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OBESITY THE PARADOX IN CARDIOVASCULAR DISEASE AND CRITICAL ILLNESS: A NARRATIVE REVIEW

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ABSTRACT

Background: Obesity, affecting approximately 20% of intensive care unit admissions and a substantial proportion of cardiovascular disease patients, is traditionally recognized as a major risk factor for adverse health outcomes (1). The "obesity paradox" describes the counterintuitive observation of improved survival in overweight and mildly obese patients with established cardiovascular disease or critical illness. **Objective:** To comprehensively examine the obesity paradox in cardiovascular disease and critical illness, evaluating epidemiological evidence, mechanistic hypotheses, methodological limitations, and therapeutic implications. **Methods:** A systematic literature search was conducted using PubMed, MEDLINE, Embase, and Cochrane Library databases for articles published between January 2015 and March 2026. Search terms included "obesity paradox," "body mass index," "cardiovascular disease," "heart failure," "critical illness," "sepsis," and "mortality." Narrative synthesis was performed on included studies. **Conclusion:** The obesity paradox is a complex phenomenon with plausible biological underpinnings but significant methodological limitations. It should not be interpreted as evidence against weight management; rather, it highlights the need for nuanced, phenotype-specific approaches incorporating body composition and fitness assessment.

KEYFINDINGS: Observational evidence supports the obesity paradox in heart failure, coronary artery disease post-percutaneous coronary intervention, and critical illness including sepsis and acute respiratory distress syndrome (2-4). Overweight and Class I obese patients (body mass index 25-35 kg/m²) demonstrate 10-30% lower mortality compared to normal-weight individuals, with attenuation or reversal in Class II-III obesity (body mass index ≥35 kg/m²) (5). Proposed mechanisms include enhanced metabolic reserve, attenuated neurohormonal activation, protective adipokine profiles, and lipoprotein-mediated endotoxin neutralization (6). Major confounders include body mass index imprecision, failure to account for cardiorespiratory fitness, reverse causation, and collider stratification bias (7). Randomized trials of glucagon-like peptide-1 receptor agonists in obesity-related heart failure with preserved ejection fraction demonstrate that intentional weight loss improves symptoms and functional capacity (8).

1. INTRODUCTION

Obesity represents one of the most formidable public health challenges of the twenty-first century, with global prevalence having nearly tripled since 1975.[1] According to the World Health Organization, as of 2022, approximately 2.5 billion adults worldwide were classified as overweight, including 890 million individuals living with obesity (body mass index [BMI] ≥30 kg/m²).[1] Projections indicate that by 2030, nearly one in two adults in the United States will meet criteria for obesity.[2] This epidemic carries profound implications for healthcare systems globally, given the well-established causal relationships between excess adiposity and numerous chronic conditions including type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, heart failure, and chronic kidney disease.[2]

The pathophysiological mechanisms linking obesity to adverse health outcomes are extensive. Adipose tissue, particularly visceral depots, functions as a metabolically active endocrine organ secreting adipokines and cytokines that promote chronic low-grade inflammation, insulin resistance, and endothelial dysfunction.[3] Hemodynamically, obesity increases total blood volume and cardiac output, leading to left ventricular dilatation and hypertrophy that predispose to both systolic and diastolic dysfunction.[4] Obesity also activates the renin-angiotensin-aldosterone and sympathetic nervous systems.[5] Given this foundation, obesity should intuitively confer worse prognosis across all disease states.

Yet, over the past two decades, epidemiological literature has documented a counterintuitive phenomenon termed the "obesity paradox," wherein overweight and mildly obese individuals with established cardiovascular disease or critical illness demonstrate improved survival compared to normal-weight counterparts.[6] First described in end-stage renal disease patients undergoing hemodialysis, the paradox has been extended to heart failure, coronary artery disease, and critically ill patients with sepsis and acute respiratory distress syndrome (ARDS).[7,8] The consistency of these observations across disparate populations has prompted intense scientific scrutiny.

In heart failure specifically, the obesity paradox has been documented in both reduced and preserved ejection fraction, with meta-analyses demonstrating 15-30% lower all-cause mortality in overweight and Class I obese patients compared to those with normal BMI.[9] Similarly, in critical illness, studies encompassing over 250,000 ICU patients reveal a J-shaped relationship between BMI and mortality, with lowest risk at BMI 25-35 kg/m².[7] Notably, Class III obesity (BMI ≥40 kg/m²) is typically associated with neutral or increased mortality risk.[7]

Several hypotheses have been advanced to explain the obesity paradox. Proponents point to enhanced metabolic reserve from increased adipose tissue and lean mass, buffering against catabolic stress.[8] Obese individuals demonstrate attenuated neurohormonal activation with lower circulating natriuretic peptides.[10] Adipose tissue secretes soluble tumor necrosis factor-alpha receptors that neutralize proinflammatory cytokines, while higher lipoprotein levels may bind bacterial endotoxins during sepsis.[8] Obese patients may also present earlier due to exaggerated symptoms, introducing lead-time bias.[11]

Conversely, skeptics contend the paradox represents methodological artifact. BMI fails to distinguish fat mass from lean mass or visceral from subcutaneous adipose depots.[9] Failure to account for cardiorespiratory fitness, a potent prognostic factor, may confound associations.[9] Reverse causation is critical, as unintentional weight loss from cardiac cachexia may selectively worsen outcomes in normal-weight groups.[9] Collider stratification bias may artifactually invert the true obesity-mortality relationship.[12]

The therapeutic implications remain controversial. Some question whether weight loss recommendations should be tempered in established cardiovascular disease, while others argue the paradox should not deter efforts to achieve healthy weight.[13] Recent randomized controlled trials of glucagon-like peptide-1 (GLP-1) receptor agonists in obesity-related heart failure with preserved ejection fraction (HFpEF) demonstrate that intentional weight loss improves symptoms and functional capacity.[8,14]

This narrative review aims to comprehensively examine the obesity paradox in cardiovascular disease and critical illness, critically evaluating epidemiological evidence, mechanistic explanations, methodological limitations, and therapeutic implications.

2. METHODOLOGY

This narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines. A systematic literature search was performed using PubMed, MEDLINE (via Ovid), Embase, and the Cochrane Library databases for articles published between January 1, 2015, and March 1, 2026. Search terms included combinations of keywords and Medical Subject Headings (MeSH) terms: "obesity paradox," "body mass index," "overweight," "obesity," "adiposity," "cardiovascular disease," "heart failure," "coronary artery disease," "percutaneous coronary intervention," "critical illness," "intensive care unit," "sepsis," "acute respiratory distress syndrome," and "mortality." Boolean operators were used to combine terms appropriately.

Studies were eligible for inclusion if they met the following criteria: (1) original research articles, systematic reviews, or meta-analyses in peer-reviewed

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English-language journals; (2) examination of associations between obesity metrics and clinical outcomes in adult patients with cardiovascular disease or critical illness; (3) publication between 2015 and 2026; and (4) full-text availability. Exclusion criteria included case reports, editorials, commentaries, pediatric studies, and duplicate publications. The initial search yielded 1,847 records; following duplicate removal and screening, 268 articles were included in the qualitative synthesis. Given the narrative nature, formal meta-analytic pooling was not performed.

3. DISCUSSION

3.1 Historical Origins and Epidemiological Foundations of the Obesity Paradox

The concept that obesity might confer survival advantages in certain disease states first emerged in nephrology literature during the late 1990s, when higher BMI was associated with improved survival among hemodialysis patients.[6] This finding contradicted the established relationship between obesity and increased mortality in the general population, prompting the designation "obesity paradox" or "reverse epidemiology." The phenomenon was subsequently extended to other chronic disease populations characterized by high metabolic stress and protein-energy wasting, including chronic heart failure and chronic obstructive pulmonary disease.[6]

In cardiovascular disease, the obesity paradox was initially described in heart failure cohorts. A seminal analysis of the Digitalis Investigation Group trial demonstrated that among 7,767 patients with stable heart failure, those with BMI 25.0-29.9 kg/m² and 30.0-34.9 kg/m² experienced 12% and 19% lower adjusted all-cause mortality, respectively, compared to normal BMI.[9] This inverse association persisted after extensive multivariable adjustment for demographic characteristics, heart failure etiology, left ventricular ejection fraction, New York Heart Association functional class, and comorbid conditions. Notably, the protective association attenuated at higher BMI ranges, establishing the characteristic U-shaped or J-shaped relationship replicated in numerous studies.[7]

The obesity paradox in critical illness has been documented more recently but with similar consistency. A large multicenter observational study involving 259,177 ICU admissions across Australia and New Zealand revealed that compared to patients with BMI <25 kg/m², those with BMI 25-30 kg/m² and 30-35 kg/m² demonstrated absolute reductions in hospital mortality of 2.0% and 3.25%, respectively.[7] This survival advantage was most pronounced in patients admitted with septic shock, where the pathophysiological rationale for enhanced metabolic reserve is particularly compelling. A meta-analysis of observational studies including over 42,000 patients with sepsis or septic shock confirmed that overweight and obesity were associated with significantly lower short-term mortality compared to normal BMI, with pooled odds ratios of 0.81 and 0.82.[8]

Geographic and ethnic variations in the obesity paradox have been increasingly recognized. A systematic review and meta-analysis of Asian cohort studies encompassing over 182,000 patients undergoing percutaneous coronary intervention (PCI) demonstrated that overweight and obese patients experienced significantly lower all-cause mortality compared to normal-weight individuals.[15] The protective BMI thresholds in Asian populations are shifted leftward relative to Western populations, consistent with World Health Organization recommendations for ethnicity-specific BMI cutoffs, reflecting greater metabolic risk at lower absolute BMI values.[1] The consistency of obesity paradox observations across diverse disease states, geographic regions, and ethnic populations has lent credence to the hypothesis that biological mechanisms, rather than methodological artifacts alone, may underlie these counterintuitive findings.

3.2 Obesity Paradox in Heart Failure: Evidence Across the Ejection Fraction Spectrum

Heart failure represents the cardiovascular condition in which the obesity paradox has been most extensively characterized, with robust evidence spanning both HFrEF and HFpEF populations. The pathophysiological relationship between obesity and heart failure is bidirectional and complex: obesity is an established independent risk factor for incident heart failure, with each 5-unit increment in BMI associated with a 41% increased risk of developing heart failure, yet once heart failure is established, obesity appears to confer prognostic advantage.[9] This apparent contradiction has important implications for understanding heart failure pathophysiology and guiding clinical management.

In HFrEF, multiple large-scale observational studies and meta-analyses have confirmed the obesity paradox. A pooled analysis of individual patient data from 13 heart failure trials including 25,819 patients demonstrated that compared to normal BMI, overweight was associated with a 16% reduction in all-cause mortality, while Class I obesity conferred a 19% reduction.[9] This protective association was independent of age, sex, left ventricular ejection fraction, heart failure etiology, and medical therapy, and was consistent across major subgroups. Importantly, the survival benefit appeared to plateau and then attenuate at higher BMI ranges, with Class III obesity demonstrating mortality rates comparable to normal-weight individuals.[9]

The obesity paradox in HFpEF has garnered particular attention given the strong epidemiological and mechanistic links between obesity and this heart failure phenotype. HFpEF is increasingly conceptualized as a cardiometabolic disease driven by systemic inflammation, endothelial dysfunction, and microvascular rarefaction, with visceral adiposity serving

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as a central pathogenic mediator.[4] Epicardial adipose tissue exerts direct paracrine effects on the underlying myocardium, promoting inflammation, fibrosis, and diastolic dysfunction through secretion of proinflammatory adipokines and cytokines.[4] Despite this pathophysiological framework, observational studies consistently demonstrate that overweight and obese HFpEF patients experience better survival than their normal-weight counterparts. Analysis of the TOPCAT trial revealed that among 3,442 patients with HFpEF, those with BMI 30.0-34.9 kg/m² had 24% lower all-cause mortality compared to those with BMI <25 kg/m².[9]

Several mechanisms may explain the paradox in heart failure. First, obese patients typically present at younger ages with less advanced disease, reflecting lead-time bias.[11] Second, circulating natriuretic peptide levels are lower in obesity due to reduced cardiac production and enhanced clearance, potentially indicating less severe hemodynamic derangement.[10] Third, obesity is associated with attenuated sympathetic and renin-angiotensin-aldosterone system activation, which may be cardioprotective.[5] Fourth, higher lipoprotein levels may bind and neutralize endotoxins, reducing inflammation.[8]

However, important limitations temper enthusiasm. BMI fails to distinguish beneficial lean mass from deleterious fat mass. Studies using dual-energy X-ray absorptiometry suggest that survival advantage may reflect preserved lean body mass rather than adiposity.[9] Sarcopenic obesity, with excess adiposity and reduced muscle mass, is associated with poor prognosis.[13] Cardiorespiratory fitness strongly modifies the obesity paradox in heart failure.[9] Recent randomized controlled trials of GLP-1 receptor agonists in obesity-related HFpEF provide crucial evidence that intentional weight loss improves outcomes. The STEP-HFpEF trial demonstrated that semaglutide 2.4 mg weekly resulted in mean weight loss of 13.3% with significant improvements in Kansas City Cardiomyopathy Questionnaire scores and 6-minute walk distance.[8] The STEP-HFpEF DM trial confirmed benefits in patients with type 2 diabetes.[14] These findings establish that pharmacologically-mediated weight loss improves symptoms and functional capacity in obesity-related HFpEF.

3.3 Obesity Paradox in Coronary Artery Disease and Percutaneous Coronary Intervention

Coronary artery disease represents another cardiovascular domain in which the obesity paradox has been consistently documented, particularly following PCI. The pathophysiological relationship between obesity and coronary atherosclerosis is unequivocal: obesity promotes endothelial dysfunction, insulin resistance, dyslipidemia, and systemic inflammation, all of which accelerate atherogenesis and increase the risk of acute coronary syndromes.[3] Paradoxically, however, numerous observational studies demonstrate that overweight and obese patients undergoing PCI experience better short- and long-term outcomes compared to normal-weight individuals.

A comprehensive meta-analysis of studies including over one million patients undergoing PCI demonstrated that compared to normal BMI, overweight and Class I obesity were associated with approximately 30% lower all-cause mortality at mean follow-up of 2.5 years.[5] This protective association was consistent across multiple subgroups including patients with stable angina, unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction. The magnitude of risk reduction was substantial, rivaling or exceeding the mortality benefits observed with established secondary prevention pharmacotherapies.

The obesity paradox in Asian PCI populations is particularly instructive given ethnic differences in body composition and cardiovascular risk profiles. A systematic review demonstrated that among 182,110 Asian patients undergoing PCI, overweight and obesity were associated with substantially lower all-cause mortality compared to normal BMI.[15] The protective BMI thresholds in Asian populations are lower than conventional Western cutoffs, reflecting greater visceral adiposity and metabolic risk at any given BMI among Asian individuals.[15] This observation underscores the importance of ethnicity-specific anthropometric assessment.

Several mechanisms specific to coronary artery disease and PCI may contribute to the obesity paradox. Obese patients undergoing PCI tend to be younger at presentation and have less extensive coronary artery disease compared to normal-weight patients, potentially reflecting lead-time bias.[11] Additionally, obese patients typically receive more aggressive secondary prevention pharmacotherapy, which may confound observed mortality associations.[12] Obese individuals also demonstrate enhanced mobilization of endothelial progenitor cells, which may promote vascular repair and reduce restenosis following PCI.[8] Higher circulating lipoprotein levels may paradoxically protect against adverse outcomes by neutralizing circulating endotoxins and reducing systemic inflammation.[8]

However, important limitations warrant consideration. BMI is an imprecise measure of body composition that fails to capture the metabolically relevant distinction between visceral and subcutaneous adiposity. Studies incorporating computed tomography-derived measures of visceral adipose tissue demonstrate that increased visceral adiposity, rather than elevated BMI, is associated with adverse cardiovascular outcomes following PCI.[9] Cardiorespiratory fitness also substantially modifies the obesity paradox in coronary artery disease; among patients with high fitness, prognosis is excellent regardless of BMI.[19] The SELECT trial demonstrated that semaglutide 2.4 mg

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weekly reduced the composite primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 20% in patients with established cardiovascular disease and overweight or obesity without diabetes, providing direct randomized evidence that pharmacologically-mediated weight loss improves cardiovascular outcomes in secondary prevention populations.[16]

3.4 Obesity Paradox in Critical Illness: Sepsis, ARDS, and General ICU Populations

The extension of the obesity paradox to critical illness has generated substantial interest and controversy within the intensive care community. Approximately 20% of patients admitted to ICUs worldwide meet criteria for obesity, and this proportion is projected to increase in parallel with population obesity trends.[7] Obesity presents unique challenges in critical care settings, including difficult airway management, challenges with vascular access, altered drug pharmacokinetics requiring weight-based dosing adjustments, increased risk of pressure injuries, and diagnostic limitations of conventional imaging modalities.[7] Despite these practical challenges, observational studies consistently demonstrate that overweight and mildly obese patients experience lower ICU and hospital mortality compared to normal-weight individuals.

A landmark multicenter observational study analyzed 259,177 ICU admissions and demonstrated a J-shaped relationship between BMI and hospital mortality, with the lowest risk observed at BMI 27.5-30.0 kg/m².[7] Compared to patients with BMI <25 kg/m², those with BMI 25-30 kg/m² and 30-35 kg/m² experienced absolute mortality reductions of 2.0% and 3.25%, respectively.[7] This protective association persisted after extensive adjustment for age, sex, admission diagnosis, severity of illness, mechanical ventilation requirements, and comorbidities. However, the survival advantage attenuated and ultimately reversed at BMI ≥40 kg/m², with Class III obesity associated with increased mortality and prolonged mechanical ventilation.[7]

In sepsis and septic shock, the obesity paradox has been particularly well-documented. A meta-analysis of over 42,000 patients with sepsis or septic shock demonstrated that overweight and obesity were associated with significantly lower short-term mortality compared to normal BMI.[8] Several mechanistic hypotheses have been proposed. Adipose tissue serves as a substantial energy reservoir that may buffer against the profound catabolic stress of critical illness, providing metabolic substrates essential for immune function and tissue repair.[8] Higher circulating lipoprotein levels in obesity may bind and neutralize bacterial endotoxins, reducing the systemic inflammatory response and mitigating organ dysfunction.[8] Adipose tissue also secretes soluble tumor necrosis factor-alpha receptors that may neutralize this key proinflammatory cytokine.[8]

In ARDS, the relationship between obesity and outcomes is complex. Obesity is associated with increased risk of developing ARDS, likely reflecting the proinflammatory state, endothelial dysfunction, and mechanical effects of increased intra-abdominal pressure on respiratory mechanics.[17] However, once ARDS is established, several studies suggest that obesity may confer survival advantages. Proposed mechanisms include the preconditioning hypothesis, wherein chronic low-grade inflammation associated with obesity induces adaptive immune responses that mitigate excessive inflammation, and mechanical advantages wherein increased chest wall elastance may paradoxically protect against ventilator-induced lung injury.[17]

Important methodological considerations specific to critical illness warrant emphasis. Reverse causation is a particularly salient concern, as critical illness induces rapid catabolism and fluid shifts that may artifactually lower BMI in the normal-weight reference group. Premorbid BMI may not accurately reflect body composition at ICU admission.[7] Fluid resuscitation may differentially affect BMI measurements across weight categories. Furthermore, decisions regarding life-sustaining therapy may be influenced by clinician perceptions of obesity-related futility, introducing selection and treatment allocation biases.[7]

3.5 Mechanistic Hypotheses: Biological Plausibility and Metabolic Reserve

The consistency of obesity paradox observations across diverse disease states has prompted extensive investigation into potential biological mechanisms that might explain how excess adiposity could confer survival advantages in the context of established cardiovascular disease or critical illness. While no single mechanism fully accounts for the paradox, several complementary hypotheses have been advanced that collectively provide a plausible biological framework.

Metabolic Reserve and Substrate Availability. The metabolic reserve hypothesis posits that increased adipose tissue and lean body mass in obesity provide a critical buffer against the catabolic stress of acute and chronic illness.[8] Heart failure and critical illness are characterized by hypermetabolism, increased resting energy expenditure, and accelerated protein catabolism, which collectively deplete energy stores and contribute to cardiac cachexia and ICU-acquired weakness. Obese patients possess substantially larger energy reserves that can be mobilized during periods of metabolic stress, preserving immune function and facilitating tissue repair.[8] Consistent with this hypothesis, unintentional weight loss and low serum albumin are among the strongest predictors of adverse outcomes, and the protective association of obesity is most pronounced when compared to underweight or cachectic patients.[6]

Attenuated Neurohormonal Activation. Obesity is associated with relative suppression of the sympathetic

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nervous system and renin-angiotensin-aldosterone system, neurohormonal axes that are pathologically activated in heart failure and contribute to adverse ventricular remodelling.[5] Obese individuals demonstrate lower circulating levels of norepinephrine, plasma renin activity, and aldosterone compared to lean individuals with comparable heart failure severity.[10] This attenuated neurohormonal profile may be cardioprotective, mitigating the deleterious effects of chronic adrenergic stimulation. Additionally, lower circulating B-type natriuretic peptide levels in obesity, reflecting reduced cardiac production and enhanced clearance via adipose tissue natriuretic peptide clearance receptors, may indicate less advanced heart failure.[10]

Protective Adipokine and Cytokine Profiles. Adipose tissue functions as an active endocrine organ secreting a complex array of bioactive mediators. Soluble tumor necrosis factor-alpha receptors, which are shed from adipocyte cell surfaces in proportion to adipose tissue mass, bind and neutralize circulating tumor necrosis factor-alpha, attenuating its proinflammatory, cardiodepressant, and catabolic effects.[8] Leptin exerts immunomodulatory actions that may enhance immune competence during critical illness. The small fraction of obese individuals with preserved adiponectin levels (metabolically healthy obesity) may account for much of the observed survival advantage.[18]

Lipoprotein-Mediated Endotoxin Neutralization. This mechanism is particularly relevant to sepsis. Bacterial endotoxin circulates bound to plasma lipoproteins, which neutralize its biological activity and facilitate hepatic clearance.[8] Obesity is associated with higher circulating lipoprotein levels, which collectively provide an expanded endotoxin-binding capacity. During sepsis, increased intestinal permeability facilitates bacterial translocation; obese individuals may more effectively neutralize this endotoxin load, attenuating the systemic inflammatory response.[8]

Endothelial Progenitor Cell Mobilization. Obesity is associated with enhanced mobilization of endothelial progenitor cells from bone marrow, a phenomenon that may promote vascular repair and angiogenesis following ischemic injury.[8] In patients undergoing PCI, higher circulating endothelial progenitor cell counts are associated with reduced rates of in-stent restenosis and target vessel revascularization. Obesity-related endothelial progenitor cell mobilization may thus confer protective effects in acute coronary syndromes and PCI.[8]

Earlier Clinical Presentation and Lead-Time Bias. Obese individuals with cardiovascular disease typically present at younger ages and with less advanced disease compared to normal-weight patients, potentially reflecting earlier diagnostic evaluation prompted by obesity-related symptoms.[11] Dyspnea and edema are more readily apparent in obese patients due to the mechanical effects of increased body mass. This may lead to earlier diagnosis and treatment initiation, introducing lead-time bias wherein survival appears prolonged from diagnosis despite no true alteration in disease natural history.[11]

3.6 Methodological Critiques: BMI Limitations, Confounding, and Selection Biases

Despite the consistency of obesity paradox observations and the biological plausibility of proposed mechanisms, substantial methodological concerns temper enthusiasm for a causal interpretation. Critical examination of study design, exposure measurement, confounding control, and potential biases is essential for appropriately contextualizing the obesity paradox.

BMI as an Imprecise Adiposity Metric. The overwhelming majority of obesity paradox literature relies on BMI, a metric with well-recognized limitations for individual-level body composition assessment.[9] BMI does not distinguish between fat mass and lean mass, nor does it provide information regarding fat distribution or ectopic fat deposition. Individuals with identical BMI may have markedly different body composition, metabolic profiles, and cardiovascular risk. Studies incorporating more precise body composition assessment using dual-energy X-ray absorptiometry or computed tomography consistently demonstrate that the protective association of elevated BMI is largely attributable to preserved lean body mass rather than adiposity per se, and that visceral adipose tissue is independently associated with adverse outcomes.[9]

Failure to Account for Cardiorespiratory Fitness. Cardiorespiratory fitness, objectively measured as peak oxygen consumption during cardiopulmonary exercise testing, is among the most powerful predictors of all-cause and cardiovascular mortality.[19] Fitness is inversely correlated with BMI in most populations, yet substantial heterogeneity exists. Failure to account for fitness in observational studies introduces substantial confounding, as fitness may be the true driver of improved outcomes while BMI serves merely as a correlated proxy. Studies stratifying by both BMI and fitness demonstrate that the obesity paradox is markedly attenuated or abolished after accounting for fitness.[19]

Reverse Causation and Cardiac Cachexia. Reverse causation refers to the phenomenon wherein the outcome influences the exposure. In the context of the obesity paradox, unintentional weight loss due to advanced cardiovascular disease or critical illness may selectively worsen outcomes in the normal-weight reference group, artifactually creating the appearance of a protective association for higher BMI.[9] Cardiac cachexia, characterized by progressive loss of lean body mass and adipose tissue in advanced heart failure, is a powerful independent predictor of mortality. Studies incorporating premorbid BMI or weight trajectory demonstrate that weight stability and intentional weight loss are associated

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with improved outcomes, while unintentional weight loss portends poor prognosis.[9]

Collider Stratification Bias. Collider stratification bias represents a fundamental threat to causal inference in studies of the obesity paradox.[12] This form of bias arises when the study sample is selected on a variable affected by both the exposure and outcome. In obesity paradox studies, the sample is typically restricted to patients with established cardiovascular disease or critical illness. Obesity is a strong risk factor for developing these conditions, meaning that obese individuals who develop disease despite elevated baseline risk may represent a selected subgroup with favorable characteristics. Conversely, normal-weight individuals who develop disease may represent a subgroup with unfavorable characteristics. This differential selection can artifactually invert the true causal relationship between obesity and mortality within the diseased population.[12]

Residual and Unmeasured Confounding. Despite extensive multivariable adjustment, residual confounding by inadequately measured or unmeasured factors remains a persistent concern. Obese patients differ systematically from normal-weight patients across numerous dimensions including age, sex, socioeconomic status, healthcare access, comorbidity burden, and treatment patterns. While statistical adjustment can partially account for measured confounders, residual confounding may substantially bias effect estimates.[12]

3.7 Therapeutic Implications: Weight Management in the Era of the Obesity Paradox

The obesity paradox presents a clinical conundrum: if observational data suggest that overweight and mild obesity confer survival advantages in patients with established cardiovascular disease and critical illness, should clinicians de-emphasize weight loss recommendations in these populations? The weight of current evidence, particularly from recent randomized controlled trials, strongly supports intentional weight loss for appropriately selected patients, while acknowledging the need for nuanced, individualized approaches.

Lifestyle Interventions and Cardiac Rehabilitation. Dietary modification and structured exercise training remain foundational components of weight management for patients with cardiovascular disease. In heart failure, the Heart Failure Society of America recommends nutritional assessment and counseling, 150 minutes of exercise per week, and caloric restriction targeting 5-10% weight loss for patients with BMI ≥35 kg/m².[20] Cardiac rehabilitation programs provide supervised exercise training and nutritional education that can facilitate safe, gradual weight loss while preserving or enhancing cardiorespiratory fitness. Observational studies suggest that heart failure patients who achieve modest weight loss through lifestyle intervention experience improvements in symptoms, functional capacity, and quality of life.[20]

Pharmacotherapy: GLP-1 Receptor Agonists and Emerging Agents. The advent of highly effective anti-obesity pharmacotherapies has fundamentally altered the landscape of obesity management. The STEP-HFpEF program demonstrated that pharmacologically-mediated weight loss of approximately 10-13% with semaglutide improves symptoms, functional capacity, and quality of life in patients with HFpEF and obesity.[8,14] The SUMMIT trial of tirzepatide in HFpEF and obesity demonstrated a 38% reduction in the composite endpoint of cardiovascular death or heart failure events.[21] Based on these data, the 2025 American College of Cardiology Scientific Statement explicitly recommends consideration of semaglutide and tirzepatide for symptom control and cardiovascular risk reduction in patients with HFpEF and obesity.[25]

Bariatric Surgery. For patients with severe obesity (BMI ≥35-40 kg/m²) who have failed non-surgical weight loss interventions, bariatric surgery represents the most effective and durable approach to weight reduction. Roux-en-Y gastric bypass and sleeve gastrectomy typically achieve 25-35% total body weight loss, with substantial improvements in obesity-related comorbidities.[23] In patients with heart failure, observational studies suggest that bariatric surgery improves left ventricular geometry and function, reduces heart failure symptoms and hospitalizations, and may facilitate candidacy for advanced therapies including heart transplantation.

Individualized, Phenotype-Guided Approaches. Rather than adopting a uniform approach based solely on BMI thresholds, emerging evidence supports individualized strategies incorporating comprehensive phenotypic assessment. Metabolically healthy obesity may confer substantially lower cardiovascular risk than metabolically unhealthy obesity, and the urgency of weight loss interventions may reasonably be tempered in such patients.[18] Conversely, sarcopenic obesity warrants interventions that prioritize preservation and augmentation of lean body mass alongside modest fat loss.[13] Cardiorespiratory fitness assessment provides valuable prognostic information and can guide exercise prescription.[19]

Avoiding Therapeutic Nihilism. Perhaps the most important clinical implication is that observational associations should not be misinterpreted as justification for therapeutic nihilism regarding obesity management. The obesity paradox describes prognostic associations within diseased populations but does not negate the well-established causal role of obesity in the development and progression of these conditions.[6] Moreover, the paradox is most evident for overweight and Class I obesity, not for the severe obesity that is unequivocally associated with adverse outcomes. Intentional weight loss achieved through lifestyle modification, pharmacotherapy, or bariatric surgery improves cardiovascular risk factors,

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symptoms, functional capacity, quality of life, and hard clinical outcomes.[24]

4. Future Directions and Recommendations

· Develop and validate precise body composition metrics beyond BMI, incorporating routine assessment of fat mass, lean mass, visceral adipose tissue, and muscle quality using accessible technologies.[20]

· Conduct longitudinal studies with serial anthropometric assessments to distinguish prognostic implications of intentional versus unintentional weight loss, stable obesity versus progressive weight gain.

· Perform dedicated randomized controlled trials of pharmacologically-mediated weight loss in HFrEF and post-PCI populations, building on evidence from HFpEF trials.[21]

· Investigate molecular mediators of potential protective effects in obesity, including adipokine signaling and lipoprotein-endotoxin interactions, to identify novel therapeutic targets.[22]

· Integrate cardiorespiratory fitness assessment into routine cardiovascular and critical illness outcome studies to clarify independent and interactive effects of adiposity and fitness.[19]

· Study ethnic and geographic variations in the obesity paradox with ethnicity-specific anthropometric assessment to define optimal BMI targets for diverse populations.[15]

· Develop clinical decision support tools incorporating body composition metrics, fitness assessment, and metabolic health parameters for individualized obesity management.

· Conduct implementation research to translate recent trial findings into real-world clinical practice, addressing barriers including medication access, cost, and clinician training.[23]

5. CONCLUSION

The obesity paradox represents a complex epidemiological phenomenon wherein overweight and mildly obese patients with established cardiovascular disease or critical illness demonstrate improved survival compared to normal-weight individuals. While observational evidence supporting this paradox is extensive and consistent across diverse populations and disease states, critical methodological limitations—including BMI imprecision, failure to account for cardiorespiratory fitness and body composition, reverse causation, and collider stratification bias—substantially complicate causal inference. The paradox does not negate the well-established adverse effects of obesity on cardiovascular structure and function, nor does it justify therapeutic nihilism regarding weight management in affected patients. Recent randomized controlled trials of GLP-1 receptor agonists in obesity-related HFpEF provide high-quality evidence that intentional, pharmacologically-mediated weight loss improves symptoms, functional capacity, quality of life, and cardiovascular outcomes. Moving forward, clinical approaches should emphasize individualized, phenotype-guided strategies incorporating precise body composition metrics, cardiorespiratory fitness assessment, and interventions that preserve lean body mass while reducing excess adiposity.[24,25]

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