Minimal plaque, low MACE risk • 11–100: Mild plaque, moderate MACE risk • 101–400: Moderate plaque, moderately high risk for MACE • Over 400: Extensive plaque, high risk for MACE	
If only evaluated with traditional CVD risk factors via common CVD risk assessment tools, the risk for atherosclerotic CVD may be underestimated. Additionally, increased CAC scores correlate better with increased visceral adiposity, rather than BMI. Once statin therapy is initiated, CAC scores may worsen in some patients such that the value of serial CAC scores in patients with elevated CAC scores at baseline treated with statins is uncertain.	
8. CT coronary angiography and calcium scoring often require higher radiation doses in individuals with larger BMI to maintain adequate image quality. Increased adipose tissue can also necessitate higher contrast volumes.	[1,125,133]
9. Obesity can make vascular access, catheter navigation, and fluoroscopic imaging more difficult, often lengthening procedures and raising the likelihood of complications. In patients with increased adiposity, transradial access (TRA) is favored over transfemoral access (TFA) because femoral access carries a significantly higher risk of retroperitoneal bleeding and hematoma. The femoral head - an essential anatomical landmark - is harder to palpate or visualize under fluoroscopy in patients with obesity, and achieving adequate post-procedural compression is more challenging. For these reasons, TRA is generally considered the safer and more dependable approach in individuals with obesity.	[125,134]
10. Obesity lowers circulating levels of B-type Natriuretic Peptide (BNP) and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) through a combination of increased clearance and reduced myocardial secretion. This suppression can mask even acute heart failure (HF), leading clinicians to miss the diagnosis when relying on standard BNP cut-points. Since BNP remains a central biomarker for identifying HF, diagnostic strategies in patients with obesity should consider lower BNP thresholds to avoid false reassurance and delayed recognition of cardiac decompensation.	[125,135,136]

adiposopathic endocrine and immune dysfunction; central “apple-shaped” body fat distribution, more common in males, promotes visceral-driven insulin resistance and dyslipidemia, whereas “pear-shaped” gluteofemoral body fat deposition is less pathogenic. Female-specific conditions - including polycystic ovary syndrome (PMOS), gestational diabetes, and the menopausal decline in estrogen - intensify insulin resistance, increased visceral adiposity, vascular dysfunction, and ultimately CVD risk. Heart failure with preserved ejection fraction (HFpEF) disproportionately affects women, especially postmenopausal women with obesity-related inflammation. Racial and ethnic differences further modify risk. Beyond obesity, Black individuals experience higher burdens of hypertension, arterial stiffness, and chronic stress-related neurohormonal activation. Those of Asian descent, particularly South Asians, often develop increased visceral adiposity and metabolic disease at lower BMI thresholds. Finally, many minority populations face structural inequities that heighten exposure to obesity, diabetes, hypertension, and dyslipidemia. Together, these factors illustrate how adiposity, metabolic vulnerability, sex-specific physiology, and social context converge to drive disparities in CVD outcomes. Essential principles include:

- Excess adiposity influences cardiometabolic and cardiovascular risk differently across the lifespan, shaped by age-related changes such as sarcopenic obesity, sex-specific physiology, and fat-distribution patterns that drive varying degrees of metabolic dysfunction.
- Women face additional risk from PMOS, gestational diabetes, menopause-related estrogen loss, and a heightened susceptibility to HFpEF, while racial and ethnic groups experience distinct vulnerabilities, including higher hypertension and arterial stiffness in Black individuals and increased visceral adiposity at lower BMI thresholds in many Asian populations.
- Structural inequities further amplify these risks, demonstrating how biology, sex, adiposity, and social context intersect to produce disparities in cardiovascular outcomes.

15. Obesity and cardiovascular diagnostic procedures (See Table 15, Fig. 15, and Chart 1)

Obesity can complicate cardiovascular evaluation and requires specific adjustments in risk assessment, diagnostic imaging, and procedural planning. Many standard risk calculators do not account for increased adiposity, perhaps making Body Mass Index (BMI) inclusive tools such as the Predicting Risk of Cardiovascular disease EVENTS (PREVENT) model or QRisk (QRISK) algorithms more appropriate. Basic diagnostic cardiovascular tests are also vulnerable to error, including blood pressure cuff-size error from incorrect cuff sizing and electrocardiogram (ECG) voltage attenuation. Excess soft tissue can degrade image quality on echocardiogram (potentially requiring ultrasound enhancing agents) or Single Photon Emission Computed Tomography (SPECT). Positron Emission Tomography (PET), Coronary Computed Tomography Angiography (CCTA), and coronary angiography frequently require higher radiation doses during imaging. Obesity may also suppress B-type Natriuretic Peptide (BNP) levels, masking acute heart failure. Finally, anatomical challenges in obesity often favor transradial over transfemoral catheterization to reduce the heightened bleeding risk associated with femoral access. Essential principles include:

- Obesity complicates cardiovascular evaluation by requiring adjustments to risk assessment tools, physical examination techniques, and imaging strategies.
- Excess adiposity can distort blood pressure readings, attenuate ECG signals, degrade SPECT and echocardiographic image quality, and suppress BNP levels.
- Positron Emission Tomography (PET), Coronary Computed Tomography Angiography (CCTA), and coronary angiography frequently require higher radiation doses during imaging of patients with obesity.
- Procedurally, anatomical considerations often make transradial catheterization safer than transfemoral access due to the increased bleeding risk associated with femoral approaches in individuals with obesity.

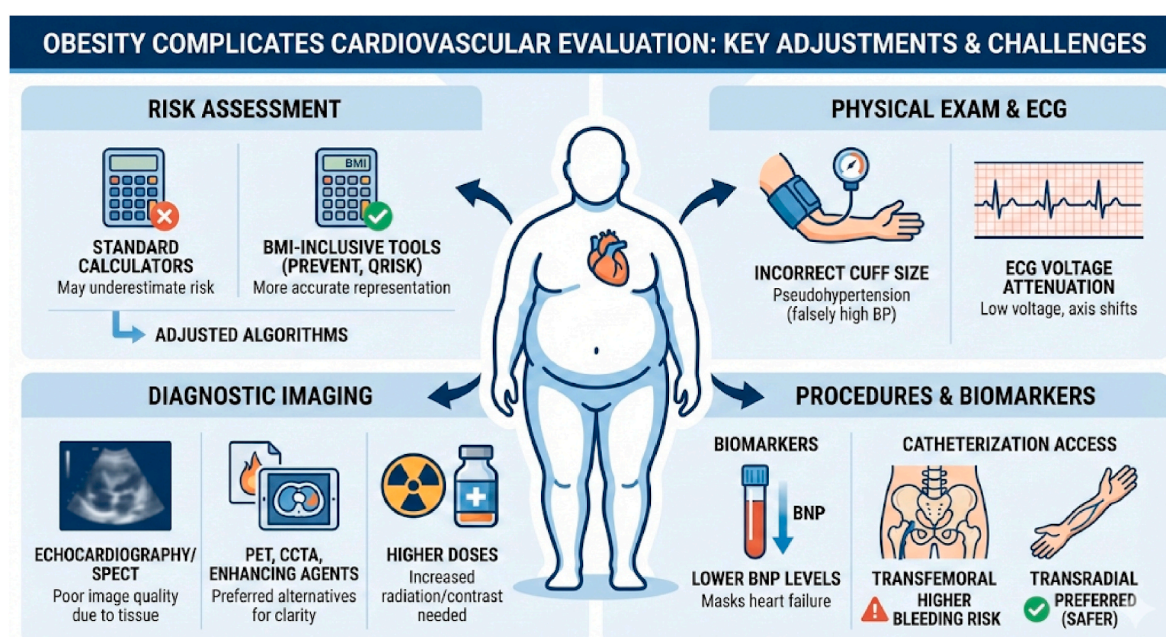


Fig. 15. Obesity and Cardiovascular Diagnostic Procedures. Obesity complicates cardiovascular evaluation by requiring adjustments to risk-prediction tools, physical examination techniques, and imaging approaches. Excess adiposity can distort blood pressure readings, reduce electrocardiogram signal strength, impair the quality of nuclear and ultrasound imaging, suppress natriuretic peptide levels, and necessitate higher radiation doses or alternative modalities such as positron emission tomography or coronary computed tomography angiography. Procedurally, anatomical considerations often make transradial catheterization safer than transfemoral access because obesity increases bleeding risk with femoral approaches.

Chart 1

Cardiac Diagnostic Testing. Cardiac diagnostic testing in patients with obesity often reveals sinus tachycardia, left ventricular hypertrophy, diastolic dysfunction, myocardial perfusion abnormalities, and increased coronary calcification. Across electrocardiogram, echocardiography, ambulatory monitoring, nuclear imaging, computed tomography, cardiac magnetic resonance imaging (CMR), and catheterization, excess adiposity contributes to technical challenges such as poor acoustic windows, soft-tissue attenuation, motion artifact, vascular access difficulty, and machine weight or gantry limits. Despite these constraints, advanced modalities like positron emission tomography (PET) and CMR maintain high accuracy, though they frequently require pharmacologic stress agents and careful consideration of equipment limitations.

Diagnostic Procedure	Key Findings in Patients With Obesity	Challenges & Limitations
Electrocardiogram (ECG)	- Sinus tachycardia, left axis deviation, left atrial enlargement (p-wave abnormalities) - Markers of left ventricular hypertrophy - False-positive “infarct” patterns (Q waves, poor R-wave progression) - QTc and/or QRS prolongation - Nonspecific ST-T wave changes (may correlate to age and blood pressure)	- Low QRS voltage due to chest mass - Lead placement difficulty - False-positive mimicking myocardial infarction
Transthoracic Echo (TTE)	- Concentric left ventricular hypertrophy & increased left ventricular mass - Diastolic dysfunction - Mild left atrial/right ventricular dilation - Preserved systolic function	- Poor acoustic windows & image quality - Lung artifact & difficulty visualizing endocardial borders - Frequent need for contrast (i.e., ultrasound enhancing agents) - Ejection fraction may be preserved at $\geq 50\%$ despite signs and symptoms of heart failure - Skin lead contact issues - Lead detachment & movement artifact
Ambulatory Rhythm Monitor	- Predominantly sinus tachycardia - High frequency of atrial and ventricular ectopy - Increased frequency of atrial fibrillation - Nocturnal brady-dysrhythmia in patients with sleep apnea	- Increased image noise & reduced signal-to-noise ratio - Higher radiation dose from computed tomography scanner may be required - Often with table weight limits (e.g., 350–450 lbs) - Often with gantry diameter limits (e.g., 70–85 cm) - Soft tissue attenuation causing high false-positive rates for myocardial infarction - Reduced image resolution - Motion artifacts - Machine weight and gantry limits - Difficulty with intravenous access - Soft tissue attenuation and artifacts with extreme obesity - Machine weight and gantry limits
Coronary Calcium (CAC)	Increased coronary artery calcification (higher cardiometabolic risk)	
Single-Photon Emission Computed Tomography (SPECT) Perfusion (e.g., technetium-99m sestamibi or tetrofosmin)	- Myocardial perfusion abnormalities - Ischemic abnormalities via nuclear contrast with treadmill testing or A2A adenosine receptor agonists (i.e., regadenoson coronary vasodilator for sestamibi stress test) if unable to walk on treadmill or with cardiac dysrhythmias/interfering ECG abnormalities - Left ventricular hypertrophy - Right ventricular dysfunction	
Positron Emission Tomography (PET) Perfusion [e.g., 50 mCi (1850 MBq) of rubidium-82 chloride (^{82}Rb) or 20 mCi (740 MBq) of ^{13}N-ammonia]	- Myocardial ischemia like SPECT through reversible defect - Irreversible defect suggestive of scar or prior myocardial infarction - High diagnostic accuracy preserved in severe obesity with lower false-positive rate vs. SPECT - If unable to physically exercise or with cardiac dysrhythmias/interfering ECG abnormalities, then pharmacologic stress testing can be achieved via the vasodilators regadenoson, adenosine, dipyridamole, or inotropic/chronotropic agents such as dobutamine with or without atropine	
Cardiac magnetic resonance imaging (CMR) with injection of contrast (i.e., gadolinium)	- As with SPECT and PET, CMR assesses myocardial ischemia - No radiation - High diagnostic quality for function & tissue characterization - Patients unable to walk on the treadmill or with cardiac dysrhythmias/interfering ECG abnormalities can receive pharmacologic agents such as adenosine, dipyridamole, or dobutamine	- Bore size & table weight limits - Signal loss from coil-to-heart distance - Difficulty with fat suppression
Coronary computed tomography Angiography (CCTA)	- Detects plaque, but distal segments are hard to evaluate - Plaque morphology (e.g., calcified, non-calcified, high risk plaque). - Coronary artery anomalies - Left ventricular hypertrophy - Other cardiac structural findings (e.g., right ventricular enlargement, aortic root dilation, aortic valve calcification, pericardial effusion or thickening)	- High image noise & streak artifacts - Higher radiation/contrast requirements - Machine weight and gantry limits
Cardiac Catheterization	Definitive evaluation of coronary anatomy	- Reduced image quality - Catheterization lab table weight limit (e.g., 350–450 lbs) - Vascular access difficulty (femoral) - Airway/sedation risks (sleep apnea) - Increased procedure time

Table 16

Ten things to know about obesity, nutrition therapy, and cardiovascular disease (CVD) [24].

Key Points	References
1. Medical nutrition therapy is most effective when dietary interventions are grounded in evidence and delivered with clear quantitative and qualitative guidance. Approaches that support long-term adherence consistently yield better outcomes in obesity and cardiovascular disease (CVD) risk reduction.	[24,137]
2. Low-calorie diets, typically providing 1200–1800 kcal per day, offer a structured reduction in energy intake to support clinically meaningful weight reduction. Very low-calorie diets (VLCDs), generally defined as <800 kcal per day, require close medical supervision due to their intensity but have demonstrated short-term improvements in cardiometabolic risk factors. Among adults with obesity and type 2 diabetes, VLCD therapy can produce short-term and rapid reductions in body weight, blood glucose, blood pressure, and blood atherogenic lipids.	[24,138]
3. Fat-restricted dietary patterns, which typically limit fat intake to 10–30% of total daily calories, can facilitate weight reduction and improve cardiometabolic risk when paired with nutrient-dense food choices. A comprehensive umbrella review of randomized trials found that reducing saturated fat intake - an essential component of fat-restricted approaches - significantly lowered CVD events.	[24,139]
4. Low-carbohydrate dietary patterns generally limit carbohydrate intake to 50–150 g per day, with very low-carbohydrate diets restricting intake to <50 g per day. In a meta-analysis of 21 randomized controlled trials involving adults with obesity and type 2 diabetes, low-carbohydrate ketogenic diets produced significantly greater improvements in key cardiovascular risk factors than non-ketogenic comparators, including reductions in body weight, body mass index, waist circumference, fasting glucose, HbA1c, and triglyceride levels, alongside increases in high density lipoprotein cholesterol levels. These diets emphasize minimizing refined and ultra-processed foods, high-glycemic carbohydrates, and trans fats. For some individuals, nutritional ketosis may also reduce hunger and facilitate sustained caloric reduction.	[24,141]
5. The Mediterranean dietary pattern emphasizes extra-virgin olive oil, vegetables, fruits, legumes, whole grains, nuts, seeds, seafood, fermented dairy, poultry, and eggs. It limits red and processed meats as well as ultra-processed carbohydrates, fostering a nutrient-dense, cardioprotective eating pattern. In the Prevención con Dieta Mediterránea (PREDIMED) randomized controlled trial, adherence to a Mediterranean diet supplemented with either extra-virgin olive oil or nuts significantly reduced major cardiovascular events compared with a low-fat control diet, establishing this approach as one of the most robustly supported dietary strategies for CVD prevention. Of note, PREDIMED was retracted and republished in 2018 following identification of randomization irregularities, with the primary finding preserved.	[24,142, 148]
6. The DASH dietary pattern emphasizes vegetables, fruits, whole grains, low-fat dairy, lean proteins, nuts, seeds, legumes, and foods naturally rich in potassium, calcium, and magnesium. It limits high-sodium foods, excessive total fat, cholesterol-dense items, red and processed meats, sugar-sweetened beverages, and added sugars. In a secondary analysis of the DASH-Sodium randomized controlled trial, the DASH diet significantly lowered estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk compared with a typical American diet, with even greater reductions when combined with sodium restriction.	[24,143]
7. Vegetarian dietary patterns center on plant-based foods - including vegetables, fruits, whole grains, legumes, seeds, and nuts - while limiting or excluding meat. Vegan diets extend this approach by eliminating all animal products and relying entirely on plant-derived nutrition. In a meta-analysis of 20 randomized clinical trials, vegetarian diets produced significant improvements in major cardiometabolic risk factors among adults with or at high risk for cardiovascular disease, including reductions in LDL cholesterol, hemoglobin A1c, and body weight. These findings support the cardioprotective potential of vegetarian eating patterns. A caveat is that beyond the absence of meat, it is the nutritional quality of the diet that most contributes to reduced CVD risk, a benefit negated if the diet consists of calorie dense, ultra-processed foods, high in refined starch and sugar, and resulting in obesity and major CVD risk factors such as type 2 diabetes mellitus, hypertension, and dyslipidemia.	[24,144]
8. Both ultra-processed carbohydrates and saturated fats increase cardiovascular disease risk when consumed in excess. Exchanging one for the other on an isocaloric basis does not meaningfully improve cardiovascular outcomes.	[24,145]
9. Dietary principles of healthful nutrition in patients with obesity include limiting ultra-processed, energy-dense, and low-nutrient foods such as sugary drinks, ultra-processed meats, trans fats, excess sodium, alcohol, and simple sugars. Nutrient rich options are encouraged and include minimally processed foods and marine oily fish, nuts, seeds, legumes, whole grains, high-fiber carbohydrates, and no-sugar-added dairy, with a focus on foods that support cardiometabolic health.	[24,146]
10. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are indicated for weight reduction, and in some cases, to reduce CVD events. In most patients with obesity who are treated with GLP-1 RA, the primary goal of nutritional therapy shifts away from guidance regarding weight reduction through additional caloric restriction. Instead, the emphasis switches to healthful nutritional intake of nutrient-dense foods that provide sufficient vitamins, minerals, and macronutrients. Adequate protein consumption helps preserve lean body mass, including skeletal muscle. As importantly, adequate hydration is necessary to support overall metabolic and renal health because reduced food intake can significantly decrease water consumption from food sources. This, combined with common side effects such as nausea, vomiting, and diminished thirst, may increase the risk of dehydration and acute kidney injury in patients treated with GLP-1 RA.	[24,147]

16. Obesity, nutrition therapy, and cardiovascular disease (CVD) [24] (See Table 16, Figs. 16a, 16b, and Chart 2)

Medical nutrition therapy is most effective when it provides clear, evidence-based guidance that patients can sustain long term. Multiple dietary patterns have demonstrated benefits for obesity and CVD risk reduction. Structured low-calorie and very low-calorie diets can produce clinically meaningful short-term improvements in weight and cardiometabolic markers, while fat-restricted and low-carbohydrate approaches - when focused on nutrient-dense, minimally processed foods - also improve key CVD risk factors. Robust trials support the cardioprotective effects of the Mediterranean diet, the “Dietary Approaches to Stop Hypertension” (DASH), and plant-based vegetarian and vegan patterns similarly reduce atherogenic lipids and improve metabolic health. Chart 2 provides an overview of some sentinel dietary patterns and their effects on CVD. Core principles for patients with obesity emphasize limiting ultra-processed, energy-dense foods and prioritizing whole, fiber-rich, nutrient-dense options. For individuals treated with GLP-1 RA, the nutritional focus shifts from further caloric restriction to ensuring adequate hydration, sufficient micronutrient and macronutrient intake, and adequate protein to help preserve lean body mass. Guidance regarding adequate hydration is also critical, given that reduced food intake, nausea, vomiting, and diminished thirst may

increase the risk of dehydration and acute kidney injury. Essential principles include:

- Medical nutrition therapy is most effective when it offers sustainable, evidence-based dietary guidance, with multiple eating patterns ranging from low-calorie plans to Mediterranean, DASH, and plant-based diets demonstrating benefits for weight and cardiovascular risk reduction.
- Core principles emphasize limiting ultra-processed, energy-dense foods while prioritizing whole, fiber-rich, nutrient-dense options that improve cardiometabolic health.
- For individuals using GLP-1 RA, the focus shifts toward maintaining adequate hydration, ensuring sufficient macro- and micronutrient intake, and consuming enough protein to preserve lean mass, given their increased vulnerability to dehydration and related complications.

17. Obesity, physical activity, and cardiovascular disease (CVD) [24] (See Table 17 and Fig. 17)

Regular physical activity improves cardiovascular health through several interconnected mechanisms: it reduces total body fat and visceral adipose tissue while preserving lean muscle, improves harmful

Chart 2
Dietary intake and risk of cardiovascular disease (CVD). Various dietary patterns influence CVD risk and body weight. Beyond CVD, greater adherence to healthy dietary patterns reduces all-cause mortality and prolongs life expectancy. A healthier dietary pattern may be associated with 18–24% lower risk of all-cause mortality, contributing to an additional life expectancy of 1.5–2.3 years for women and 1.9–3.0 years for men at the age of 45 years [166].

Dietary Pattern	Effect on cardiovascular disease	Effect on body weight	Reference
Mediterranean Diet [e.g., PREDIMED (Prevention with Mediterranean Diet), Lyon Diet Heart, and CORDIOPREV (Coronary Diet Intervention with Olive oil and cardiovascular PREvention) trials]	Implementation of the Mediterranean diet contributes to up to a ~30% reduction in cardiovascular events compared to a low fat diet	Implementation of Mediterranean Diet may promote ~5% weight reduction	[24, 148–150]
Dietary Approaches to Stop Hypertension (DASH): (e.g., PREMIER Trial)	Implementation of the DASH diet contributes to ~20% reduction in overall cardiovascular disease risk (e.g., coronary artery disease, and stroke).	Implementation of DASH Diet may promote ~5% weight reduction	[24, 151–154]
Healthful Plant-Based Diet [e.g., Mediterranean Diets (see above), Ornish Lifestyle Heart Trial, Esselstyn Cohort]	Implementation of a healthful plant-based diet contributes to ~13% reduction in cardiovascular disease, coronary artery disease, and stroke.	Implementation of healthful plant-based diet may promote ~3% weight reduction	[24,144, 155–160]
Low fat diet	Depending on composition, implementation of low fat diet may not reduce risk of cardiovascular disease	Implementation of low fat diet may promote ~3% weight reduction	[24,161, 162]
Modified fat intake	Replacement of saturated fats with polyunsaturated fats may contribute to ~17% reduction in cardiovascular disease.	Replacement of saturated fats with polyunsaturated fats may contribute to ~1% reduction in body weight.	[24,140, 163,164]
Low Carbohydrate Diet without modified fat intake	Implementation of a low carbohydrate diet without modified fat intake has not been shown to reduce CVD events.	Implementation of low carbohydrate diet may contribute to ~5% reduction in body weight.	[24,150, 165]

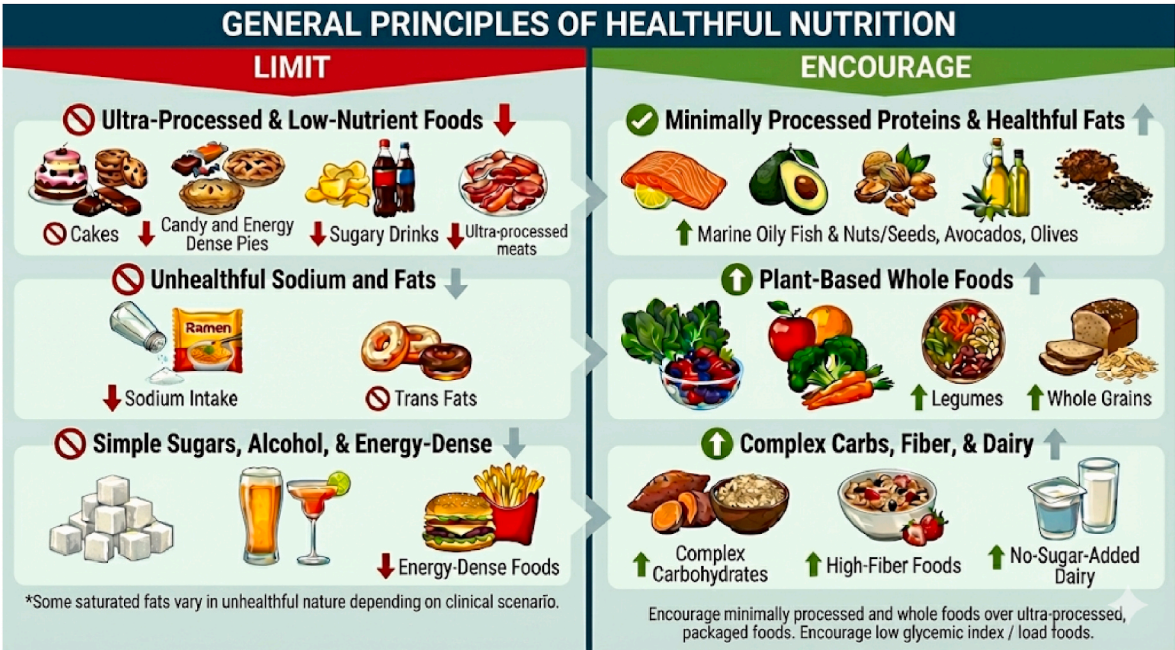


Fig. 16a. Obesity, Nutrition Therapy, and Cardiovascular Disease (CVD). Medical nutrition therapy works best when it offers clear, evidence-based recommendations that patients can maintain over time. A variety of dietary patterns - including low-calorie plans, low-carbohydrate or fat-restricted approaches centered on minimally processed foods, the Mediterranean diet, the Dietary Approaches to Stop Hypertension eating pattern, and plant-based - have all been shown to improve weight, lipid levels, and overall cardiometabolic health. Across all approaches, the unifying principle is to limit ultra-processed, energy-dense foods and prioritize whole, fiber-rich, nutrient-dense options.

endocrine and immune disturbances associated with excess adiposity, and strengthens metabolic, musculoskeletal, heart, lung, cognitive, mental, and sexual health. These whole-body benefits enhance functional capacity and resilience against cardiometabolic disease, and higher levels of cardiorespiratory fitness are strongly associated with lower mortality even when body weight does not change. Physical activity also helps prevent weight gain and weight regain, while resistance training preserves muscle mass, muscle function, and resting metabolic rate, all which protect against insulin resistance and unhealthy blood lipid patterns. Because prolonged sitting and inactivity independently increase cardiovascular risk, increasing total daily movement and interrupting long periods of inactivity through leisure activity and everyday movement is essential. Sustainable exercise programs follow principles that address frequency, intensity, duration, type, and

enjoyment, and individuals with excess adiposity or existing cardiovascular risk should undergo appropriate medical evaluation before beginning a demanding exercise plan. Tracking activity through logs, wearable devices, or periodic body composition measurements supports adherence and highlights early improvements relevant to cardiovascular prevention. Professional guidelines recommend 150–300 min of moderate-intensity dynamic activity per week or 75–150 min of vigorous-intensity aerobic activity per week, along with resistance training at least twice weekly, and they also encourage step goals beginning at a minimum of 5000 steps per day and progressing toward 10,000 or more steps per day to promote accessible and scalable cardiovascular protection. Essential principles include:

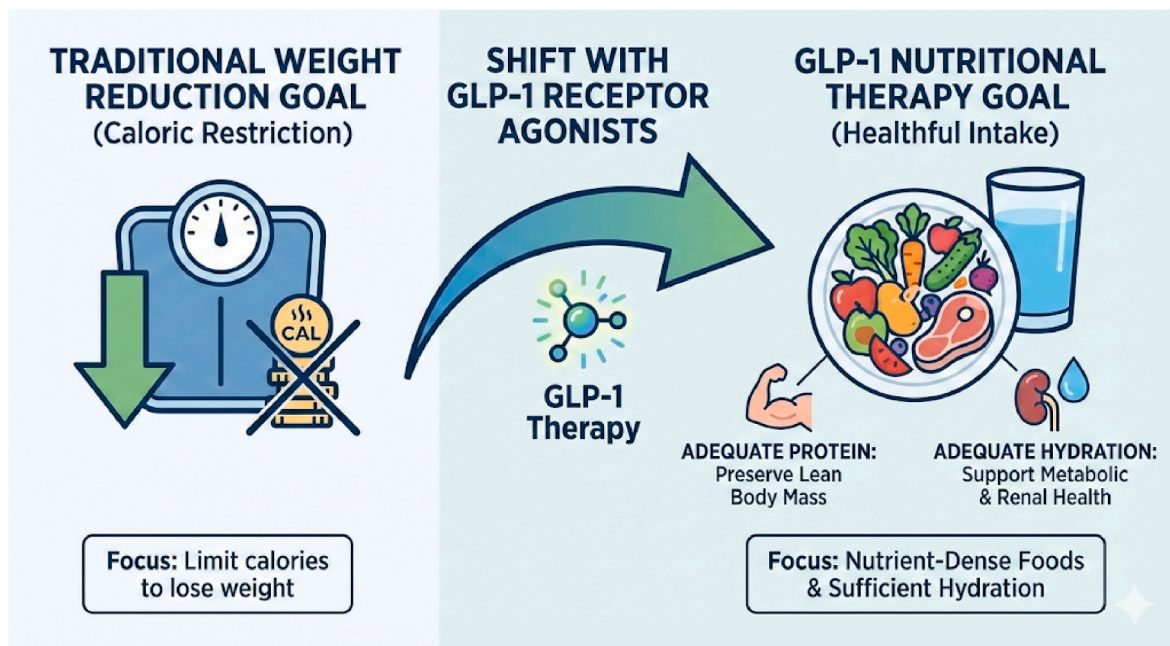


Fig. 16b. Obesity, Nutrition Therapy, and Cardiovascular Disease (CVD) in Patients Treated With Incretin Mimetics, such as Glucagon-like Peptide-1 Receptor Agonist (GLP-1 RA) Based Therapies. For individuals using GLP-1 RA, the nutritional priority shifts away from further calorie restriction and toward ensuring adequate hydration, healthful micronutrient and macronutrient intake, and enough protein to preserve lean body mass. Because these medications often reduce appetite and thirst—and may cause nausea or vomiting—patients are at increased risk of dehydration and acute kidney injury without intentional fluid intake. Overall, nutrition therapy focuses on nutrient-dense foods, adequate protein, and vigilant hydration to support metabolic and renal health while the medication drives weight reduction.

- Regular physical activity improves cardiovascular health by reducing excess adiposity, preserving lean mass, correcting endocrine and immune disturbances, and strengthening metabolic, musculoskeletal, cardiovascular, pulmonary, and cognitive systems.
- Physical exercise benefits include enhanced functional capacity and reduced cardiometabolic risk, with higher cardiorespiratory fitness linked to lower mortality regardless of weight change, while minimizing sedentary time and incorporating resistance training further protect against insulin resistance and adverse lipid patterns.
- Sustainable programs emphasize individualized frequency, intensity, duration, and enjoyment, supported by activity tracking, and align with guidelines recommending 150–300 min of moderate or 75–150 min of vigorous aerobic activity weekly, plus twice-weekly resistance training, with an alternative of step goals progressing from 5000 toward 10,000 or more per day.

18. Obesity, behavioral modification, eating disorders, and cardiovascular disease (CVD) [25] (See Table 18 and Fig. 18)

Eating and activity patterns in individuals with overweight or obesity arise from a complex interplay of genetic, physiologic, psychological, sensory, and environmental forces that strongly promote weight gain, weakly defend against weight reduction, and accelerate cardiovascular disease (CVD) through both fat-mass related cardiac strain and adiposopathic cardiometabolic risk. Sensory cues, stress, sleep loss, stigma, emotions, socioeconomic barriers, medications, psychiatric conditions, and reward pathways can intensify overeating and undermine adherence to heart-healthy nutrition, while eating disorders further worsen metabolic parameters relevant to CVD prevention and treatment. Physical inactivity, driven by medical conditions, immobility, fatigue, disinterest, or sedentary environments, exacerbates CVD by impairing fitness, worsening cardiometabolic risk factors, and promoting increased visceral adiposity. Behavioral contributors to weight

gain, including perceived time scarcity and inherited tendencies toward higher energy intake or lower expenditure, can derail CVD management unless addressed through tailored, supportive interventions. Effective behavior therapy relies on structured strategies such as education, stimulus control, cognitive restructuring, goal setting, self-monitoring, and social support, and may be enhanced by pharmacotherapy or metabolic treatments that reduce intrusive food thoughts. While technologies and supportive environments can help motivated patients adopt healthier behaviors, meaningful CVD risk reduction ultimately requires readiness for change and sustained engagement with evidence-based treatments, reinforced through ongoing monitoring, clinical follow-up, and social reinforcement. Essential principles include:

- Eating and activity patterns in individuals with overweight or obesity reflect a complex mix of biological, psychological, and environmental forces that promote weight gain, hinder attainment of healthy body weight, and heighten CVD risk through both excess fat mass and adiposopathic metabolic dysfunction.
- Stressors such as sensory cues, sleep loss, stigma, psychiatric conditions, medications, socioeconomic barriers, and physical inactivity further intensify overeating, impair fitness, worsen cardiometabolic markers, and contribute to increased visceral adiposity.
- Effective CVD risk reduction requires tailored behavioral strategies—education, stimulus control, cognitive restructuring, goal setting, self-monitoring, and social support—potentially augmented by pharmacotherapy, along with sustained readiness for change and ongoing clinical reinforcement.

19. Obesity and cardiovascular disease medications [26] (See Table 19 and Fig. 19)

In patients with obesity, choice of pharmacologic management of cardiovascular and metabolic disease should consider drug-specific

Table 17
Ten things to know about obesity, physical activity, and cardiovascular disease (CVD) [24].

Key Points	References
1. Routine physical activity may improve body composition by reducing overall adiposity, reducing visceral adiposity, and preserving lean mass. These improvements directly support cardiovascular health by lowering cardiometabolic risk factors that drive atherosclerotic disease.	[24,167]
2. Routine physical activity may improve adiposopathic endocrine and immune body processes, reducing inflammatory and hormonal disturbances associated with obesity. This reduction in adiposopathy is critical for cardiovascular disease prevention because chronic inflammation accelerates vascular injury. Routine physical activity may also favorably affect adipose tissue and muscle interactions and crosstalk (i.e., adipo-myokine profile).	[24,168]
3. Physical activity supports metabolic, musculoskeletal, cardiovascular, pulmonary, mental, sexual, and cognitive health. Together, these multisystem benefits lessen cardiovascular disease burden by enhancing functional capacity and strengthening cardiometabolic resilience. Moreover, higher cardiorespiratory fitness independently predicts lower mortality, often irrespective of weight change. Therefore, when regular physical activity improves a patient's fitness, it confers meaningful health benefits even in the absence of weight reduction – which can be an important patient motivator.	[24,169]
4. While dynamic training may promote weight reduction, physical exercise is especially beneficial in preventing weight gain or weight regain. Stabilizing weight trajectories is essential for cardiovascular disease prevention because progressive increased adiposity worsens cardiometabolic risk.	[24,101]
5. Resistance training may improve body composition, prevent muscle loss during weight reduction, and increase resting energy expenditure. Preserving muscle mass and function contributes to cardiovascular health because sarcopenia and reduced metabolic rate contribute to insulin resistance and dyslipidemia.	[24,170]
6. Prolonged physical inactivity is an independent risk factor for CVD. In addition to structured and scheduled physical exercise, increased energy expenditure can be achieved via increased leisure-time physical activity and non-exercise activity thermogenesis (NEAT). Higher total daily movement and breaking up prolonged periods of physical inactivity reduces CVD risk.	[24,171]
7. A common physical exercise prescription (FITTE) includes frequency, intensity, time, type, and enjoyment. Using FITTE principles ensures sustainable activity patterns that meaningfully reduce cardiovascular disease risk over time. Prior to implementing any rigorous physical exercise program, individuals with obesity and existing CVD risk factors, should undergo an evaluation of overall health and potential risk, especially from a cardiopulmonary and musculoskeletal standpoint.	[24,172]
8. Tracking physical activity can be done through activity logs, wearable devices, and periodic body composition measurements using reliable techniques. Monitoring progress reinforces adherence and allows early identification of cardiometabolic improvements relevant to cardiovascular disease prevention.	[24,173]
9. The Obesity Medicine Association (OMA) recommends 150–300 min or more of moderate-intensity dynamic activity per week or 75–150 min or more of vigorous-intensity aerobic activity per week, plus resistance training at least twice weekly. These targets align with cardiovascular disease prevention guidelines and ensure adequate stimulus for cardiometabolic benefit. Where the OMA differs is the specified inclusion of at least 5000 steps per day, progressing toward 10,000 or more steps per day to meet dynamic training goals. Step-based targets are particularly valuable for cardiovascular disease prevention because they increase daily movement in accessible, scalable ways.	[24,174]
10. Obesity and physical inactivity act synergistically to worsen insulin resistance, dyslipidemia, hypertension, and systemic inflammation, amplifying the risk of cardiovascular disease. Regular physical activity—whether structured exercise, NEAT, or step-based movement—improves endothelial function, autonomic balance, and myocardial efficiency, thereby enhancing vascular health and reducing cardiac workload. Because these physiologic adaptations accumulate over time, sustained long-term adherence to physical activity is one of the strongest predictors of reduced cardiovascular disease morbidity and mortality.	[24,167]

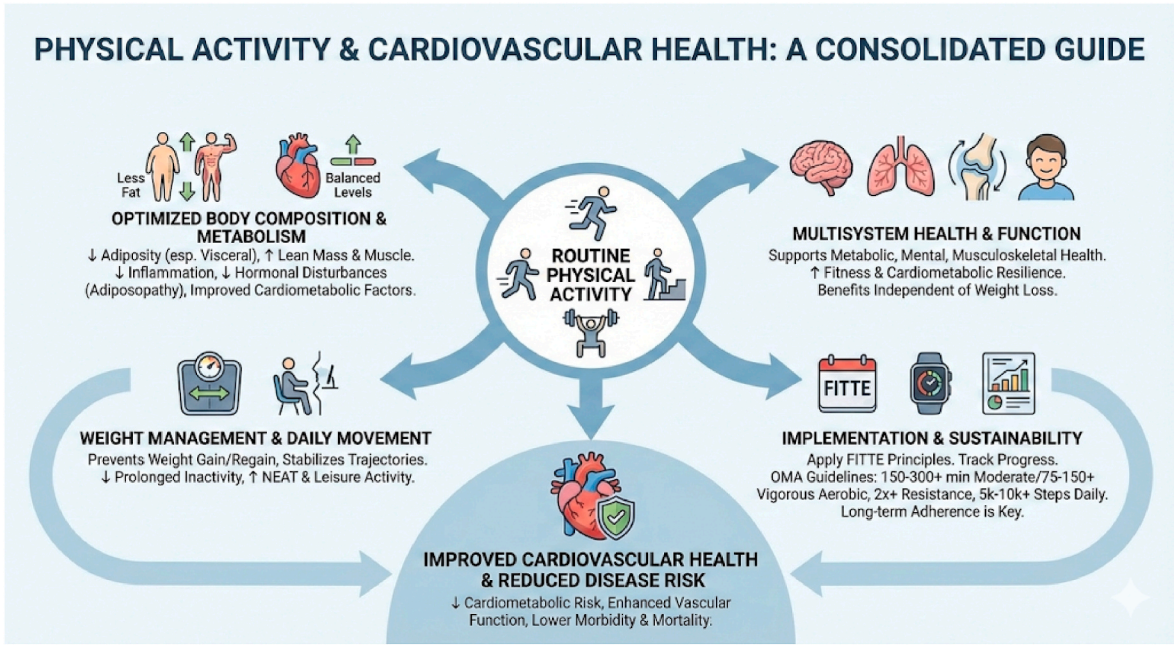


Fig. 17. Obesity, Physical Activity, and Cardiovascular Disease. Regular physical activity improves cardiovascular health by reducing excess body fat, preserving lean muscle, and correcting harmful endocrine and immune disturbances while strengthening multiple organ systems. Higher cardiorespiratory fitness lowers cardiometabolic risk and mortality even without weight reduction and minimizing sedentary time - along with resistance training - helps prevent insulin resistance and unhealthy lipid patterns. Sustainable exercise programs tailor FITTE (frequency, intensity, time, type, enjoyment) to the individual, supported by activity tracking, and generally follow guidelines recommending 150–300 min of moderate or 75–150 min of vigorous aerobic activity weekly plus twice-weekly resistance training or step goals progressing from 5000 toward 10,000 or more per day.

Table 18
Ten things to know about obesity, behavioral modification, eating disorders, and cardiovascular disease (CVD) [25].

Key Points	References
1. Eating behavior in individuals with overweight or obesity often reflects an imbalance of genetic, physiologic, psychologic, and environmental forces that strongly promote weight gain and weakly resist weight reduction - an imbalance analogous to the strong physiologic symptoms (e.g., tachycardia, diaphoresis, diminished mental status) of hypoglycemia versus the often weak or absent signals of hyperglycemia. These same biologic pressures contribute to excess adiposity that accelerates CVD through both adverse biomechanical “fat mass disease” (cardiac effects) and adverse adiposopathic “sick fat disease” (generation of cardiometabolic risk factors).	[25,175]
2. Because eating behavior is shaped by sight, smell, hearing, taste, and tactile cues, individuals living with obesity may experience intensified sensory-driven eating that promotes caloric excess. In the context of cardiovascular disease, these sensory triggers can perpetuate unhealthful dietary patterns high in sodium, saturated fat, and refined carbohydrates, thereby worsening cardiometabolic risk.	[25,176]
3. Genetic predisposition, chronic sleep deprivation, mental stress, experiences of weight stigma, emotions, habitual time cues, environmental exposures (including socioeconomic barriers and food insecurity), weight-promoting medications, information gaps, reward pathways, and psychiatric disease all influence eating behavior. These factors can compound CVD risk by reinforcing maladaptive dietary patterns and limiting adherence to heart-healthy nutrition strategies and options.	[25,146, 177]
4. Eating disorders (e.g., binge-eating disorder, bulimia nervosa, night-eating syndrome, and sleep-related eating disorder) can significantly disrupt energy balance and metabolic health. When present in patients with CVD or at CVD risk, these conditions may worsen insulin resistance, blood glucose, blood pressure, and atherogenic blood lipids, complicating both CVD prevention and treatment.	[25,178]
5. Physical inactivity may stem from musculoskeletal, neurologic, pulmonary (including obstructive sleep apnea), cardiac, and other health disorders, as well as fatigue, disinterest, or unhealthful environments that promote sedentary behavior. Reduced physical activity directly contributes to CVD progression by impairing cardiorespiratory fitness, adversely affecting cardiometabolic risk factors (insulin resistance, high blood glucose, high blood pressure, high atherogenic blood lipids), impairing endothelial function, increasing systemic inflammation and thrombosis, and facilitating a body composition associated with increased CVD risk (i. e., increased visceral adiposity).	[25,171]
6. Behaviors contributing to weight gain or regain often reflect personal and physiologic priority imbalances - such as perceived “lack of time” - that can disrupt nutritional intake and energy expenditure. These imbalances can undermine CVD management by limiting engagement in heart-healthy eating and regular physical activity.	[25,179]
7. Eating habits and physical activity behaviors may be substantially influenced by genetic predisposition, shaping an individual's baseline tendencies toward energy intake and expenditure. In CVD, these inherited behavioral patterns can amplify risk trajectories unless addressed through tailored, supportive interventions.	[25,180]
8. Optimal behavior therapies are feasible, efficacious, measurable, and promote self-ownership, with enhanced outcomes achieved through frequent professional encounters, education, stimulus control, cognitive restructuring, goal setting, self-monitoring, behavioral contracting, and social support. For patients with CVD, combining these behavioral approaches with appropriate pharmacotherapy or metabolic interventions can suppress intrusive food thoughts (“food noise”), allowing patients to meaningfully improve dietary quality, physical activity, and long-term CVD risk reduction.	[25,181]
9. For patients ready for change, weight-management technologies, access to healthful food environments, and availability of physical activity resources can support improved nutrition and exercise behaviors that reduce CVD risk. However, in individuals not yet ready for change, simply providing these resources rarely produces meaningful or sustained cardiometabolic benefit. Clinically meaningful change in CVD risk requires clinically meaningful changes in behavior and willingness to accept and adhere to evidence-based treatments.	[25,182]
10. Healthful behavior change is more effective and consistent when supported by self-monitoring, record-keeping, education, routine clinical assessment, and social reinforcement. In CVD care, these strategies help patients maintain adherence to nutrition, activity, and medication plans that are essential for long-term risk reduction.	[25,183]

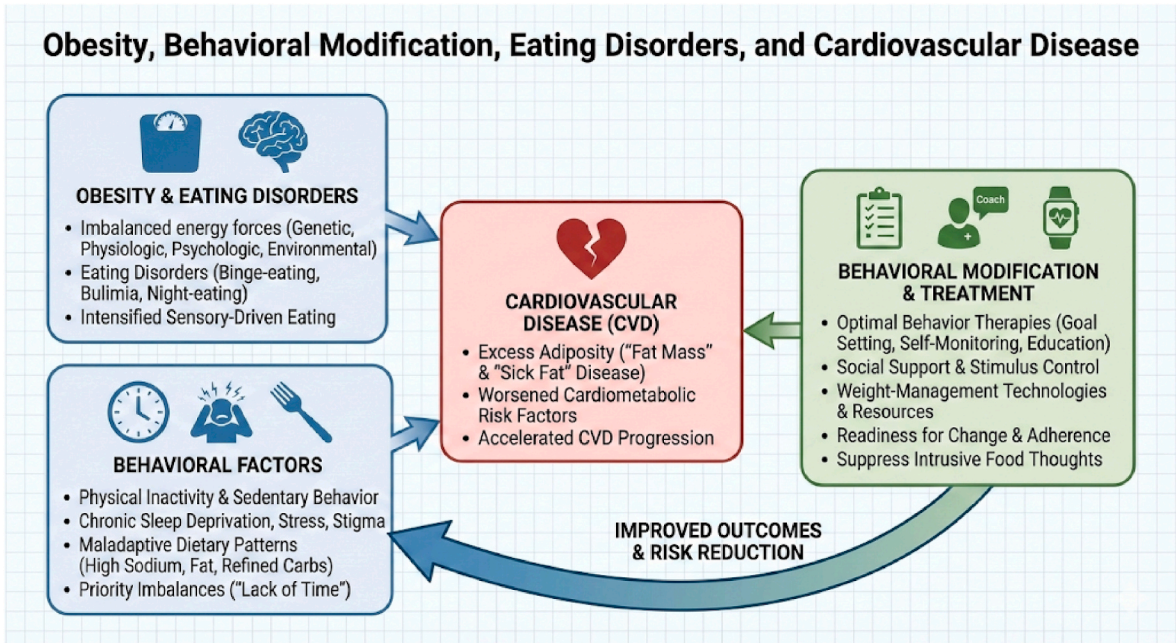


Fig. 18. Obesity, Behavioral Modification, Eating Disorders, and Cardiovascular Disease (CVD). Eating and physical activity patterns in individuals with overweight or obesity arise from intertwined biological, psychological, and environmental forces that promote weight gain, resist weight reduction, and elevate cardiovascular risk through both excess fat mass and adiposopathic metabolic dysfunction. Stressors such as sensory cues, sleep loss, stigma, psychiatric conditions, medications, socioeconomic barriers, and physical inactivity further intensify overeating, worsen cardiometabolic markers, and promote increased visceral adiposity. Meaningful cardiovascular risk reduction requires tailored behavioral strategies—such as education, stimulus control, cognitive restructuring, goal setting, self-monitoring, and social support—often complemented by pharmacotherapy and sustained engagement with evidence-based treatment.

Table 19

Ten things to know about obesity and cardiovascular disease medications [26].

Key Points	References
1. Older beta blockers such as propranolol, atenolol, and metoprolol can promote weight gain by lowering metabolic rate and reducing energy expenditure. Carvedilol and nebivolol are generally weight-neutral and do not have the same metabolic effects. Bisoprolol is generally β 1-selective (like metoprolol) and lacks the vasodilatory properties of carvedilol/nebivolol, so it is typically grouped with the agents that can reduce metabolic rate, though clinical weight gain is often less pronounced than with atenolol. Choosing a weight-neutral agent can help avoid worsening cardiometabolic risk in individuals with obesity and cardiovascular disease (CVD).	[26,86,184]
2. Dihydropyridine calcium channel blockers such as nifedipine and amlodipine frequently cause peripheral edema, which increases body weight through fluid retention rather than adipose tissue accumulation. This edema results from precapillary vasodilation and increases hydrostatic pressure. In individuals with obesity, the edema can be more pronounced and complicate assessment of true volume status.	[26,185]
3. Insulins, sulfonylureas, thiazolidinediones (e.g., TZDs such as pioglitazone), and meglitinides (e.g., nateglinide and repaglinide) can all contribute to weight gain, either by enhancing insulin signaling or by causing fluid retention. Notably, TZDs are contraindicated in patients with NYHA Class III or IV heart failure.	[26,186]
4. Diabetes medications such as metformin, glucagon-like peptide-1 receptor agonist (GLP-1 RA), SGLT2 inhibitors, α -glucosidase inhibitors, and amylin analogs promote weight reduction. Semaglutide, liraglutide, and tirzepatide are examples of diabetes medications that also produce clinically meaningful weight reduction. Among patients with diabetes, semaglutide, liraglutide, and SGLT2 inhibitors have cardiovascular outcomes trials demonstrating reductions in major adverse cardiovascular events (MACE) such as "Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes" or SUSTAIN-6, "Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results" or LEADER, and for SGLT2 inhibitors, the "SGLT2i Meta-Analysis Cardio-Renal Trialists Consortium" or SMART-C meta-analysis. A cohort study also links tirzepatide to reduced all-cause mortality, MACE, and kidney events compared with GLP-1 receptor agonists.	[26,27,187]
5. Obesity increases intra-abdominal pressure, impairs renal venous return, and diminishes the effectiveness of loop diuretics. As a result, clinicians may need higher doses or sequential nephron blockade with agents like metolazone to maintain fluid balance, although this approach raises the risk of electrolyte abnormalities and kidney injury. Obesity also promotes elevated aldosterone levels, making spironolactone a consideration in cases of resistant hypertension, albeit one that requires careful monitoring for hyperkalemia, especially in patients taking renin-angiotensin system inhibitors or those with obesity-related chronic kidney disease (CKD). Finerenone is indicated for adults with type 2 diabetes mellitus and chronic kidney disease (CKD) to slow renal decline and reduce cardiovascular events. Finerenone is also indicated for patients with heart failure with left ventricular ejection fraction $\geq 40\%$. As a non-steroidal mineralocorticoid receptor antagonist (nsMRA), it offers high selectivity for the mineralocorticoid receptor with minimal affinity for androgen and progesterone receptors, leading to a lower risk of gynecostasia compared to spironolactone. Finally, obesity suppresses circulating B-type natriuretic peptide (BNP) levels because adipose tissue increases natriuretic peptide clearance and expresses receptors that degrade them, which can lead to "normal" or only mildly elevated BNP values in patients with obesity and acute heart failure, contributing to under-recognition of congestion. Some evidence suggests obesity may reduce production of BNP. These BNP imbalances further support the use of ARNIs such as sacubitril/valsartan, which inhibit neprilysin and help restore effective natriuretic peptide activity.	[26,188,189]
6. Antithrombotic therapy in individuals with obesity requires careful adjustment to account for altered pharmacokinetics. Among direct oral anticoagulants, apixaban and rivaroxaban are preferred in patients with very high BMI ($>40 \text{ kg/m}^2$ or weight $>120 \text{ kg}$), because standard dosing is supported by stronger evidence, whereas dabigatran and edoxaban are generally avoided due to less predictable drug handling and limited data in this population. In patients with a BMI above 50 kg/m^2 or those who have undergone bariatric surgery, absorption becomes increasingly variable, prompting the use of drug-specific peak and trough anti-Xa monitoring to confirm therapeutic levels. Similar concerns apply to antiplatelet therapy: standard low-dose aspirin (81 mg) may provide inadequate platelet inhibition in individuals with higher body weight because of increased esterase activity and a larger volume of distribution. Although not currently in established guidelines, some evidence indicates that patients weighing more than 70–90 kg may require higher or more frequent dosing - such as 325 mg or twice-daily regimens - to achieve sufficient antiplatelet effect; however, such adjustments may increase bleeding risk and should be framed as pharmacokinetic considerations or areas of ongoing debate rather than established guideline standards.	[9,26,86]
7. Highly lipophilic drugs such as amiodarone have a substantially increased volume of distribution in obesity, as expanded adipose tissue acts as a reservoir that prolongs their elimination half-life (a process less pronounced for moderately lipophilic drugs like lidocaine). While loading doses for lipophilic drugs often require scaling toward total body weight to achieve therapeutic concentrations, amiodarone loading is typically capped or calculated using ideal or adjusted body weight to prevent toxicity. Maintenance dosing requires caution and should be based primarily on metabolic clearance rather than total body weight. Hydrophilic agents like digoxin and sotalol distribute chiefly into lean tissue and body water rather than fat, so their volume of distribution rises little with excess adiposity and dosing is more accurately based on ideal or lean body weight. Statins vary in their lipophilicity, with lipophilic agents entering cells by passive diffusion and hydrophilic agents relying on transporters. Both moderate intensity and high intensity statins are sometimes associated with small increases in body weight, and high-intensity statins (e.g., lipophilic atorvastatin and the hydrophilic agent rosuvastatin) are sometimes associated with small increases in fasting glucose and hemoglobin A1c, occasionally contributing to type 2 diabetes. That said, the cardiovascular benefits of statins overwhelmingly outweigh these potential adverse metabolic effects. Pravastatin and pitavastatin appear to have the least influence on glycemic parameters. The fact that rosuvastatin, despite being hydrophilic, still carries a risk of glycemic worsening underscores that statin intensity, rather than solubility characteristics, is the principal determinant of new-onset diabetes risk.	[26,86,190,191]
8. Using total body weight in the Cockcroft–Gault equation overestimates creatinine clearance in individuals with morbid obesity, increasing the risk of overdosing renally cleared medications. In contrast, the CKD-EPI equation is less biased by body size and is the most widely used method for estimating glomerular filtration rate; its accuracy for drug dosing can be improved by de-indexing, which converts the laboratory-reported eGFR (normalized to 1.73 m^2) to an absolute GFR (mL/min) based on the patient's actual body surface area. De-indexed CKD-EPI is particularly relevant for medications whose pharmacokinetics depend on true renal clearance, including metabolic and endocrine agents such as metformin, renally cleared GLP-1 RA (e.g., exenatide, lixisenatide), insulin, and most DPP-4 inhibitors (except linagliptin), as well as cardiovascular and heart-failure therapies such as SGLT2 inhibitors, ACE inhibitors and ARBs, sacubitril/valsartan, mineralocorticoid receptor antagonists, loop and thiazide-type diuretics, renally cleared beta-blockers (atenolol, nadolol, sotalol); direct oral anticoagulant dosing are based on the Cockcroft–Gault equation.	[26,192]
9. Sodium–glucose cotransporter-2 inhibitors reduce the incidence of major adverse cardiovascular events; empagliflozin and dapagliflozin markedly reduce hospitalizations for heart failure (especially heart failure with preserved ejection fraction) among individuals with obesity and type 2 diabetes. Emerging evidence indicates that people with obesity may derive even greater cardiovascular benefit than those with lower body weight. This pattern underscores the substantial cardiometabolic value of this drug class in a high-risk population, likely due to improved myocardial energy utilization, reduced inflammation, enhanced autophagy, and favorable influences on blood pressure, arterial stiffness, and reduction in body weight. Collectively, these pathways promote healthier cardiac structure and function and may also lessen the risk of myocardial infarction, dysrhythmias, and vascular dysfunction.	[26,193]
10. Pharmacological management of CVD in patients with obesity requires a strategic shift from treating isolated complications of obesity to prioritizing agents that synergistically treat both the cause (i.e., obesity) and the adverse consequences (e.g., type 2 diabetes mellitus, hypertension, and dyslipidemia). For example, for treatment of type 2 diabetes mellitus, clinicians should preferentially select medications that substantially reduce body weight (e.g., GLP-1 RA) or therapies that modestly reduce body weight or that are weight neutral (e.g., SGLT2 inhibitors, metformin, α glucosidase inhibitors, amylin) while avoiding weight-promoting agents (e.g., sulfonylureas, insulin, thiazolidinediones, meglitinides) whenever possible. Furthermore, standard dosing regimens must be rigorously adjusted to account for obesity-altered pharmacokinetics to ensure therapeutic efficacy and safety. Finally, beyond cardiometabolic drug treatment, bariatric surgeries such as Roux-en-Y gastric bypass may impair gastrointestinal absorption of extended-release formulations and should often be replaced with immediate-release alternatives.	[26,40]

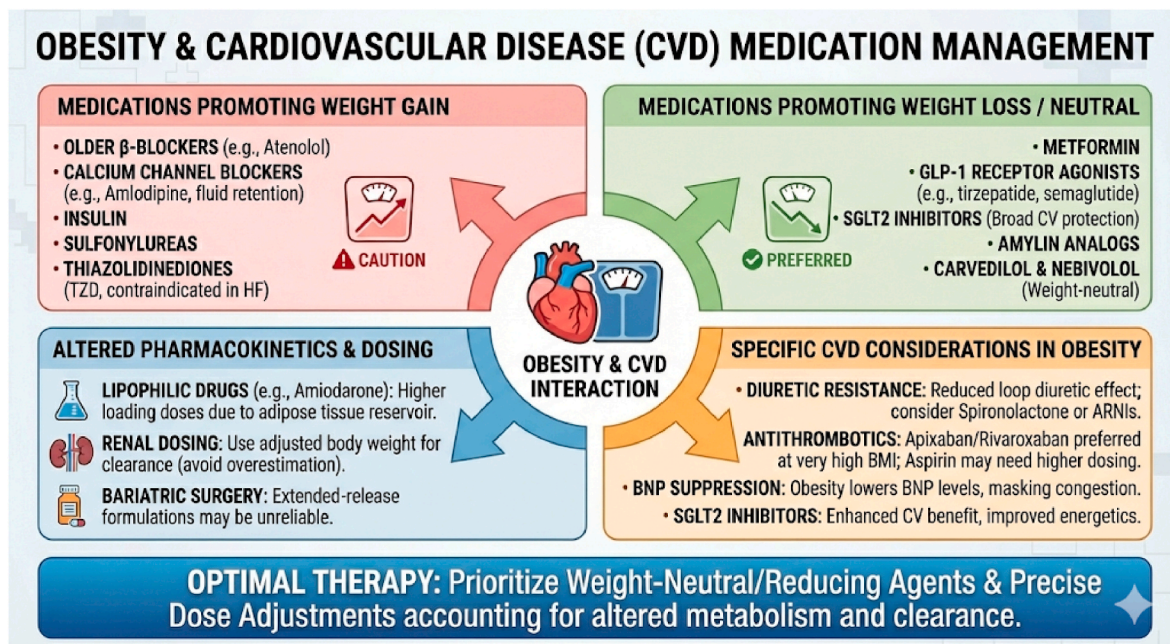


Fig. 19. Obesity and Cardiovascular Disease Medications. Pharmacologic management in individuals with obesity must account for drug-specific metabolic effects, fluid balance, and altered pharmacokinetics, since several medications—including older beta-blockers, certain calcium channel blockers, and multiple glucose-lowering agents—can promote weight gain or edema, whereas metformin, glucagon-like peptide-1 receptor agonists, and sodium–glucose cotransporter-2 inhibitors support weight reduction and improve cardiovascular outcomes. Obesity also alters drug handling by reducing loop-diuretic effectiveness, increasing aldosterone-driven hypertension, suppressing natriuretic peptide levels, modifying antithrombotic pharmacokinetics, and changing dosing requirements for lipophilic and hydrophilic drugs, with renal dosing requiring adjusted body weight, or more accurately, deindexed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); extended-release formulations may be unreliable after Roux-en-Y gastric bypass. Overall, optimal cardiovascular therapy emphasizes weight-neutral or weight-reducing medications and careful dose adjustment to accommodate obesity-related changes in drug distribution, metabolism, and clearance.

metabolic effects, fluid balance, and altered pharmacokinetics. Older β -blockers such as propranolol, atenolol, and metoprolol can promote weight gain by lowering metabolic rate, reducing energy expenditure, and decreasing lipolysis through blocking beta-adrenergic receptors; carvedilol and nebivolol are generally weight-neutral. Dihydropyridine calcium channel blockers often cause edema from precapillary vasodilation, which is more pronounced in obesity.

Several glucose-lowering agents [(e.g., insulin, sulfonylureas, thiazolidinediones (TZD), and meglitinides)] also contribute to weight gain, with TZDs contraindicated in advanced heart failure. In contrast, metformin, GLP-1 RA, SGLT2 inhibitors, α -glucosidase inhibitors, and amylin analogs promote weight reduction and improve cardiovascular risk factors, with semaglutide and SGLT2 inhibitors [27] demonstrating reduction in major adverse cardiovascular events (MACE) and tirzepatide undergoing CVD outcome clinical trials in patients with obesity. Obesity also reduces loop diuretic effectiveness, increases aldosterone-driven resistant hypertension, and suppresses B-type natriuretic peptide (BNP) levels, supporting the use of spironolactone, finerenone, and angiotensin receptor-neprilysin inhibitors (ARNIs) such as sacubitril/valsartan.

Antithrombotic therapy must account for altered drug pharmacokinetics, with apixaban and rivaroxaban preferred at very high BMI and aspirin potentially requiring higher or more frequent dosing due to pharmacokinetic dilution. Lipophilic drugs like amiodarone and lidocaine require higher loading doses, while hydrophilic agents such as digoxin and sotalol should be dosed using ideal or lean body weight. High-intensity statins may modestly worsen glycemia (and potentially increase appetite), though the CVD benefits outweigh risks. Renal dosing

must avoid overestimation of creatinine clearance by using adjusted body weight, or more accurately by deindexed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); extended-release formulations may be unreliable after Roux-en-Y gastric bypass.

SGLT2 inhibitors provide broad cardiovascular protection - particularly in individuals with obesity - through mechanisms including improved myocardial energetics, reduced inflammation, and favorable hemodynamic effects. Overall, optimal concomitant CVD therapy emphasizes weight-neutral or weight-reducing agents and precise dose adjustment to accommodate obesity-related changes in drug distribution, metabolism, and clearance. Essential principles include:

- Pharmacologic management in individuals with obesity requires attention to drug-specific metabolic effects and altered pharmacokinetics, as several agents - including older β -blockers, certain calcium channel blockers, and multiple glucose-lowering drugs - can promote weight gain or fluid retention, where metformin, GLP-1 RA, SGLT2 inhibitors, and related agents support weight reduction and improve cardiovascular outcomes.
- Obesity also affects drug handling by reducing loop diuretic effectiveness, increasing aldosterone-driven hypertension, suppressing BNP levels, altering antithrombotic pharmacokinetics, and changing dosing needs for lipophilic and hydrophilic medications, with renal dosing requiring adjusted body weight and extended-release formulations becoming unreliable after gastric bypass.
- Optimal therapy prioritizes weight-neutral or weight-reducing medications and precise dose adjustments that account for obesity-related changes in drug distribution, metabolism, and clearance.

Table 20
Ten things to know about obesity medications and cardiovascular disease (CVD) [28].

Key Points	References
1. Among patients with obesity, modest weight reduction (e.g., 5%–10% of total body weight) is often sufficient to improve cardiometabolic risk factors, including blood glucose, blood pressure, and blood lipid levels (i.e., decreases triglyceride levels and increases in high density lipoprotein cholesterol levels). Larger reductions in body weight (>10%) more reliably reduce CVD events and mortality.	[1,28,175,194,195]
2. Tirzepatide is an unimolecular glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA) that at a maximum dose of 15 mg injectable once a week is approved for chronic weight management in adults with obesity or overweight. Tirzepatide not only reduces body weight, but also improves cardiometabolic risk factors such as blood glucose, blood pressure, and atherogenic blood lipids. In the SUMMIT trial [Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity], tirzepatide produced substantial weight reduction and a significant reduction in the composite risk of heart-failure events and cardiovascular death. Tirzepatide has undergone and continues to undergo clinical trials to evaluate obesity and weight management (SURMOUNT), as well as diabetes mellitus (Study of Tirzepatide in Participants with Type 2 Diabetes or SURPASS). The SURMOUNT Morbidity and Mortality Outcomes (MMO) trial will assess CVD events, with an estimated study completion date of October 2027.	[28,78,112,194]
3. Semaglutide is a GLP-1 RA with robust evidence for cardiovascular protection. In the landmark SELECT trial, semaglutide at a maximum dose of 2.4 mg injectable weekly reduced major adverse cardiovascular events (MACE) such as heart attack and stroke by 20% in adults with overweight or obesity and established cardiovascular disease and without diabetes mellitus. In 2024, semaglutide was the first obesity medication to achieve an FDA indication to reduce cardiovascular death, heart-attack, and stroke risk. Beyond MACE reduction, semaglutide has demonstrated meaningful benefits across other high-risk cardiometabolic conditions. As assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and 6-min walk distance, the “Semaglutide Treatment Effect in People with Obesity (STEP) – HFpEF” trial showed significant improvements in symptoms, functional capacity, and quality of life in patients with HFpEF and obesity. Regarding patients with chronic kidney disease and type 2 diabetes mellitus, the FLOW trial was stopped early for efficacy after achieving a 24% reduction in the primary endpoint of a composite that included: onset of kidney failure, a $\geq 50\%$ reduction in estimated glomerular filtration rate, and death from kidney or cardiovascular causes.	[28,194,196–198]
4. Liraglutide is a GLP-1 RA approved at lower doses (1.8 mg injectable per day) for the treatment of type 2 diabetes mellitus and at higher doses (3.0 mg injectable per day) for the treatment of obesity. While liraglutide improves cardiometabolic parameters including blood glucose, blood pressure, and atherogenic lipid levels, clinical evidence for cardiovascular risk reduction is currently limited to the diabetes population. Specifically, in the “Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)” trial, the drug significantly reduced major adverse cardiovascular events (MACE) and cardiovascular death in patients with type 2 diabetes using the 1.8 mg per day dose. However, unlike semaglutide, liraglutide does not carry an FDA indication for cardiovascular risk reduction in individuals with obesity but without diabetes, as no trial analogous to the SELECT study has been conducted to evaluate outcomes in this population. That said, liraglutide is approved for the treatment of obesity and is available as a generic formulation.	[28,78,194]
5. Cardiovascular outcome trials suggest that GLP-1 RA deliver cardiovascular benefits prior to clinically meaningful weight reduction, with event-curve separation apparent within the first year. Acute negative caloric balance contributes to rapid improvements in cardiometabolic risk factors (glucose, BP, lipids). While speculative and yet to be proven, some authors suggest that early CVD benefit may also be driven by direct vascular and anti-inflammatory actions independent of weight reduction. These include reduced vascular inflammation, improved endothelial function, enhanced endothelial-dependent vasodilation, decreased arterial stiffness, renal protection, and enhanced atherosclerotic plaque stability. Finally, while GLP-1 RA therapies generally lower blood pressure, they can modestly increase resting heart rate, a well-recognized class effect.	[28,194,199–201]
6. While much needs to be confirmed in humans, rodent studies suggest that GLP-1 RA can favorably affect “sick fat.” Adiposopathy describes hypertrophic, hypoxic, fibrotic adipose tissue infiltrated by pro-inflammatory immune cells that release cytokines and maladaptive adipokines which results in adipocyte and adipose tissue dysfunction, insulin resistance, ectopic lipid deposition, and elevated cardiometabolic and CVD risk. GLP-1 receptors are found in the beta cells of the pancreas, brain, gastrointestinal tract, liver, kidneys, and heart, as well as adipose tissue. Human adipocytes express fewer GLP-1 receptors compared with the pancreas and brain; thus, the effects of GLP-1 RA on adipocytes likely reflect both direct effect as well as indirect effects via sympathetic pathways. Direct effects of GLP-1 RA may include cellular signaling, reduced adipose inflammation and relief of adipocyte endoplasmic reticulum (ER) stress. Facilitated by weight reduction, as adipose tissue function normalizes, insulin sensitivity improves, peripheral subcutaneous adipose tissue can store energy appropriately, visceral adipose tissue declines, and ectopic fat is reduced. By correcting adiposopathic endocrine and immune signaling, GLP-1 RAs improve cardiometabolic risk factors, enhance vascular function, and lower CVD risk. Additionally, GLP-1 RA may remodel adipose tissue, shifting it from energy storage toward energy expenditure and stimulating lipolysis, suppressing de novo lipogenesis, shrinking adipocyte size, and promoting browning of white fat to increase thermogenesis. Thus, beyond reducing fat mass, GLP-1 RA may improve adipose function by decreasing chronic inflammation and increasing glucose uptake via glucose transporter 4 translocation, producing smaller, more insulin-sensitive, less toxic, and more thermogenic adipocytes.	[28,194,202,203]
7. Phentermine is a sympathomimetic amine that suppresses appetite and is FDA-approved only for short-term use - typically up to 12 weeks - for the treatment of obesity. Because it increases norepinephrine release, phentermine can raise both heart rate and blood pressure, requiring caution in individuals with uncontrolled hypertension or established cardiovascular disease. No prospective, randomized, long-term cardiovascular outcome trial has shown that phentermine monotherapy reduces major adverse CVD events.	[28,194,204,205]
8. The combination of phentermine and topiramate in an extended-release formulation is approved for chronic weight management and typically achieves greater weight reduction than either agent alone. It has been associated with improvements in cardiometabolic risk factors, including blood glucose, blood pressure and atherogenic blood lipid levels; however, the phentermine component can produce a modest rise in heart rate, warranting routine monitoring. Although observational studies support its overall safety, no prospective, randomized cardiovascular outcome trial has yet demonstrated that this combination reduces cardiovascular morbidity or mortality.	[28,194]
9. The naltrexone/bupropion combination works centrally to reduce appetite and food cravings, producing modest weight loss in many patients. Its cardiovascular safety was evaluated in the “Light” trial, but the study was stopped early, leaving the long-term cardiovascular benefits or risks inconclusive. While it has the potential for several drug interactions, naltrexone/bupropion can improve cardiometabolic risk factors. That said, the bupropion component can cause transient increases in blood pressure and is contraindicated in patients with uncontrolled hypertension.	[28,194]
10. Orlistat is a reversible gastrointestinal lipase inhibitor that inhibits the absorption of dietary fats, resulting in modest weight reduction and modest improvements in blood pressure. Orlistat may lower low density lipoprotein cholesterol beyond what weight reduction alone would predict, likely due to reduced intestinal lipid absorption. No large-scale cardiovascular outcome trial has demonstrated that orlistat reduces major CVD such as myocardial infarction or stroke.	[28,194]

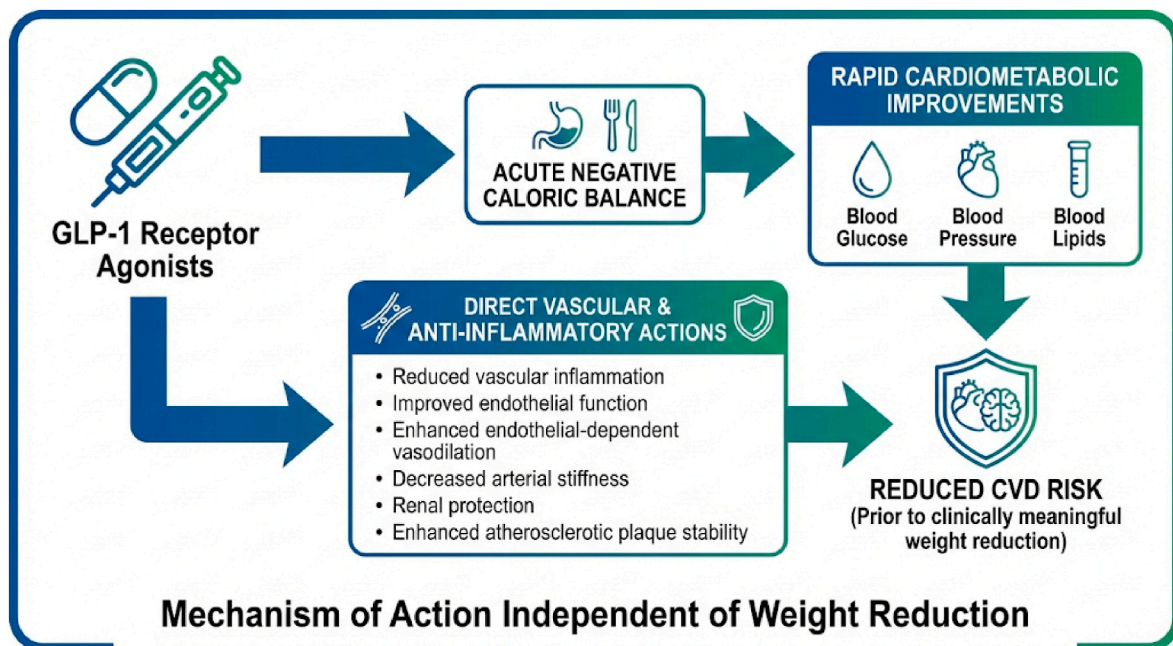


Fig. 20a. Glucagon-like peptide-1 receptor agonists demonstrate cardiovascular benefits often within months, before substantial weight reduction occurs. While rapid improvements in glucose, blood pressure, and lipids from acute caloric deficit may play a role, and while yet to be proven [199–201], some authors suggest that any early cardiovascular protection may also stem from weight-independent mechanisms. These include reduced vascular inflammation, improved endothelial function and vasodilation, decreased arterial stiffness, renal benefits, and greater atherosclerotic plaque stability.

20. Obesity medications and cardiovascular disease (CVD) [28] (See Table 20, Figs. 20a and 20b)

Among patients with obesity, modest weight reduction of 5%–10% via evidence-based interventions can reduce cardiometabolic risk

factors. Greater weight reduction is usually required (>10%) for more consistent and demonstrable reduction in CVD events. In the Look AHEAD (Action for Health in Diabetes) Lifestyle study, mostly lifestyle-only interventions did not reduce CVD events despite 3–8% weight reduction at various points during the ~10 years of follow-up. However,

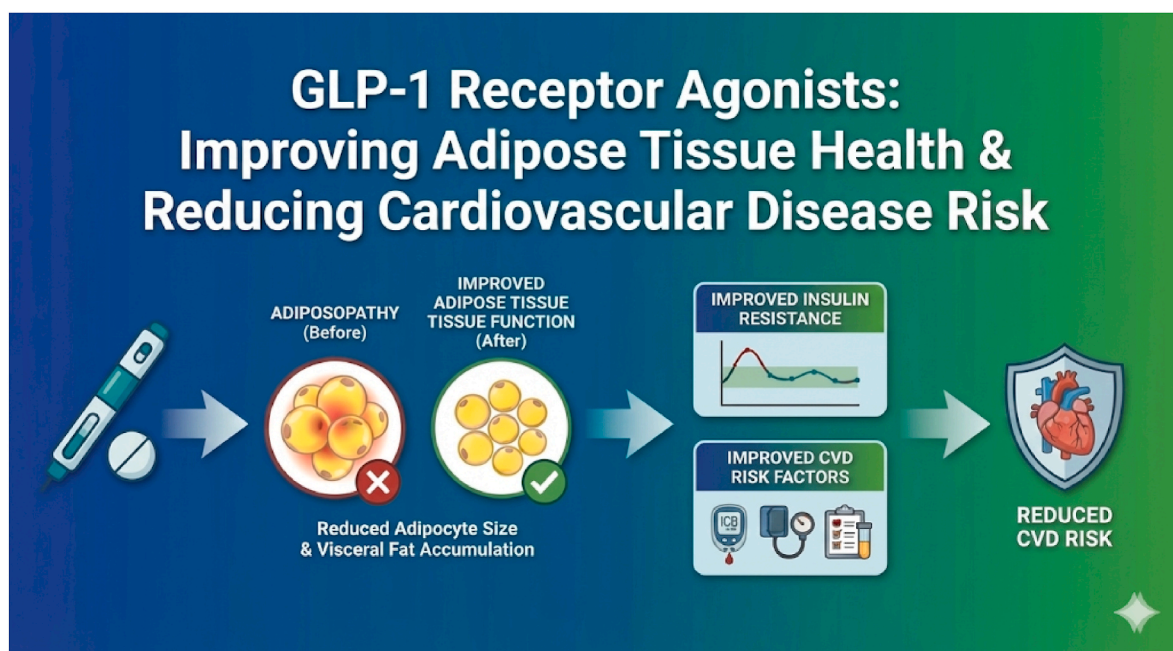


Fig. 20b. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) treat the adiposopathic consequences of obesity that lead to cardiovascular disease (CVD). While effects in humans await confirmation, rodent studies suggest that GLP-1 RA improve the structure and function of hypertrophic, inflamed, and metabolically harmful “sick” adipose tissue. Although adipocytes express relatively few GLP-1 receptors, GLP-1 RA act through both direct cellular effects by reducing adipose tissue inflammation, easing endoplasmic reticulum (ER) stress, and improving cellular signaling, as well as promoting lipolysis via sympathetic pathways. As weight decreases and adipose tissue size and function normalizes, insulin sensitivity improves, subcutaneous adipose tissue has greater capacity to store more energy, visceral and ectopic fat decline, and cardiometabolic risk is improved. Finally, GLP-1 RA may promote the browning of white fat cells, ultimately producing smaller, less inflammatory, more insulin-sensitive, and more thermogenic adipocytes.

Table 21

Ten things to know about obesity, bariatric procedures, and cardiovascular disease (CVD) [29].

Key Points	References
1. Bariatric surgeries such as gastric bypass and sleeve gastrectomy are the most durable intervention for achieving and maintaining substantial weight reduction, with metabolic and anti-inflammatory effects that translate into cardiovascular benefit. By limiting the weight regain common with lifestyle or obesity medications alone, bariatric surgery preserves improvements in cardiometabolic risk factors and meaningfully reduces long-term cardiovascular risk. Specifically, bariatric procedures can facilitate remission of type 2 diabetes mellitus, with less durable remission of hypertension (although control of both are more easily achieved with fewer medications).	[29,206,207]
2. Bariatric surgery addresses both major dimensions of adiposity: it decreases total fat mass ("fat mass disease") and simultaneously improves adiposopathic "sick fat disease". By shrinking adipose depots and restoring healthier endocrine and inflammatory signaling, bariatric surgeries produce metabolic and immunologic improvements that contribute to broad cardiometabolic benefits.	[29,208–210]
3. Specifically, bariatric surgery lowers long-term myocardial infarction risk and stroke by improving the atherosclerotic environment. Early improvements in glycemic control, blood pressure, and atherogenic lipids, along with sharp reductions in systemic inflammation (as evidenced by rapid declines in highly sensitive C-reactive protein and interleukin 6) reflect decreased adipose-tissue inflammation and healthier metabolic signaling, collectively mitigating the atherosclerotic process.	[29,211]
4. Longitudinal studies demonstrate that bariatric surgery patients outperform matched non-surgical cohorts in weight trajectories, metabolic parameters, and cardiovascular outcomes, with advantages that endure for ten years or more.	[29,212]
5. Bariatric procedures can sometimes be used in combination with obesity medications. Obesity medications prior to bariatric surgery can reduce surgical risk (e. g., hepatomegaly). Obesity medications after bariatric procedures can improve the weight reduction and maintenance of weight reduction. Either way, the combined use of obesity medications with bariatric procedures can help maintain weight reduction and persistence in improved CVD risk factors.	[29,213]
6. Long-term evidence consistently demonstrates that bariatric surgery is associated with substantial reductions in all-cause mortality, driven in part by significant decreases in cardiovascular, metabolic, and cancer-related deaths. Because obesity accelerates both atherosclerosis and chronic kidney disease, the renal improvements seen after surgery - such as slower progression of albuminuria and a reduced risk of end-stage renal disease - add to its cardiovascular benefits and underscore its value as a comprehensive cardiometabolic intervention. Specifically, regarding the heart, bariatric surgery improves heart failure with preserved ejection fraction, reduces the risk of new onset atrial fibrillation, and improves the success rate of cardiac ablation procedures.	[29,175,214]
7. Current clinical guidelines support bariatric surgery for individuals with severe obesity, particularly when cardiovascular risk is increased by conditions such as diabetes, high blood pressure, or obstructive sleep apnea. Surgery may also be considered for people with Class I obesity, defined as a body mass index of 30–34.9 kg/m ² , when metabolic disease remains insufficiently controlled. The 2022 guidelines from the American Society for Metabolic and Bariatric Surgery and the International Federation for the Surgery of Obesity and Metabolic Disorders broadened eligibility by recommending surgery for all individuals with a body mass index of 35 kg/m ² or higher, regardless of accompanying medical conditions, and by considering surgery for those with a body mass index of 30 kg/m ² or higher when cardiometabolic disease is present.	[29,215]
8. Although bariatric surgeries are generally safe and deliver substantial cardiovascular benefit, they are associated with distinct long-term risks. Nutritional deficiencies are common - particularly of vitamin D, vitamin A, vitamin B1 (thiamine), vitamin B9 (folate), vitamin B12 (cobalamin), as well as minerals and trace elements such as calcium, magnesium, iron and zinc - often requiring lifelong supplementation and monitoring. Patients also face an elevated risk of bone fractures and, in some cases, may require reoperation for complications or anatomical issues that arise over time. Procedure selection must be aligned with broader cardiometabolic management. For example, the presence of gastroesophageal reflux disease is a key determinant: Sleeve Gastrectomy can worsen reflux symptoms, whereas Roux-en-Y Gastric Bypass often leads to meaningful improvement.	[29,97,216, 217]
9. Long-term cardiovascular benefits of bariatric procedures depend on structured follow-up that ensures nutritional monitoring, behavioral support, and ongoing management of cardiometabolic comorbidities. Sustained engagement with a multidisciplinary team is essential to preserve these gains.	[29,218]
10. Roux-en-Y gastric bypass and sleeve gastrectomy lead to substantial and durable reductions in major adverse cardiovascular events, with Roux-en-Y gastric bypass supported by the most extensive long-term data showing marked decreases in myocardial infarction, heart failure, and all-cause mortality. Sleeve gastrectomy - now the most performed procedure - achieves comparable cardiometabolic improvements with a more favorable safety profile, although Roux-en-Y gastric bypass often yields superior long-term remission of type 2 diabetes and dyslipidemia. Hypoabsorptive procedures such as the Duodenal Switch, while used less frequently, remain important options for patients with super-obesity or marked metabolic resistance.	[29,206]

a post hoc analysis of participants in Look AHEAD who reduced at least 10% of their body weight in the first year had a 21% lower risk of the primary outcome (heart attack, stroke, or cardiovascular death) compared to those who had stable weight or gained weight. Thus, among patients with obesity, a >10% reduction of body weight may be considered a clinical threshold for improvement in CVD.

In the SUMMIT trial, tirzepatide produced substantial weight reduction and significantly reduced the composite endpoint of cardiovascular death or worsening heart-failure events in patients with obesity-related HFpEF. The composite benefit was driven mainly by fewer worsening heart-failure events, with no significant difference in cardiovascular death alone. In the "Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity" (SELECT) trial, semaglutide demonstrated a 20% reduction in major adverse cardiovascular events (MACE). In the "Semaglutide Treatment Effect in People with Obesity (STEP) – HFpEF", semaglutide improved HFpEF symptoms. Finally, in the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, semaglutide provided renal protection. In the "Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)" trial at diabetes-doses, liraglutide improved cardiometabolic risk factors and reduced MACE. No SELECT-equivalent trial exists for obesity-dose liraglutide. Prior obesity medications such as phentermine, phentermine/topiramate, naltrexone/bupropion, and orlistat can support modest weight reduction and improve select risk factors, but none have demonstrated definitive reductions in MACE. Essential principles include:

- Among patients with obesity, modest weight reduction of 5%–10% with healthful evidence-based interventions improve key cardiometabolic risk factors. However, weight reduction of >10% is more consistently associated with reduced CVD events.
- Tirzepatide and semaglutide have demonstrated substantial weight reduction along with significant reductions in heart failure events, cardiovascular death, and major adverse cardiovascular events, with additional renal benefits.
- While older agents can produce modest weight reduction and improve select risk factors, none have shown definitive CVD event reduction.

21. Obesity, bariatric procedures, and cardiovascular disease (CVD) [29] (See Table 21 and Fig. 21)

Examples of bariatric interventions include bariatric surgeries such as Roux-en-Y gastric bypass and sleeve gastrectomy, along with other procedural options such as intragastric balloon therapy, transoral gastric volume-reduction techniques (e.g., endoscopic sleeve gastroplasty), and emerging ablation-based technologies. Among operative approaches, Roux-en-Y gastric bypass and sleeve gastrectomy have the most consistent and compelling evidence for long-term cardiovascular benefit. Roux-en-Y gastric bypass provides the most extensive longitudinal data and demonstrates superior remission rates for type 2 diabetes and dyslipidemia, while sleeve gastrectomy achieves comparable metabolic improvements with a more favorable safety profile. Surgical interventions such as the Duodenal Switch remain important options for

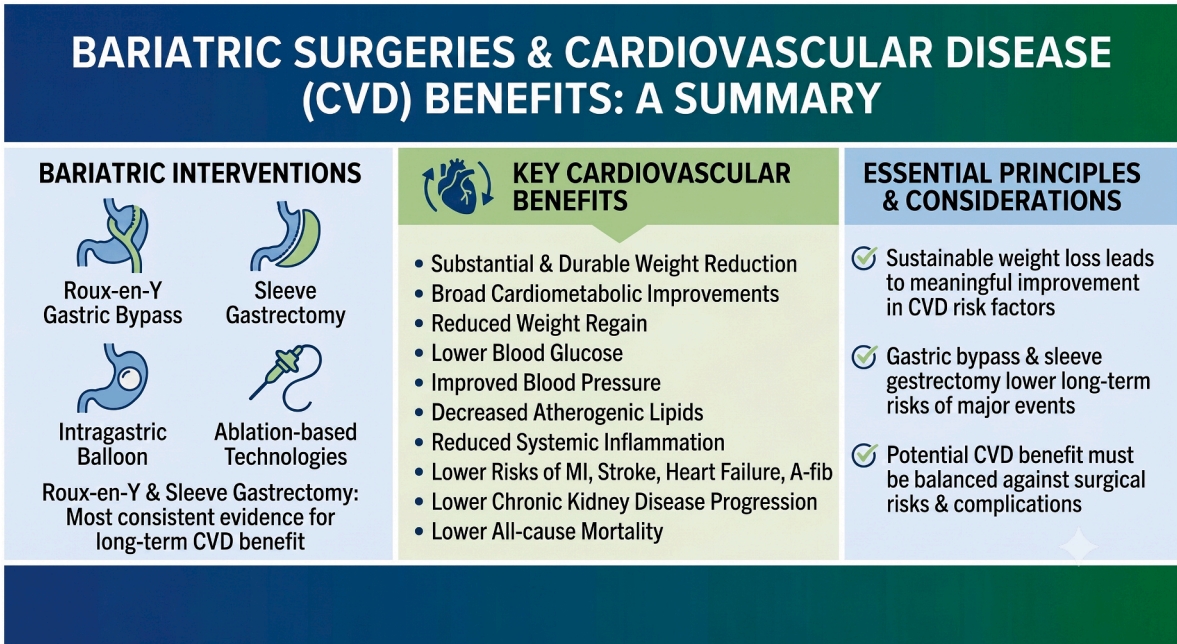


Fig. 21. Obesity, Bariatric Procedures, and Cardiovascular Disease (CVD). Bariatric procedures - particularly gastric bypass and sleeve gastrectomy - produce durable weight reduction that drives broad improvements in cardiovascular risk profiles. These cardiometabolic benefits include enhanced glycemic control, lower blood pressure, improved lipid patterns, and reduced systemic inflammation, collectively mitigating the cardiometabolic burden of obesity. Long-term evidence shows that gastric bypass and sleeve gastrectomy substantially decrease the incidence of myocardial infarction, stroke, heart failure, atrial fibrillation, chronic kidney disease progression, and cardiovascular mortality. For each patient with obesity, however, these cardiovascular gains must be weighed against the procedural risks and the potential for long-term surgical complications.

individuals with extreme obesity or pronounced metabolic resistance. Most of the documented reduction in cardiovascular disease risk with bariatric surgery comes from studies of gastric bypass and sleeve gastrectomy. These procedures reliably produce substantial and durable weight reduction accompanied by broad cardiometabolic improvements, including reduced weight regain, lower blood glucose, improved blood pressure, decreased concentrations of atherogenic lipids, reduced systemic inflammation, and lower long-term risks of myocardial infarction, stroke, heart failure, atrial fibrillation, chronic kidney disease progression, and all-cause mortality. By decreasing total fat mass and correcting dysfunctional adipose-tissue biology, bariatric surgery promotes remission of type 2 diabetes and improves hypertension control. Current clinical guidelines recommend bariatric surgery for individuals with severe obesity and for selected individuals with obesity defined by a body mass index of 30–34.9 kg per square meter who have uncontrolled metabolic disease, with expanded eligibility under the 2022 American Society for Metabolic and Bariatric Surgery and International Federation for the Surgery of Obesity and Metabolic Disorders criteria. For the individual patient with obesity, the potential adverse complications of bariatric surgery should be weighed against the potential reduction in CVD events. Essential principles include:

- Bariatric surgeries such as gastric bypass and sleeve gastrectomy produce substantial and lasting weight reduction that leads to meaningful improvements in major cardiovascular risk factors such as improving blood glucose, blood pressure, lipid levels, and systemic inflammation.
- Gastric bypass and sleeve gastrectomy lower long-term risks of heart attack, stroke, heart failure, atrial fibrillation, chronic kidney disease progression, and cardiovascular-related death.
- For the individual patient with obesity, the potential cardiovascular benefit must be balanced against the surgical risks and long-term complications of bariatric procedures.

22. Obesity, cancer, and cardiovascular disease (CVD) [30] (See Table 22 and Fig. 22)

Obesity is a leading preventable cause of cancer and a dominant driver of cardiovascular disease, acting through intertwined metabolic, inflammatory, hormonal, and hemodynamic pathways that elevate risk for gastrointestinal and hormonally driven cancers as well as lifelong CVD. Excess adiposity contributes to 5% of cancers in US men and 11% in women, parallels rising early-onset cancer and cardiometabolic disease in younger adults, and fuels carcinogenesis and vascular injury through cytokine excess, oxidative stress, hypoxia, hormonal dysregulation, and hyperinsulinemia. These same mechanisms worsen endothelial dysfunction, atherosclerosis, arterial stiffness, and vulnerability to chemotherapy-related cardiotoxicity, particularly in phenotypes such as sarcopenic obesity. While GLP-1 RA now reduce cardiovascular events in people with obesity, no therapy is yet indicated to simultaneously treat obesity and prevent cancer, even as emerging obesity medications show promise across both domains. Diets high in processed meats, sugars, and pro-oxidative exposures amplify cancer and CVD risk, whereas nutrition rich in fiber, antioxidants, and phytochemicals, along with sustained weight reduction and physical activity, reduces inflammation, improves cardiometabolic health, and lowers both cancer incidence and recurrence—positioning lifestyle and weight management as shared, foundational prevention strategies. Essential principles include:

- Obesity is a leading preventable cause of both cancer and cardiovascular disease, driven by shared metabolic, inflammatory, hormonal, and oxidative mechanisms.
- These pathways accelerate carcinogenesis, atherosclerosis, cardiotoxicity vulnerability, and early-onset disease, while lifestyle and dietary factors can either worsen or mitigate risk.
- Weight reduction, improved nutrition, physical activity, and emerging obesity medications provide overlapping protection across cancer and cardiovascular outcomes.

Table 22
Ten things to know about obesity, cancer, and cardiovascular disease (CVD) [30].

Key Points	References
1. Obesity is a major preventable cause of cancer and a dominant driver of CVD through metabolic, inflammatory, and hemodynamic pathways. For nonsmokers, obesity is the leading preventable cause of cancer and a major modifiable determinant of cardiometabolic risk. While the specific cancer types are heterogeneous, the risk appears highest in gastrointestinal and hormonally driven cancers such as esophageal adenocarcinoma, colorectal, pancreatic, liver, postmenopausal breast cancers, endometrial, and kidney cancers.	[30,219]
2. Excess body weight accounts for ~5% of cancers in US men and ~11% in women, while also substantially increasing lifetime CVD risk. Rising obesity rates in young adults parallel the increase in early-onset cancer and earlier onset of type 2 diabetes mellitus, hypertension, and dyslipidemia.	[30,220]
3. Obesity-related cytokine production (e.g., tumor necrosis factor, interleukin-6) promotes DNA damage and carcinogenesis while simultaneously driving endothelial dysfunction, atherosclerosis, and plaque instability. Increased reactive oxygen species (ROS) contribute to both tumorigenesis and oxidative vascular injury.	[30,219]
4. Adipose tissue expansion beyond its vascular supply creates hypoxia that accelerates cancer progression and worsens cardiometabolic inflammation. Obesity-related sleep apnea adds intermittent hypoxia that increases cancer risk and is a well-established contributor to hypertension, dysrhythmias (e.g., atrial fibrillation), and heart failure.	[30,221]
5. Obesity, as well as cigarette smoking, inactivity, excessive alcohol consumption, and low-antioxidant diets, increase ROS generation, promoting carcinogenesis and vascular injury. This oxidative imbalance also contributes to endothelial dysfunction, low density lipoprotein oxidation, and the progression of atherosclerotic cardiovascular disease.	[30,222]
6. Obesity increases estrogens, leptin, and insulin-like growth factor-1, while suppressing protective adiponectin and thus promoting cancer growth while also worsening insulin resistance, dyslipidemia, and vascular inflammation. Hyperinsulinemia - linked to both tumorigenesis and CVD - amplifies atherogenic and prothrombotic pathways. Adiposopathic cytokines promote extracellular matrix abnormalities and intravasation, facilitating metastasis. These same processes impair vascular integrity, promote arterial stiffness, and accelerate the development of CVD.	[30,223]
7. Obesity independently increases vulnerability to chemotherapy-related cardiotoxicity, thus contributing to a potential “double hit” insult. Individuals with obesity face a substantially higher risk of developing heart failure when exposed to anthracyclines (such as doxorubicin used in breast cancer and lymphoma) or trastuzumab. The chronic hemodynamic burden imposed by obesity diminishes cardiac reserve, leaving the heart less able to tolerate the toxic effects of cancer therapies. As a result, obesity complicates oncologic care by elevating the likelihood of chemotherapy-induced heart failure and perioperative complications. Notably, phenotypes like sarcopenic obesity - characterized by low muscle mass despite high adiposity - carry the worst outcomes, accelerating both tumor progression and cardiovascular deterioration.	[30,224]
8. Processed meats, high-temperature cooking, and simple sugars increase cancer risk and worsen cardiometabolic health through insulin resistance, hypertension, and dyslipidemia. Conversely, diets rich in phytochemicals, fiber, and antioxidants modulate the gut microbiome, reduce inflammation, and support both cancer prevention and cardiovascular protection. Weight reduction via healthful nutrition, and physical activity reduce obesity-related cancer risk and recurrence while also producing robust improvements in blood glucose, blood pressure, and blood atherogenic lipids, and overall CVD outcomes. Lifestyle and weight-management interventions therefore serve as a shared preventive strategy across obesity-related cancer and cardiovascular disease.	[30,225]
9. Glucagon-like peptide-1 receptor agonists have been indicated to reduce cardiovascular events in patients with obesity, marking a shift in therapeutic strategy. However, no medication is currently indicated to treat both obesity and prevent or treat cancer, despite obesity’s central role in both diseases. In contrast, obesity medications consistently improve multiple CVD risk factors, underscoring a clearer therapeutic pathway for cardiovascular prevention. Thus, while no <i>single</i> indication exists, highly effective obesity medications demonstrate CVD benefits, with the potential for a reduction of cancer risk.	[30,226]
10. Obesity-related cancers, particularly endometrial and postmenopausal breast, are reduced after bariatric surgery. Although a possible early post-gastric-bypass increase in colorectal cancer risk has been reported, longer-term data are inconsistent. While bariatric surgery in people with obesity consistently reduces cardiovascular disease events and mortality, the evidence of benefit for cancer is more heterogeneous. Bariatric surgery seems to reduce the risk of obesity-related cancers such as postmenopausal breast, endometrial, and some gastrointestinal cancers. Taken together, bariatric surgery appears to confer clear long-term cardiovascular benefit and likely reduces the burden of many obesity-related cancers, while not showing a consistent increase in any specific cancer type.	[30,227, 228]

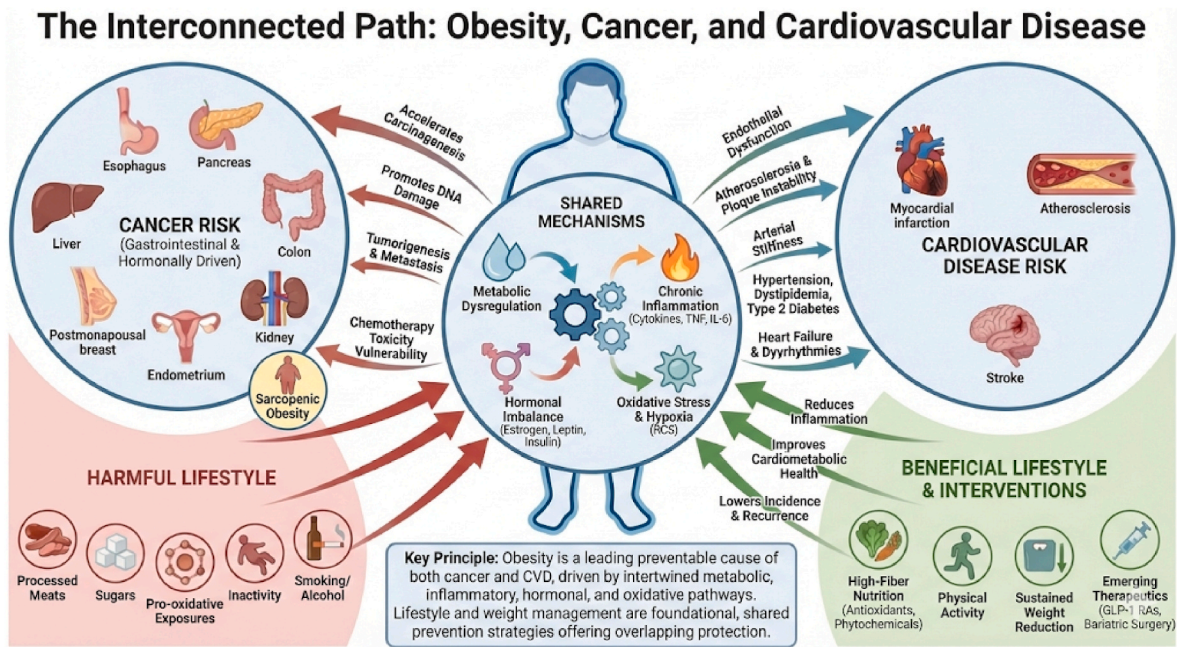


Fig. 22. Obesity, Cancer, and Cardiovascular Disease (CVD). Obesity is a major preventable driver of both cancer and cardiovascular disease, fueled by overlapping metabolic, inflammatory, hormonal, and oxidative pathways. These biologic disturbances accelerate carcinogenesis, atherosclerosis, vulnerability to cardiotoxicity, and earlier onset of chronic disease, while lifestyle and dietary patterns can either amplify or counteract this risk. Weight reduction, achieved through improved nutrition, physical activity, or highly effective obesity medications, consistently reduces these shared mechanisms, offering simultaneous protection against both cancer development and adverse cardiovascular outcomes.

Table 23
Ten things to know about obesity, psychiatric disease, and cardiovascular disease (CVD) [31].

Key Points	References
1. Obesity acts as a chronic physiologic stressor that heightens sympathetic tone, elevates blood pressure, and increases cardiometabolic workload. This sustained stress response accelerates atherosclerosis and establishes a baseline of cardiovascular strain that becomes even more vulnerable to amplification by psychological stress.	[1,31]
2. Chronic stress induces adiposopathic endocrine and immune dysfunction—such as hypercortisolemia and persistent low-grade inflammation that worsens glucose regulation, raises blood pressure, increases inflammatory burden, and may disrupt the microbiome. These stress-driven abnormalities impair endothelial function and accelerate atherosclerotic plaque development, thereby promoting cardiovascular disease progression.	[31,229]
3. Stress-related limbic dysregulation disrupts appetite control and reward processing, fostering a preference for hyper-palatable, calorie-dense foods that drive weight gain, increased visceral adiposity, insulin resistance, hypertension, and dyslipidemia. Mood and anxiety disorders add further autonomic and inflammatory strain, and when layered onto obesity, these behavioral and biologic disturbances compound to markedly elevate cardiovascular disease (CVD) risk.	[31,229]
4. Obesity and depression reinforce one another—obesity increases depression through inflammatory and psychosocial pathways, while depression promotes obesity through inactivity and neuroendocrine disruption. This bidirectional cycle amplifies inflammation, metabolic dysfunction, and physical inactivity, creating a self-perpetuating decline that independently heightens the risk for CVD.	[31,230]
5. Serious mental illness - particularly schizophrenia and bipolar disorder - carries intrinsic metabolic vulnerability even before psychotropic medications are introduced, predisposing patients to obesity, insulin resistance, dyslipidemia, and hypertension. These metabolic disturbances contribute to the well-documented 10–25-year mortality gap, driven predominantly by accelerated cardiovascular disease rather than suicide.	[31,231]
6. Many psychiatric medications - especially second-generation antipsychotics, mood stabilizers, and some anti-depressants - can promote weight gain, insulin resistance, hypertension, and dyslipidemia. Even agents considered “weight-neutral” may have variable and unexpected weight and metabolic effects in individual patients. Yet untreated psychiatric illness itself increases cardiovascular risk, making a careful risk–benefit assessment and proactive metabolic monitoring essential for patients with or at risk for CVD.	[31,231, 232]
7. Binge Eating Disorder and Night Eating Syndrome are common but often underrecognized conditions that drive excess caloric intake and significant metabolic dysregulation, worsening obesity-related cardiovascular risk. Their impact typically exceeds what standard dietary counseling can address, requiring integrated psychiatric and metabolic treatment. This may include targeted behavioral therapies or obesity medications such as glucagon-like peptide-1 receptor agonist based agents to prevent further cardiometabolic deterioration.	[31,178]
8. Chronic stress and psychiatric illness disrupt sleep and undermine core health behaviors, driving dysregulated appetite, impaired glucose metabolism, elevated blood pressure, and progressive weight gain. As obesity develops or worsens, it further amplifies psychological stress and contributes to obstructive sleep apnea, where intermittent hypoxia becomes a powerful physiological stressor that promotes resistant hypertension, atrial fibrillation, systemic inflammation, and worsening mood and cognitive symptoms. These mutually reinforcing pathways create a cycle of metabolic, psychological, and cardiovascular deterioration that requires coordinated cardiometabolic, psychiatric, and behavioral intervention.	[31,231]
9. Early-life trauma and Adverse Childhood Experiences create lasting neuroendocrine dysregulation that “biologically embeds” vulnerability to obesity, mood disorders, and early-onset cardiovascular disease. These early insults interact with stigma-related stress and maladaptive coping to accelerate cardiometabolic decline across the lifespan. Genetic pleiotropy further reinforces this clustering: the same variants that influence synaptic plasticity also regulate appetite and metabolic function, predisposing some individuals to obesity, depression, and schizophrenia independent of behavior. Socioeconomic conditions then shape the broader environment, amplifying or buffering these inherited and trauma-related risks.	[31,233, 234]
10. Weight stigma and mental health discrimination act as potent toxic stressors that elevate allostatic load in individuals with obesity, particularly those with co-occurring psychiatric illness. These social pressures reduce engagement with preventive cardiology and contribute to delayed diagnosis and worse cardiovascular outcomes. At the same time, chronic stress fosters maladaptive coping behaviors such as smoking and alcohol use, which further amplify obesity-related insulin resistance, hypertension, and dyslipidemia, compounding overall CVD risk.	[31,235]

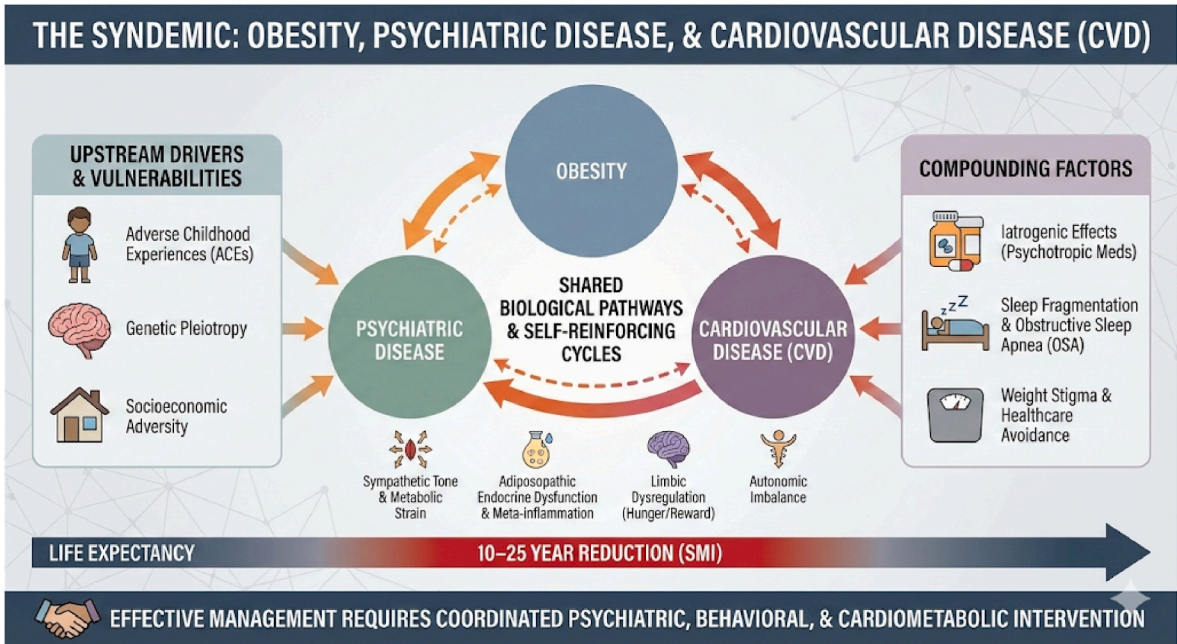


Fig. 23. Obesity, Psychiatric Disease, and Cardiovascular Disease (CVD). Patients with psychiatric disorders - particularly depression and serious mental illness (SMI) such as schizophrenia - face a uniquely high burden of obesity driven by both disease-related behavioral changes and the obesogenic effects of many essential psychiatric medications. Antidepressants, mood stabilizers, and second-generation antipsychotics can promote weight gain, insulin resistance, and dyslipidemia, compounding the metabolic vulnerability already present in mood disorders. This convergence of biological, behavioral, and medication-related factors accelerates cardiometabolic deterioration and heightens long-term cardiovascular disease risk, underscoring the need for integrated psychiatric and metabolic management. Additionally, weight stigma and mental health discrimination act as chronic toxic stressors that elevate allostatic load and reduce engagement with preventive cardiology, leading to delayed detection and worsening of cardiovascular disease. These social pressures also drive maladaptive coping behaviors—such as smoking and alcohol use—that compound obesity-related hypertension, dyslipidemia, and metabolic dysfunction. Together, these forces create a self-reinforcing pathway that accelerates cardiometabolic deterioration and heightens long-term CVD risk.

23. Obesity, psychiatric disease, and cardiovascular disease (CVD) [31] (See Table 23 and Fig. 23)

Obesity, chronic mental stress, and psychiatric illness form a tightly interwoven network of physiological, behavioral, and social forces that accelerate cardiovascular disease (CVD). This relationship is driven by shared biological pathways: obesity increases sympathetic tone and metabolic strain, while chronic stress drives adiposopathic endocrine dysfunction and meta-inflammation that degrade endothelial health. Stress-induced limbic dysregulation alters hunger and reward pathways, promoting high-caloric intake and insulin resistance. Meanwhile, mood disorders and Serious Mental Illness (SMI) independently raise CVD risk through autonomic imbalance and intrinsic metabolic disturbances - contributing to a 10–25 year reduction in life expectancy for patients with SMI. These cycles are compounded by iatrogenic effects from psychotropic medications, sleep fragmentation, and obstructive sleep

apnea, which introduces intermittent hypoxia that drives resistant hypertension and dysrhythmias. Rooted in upstream drivers like adverse childhood experiences, genetic pleiotropy, and socioeconomic adversity, these vulnerabilities are often exacerbated by weight stigma and healthcare avoidance. Consequently, effective management requires dismantling these self-reinforcing cycles through coordinated psychiatric, behavioral, and cardiometabolic intervention. Essential principles include:

- Obesity, stress, and psychiatric illness heighten sympathetic activation, systemic inflammation, and metabolic dysfunction via overlapping pathways.
- Early-life trauma, genetic overlaps, and socioeconomic adversity embed biological vulnerability, creating self-reinforcing cycles of weight gain, mood disturbance, and cardiometabolic decline.

Table 24

Ten things to know about obesity, pediatrics, and cardiovascular disease (CVD) [32,239].

Key Points	References
1. Childhood obesity accelerates the development of atherosclerosis by promoting inflammation, endothelial dysfunction, and metabolic abnormalities, often beginning in utero through maternal obesity, gestational diabetes, and other epigenetic influences. Rapid weight gain in the first six months of life is one of the strongest predictors of adolescent obesity and later cardiovascular disease (CVD), and maternal conditions such as preeclampsia further elevate long-term CVD risk independent of birth weight. Together, these findings highlight the need for prenatal prevention, early-life intervention, and strategies that interrupt intergenerational transmission of cardiometabolic disease.	[32,236]
2. Not all pediatric cardiovascular disease is caused by obesity. Important non-obesity causes include congenital heart defects, abnormal heart rhythms such as Wolff-Parkinson-White syndrome and long-QT syndrome, inflammation of the heart muscle, and inherited or acquired heart muscle disorders such as hypertrophic and dilated cardiomyopathy. Cardiovascular injury can also result from chemotherapy medicines such as anthracyclines, complications of Kawasaki disease, rheumatic heart disease, and early atherosclerosis caused by familial hypercholesterolemia. Additional contributors include the use of stimulants such as cocaine and amphetamines, congenital abnormalities of the coronary arteries, and inflammatory or autoimmune conditions. Routine sports physical examinations play a role in identifying hypertrophic cardiomyopathy, historically regarded as the leading cause of sudden cardiac death in young athletes, although more recent autopsy series identify autopsy-negative sudden unexplained death and congenital coronary anomalies at least as frequently.	[32,237]
3. Children should have body mass index (BMI) measured once a year starting at age 2. Children without diabetes but at risk for diabetes (e.g., obesity, family history of type 2 diabetes mellitus, or physical findings of insulin resistance) should have glucose screening at age 10 or at puberty onset (whichever comes first). Blood pressure screening should begin annually at age 3 to support early detection of cardiometabolic risk. All children should undergo cholesterol screening at ages 9–11 and again at 17–21, with testing beginning as early as age 2 when there is a family history of premature cardiovascular disease or dyslipidemia. Physical examination should include evaluation for acanthosis nigricans and violaceous striae as markers of insulin resistance or Cushing syndrome. Children with elevated low density lipoprotein levels and without obesity should prompt an examination for tendon xanthomas or xanthelasma to identify possible Familial Hypercholesterolemia.	[32,65,238]
4. Weight stigma can act as a chronic stressor - raising cortisol and inflammation - and further amplifies cardiometabolic vulnerability. Emerging evidence points to additional determinants, including the gut microbiome, inflammatory biomarkers, and advanced imaging, that may eventually sharpen pediatric CVD risk prediction and enable more personalized prevention strategies. Long-term studies consistently show that childhood BMI, blood pressure, and lipid levels strongly forecast adult cardiovascular events, and that youth with obesity are likely to maintain obesity into adulthood, reinforcing the need for early identification and intervention.	[32,239]
5. High daily screen time (>2 h) is independently associated with hypertension and endothelial dysfunction, even among otherwise active children. Although sedentary behavior and screen use overlap, screen exposure also promotes mindless eating and increases contact with food marketing—mechanisms that operate separately from physical inactivity. Screen time beyond 2h/day is also strongly linked to reduced sleep duration and poorer sleep quality. Insufficient sleep disrupts appetite-regulating hormones (raising ghrelin and lowering leptin) and increases insulin resistance, creating an additional, distinct pathway contributing to CVD risk.	[32,240]
6. Children with obesity show increased arterial stiffness, impaired endothelial function, and thicker carotid intima-media layers. These measurable vascular changes predict higher adult CVD risk.	[32,241, 242]
7. Obesity in youth clusters with insulin resistance, type 2 diabetes mellitus, hypertension, and dyslipidemia, which are often accompanied by metabolic-dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, and polyendocrine metabolic ovarian syndrome (PMOS). These conditions amplify long-term CVD risk and often persist into adulthood.	[32,243]
8. Social determinants of health - specifically food insecurity and neighborhood disadvantage - often coexist with systemic bias and weight stigma to intensify cardiometabolic risk in children. This risk is further amplified by Adverse Childhood Experiences (ACEs), including abuse, and mental health disorders such as depression and anxiety. These factors are not merely comorbidities but independent drivers of CVD that operate through dual pathways: behaviorally, by creating barriers to lifestyle adherence and fostering healthcare avoidance due to perceived judgment, and physiologically, where the chronic stress of discrimination and stigma acts as an allostatic load, upregulating systemic inflammation. Children with behavioral or mental health issues treated with atypical antipsychotics (e.g., risperidone, aripiprazole, olanzapine) can experience significant metabolic side effects, including rapid weight gain, insulin resistance and dyslipidemia.	[32,234]
9. Beyond obesity, major modifiable CVD risk factors include consumption of caloric dense, ultra-processed foods, physical inactivity, hyperglycemia, hypertension, elevated low density lipoprotein cholesterol, cigarette smoking, vaping and e-cigarette use and excessive alcohol intake. Non-modifiable CVD risk factors include genetic abnormalities and adverse consequences of chronic structural heart diseases or chronic metabolic and immune diseases. While childhood risk factors track strongly into adulthood, normalizing weight before adulthood can significantly mitigate this excess CVD risk.	[32,244]
10. Healthful nutrition, routine physical activity and behavior modification are foundational in the treatment paradigm of childhood obesity. Unfortunately, these approaches are often insufficient for severe pediatric obesity, prompting the use of obesity medications. Current FDA-approved options include semaglutide, liraglutide, orlistat, and phentermine/topiramate (all approved for ages 12 and older), as well as short-term phentermine (approved >16 years). Setmelanotide is approved for ages 2 and older for specific genetic conditions. Tirzepatide and naltrexone/bupropion are currently approved only for adults (18+) for weight management, although tirzepatide has been approved in children and adolescents 10 years and older with type 2 diabetes mellitus. In select cases of severe obesity, metabolic surgery is considered for adolescents (generally age 13+) with BMI ≥120% of the 95th percentile with an obesity driven disease or BMI ≥140% of the 95th percentile. Such interventions can substantially reduce CVD risk factors. Early intervention is recommended because the longer the exposure to obesity, then the longer the individual is exposed to adiposopathic endocrinopathies and immunopathies, which often leads to insulin resistance, vascular aging, and end-organ injury. Early identification and treatment in childhood can meaningfully alter this trajectory, preventing the cumulative burden of complications that otherwise accelerate across adolescence and adulthood.	[32,245, 246]

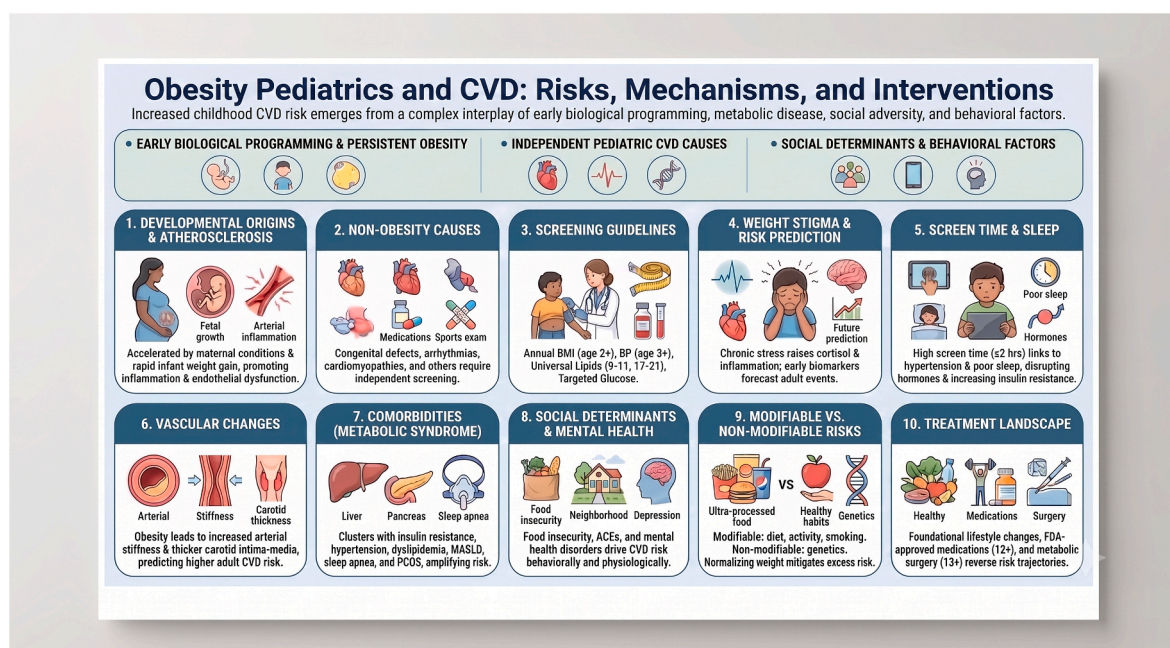


Fig. 24. Obesity, Pediatrics, and Cardiovascular Disease (CVD). Childhood cardiovascular risk emerges from early biological programming, persistent obesity, and clustered metabolic conditions that accelerate vascular aging. Many pediatric cardiovascular diseases occur independently of obesity, underscoring the importance of universal lipid screening, early evaluation in high-risk families, and careful physical examination. Social and behavioral factors further heighten vulnerability, while timely lifestyle therapy, appropriate pharmacotherapy, and selective metabolic surgery can alter long-term risk trajectories.

- The compounding force of these factors accelerates atherosclerosis and shortens life expectancy, necessitating integrated care that addresses metabolic and mental health simultaneously.

24. Obesity, pediatrics, and cardiovascular disease (CVD) (See Table 24 and Fig. 24)

Increased childhood CVD risk emerges from a complex interplay of early biological programming (e.g., genetics, epigenetics), metabolic disease, social adversity, and behavioral factors. Excessive maternal adiposity in fetal life accelerates atherosclerosis through inflammation, endothelial dysfunction, and metabolic derangements, while rapid infant weight gain and persistent obesity in childhood can amplify CVD risk via adiposopathic consequences such as insulin resistance, hypertension, dyslipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD), sleep apnea, and polyendocrine metabolic ovarian syndrome (PMOS). That said, as part of the differential diagnosis, it is important to note that pediatric cardiovascular diseases arise independently of obesity. Examples include congenital heart disease, cardiac dysrhythmias, myocarditis, cardiomyopathies, Kawasaki disease sequelae, rheumatic heart disease, chemotherapy-induced cardiotoxicity, familial hypercholesterolemia, congenital coronary anomalies, autoimmune conditions, and substance-related injury. Both the potential for obesity dependent and obesity independent CVD underscores the need for universal and routine screening (including targeted physical exam evaluation) for CVD risk factors. Traditional screening tools such as body mass index trajectory, blood glucose, blood pressure, and blood lipid panel can help assess early CVD risk. However, CVD risk factors such as these are often inadequate in fully predicting CVD risk, prompting interest in other assessments in select cases, such as inflammatory biomarkers and advanced imaging. Complicating CVD risk is that weight stigma itself acts as a toxic stressor that raises cortisol and inflammation. Excessive screen time, poor sleep, food insecurity, neighborhood disadvantage, adverse childhood experiences, mental health disorders, and the metabolic effects of some medications (e.g., atypical antipsychotics) may further elevate CVD vulnerability. In many cases, reduction of body mass index to normal range in childhood and

adolescence in individuals with obesity can lower cardiometabolic risk in adulthood similar to that of an adult who never had obesity [32]. Treatment with healthful nutrition, physical activity, and behavior modification are foundational. In addition, use of evidence-based obesity medications and, in select adolescents, metabolic surgery can meaningfully reverse risk trajectories and improve long-term CVD outcomes. Essential principles include:

- Childhood CVD risk develops through early biological programming, persistent obesity, and clustering conditions such as insulin resistance, hypertension, and dyslipidemia, often associated with MASLD, sleep apnea, and PMOS, all which accelerate vascular aging.
- Many pediatric cardiovascular diseases are independent of obesity, highlighting the need for universal CVD risk screening, with earlier testing in individuals with family history of premature CVD, along with a targeted physical examination.
- Social determinants, weight stigma, mental health conditions, excessive screen time, poor sleep, and the metabolic effects of atypical antipsychotics further amplify cardiometabolic vulnerability, while early lifestyle therapy, evidence-based pharmacotherapy, and selective metabolic surgery can meaningfully reverse long-term cardiovascular risk trajectories.

25. Obesity, social determinants of health, and cardiovascular disease (CVD) [33–35] (See Table 25 and Fig. 25)

Obesity is a chronic, biologically mediated disease involving disrupted appetite regulation, altered energy balance, and dysfunctional adipose tissue, but its expression is profoundly shaped by social conditions such as access to nutritious foods, safe activity spaces, and stable housing. Lower-income communities face disproportionate exposure to ultra-processed “food swamps,” food insecurity, and feast-or-famine cycles that promote fat storage and insulin resistance. These inequities begin early: maternal stress, inadequate nutrition, environmental exposures, and epigenetic programming heighten lifelong susceptibility to obesity and CVD, compounded by genetic–environment mismatches like the “thrifty gene” hypothesis. Minority youth are targeted with

Table 25

Ten things to know about obesity, social determinants of health, and cardiovascular disease (CVD) [33–35].

Key Points	References
1. Obesity is a chronic, biologically mediated disease marked by disrupted appetite regulation, altered energy balance, and dysfunctional adipose tissue. As excess adipose tissue accumulates, lipotoxicity allows lipid deposition in non-adipose organs - including the heart - driving cardiometabolic stress and accelerating the pathways that lead to CVD. CVD often reflects years of metabolic dysfunction rooted in excess adiposity, with chronic inflammation, insulin resistance, and endothelial injury forming the core mechanistic link between obesity and cardiovascular pathology. While traditional risk factors such as type 2 diabetes, hypertension, and dyslipidemia are important, social determinants also critically shape the onset of CVD risk factors, CVD risk, and CVD outcomes.	[33–35]
2. Structural conditions such as access to nutritious foods, safe spaces for physical activity, and stable housing - strongly shape the prevalence of obesity and long-term CVD risk. Among socioeconomically disadvantaged individuals, living locations may have unavailability of healthful foods (i.e., “food deserts”), inability to access healthful foods (“food insecurity”), or a disproportionate exposure to promotion and access to unhealthful, ultra-processed, energy-dense foods (i.e., “food swamps”). These inequities are reflected in obesity rates, with ~50% obesity among Non-Hispanic Black adults and ~46% among Hispanic adults versus 41% among Non-Hispanic White adults. Many Asian populations may develop complications at lower body mass index (i.e., often ≥ 23 kg/m ²) due to genetic predisposition to adiposopathy manifested by increased visceral adiposity accumulation. Another potential food access contributor to obesity includes the feast-or-famine cycle, which involves periods of scarcity followed by access to calorie-dense foods, which drives metabolic adaptations that favor fat storage and insulin resistance, effects more pronounced than steady overeating. Based on 2022 data, although food insecurity affects 12.8% of US households overall, rates are far higher among Black (22.4%) and Hispanic (20.8%) households, reinforcing disparities in obesity and CVD.	[33–35]
3. Minority youth are disproportionately exposed to marketing of sugar-sweetened beverages and ultra-processed foods — products consistently linked to excess adiposity and to early cardiometabolic dysfunction. These patterns illustrate the commercial determinants of health: food and beverage companies invest heavily to shape dietary preferences within specific demographic groups, competing with - and often outweighing - parental guidance, clinician counseling, and public health messaging, and helping entrench eating habits associated with greater lifelong obesity risk and, plausibly, higher downstream CVD burden. A 2022 Rudd Center analysis found that in 2021 Black youth and adults viewed 9% to 21% more food and beverage TV ads than their White counterparts after adjusting for total TV viewing time, and an earlier analysis of 2017 data found more than \$1 billion spent in a single year on Spanish-language and Black-targeted TV advertising, overwhelmingly for candy, sugary drinks, and snacks.	[33–35]
4. Structural racism shapes the environments in which people live, the healthcare they can access, and the chronic stress they endure. These forces elevate allostatic load, which represents the cumulative physiologic stress that raises cortisol, blood pressure, and metabolic dysfunction - driving higher rates of both obesity and cardiovascular disease. Black Americans ages 35–64, for example, are about 50% more likely to have hypertension than White Americans, reflecting the cumulative physiologic burden of structural stressors, differences in health-care access, and social and economic conditions. Pregnancy also functions as a metabolic “stress test,” and complications such as gestational diabetes and preeclampsia independently predict future CVD. Women with prior GDM face a seven-fold increased risk of developing type 2 diabetes and substantially higher lifetime CVD risk. These burdens fall disproportionately on Black women, who are nearly three times more likely to die from pregnancy-related causes than White women - underscoring the intersection of structural racism, maternal health, and obesity-related cardiometabolic vulnerability.	[33–35]
5. Health disparities often originate before birth and in early childhood, when maternal stress, unhealthful nutrition, and environmental exposures shape lifelong metabolic vulnerability. Epigenetic changes arising during these periods can “program” increased susceptibility to obesity and cardiovascular disease, helping explain why equalizing healthcare access in adulthood does not immediately erase disparities. The “thrifty gene” hypothesis adds important context: some populations carry genetic traits that historically promoted efficient fat storage - a survival advantage in environments marked by scarcity. In calorie-dense, highly processed food environment, those same traits can become liabilities. Emphasizing this mismatch helps reduce stigma by underscoring that many individuals are biologically predisposed to struggle in a modern obesogenic landscape, rather than being at fault for their physiology.	[33–35]
6. Adverse Childhood Experiences (ACEs) are a defined clinical framework encompassing abuse, neglect, and household dysfunction. ACEs are a powerful, independent predictor of both obesity and CVD risk. High ACE scores are associated with a persistent “fight-or-flight” physiological state, leading to dopamine resistance that promotes comfort-seeking eating behaviors and cortisol dysregulation that accelerates visceral adipose tissue accumulation. These biologic effects compound over time, contributing to severe obesity and heightened cardiometabolic strain. Adults with four or more ACEs face a two- to three-fold increased risk of heart disease and are substantially more likely to develop severe obesity compared with individuals reporting no ACEs.	[33–35]
7. Limited access to preventive care and pharmacotherapy (such as glucagon-like peptide-1 receptor agonists) widens the gap. When effective obesity treatments are restricted by cost or insurance tiers, metabolic dysfunction progresses unchecked in lower-income populations, leading to preventable obesity-related conditions such as type 2 diabetes mellitus, hypertension, and dyslipidemia, and thus limits prevention of CVD. Late detection allows metabolic dysfunction to progress unchecked, increasing the likelihood of clinically significant CVD. These gaps disproportionately affect underserved populations. It is the official position of the Obesity Medicine Association that all individuals with obesity have access to health improving, if not lifesaving, evidence-based obesity treatments – across the socioeconomic spectrum.	[33–35]
8. Weight stigma and bias within healthcare systems erode trust, reduce patient engagement, and contribute to therapeutic inertia. At the same time, many underserved communities face environmental stressors such as noise, light pollution, and the demands of shift work - that disrupt circadian rhythms and worsen insulin resistance. Poor sleep and chronic stress can reinforce one another, creating a metabolic feedback loop that accelerates both obesity and CVD. When coupled with the disproportionate environment of “food deserts,” “food insecurity,” and “food swamps,” all these social determinants translate into measurable disparities. CDC data show obesity prevalence is substantially higher in rural counties (34.2%) than in metropolitan areas (28.7%), with rural residents experiencing a 40% higher rate of preventable CVD deaths compared with their urban counterparts.	[33–35]
9. Communities without sidewalks, parks, or safe transportation options are effectively forced into sedentary patterns, limiting energy expenditure regardless of individual motivation. This constrained physical activity accelerates obesity progression and erodes cardiovascular resilience. Beyond the absence of supportive infrastructure, many lower-income and minoritized neighborhoods face an added burden: environmental toxicity. These communities are disproportionately located near highways, factories, and industrial zones, where exposure to obesogens and endocrine disruptors [e.g., bisphenols (BPA, BPS, BPF), phthalates, certain pesticides (atrazine, DDT), perfluorooctanoic acid (PFOA), and organotins] trigger insulin resistance, systemic inflammation, and endothelial dysfunction, which increase the risk of CVD.	[33–35]
10. Addressing obesity, social determinants of health and CVD together yields greater impact than treating each in isolation. Effective strategies require moving beyond individual “advice” toward coordinated clinical, community, and policy interventions. Such multilevel approaches can meaningfully reduce disparities and improve cardiometabolic health.	[33–35]

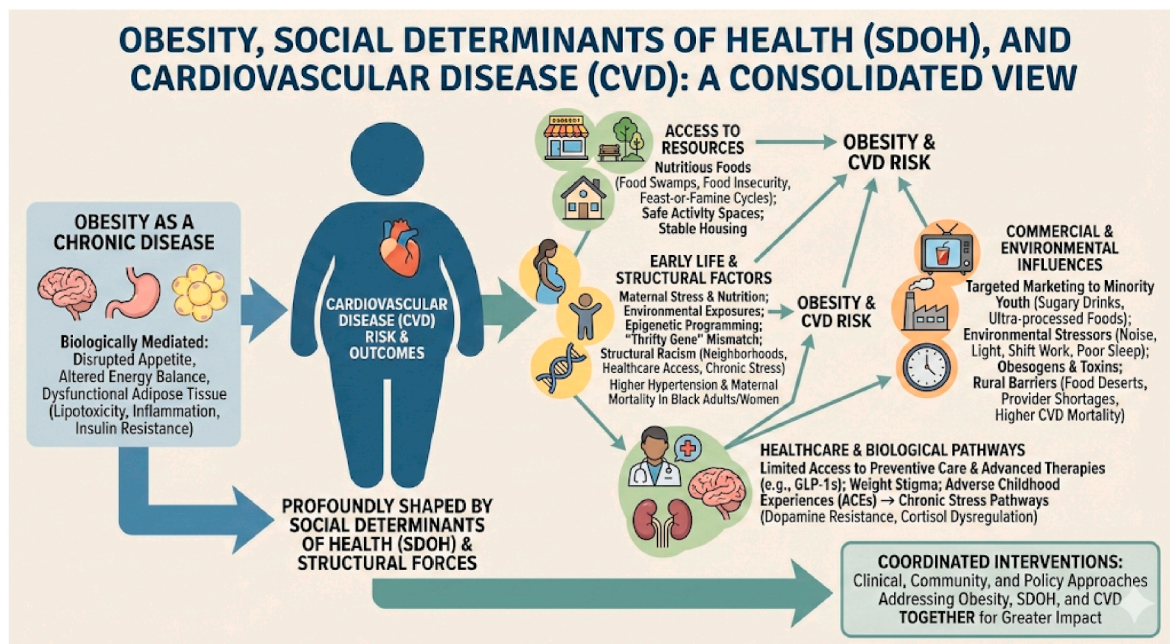


Fig. 25. Obesity, Social Determinants of Health, and Cardiovascular Disease (CVD). Obesity is a biologically rooted disease whose expression and subsequent CVD risk is accelerated by structural conditions such as food environments, housing stability, neighborhood safety, chronic stress, and targeted commercial influences, all of which disproportionately burden lower-income and minoritized communities. Early-life adversity, environmental exposures, structural racism, limited access to preventive and advanced care, and cumulative stress physiology embed lifelong vulnerability to obesity and CVD in ways that go beyond individual behavior. Meaningful progress requires coordinated clinical, community, and policy strategies that address biological mechanisms and social determinants together to reduce entrenched cardiometabolic disparities.

marketing of sugar-sweetened beverages and ultra-processed foods, while structural racism shapes neighborhood conditions, healthcare access, and chronic stress, contributing to disparities such as markedly higher hypertension and maternal mortality among Black adults and women. Adverse Childhood Experiences further embed biologic risk through chronic stress pathways that drive dopamine resistance, cortisol dysregulation, increased visceral adiposity, and elevated heart disease risk. Limited access to preventive care and advanced therapies, along with weight stigma in healthcare, allows metabolic dysfunction to progress in underserved populations. Environmental stressors include noise, light pollution, shift work, and poor sleep that disrupts circadian rhythms, as well as impoverished communities that face additional barriers such as food deserts, provider shortages, and higher preventable CVD mortality. Structural constraints on physical activity and disproportionate exposure to obesogens (i.e., chemicals, often called “endocrine disruptors,” that disrupt normal metabolic, endocrine, or developmental processes in ways that increase the risk of excess adiposity) and environmental toxins add inflammatory and endothelial injury burdens that cannot be overcome by individual behavior alone. Coordinated clinical, community, and policy interventions addressing obesity, social determinants, and CVD together offer far greater impact than treating each in isolation. Essential principles include:

- Obesity and cardiovascular disease share deep biological roots, but their expression is powerfully shaped by structural forces, from lack of promotion and/or access to healthful foods and environmental exposures to chronic stress, racism, and limited access to overall medical care.
- The adverse consequences of unhealthful social determinants of health begin early in life, are reinforced by targeted commercial influences and neighborhood environments, and are amplified when advanced treatments and preventive services are inaccessible.
- Meaningful progress requires addressing biology and social determinants together, because no single intervention can overcome

the cumulative, lifelong pressures that drive cardiometabolic disparities.

26. Obesity, future directions, paradigm shift, and cardiovascular disease (CVD) [36,37] (See Table 26, Figs. 26a and 26b)

Obesity is a generational disease. Optimal management of obesity should begin no later than during the prenatal period, extending through childhood, and continued into adulthood. Given that CVD risk is shaped by epigenetic and generational influences, then one might argue that “optimal” obesity management might best begin with grandparents or earlier. In the past, adipose tissue was considered as little more than an energy storage organ. However, adipose tissue is now recognized as an active endocrine and immune organ. Additionally, since adipose tissue is like other organs (such as the heart) where anatomy often reflects function, this reinforces the diagnostic need to move beyond body mass index alone towards a more detailed assessment of body composition. Evidence acquired over decades supports some anthropometric measurements as being superior to BMI in assessing CVD risk. While BMI is sufficient in population studies, it may lack precision in the individual. For example, an increase in BMI can be due to increased muscle mass and not necessarily fat mass. A normal BMI may be misleading in a patient with sarcopenic obesity. Thus, percent body fat is a better diagnostic measure than BMI. That said, among the most validated prognostic anatomic measure for CVD risk is the accumulation of visceral (and epicardial) adipose tissue, which is an anatomical reflection of global adipose tissue dysfunction. It is the combination of both “fat mass disease” and “sick fat disease” that are the most common contributors to the most common cardiometabolic complications encountered by clinicians. Obesity commonly leads to fat mass and adiposopathic multisystem adverse consequences, such as multiple CVD complications (e.g., atherosclerotic coronary artery disease, heart failure, cardiac dysrhythmias, and stroke), MASLD, as well as Cardiovascular-Kidney-Metabolic (CKM) Syndrome. Because most of the

Table 26
Ten things to know about obesity, future directions, paradigm shift, and cardiovascular disease (CVD) [36,37].

Key Points	References
1. Early intervention, beginning prenatally and extending through childhood, can alter cardiometabolic trajectories before the complications of the disease of obesity become irreversible. Epigenetic and generational influences underscore the need for preventive strategies that start before conception.	[36,37]
2. Adipose tissue is an active endocrine and immune organ whose dysfunction fuels inflammation, insulin resistance, and atherogenesis. This understanding underscores the need to move beyond a simplistic “fat-mass” framework and toward true body-composition assessment for more accurate risk stratification and targeted treatment. Some guidances emphasize anthropometric assessments such as waist circumference (previously discussed in metabolic syndrome section), waist-to-hip ratio of ≥ 0.9 for men and ≥ 0.85 for women, waist to height ratio ≥ 0.5 , and direct measures of body composition (i.e., percent body fat and visceral adipose tissue assessment), rather than body mass index (BMI) alone. A sole focus on BMI may overestimate the degree of adiposity in muscular individuals, underestimate the cardiometabolic risk in many Asian populations, and underestimate the amount of body fat in patients with sarcopenic obesity.	[36,37, 247]
3. Obesity affects multiple interdependent organ systems, leading to not only CVD and metabolic dysfunction-associated steatotic liver disease (MASLD), but also chronic kidney disease and cardiometabolic risk factors (i.e., Cardiovascular-Kidney-Metabolic (CKM) Syndrome framework). One of the more compelling developments within this framework is the emerging recognition of the obesity – heart failure with preserved ejection fraction (HFpEF) connection – which disproportionately affects females, and like obesity, illustrates how a single measure (i.e., BMI in obesity and ejection fraction with HFpEF) is often inadequate in clinical assessments.	[36,37]
4. Among those with obesity, CVD risk assessment has value because, especially when due to obesity, cardiometabolic complications such as type 2 diabetes mellitus, hypertension, and dyslipidemia can be improved with evidence-based weight reduction – which in some cases – can result in remission of type 2 diabetes mellitus and hypertension, and clinically meaningful CVD risk reduction.	[36,37]
5. Confronting obesity early and decisively reshapes the trajectory of CVD by targeting the upstream metabolic disturbances that drive cardiometabolic risk. Making obesity treatment the first therapeutic priority (“treat obesity first”) reframes it as the foundational intervention- one that strengthens and amplifies every downstream component of CVD management rather than functioning as an optional add-on. (See Fig. 26b)	[36,37]
6. With rare exception, treatment of obesity requires sustained, lifelong management comparable to treatment of other chronic conditions like diabetes mellitus, hypertension, and dyslipidemia. Recognizing its relapsing course enables clinicians and patients to adopt care strategies that are durable, compassionate, and grounded in evidence. Describing obesity medications as disease-modifying agents - much like statins – more accurately reflects an evolution in priorities, with the goal being improvements in health (and not just weight), which may help mitigate a key conceptual gap that treatment of obesity is mainly for cosmetic purposes.	[36,37]
7. Emerging biomarkers (e.g., inflammatory markers, metabolic signatures, and genetic indicators) have the potential to refine cardiovascular risk prediction in individuals with obesity. Incorporating these tools supports a precision-medicine approach with tailored therapy to biological phenotype rather than population averages.	[36,37]
8. Obesity and CVD risk manifest differently across racial, ethnic, socioeconomic, and biological groups, requiring individualized assessment and therapy. Tailored approaches improve equity, relevance, and clinical effectiveness.	[36,37]
9. Treatment of obesity must integrate the management of blood glucose, blood pressure, and blood atherogenic lipids, as well as healthful nutrition and routine physical activity, which may have health benefits beyond weight reduction. Assessment and management of other obesity complications, such as obstructive sleep apnea (OSA), are key in reducing CVD risk (especially atrial fibrillation and resistant hypertension), making sleep hygiene and routine OSA screening essential components of any truly comprehensive approach.	[36,37]
10. Optimal care for obesity-related cardiovascular disease relies on a coordinated, multidisciplinary team including clinicians, nurses, dietitians, behavioral specialists, exercise physiologists, psychologists, pharmacists, obesity medicine experts and often bariatric surgeons, all working together to deliver patient-centered treatment. This collaborative model improves adherence, enhances outcomes, and minimizes fragmented care. Expanding access to evidence-based obesity medications further supports this approach by helping improve cardiometabolic risk factors and lowering overall CVD risk.	[36,37]

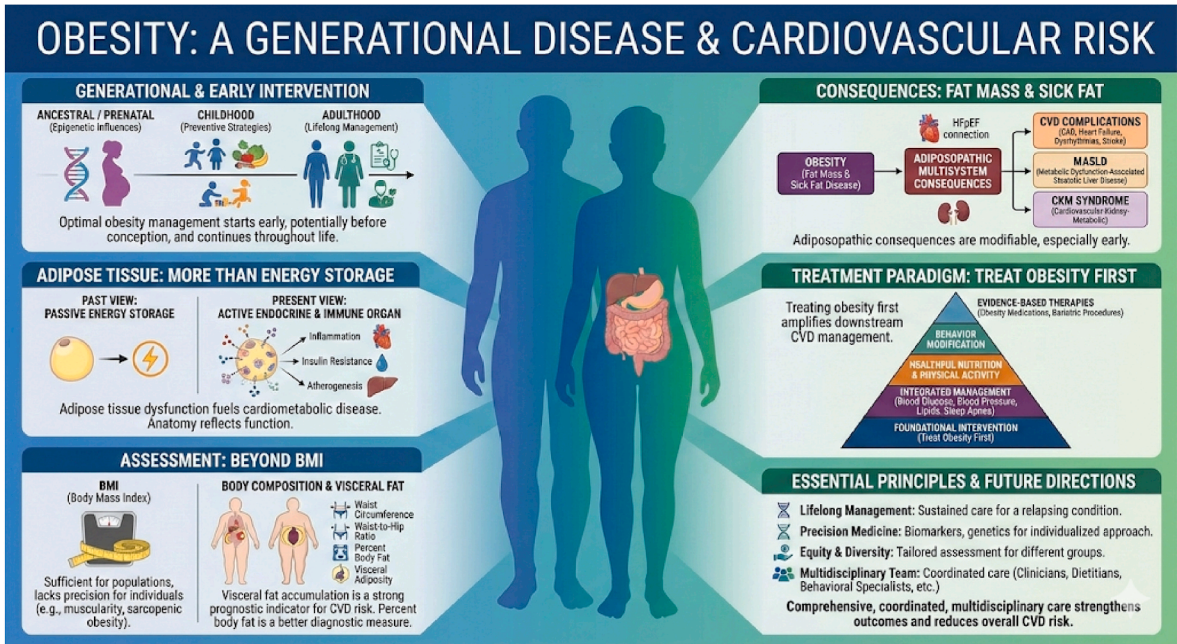


Fig. 26a. Future Directions of Obesity, Paradigm Shift, and Cardiovascular Disease (CVD). Early, lifelong obesity management is emerging as a cornerstone of future cardiometabolic care, reflecting a paradigm shift toward intervening before CVD risk becomes entrenched. Treating obesity first - using evidence-based, disease-modifying strategies - positions clinicians to meaningfully reduce long-term cardiovascular risk, especially when initiated early in life. Accurate body composition analyses, precision tools, individualized phenotyping, integrated Cardiovascular-Kidney-Metabolic (CKM) - aligned management, and coordinated multidisciplinary care represent the next generation of CVD prevention, strengthening outcomes by targeting the full spectrum of cardiometabolic drivers, including sleep apnea.

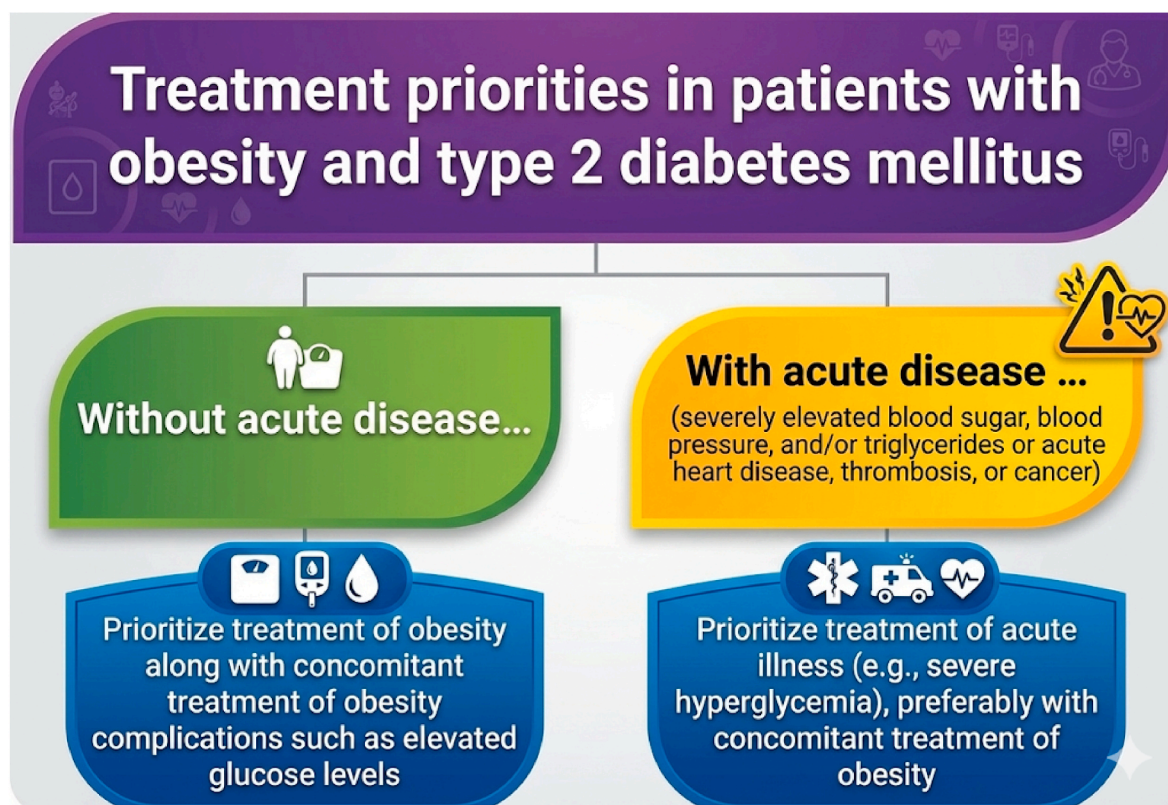


Fig. 26b. Treat obesity first. Treatment priorities for patients with co-occurring obesity and complications such as type 2 diabetes (and other cardiometabolic diseases) may best be based on the severity and immediacy of the cardiometabolic abnormality. For patients without acute disease, the primary goal is treating obesity, preferably with evidence-based treatment known to improve glucose and other cardiometabolic risk factors. For patients presenting severe acute illnesses like very high blood glucose, blood pressure, or triglycerides, the immediate priority shifts to stabilizing the acute condition, preferably while also addressing obesity.

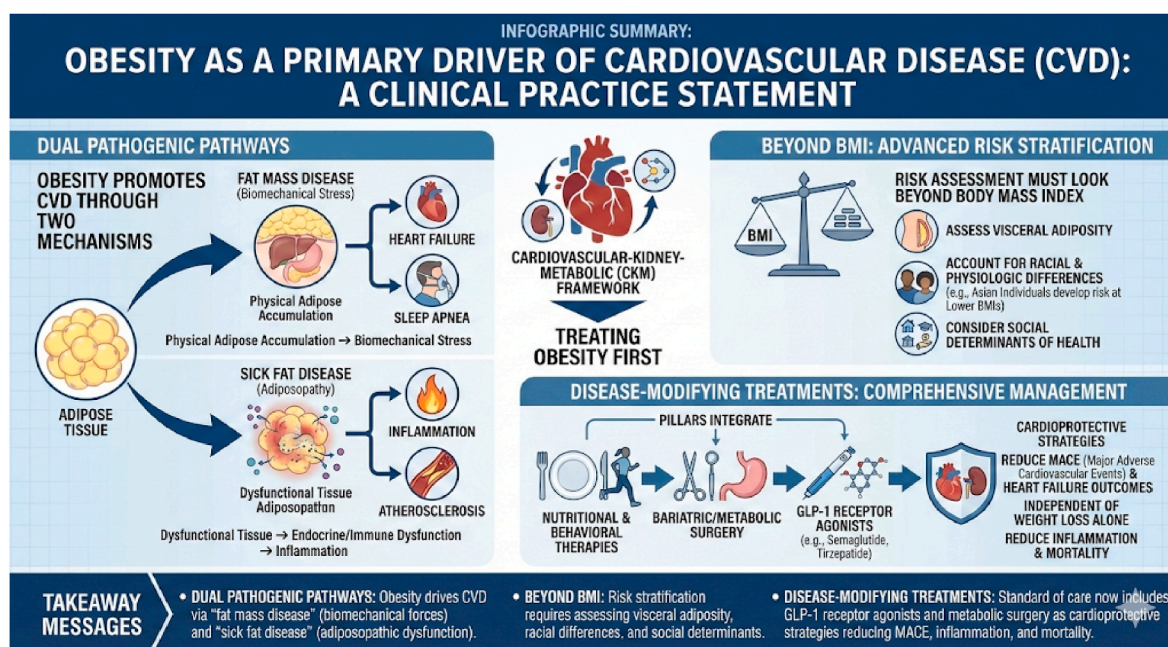


Fig. 27. Overall Summary of Obesity and Cardiovascular Disease (CVD). Obesity drives cardiovascular disease through two primary pathways: "fat mass disease" causing biomechanical stress and "sick fat disease" (adiposopathy) leading to endocrinopathies and immunopathies. Determining CVD risk among patients with obesity goes beyond simple body mass index to include factors like body composition, racial, sex and age differences, assessing obesity complications (e.g., insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, metabolic dysfunction-associated steatotic liver disease, chronic kidney disease), and social determinants of health. Finally, optimal CVD risk reduction includes the engagement of a team approach, whose collective goal is to integrate healthful nutrition, physical activity, behavioral modification, evidence-based obesity medications, and bariatric surgery to improve the health of patients, and reduce CVD risk.

increase in CVD risk due to obesity is due to the adverse consequences of obesity itself, and because obesity-related adverse consequences are modifiable (at least early in the disease process), then this often supports the “treat obesity first” paradigm. Comprehensive obesity management integrates the control of blood glucose, blood pressure, and blood atherogenic lipids, as well as sleep apnea. Optimal care depends on coordinated, multidisciplinary teams and expanded access to evidence-based obesity therapies that include access to, and education regarding healthful nutrition, routine physical activity, behavior modification, obesity medications and bariatric procedures. Essential principles include:

- Optimal obesity management begins early and is best maintained lifelong.
- CVD risk in patients with obesity is often modifiable, especially when treatment is initiated early in life; when appropriate, treating obesity first with evidence-based strategies has the greatest likelihood to produce successful long-term improvement in CVD risk reduction.
- Precision tools, individualized approaches, integrated management of all cardiometabolic factors (including sleep apnea), and coordinated multidisciplinary care collectively strengthen outcomes and might best reduce overall CVD risk.

27. Conclusion (See Fig. 27)

This Obesity Medicine Association Clinical Practice Statement characterizes obesity as a primary driver of cardiovascular disease (CVD) operating through two distinct but complementary mechanisms. First, “fat mass disease” refers to the direct mechanical effects of excess adipose tissue, which impose biomechanical stress and contribute to conditions such as heart failure and sleep apnea. Second, “sick fat disease” (adiposopathy) reflects dysfunction of adipose tissue, which indirectly elevates CVD risk by promoting major risk factors such as diabetes mellitus, hypertension, and dyslipidemia, and directly increases CVD risk through the adverse immune and endocrine activity of epicardial adipose tissue. The overall risk of CVD is strongly influenced by age, race, and sex, as well as by social determinants of health. For many individuals with excess adiposity, a rational clinical approach follows a “treat obesity first” paradigm, which includes healthful nutrition, physical activity, behavioral modification, and evidence-based medical and surgical interventions.

27.1. Takeaway messages

- Obesity promotes CVD through “fat mass disease” (biomechanical forces) and “sick fat disease” (adiposopathic endocrine and immune dysfunction).
- CVD risk stratification best involves assessment of body composition, while accounting for racial, sex, and age influences, as well as social determinants of health.
- The standard of care for obesity has evolved to include healthful nutrition, routine physical activity, behavior modification, and highly effective obesity medications and metabolic surgery as treatment strategies that reduce CVD risk.

Author contributions

HEB drafted the initial manuscript and created the figures and tables. All authors reviewed and edited the initial draft, and all authors reviewed, edited, and approved the final draft.

Review

Although certain authors hold or previously held editorial or reviewer roles with Obesity Pillars, all aspects of editorial oversight were handled independently. The Managing Editor (who was not an

author and not on the OMA Board of Trustees) retained full authority for final editorial decisions. Peer review was performed by Obesity Medicine Association Board of Trustee members who were not authors of the manuscript.

Disclaimer and limitations

This Clinical Practice Statement is not a Guideline, in that it does not provide graded clinical recommendations. Instead, this expert review was developed by the Obesity Medicine Association members to assist clinicians in providing care for patients living with obesity, drawing upon the best available evidence. In areas where scientific data were inconclusive or insufficient, then the authors applied their professional judgment, and portions of this Statement necessarily reflect their expert interpretation of the evidence. This Clinical Practice Statement represents the state of obesity medicine at the time of publication and should not be considered a substitute for ongoing review of emerging research. Decisions by practitioners to apply the principles outlined herein are best made by considering local resources, individual patient circumstances, patient preferences, and applicable federal, state, and local laws and guidance.

Declaration of use of artificial intelligence

Artificial Intelligence was employed to support categorization, phrasing, spelling, accuracy, and image generation. The authors reviewed and edited the content and accept responsibility for the manuscript content.

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CV: Eli Lilly, Advisory Board and Speakers Bureau; Boehringer Ingelheim, Advisory Board.

LA: Novo Nordisk Advisory Board and Speaker's bureau; Eli Lilly Advisory Board and Speaker's bureau; Amgen consulting; Currax Speaker's bureau; Genentech Advisory Board.

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