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Beyond Body Mass Index (BMI): A Systematic Review of Central Adiposity and the Obesity Survival Paradox Across Heart Failure Phenotypes

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Abstract

Obesity contributes to the development of heart failure (HF), yet a higher body mass index (BMI) has frequently been associated with improved survival after HF is established, giving rise to the obesity paradox. This systematic review examined whether this paradox persists when adiposity is assessed using central anthropometric measures and whether associations differ across HF phenotypes and clinical outcomes. MEDLINE through PubMed, Embase, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials were searched from inception through September 5, 2026. Longitudinal studies of adults with established HF that evaluated waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), or related indices alongside BMI were eligible. Owing to clinical and methodological heterogeneity, the findings were synthesized narratively. Seven studies comprising 25,408 participants were included, although the availability of central anthropometric measurements varied. Higher BMI was frequently associated with neutral or improved survival in unadjusted analyses, but this apparent benefit was attenuated or eliminated after comprehensive adjustment in several large cohorts. Central adiposity generally identified greater clinical risk, with the most consistent associations observed for HF hospitalization. In heart failure with preserved ejection fraction (HFpEF), abdominal obesity was associated with increased mortality, while WHtR identified widespread central adiposity and greater HF event risk. In heart failure with reduced ejection fraction (HFrEF), increasing WHtR was associated with hospitalization, although its adjusted relationship with mortality varied across populations and follow-up periods. A high-risk phenotype characterized by low BMI and elevated WHtR was identified in Asian patients, while higher WHR predicted mortality among women but not men in a mixed-ejection fraction (EF) cohort. Five studies had moderate and two had high overall risk of bias. The obesity paradox therefore appears to depend on adiposity measurement, outcome selection, and HF population rather than representing a uniform protective effect of excess fat. Combining BMI with central anthropometric measures may provide a more clinically informative characterization of obesity-related risk in HF.

Categories: Other, Internal Medicine, Endocrinology/Diabetes/Metabolism
Keywords: abdominal obesity, body mass index, central adiposity, heart failure, heart failure hospitalization, mortality, obesity paradox, waist circumference, waist-to-height ratio, waist-to-hip ratio

Introduction And Background

Obesity is a major risk factor for the development and progression of heart failure (HF), acting through interconnected hemodynamic, metabolic, inflammatory, and structural pathways [1,2]. Excess adiposity leads to hypertension, insulin resistance, renal dysfunction, myocardial fibrosis, and impaired ventricular relaxation while increasing circulatory volume and cardiac workload [1-4]. These mechanisms are particularly prominent in obesity-related heart failure with preserved ejection fraction (HFpEF), although obesity is also common among patients with heart failure with reduced ejection fraction (HFrEF) [2-4]. Despite its established contribution to incident HF, the prognostic significance of obesity once HF is established remains uncertain.

Numerous observational studies have reported that patients with established HF and a higher body mass index (BMI) experience similar or better survival than those with a normal or low BMI, an observation commonly described as the obesity paradox [4,5]. This association has been interpreted as possibly reflecting greater metabolic reserve, preserved muscle mass, or improved tolerance of disease-modifying therapy. However, alternative explanations include reverse causation from cardiac cachexia, confounding by disease severity and physical fitness, earlier clinical recognition among patients with obesity, and selection bias arising from the restriction of analyses to individuals who have already developed HF [4,5]. The obesity paradox should therefore be interpreted as a prognostic association rather than evidence that excess adipose

tissue confers a causal survival benefit.

An important limitation is that BMI measures overall body size rather than adiposity itself. It cannot distinguish adipose tissue from skeletal muscle, bone mass, or extracellular fluid, nor can it characterize the distribution of body fat [6]. Central anthropometric measures, including waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), may provide complementary information about abdominal fat distribution and cardiometabolic risk [3,4,6]. Emerging evidence suggests that these measures can identify high-risk patients who are not classified as obese by BMI and that their prognostic associations may vary according to HF phenotype, sex, ethnicity, disease stage, and the outcome examined. Nevertheless, central anthropometric indices remain indirect measures of adiposity, and the available evidence is heterogeneous and occasionally conflicting [3,4,7].

This systematic review aimed to determine whether the apparent obesity survival paradox in adults with established HF persists when adiposity is evaluated using central anthropometric measures rather than BMI. It also sought to compare associations with mortality and HF hospitalization and to examine whether these relationships vary across HFrEF, heart failure with mildly reduced ejection fraction (HFmrEF), and HFpEF, as well as by sex, geographical context, HF etiology, and disease stage. By distinguishing overall body size from abdominal fat distribution, this review aimed to provide a more clinically informative interpretation of obesity-related prognosis across the HF spectrum.

Review

Methodology

Study Design and Reporting Framework

This systematic review evaluated whether the apparent obesity survival paradox in established HF persists when adiposity is assessed using central anthropometric measures rather than BMI. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [8]. The eligibility criteria, outcomes, search strategy, screening procedures, and planned approach to evidence synthesis were specified before formal study selection. Because adiposity was evaluated as a prognostic exposure rather than an intervention, the review was structured as a systematic review of prognostic factor studies.

Review Question and PICO Framework

The review question was formulated according to the Population, Index prognostic factor, Comparator, and Outcome (PICO) framework. The population comprised adults aged 18 years or older, with no upper age limit, who had established HF, including HFrEF, HFmrEF, HFpEF, and mixed ejection fraction populations. An index prognostic factor was defined as a baseline characteristic evaluated for its association with subsequent clinical outcomes. In this review, the index prognostic factors were central anthropometric measures, including WC, WHR, and WHtR, together with related indices derived from WC, hip circumference, height, or weight. Comparators included BMI, conventional BMI categories, or the reference category used in each study for the corresponding central adiposity measure. Outcomes of interest were all-cause mortality, defined as death from any cause; cardiovascular mortality, defined as death attributed to cardiovascular causes; and noncardiovascular mortality, defined as death attributed to causes outside the cardiovascular system. Cause-specific mortality was classified according to the definitions used in each included study. Additional outcomes included HF hospitalization, composites of HF hospitalization and death, and the composite of death or urgent heart transplantation.

Eligibility Criteria

Studies were eligible if they enrolled adults aged 18 years or older, with no upper age limit, who had an established clinical diagnosis of HF and reported a longitudinal association between at least one central anthropometric measure and a relevant clinical outcome. To ensure alignment with the review question, studies were required either to compare BMI with a central adiposity measure within the same cohort or to evaluate a central measure while incorporating BMI through multivariable adjustment, stratification, or combined adiposity phenotypes. Studies involving HFrEF, HFmrEF, HFpEF, advanced systolic HF, or mixed ejection fraction populations were eligible because HF phenotype, etiology, and disease stage were prespecified sources of clinical heterogeneity. Eligible designs included prospective and retrospective cohort studies, multicenter registries, comparative observational studies, and secondary or post hoc analyses of randomized trial cohorts. Trial-derived analyses were treated as observational studies because BMI and central adiposity were not randomized exposures.

Studies were excluded if they evaluated BMI without a central anthropometric measure, examined incident HF in populations without established disease, lacked longitudinal clinical outcomes, or did not provide an interpretable association estimate. Cross-sectional studies, case reports, small case series, reviews, meta-analyses, editorials, conference abstracts with insufficient data, animal studies, and pediatric studies were excluded. Studies reporting imaging-based or direct body-composition measures without the required BMI

or central anthropometric data were reserved for contextual discussion rather than primary synthesis. No restrictions were imposed according to sex, ethnicity, geographical region, HF etiology, or care setting, and no lower publication-date limit was applied.

Information Sources and Search Strategy

MEDLINE through PubMed, Embase, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials were searched from database inception through September 5, 2026. The database-specific search strategies are summarized in Table *1*. Controlled vocabulary and field syntax were adapted for each database. Reference lists of eligible studies and relevant reviews were screened manually, and forward citation searching was undertaken to identify additional eligible reports. Searches were limited to adult human studies, with no language restriction. No study-design filter was applied.

Database	Heart failure terms	Adiposity terms	Outcome terms	Combination
MEDLINE through PubMed	("heart failure" OR HFpEF OR HFmrEF OR HFrEF)	(obesity OR adiposity OR BMI OR "body mass index" OR "central obesity" OR "abdominal obesity" OR "waist circumference" OR WHtR OR WHR OR "body composition" OR "obesity paradox")	(mortality OR survival OR "heart failure hospitalization" OR "cardiovascular outcomes")	(Heart-failure terms) AND (Adiposity terms) AND (Outcome terms)
Embase	('heart failure'/exp OR HFpEF OR HFmrEF OR HFrEF)	('obesity'/exp OR adiposity OR BMI OR "central obesity" OR "abdominal obesity" OR "waist circumference" OR WHtR OR WHR OR "body composition" OR "obesity paradox")	(mortality OR survival OR "heart failure hospitalization" OR "cardiovascular outcomes")	(Heart-failure terms) AND (Adiposity terms) AND (Outcome terms)
Scopus	("heart failure" OR HFpEF OR HFmrEF OR HFrEF)	(obesity OR adiposity OR BMI OR "central obesity" OR "abdominal obesity" OR "waist circumference" OR WHtR OR WHR OR "body composition" OR "obesity paradox")	(mortality OR survival OR "heart failure hospitalization" OR "cardiovascular outcomes")	(Heart-failure terms) AND (Adiposity terms) AND (Outcome terms)
Web of Science Core Collection	("heart failure" OR HFpEF OR HFmrEF OR HFrEF)	(obesity OR adiposity OR BMI OR "central obesity" OR "abdominal obesity" OR "waist circumference" OR WHtR OR WHR OR "body composition" OR "obesity paradox")	(mortality OR survival OR "heart failure hospitalization" OR "cardiovascular outcomes")	(Heart-failure terms) AND (Adiposity terms) AND (Outcome terms)
Cochrane CENTRAL	("heart failure" OR HFpEF OR HFmrEF OR HFrEF)	(obesity OR adiposity OR BMI OR "central obesity" OR "abdominal obesity" OR "waist circumference" OR WHtR OR WHR OR "body composition" OR "obesity paradox")	(mortality OR survival OR "heart failure hospitalization" OR "cardiovascular outcomes")	(Heart-failure terms) AND (Adiposity terms) AND (Outcome terms)
Complete Boolean example	Combined search across all three concept groups →	("heart failure" OR HFpEF OR HFmrEF OR HFrEF) AND (obesity OR adiposity OR BMI OR "body mass index" OR "central obesity" OR "abdominal obesity" OR "waist circumference" OR WHtR OR WHR OR "body composition" OR "obesity paradox") AND (mortality OR survival OR "heart failure hospitalization" OR "cardiovascular outcomes")	—	—

TABLE 1: Summary of the database search strategy.

Terms within each column were combined using OR, and the three concept groups were combined using AND. Controlled vocabulary and title, abstract, keyword, or topic-field syntax were applied as appropriate for each database.

BMI, body mass index; CENTRAL, Cochrane Central Register of Controlled Trials; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

Study Selection

All retrieved records were imported into reference-management software, and duplicates were removed before screening. Two reviewers independently screened the titles and abstracts against the prespecified eligibility criteria. The full texts of potentially eligible reports were then evaluated independently by the

same reviewers. Disagreements at either stage were resolved through discussion, with consultation of a third reviewer when consensus could not be reached. Multiple publications derived from the same parent cohort were linked and retained as separate reports only when they evaluated distinct adiposity measures, HF phenotypes, follow-up periods, or outcomes. Reasons for exclusion during full-text assessment were recorded, and the study-selection process was summarized using a PRISMA 2020 flow diagram.

Data Extraction

Two reviewers independently extracted data using a standardized form. Extracted information included the author and publication year, parent cohort or trial, country and setting, study design, sample size, participant age and sex, HF phenotype and EF definition, HF etiology, adiposity measures and thresholds, comparator categories, follow-up duration, outcome definitions, event counts, adjusted and unadjusted effect estimates, confidence intervals, and covariates included in multivariable models. Data on effect modification by sex, HF phenotype, ethnicity, or geographical region were also collected. Maximally adjusted estimates were prioritized for the primary interpretation, while unadjusted estimates were retained when required to determine whether statistical adjustment altered the apparent obesity paradox.

Risk-of-Bias Assessment

Two reviewers independently assessed risk of bias using the Quality In Prognosis Studies (QUIPS) tool [9]. The six domains evaluated were study participation, study attrition, prognostic-factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain was judged as having a low, moderate, or high risk of bias. Disagreements were resolved through consensus, with consultation of a third reviewer when necessary. Particular attention was given to missing central anthropometric measurements, reliance on a single baseline assessment, adjustment for HF severity and N-terminal pro-B-type natriuretic peptide (NT-proBNP), reverse causation related to cardiac cachexia, and residual confounding by muscle mass, physical fitness, frailty, and congestion. The Cochrane Risk of Bias 2 (RoB 2) tool was not applied to trial-derived cohorts because the review evaluated nonrandomized adiposity exposures rather than randomized treatment comparisons. No numerical quality score was calculated.

Data Synthesis

Clinical and methodological heterogeneity was evaluated according to HF phenotype, disease stage, adiposity measure, threshold definition, clinical outcome, and follow-up duration. Findings were synthesized narratively and organized according to mortality and HF morbidity, with separate consideration of HFrEF, HFpEF, and mixed ejection fraction populations. Associations based on BMI were compared with those based on WHtR, WHR, and WC, while discordant BMI and central adiposity phenotypes were examined separately where reported. Quantitative meta-analysis was not considered appropriate because of substantial variation in reference categories, adiposity thresholds, effect measures, covariate adjustment, and outcome definitions. Publication bias was not assessed statistically because fewer than 10 sufficiently comparable studies were available for any individual outcome. The certainty of the overall conclusions was considered qualitatively according to risk of bias, consistency, directness, precision, and the possibility of publication bias.

Results

Study Selection Process

The database search identified 596 records, of which 26 duplicates were removed, leaving 570 records for title and abstract screening. Following the exclusion of 398 records, 172 reports were sought for retrieval; 16 could not be obtained, and 156 full-text reports were assessed for eligibility. Of these, 149 were excluded, most commonly because they evaluated BMI without a central anthropometric measure (n = 42), examined incident HF rather than established disease (n = 21), lacked longitudinal outcomes (n = 18), represented reviews, meta-analyses, or editorials (n = 16), or did not provide an interpretable association estimate (n = 14). Other exclusions included cross-sectional studies, case reports, conference abstracts with insufficient data, pediatric or animal studies, and imaging-based studies without the required anthropometric comparison. Seven studies ultimately satisfied the eligibility criteria and were included in the systematic review (Figure *1*).

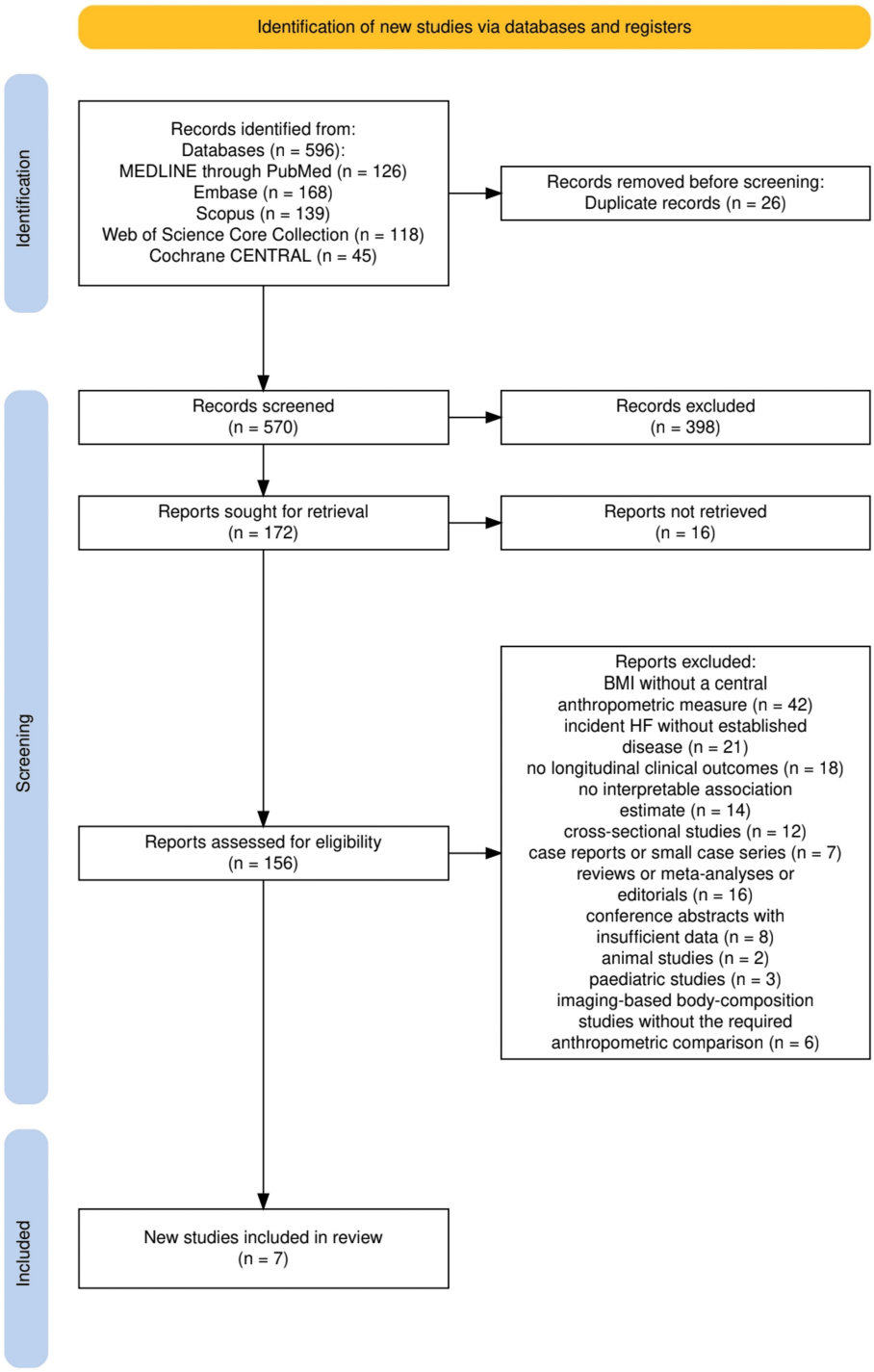


FIGURE 1: PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Characteristics of the Selected Studies

Seven studies published between 2011 and 2025, comprising 25,408 participants, were included [10-16]. Sample sizes ranged from 344 to 8,399 participants, and study designs included prospective registries, observational cohorts, and secondary analyses of randomized trial populations. The studies represented HFrEF, HFmrEF, HFpEF, and mixed ejection fraction populations across diverse geographical settings. BMI was evaluated alongside WC, WHR, WHtR, or related anthropometric indices. Reported outcomes included all-cause and cardiovascular mortality, HF hospitalization, urgent heart transplantation, and composite clinical endpoints, with follow-up ranging from 1 to 9.5 years (Table *2*).

Study and cohort	Design and population	HF phenotype	Adiposity measures	Outcomes and follow-up	Key statistical findings	Landmark interpretation
Peikert et al., 2025; PARAGON-HF [10]	Secondary analysis of an international RCT cohort; 4,796 patients, with WHtR available in 4,534	HFpEF/HFmrEF; LVEF ≥ 45%	BMI and WHtR	Total HF hospitalizations, CV death and all-cause death; median 35 months	Obesity prevalence was 49% by BMI, while 96% had WHtR ≥ 0.50. Among patients with BMI < 30, 37% had WHtR ≥ 0.60. WHtR showed a linear relationship with HF events, mainly hospitalizations	The unadjusted BMI-based survival paradox was not observed with WHtR. Central adiposity was almost universal and more closely reflected HF morbidity
Butt et al., 2025; DANISH [11]	Secondary prognostic analysis of a multicenter RCT cohort; 1,116 patients with non-ischemic HFrEF	Non-ischemic HFrEF	BMI and multiple alternative indices; WHtR was the principal central measure	All-cause and CV mortality; median 9.5 years	BMI ≥ 35 vs. 18.5-24.9 kg/m²: all-cause mortality HR 1.78 (95% CI 1.28-2.48) and CV mortality HR 2.46 (1.69-3.58). Highest vs. lowest WHtR quintile: all-cause mortality HR 2.11 (1.53-2.92) and CV mortality HR 2.17 (1.49-3.15)	Both BMI and WHtR showed that greater adiposity predicted higher long-term mortality, providing no support for an obesity-survival paradox
Butt et al., 2023; PARADIGM-HF [12]	Secondary analysis of an international RCT cohort; 8,399 patients, with WHtR available in 98.6%	HFrEF	BMI, WHtR, WC, WHR, and other derived indices	HF hospitalization or CV death; mortality outcomes; median 27 months	Highest vs. lowest WHtR quintile: all-cause mortality aHR 1.10 (0.87-1.39) and HF hospitalization aHR 1.39 (1.06-1.81). The BMI survival advantage disappeared after comprehensive adjustment	Central adiposity did not independently predict mortality but was associated with a higher risk of HF hospitalization. The BMI paradox was largely explained by other prognostic differences
Chandramouli et al., 2019; ASIAN-HF [13]	Prospective registry across 46 centers in 11 Asian regions; 5,964 patients, with WHtR available in 2,051	Mixed HFrEF and HFpEF	BMI and WHtR; combined lean/thin, lean/fat, obese/thin and obese/fat phenotypes	HF hospitalization or death at 1 year	Increasing BMI predicted lower risk, whereas increasing WHtR predicted higher risk. Lean-fat patients had a 22% event rate and higher adjusted risk than obese-thin patients: HR 1.93 (1.17-3.18; $P = 0.01$). EF interaction: $P = 0.355$	The obesity paradox appeared only with BMI. WHtR identified a high-risk lean-fat phenotype that BMI failed to detect
Streng et al., 2018; BIOSTAT-CHF [14]	Observational analysis of 1,479 patients with chronic or worsening HF; mean age 75 years, 33% women	Mixed HFrEF, HFmrEF and HFpEF	BMI and sex-specific WHR tertiles	All-cause mortality; median 21 months	Significant sex interaction: $P < 0.001$. Highest vs. lowest WHR tertile predicted mortality in women: aHR 2.23 (1.37-3.63; $P = 0.001$), but not men: aHR 0.87 (0.63-1.20; $P = 0.409$). No EF interaction was detected.	The prognostic effect of central adiposity differed by sex. BMI suggested an obesity paradox, while high WHR identified increased mortality specifically among women
Tsujimoto and Kajio, 2017; TOPCAT [15]	Post hoc observational analysis of an international RCT cohort; 3,310 patients, including 2,413 with abdominal obesity	HFpEF	WC-defined abdominal obesity; BMI included in adjustment and supporting analyses	All-cause, CV and non-CV mortality; mean 3.4 ± 1.7 years	Abdominal obesity predicted all-cause mortality: aHR 1.52 (1.16-1.99; $P = 0.002$); CV mortality: aHR 1.50 (1.08-2.08; $P = 0.01$); and non-CV mortality: aHR 1.58 (1.00-2.51; $P = 0.04$)	Abdominal adiposity predicted worse survival in HFpEF, challenging the protective interpretation associated with higher BMI
Clark et al., 2011; UCLA advanced HF cohort [16]	Observational comparative cohort of 344 patients with advanced systolic HF	Advanced HFrEF	BMI and WC; combined BMI-WC groups	All-cause mortality and death or urgent transplantation over 2 years	Transplant-free survival was higher with high vs. normal WC: 77.9% vs. 64.3% ($P = 0.025$), and high vs. normal BMI: 89.8% vs. 58.2% ($P < 0.001$). Normal vs. high WC predicted mortality: adjusted RR 2.76 (1.34-5.71)	Unlike the newer studies, both greater BMI and larger WC predicted better outcomes, supporting an obesity paradox in advanced systolic HF

TABLE 2: Characteristics and principal findings of the included studies.

aHR, adjusted hazard ratio; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; BIOSTAT-CHF, A Systems Biology Study to Tailored Treatment in Chronic Heart Failure; BMI, body mass index; CI, confidence interval; CV, cardiovascular; DANISH, Danish Study to Assess the Efficacy of Implantable Cardioverter-Defibrillators in Patients with Nonischemic Systolic Heart Failure on Mortality; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; n, number of participants; non-CV, noncardiovascular; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAGON-HF, Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin Receptor Blockers Global Outcomes in Heart Failure with Preserved Ejection Fraction; RCT, randomized controlled trial; RR, risk ratio; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; UCLA, University of California, Los Angeles; vs, versus; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

Quality Assessment

Using the QUIPS tool, five studies were judged to have a moderate overall risk of bias, and two were judged to have a high risk, while none met the criteria for low overall risk. Outcome measurement was generally robust, particularly in trial-derived cohorts with adjudicated endpoints. The principal concerns were the selective availability of central adiposity measurements, restricted or highly selected populations, reliance on a single baseline anthropometric assessment, and residual confounding by congestion, frailty, muscle mass, physical fitness, and disease-related weight loss. The high-risk judgments were driven primarily by the limited availability of WHtR measurements in one registry and concerns regarding participant selection and residual confounding in a small advanced HF cohort (Table *3*).

Study	Participation	Attrition	Adiposity measurement	Outcome measurement	Confounding	Analysis and reporting	Overall risk
Peikert et al., 2025; PARAGON-HF [10]	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Butt et al., 2025; DANISH [11]	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Butt et al., 2023; PARADIGM-HF [12]	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Chandramouli et al., 2019; ASIAN-HF [13]	High	Moderate	Moderate	Low	Moderate	Moderate	High
Streng et al., 2018; BIOSTAT-CHF [14]	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Tsujimoto and Kajio, 2017; TOPCAT [15]	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
Clark et al., 2011; UCLA advanced HF cohort [16]	High	Moderate	Moderate	Low	High	Moderate	High

TABLE 3: Risk of bias assessment of the included studies using the QUIPS tool.

ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; BIOSTAT-CHF, A Systems Biology Study to Tailored Treatment in Chronic Heart Failure; DANISH, Danish Study to Assess the Efficacy of Implantable Cardioverter-Defibrillators in Patients with Nonischemic Systolic Heart Failure on Mortality; HF, heart failure; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAGON-HF, Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin Receptor Blockers Global Outcomes in Heart Failure with Preserved Ejection Fraction; QUIPS, Quality In Prognosis Studies; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; UCLA, University of California, Los Angeles

Discussion

Principal Findings: A Measurement-Dependent Paradox

Across the included studies, the prognostic significance of obesity varied substantially according to how adiposity was defined. A higher BMI was often associated with neutral or improved survival in patients with HF, but this apparent advantage disappeared after comprehensive adjustment in the PARADIGM-HF analysis by Butt et al. [12] and was not supported by the long-term DANISH findings [11]. In contrast, WHtR, WHR, and WC generally identified greater clinical risk, with more consistent associations for HF hospitalization than for mortality [10-15]. The study by Clark et al. was an important exception, as both

higher BMI and larger WC were associated with better outcomes in advanced systolic HF [16]. Collectively, these findings suggest that the obesity paradox is neither a universally reproducible biological phenomenon nor an observation that can be dismissed entirely. Rather, its appearance appears to depend on the adiposity measure, clinical outcome, study population, and extent of adjustment for disease severity. The paradox may therefore be better understood as a discordance between body size, fat distribution, and disease-related wasting than as evidence that excess adiposity is intrinsically protective in established HF.

Why BMI May Produce an Apparent Survival Advantage

BMI is an accessible and reproducible measure of body size, but it cannot distinguish adipose tissue from skeletal muscle, bone mass, or extracellular fluid [6]. Consequently, a higher BMI in patients with HF may reflect preserved muscle mass, greater nutritional reserve, or fluid retention rather than a greater burden of metabolically harmful adipose tissue. Conversely, a low BMI may result from cardiac cachexia, sarcopenia, frailty, or advanced systemic illness, all of which are associated with an adverse prognosis [5]. These competing influences create substantial potential for reverse causation, particularly when body weight is measured after HF is established. Interpretation is further complicated by the inverse relationship between obesity and natriuretic peptide concentrations, as these biomarkers are powerful indicators of HF severity and can substantially alter risk estimates when incorporated into multivariable models [12]. Therefore, an association between higher BMI and survival should be interpreted as an association involving overall body size and underlying illness status rather than as direct evidence that excess adipose tissue confers a causal survival benefit.

Central Adiposity Exposes Risk Concealed by BMI

A central finding of this review is that measures of abdominal adiposity may identify clinically important risk that remains concealed when obesity is defined by BMI alone. In ASIAN-HF, Chandramouli et al. identified a high-risk “lean-fat” phenotype characterized by a low BMI but elevated WHtR, illustrating that patients may appear lean by conventional criteria while carrying substantial central adiposity [13]. Similarly, Peikert et al. reported central adiposity in 96% of PARAGON-HF participants, although only 49% met the BMI definition of obesity [10]. In PARADIGM-HF, Butt et al. found that nearly half of participants not classified as overweight or obese by BMI were outside the healthiest WHtR category [12]. These observations suggest that BMI may underestimate adiposity-related risk in patients with relatively low body weight but an unfavorable distribution of body fat. Nevertheless, central anthropometric measures are neither interchangeable nor direct measurements of visceral adiposity. WHtR adjusts waist size for stature, WHR reflects the relationship between abdominal and gluteofemoral dimensions, and WC does not account for overall body size [6,12,13]. These methodological differences may partly explain variation across studies and suggest that WHtR could provide a practical, although still imperfect, complement to BMI.

Survival and HF Morbidity Tell Different Stories

The prognostic consequences of central adiposity differed according to the outcome examined. In the PARADIGM-HF analysis by Butt et al. and the PARAGON-HF analysis by Peikert et al., greater central adiposity was more consistently associated with HF hospitalization than with adjusted mortality [10,12]. This pattern was not universal, as Tsujimoto and Kajio in TOPCAT and Butt et al. in DANISH also identified associations with mortality [11,15]. Nevertheless, abdominal adiposity may influence HF morbidity through adverse metabolic, inflammatory, and hemodynamic pathways that contribute to elevated filling pressures, congestion, functional limitation, and recurrent hospitalization [1-4]. Mortality may be less specific to this burden because it is also shaped by cachexia, frailty, noncardiovascular illness, competing risks, and tolerance of disease-modifying treatment [5]. HF hospitalization may therefore provide a more sensitive, although healthcare-dependent, indication of the clinical burden associated with central adiposity [4,5]. From this perspective, the obesity paradox represents a survival observation that can coexist with greater symptoms, poorer functional status, and more frequent hospitalization. An apparent mortality advantage should not be interpreted as evidence that obesity is clinically benign.

HF Phenotype, Etiology, and Disease Stage

The relationship between adiposity and prognosis varied across HF populations, but this heterogeneity could not be explained by ejection fraction alone. In HFpEF, Tsujimoto and Kajio found that abdominal obesity was associated with higher mortality in TOPCAT, whereas Peikert et al. observed a clearer relationship between WHtR and HF events than mortality in PARAGON-HF [10,15]. Among patients with HFrEF, the PARADIGM-HF analysis by Butt et al. showed that increasing WHtR was associated with HF hospitalization but not adjusted mortality [12]. Their subsequent DANISH analysis associated both higher BMI and WHtR with increased long-term mortality in nonischemic HFrEF [11]. In contrast, Clark et al. found that greater BMI and WC predicted better survival in advanced systolic HF [16]. These differences may reflect variation in disease stage, etiology, treatment era, population selection, and duration of follow-up. In advanced HF, lower body size and WC may increasingly reflect disease-related wasting rather than the absence of harmful adiposity. Disease stage and the competing prognostic influence of cachexia may therefore modify the observed association as strongly as EF phenotype itself.

Sex, Ethnicity, and Regional Context

Sex and regional context provide additional dimensions through which the prognostic significance of adiposity may vary. In BIOSTAT-CHF, Streng et al. found that higher WHR independently predicted mortality in women but not in men, with exploratory biomarker findings suggesting stronger inflammatory and metabolic associations among women [14]. This difference may reflect sex-specific patterns of visceral, subcutaneous, and gluteofemoral fat distribution, although the observational analysis cannot establish the underlying biological mechanism. In ASIAN-HF, Chandramouli et al. demonstrated that clinically important central adiposity and adverse outcomes could occur at BMI levels not conventionally classified as obese, highlighting the limitations of applying universal BMI thresholds across populations with differences in stature and body composition [13]. Although neither study detected significant effect modification by EF category, this should not be interpreted as evidence that the associations were identical, particularly because the relevant subgroups were limited in size [13,14]. A clinically informative HF phenotype may therefore need to incorporate sex, ethnicity, geographical context, and fat distribution alongside conventional classification by ejection fraction.

Causal Interpretation and Limitations of the Evidence

The findings should be interpreted as prognostic associations rather than evidence that adiposity causally affects survival. All included studies were observational analyses, even when their populations originated from randomized trials, because body size and fat distribution were not randomized exposures [10-16]. Reverse causation is particularly important in established HF, where progressive disease may cause involuntary weight loss, sarcopenia, and cardiac cachexia, thereby creating an apparent survival advantage among patients who retain a higher BMI [5]. Restricting analyses to individuals with established HF may also introduce index-event bias, a form of collider bias. A collider is a variable influenced by two or more factors; in this setting, HF development may be influenced by both obesity and other determinants of subsequent mortality. Selecting only patients who have developed HF can create an association between obesity and these other determinants, even if they were unrelated in the source population. For example, patients without obesity who develop HF may have a greater burden of other adverse factors, such as underlying myocardial disease, than patients whose obesity contributed to HF development. This imbalance could make obesity appear protective after HF diagnosis without adiposity itself providing a survival benefit. This represents a potential source of bias rather than a mechanism demonstrated by the included studies. Most studies relied on a single baseline anthropometric assessment and could not account for subsequent changes in weight, congestion, muscle mass, or fat distribution [10-16]. Trial populations may also underrepresent frail, multimorbid, or undertreated patients encountered in routine practice, while residual confounding by physical fitness, socioeconomic circumstances, nutritional status, and unintentional weight loss cannot be excluded. Adjustment for NT-proBNP introduces further complexity. Although NT-proBNP is an important marker of HF severity, obesity itself is associated with lower natriuretic peptide concentrations [12]. Its inclusion may improve control of prognostic imbalance while simultaneously adjusting for a factor partly influenced by the exposure under investigation. The disappearance of the BMI paradox after such adjustment is consistent with confounding but does not establish that the unadjusted association is entirely artificial.

Clinical Implications and Future Research

The present findings support a more comprehensive assessment of adiposity in HF rather than the abandonment of BMI. BMI remains inexpensive, reproducible, and clinically familiar, but its interpretation may be improved by adding a measure of central adiposity [6]. WC is simple to obtain, while WHtR accounts for differences in stature and may identify patients whose abdominal adiposity is underestimated by BMI [10,12,13]. At present, however, these measures should complement clinical risk characterization rather than independently determine treatment or justify intentional weight loss. The available evidence does not establish that reducing body weight improves survival across all HF phenotypes, nor does it distinguish the effects of reducing visceral adiposity from those of losing skeletal muscle. Future studies should combine repeated anthropometric assessments with direct measurements of visceral fat and lean mass using dual-energy X-ray absorptiometry, computed tomography, or magnetic resonance imaging. These studies should also account for congestion, sarcopenia, and unintentional weight change. Individual-participant data analyses should investigate effect modification by EF, sex, ethnicity, HF etiology, and disease stage, while trials of weight-management interventions should report functional capacity, quality of life, HF hospitalization, and mortality separately. Ultimately, the most clinically informative question is not whether obesity is uniformly protective or harmful, but which component of body size is being measured, in which HF phenotype, and in relation to which clinical outcome.

Conclusions

The apparent obesity paradox in HF is not a uniform biological phenomenon but a context-dependent association shaped by how adiposity is measured, which outcome is examined, and which patient phenotype is studied. BMI may suggest a survival advantage because it combines adipose tissue with muscle mass, skeletal structure, fluid status, and disease-related wasting, whereas central anthropometric measures more often identify increased risks of hospitalization, functional burden, and, in some populations, mortality.

These findings do not establish that intentional weight loss improves survival, nor do they justify abandoning BMI. Rather, they support interpreting BMI alongside waist-based measures, particularly WHtR, while accounting for HF phenotype, sex, ethnicity, and disease stage. The principal take-home message is that higher body weight should not be mistaken for biologically protective adiposity, and an apparent survival advantage should not obscure the clinical burden associated with central fat accumulation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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