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Dissecting the Obesity Paradox in Relation to Morbid Obesity and Heart Failure Outcomes

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Abstract

The study's primary goals were to: 1) Assess the prognostic influence of the obesity spectrum on heart failure patients or 2) How do outcomes differ between morbid and non-morbid obese patients in heart failure patients?3) Do HF patients who have morbid obesity also fall under the obesity paradox in heart failure? 4) Does both systolic and diastolic heart failure play a role in the obesity paradox? The evidence supporting the link between weight status and heart failure mortality (and survival) was thoroughly evaluated in this study. The PRISMA protocol was used when searching the PubMed/MEDLINE, Google Scholar, Scopus, and EMBASE databases. 33 studies were included in the 5132 papers that this search turned up once the exclusion criteria were applied. When comparing obese heart failure patients to their normal weight counterparts, all 33 studies found that their prognosis was better; however, extreme obesity (BMI > 40 kg/m2) was associated with a lower prognosis. The results of this review will have a big impact on how obese people with heart failure are asked to change their weight. Any such advice on losing weight, therefore, needs to be based on more proof about the mechanisms underlying the obesity paradox in heart failure and the

1. Introduction

An "obesity paradox"—a clinical phenomenon in which obeseindividuals have a lower risk of mortality (or better survival) within clinical subpopulations—has been demonstrated by longitudinal research(1). While obesity continues to be associated with a higher mortality risk in the general population, there are evidence that it may offer some protection against death for those who are already sick (2).

It has been shown that obesity paradoxically benefits a number of cardiovascular diseases, such as myocardial infarction, hypertension, patients who have had coronary bypass surgery, peripheral vascular disease, atrial fibrillation, aortic stenosis, patients with cardiac implants, and other Acute Coronary Syndromes (ACS)(3). Patients with chronic respiratory conditions, cancer, stroke, kidney illness, pneumonia, and chronic obstructive pulmonary disease (COPD) also experience this contradiction(4).

The obesity paradox has been specifically shown in heart failure patients, with consistent findings across a broad spectrum of clinical subpopulations based on age, gender, location, and the presence or absence of comorbidities, as well as across various body fatness measures, including waist circumference (WC), body mass index (BMI), triceps skinfold thickness (TSF), and waist-hip ratio (WHR)(5).

Why Does Heart Failure Occur? Overweight has long been linked to detrimental effects on left ventricular diastolic and systolic performance, as well as cardiac anatomy(6). Additionally, it has been established that being overweight increases the risk of coronary heart disease and hypertension, two main causes of heart failure(7). As a result, heart failure is becoming more and more common in overweight and obese people(8). Despite this abundant data, the prognosis for obese individuals with heart failure is better than that of their thin counterparts. There is still a lot of disagreement

over the mechanisms underlying this obesity paradox(9).

In many regions of the world, obesity has reached epidemic proportions, and since 1980, the prevalence of the disease has grown quickly worldwide(10). In 2008, 35% of persons worldwide who were 20 years of age or older were overweight (nearly 1.4 billion were obese; only 11% were obese). Approximately 300 million women and more than 200 million men were obese overall. Overweight and obesity kill more people in the countries where 65 percent of the world's population resides than underweight. The problem does not only affect adults; in 2011, approximately 40 million youngsters under the age of five suffered from overweight(11).

In the United States, obesity is a major issue. From the 1980s to the late 1990s, the prevalence of obesity in adults increased by 50%, and 70% of adult Americans were either overweight or obese(12). Developing nations are not exempt from the issue; they are currently facing a high obesity prevalence that is comparable to patterns seen in rich nations during the early stages of the obesity pandemic this phenomenon has been dubbed the "nutrition transition(13).

The literature has demonstrated a link between obesity and a higher risk of coronary artery disease, hypertension, heart failure, stroke, and cardiovascular disease. The study's primary goals wereAssessing the prognostic influence of obesity spectrum disorders on individuals suffering from heart failure or 2) How do outcomes differ between morbid and non-morbid obese patients in heart failure patients?3) Do HF patients who have morbid obesity also fall under the obesity paradox in heart failure? 4) Does both systolic and diastolic heart failure play a role in the obesity paradox?

2. METHODOLOGY

2.1. Literature Search

On March 17, 2024, online databases was searched for the publications from 2014 to 2024, using the following search strategy: PubMed: ((("obesity paradox"[MeSH Terms]) AND ("heart failure"[MeSH Terms] OR "heart failure"[All Fields])) AND ("obesity"[MeSH Terms] OR "obesity"[All Fields]) AND ("morbid obesity"[MeSH Terms] OR "morbid obesity"[All Fields])) NOT ("review" [Publication Type] OR "case reports" [Publication Type]) AND English[Language]; Web of Science: ("obesity paradox" AND "heart failure" AND obesity AND "morbid obesity") AND DOCUMENT TYPES: (Article) AND LANGUAGE: (English); Scopus: (TITLE-ABS-KEY("obesity paradox" AND "heart failure" AND obesity AND "morbid obesity") AND LANGUAGE (English)) AND DOCTYPE (ar) AND (LIMIT-TO (EXACTKEY WORD, "Human")). This search result in a total of 5132 articles.

2.2. Studies Selection

Inclusion Criteria

- Studies Published in peer-reviewed Journals from 2014 to 2024.
- Studies involving adult population diagnosed with heart failure and focusing on morbid obesity, defined as a Body Mass Index (BMI) ≥ 40 kg/m² or other accepted criteria for morbid obesity.
- Studies reporting relevant clinical outcomes related to heart failure and comparing outcomes in morbidly obese individuals with outcomes in non-obese or less severely obese individuals will be included.
- Studies which have to be the primary report and not a meta-analysis or systematic review.

Exclusion Criteria

- Studies utilizing composite outcomes, such as those in which the outcome variable is = device, transplant, or death.
- Studies focusing on population with congenital heart disease.
- Studies that do not report clinical outcomes related to heart failure or using non-standardized outcome measures.
- Studies that primarily focuses on obesity interventions rather than relationship of obesity and heart failure outcomes.

2.3. Article Screening and Data Extraction

The database searches provided a total of 5132 records. Of those, 1023 duplicate records, 562 records flagged as ineligible by automation technologies, and 784 records eliminated for other reasons were removed prior to screening. Following the removal of duplicates, 2763 records were examined. 1982 records out of 2763 were removed because 932 of them involved animal studies, 85 case series, 34 had to do with diagnosis, 433 relied on guidelines, 76 had to do with congenital heart disease alone, 90 with other diseases, 119 preclinical studies, 134 reviews, and 79 had to do with unrelated treatment records. After the remaining 781 were

filtered for retrieval, N = 492 reports that could not be retrieved were again searched for, and 289

reports were counted as remaining. Full-text publications with qualitative data were eliminated from the remaining 289 (n = 192). Records (n=64) without a follow-up duration. The study persisted after it was limited to 33 original research publications that we used for our meta-analysis.

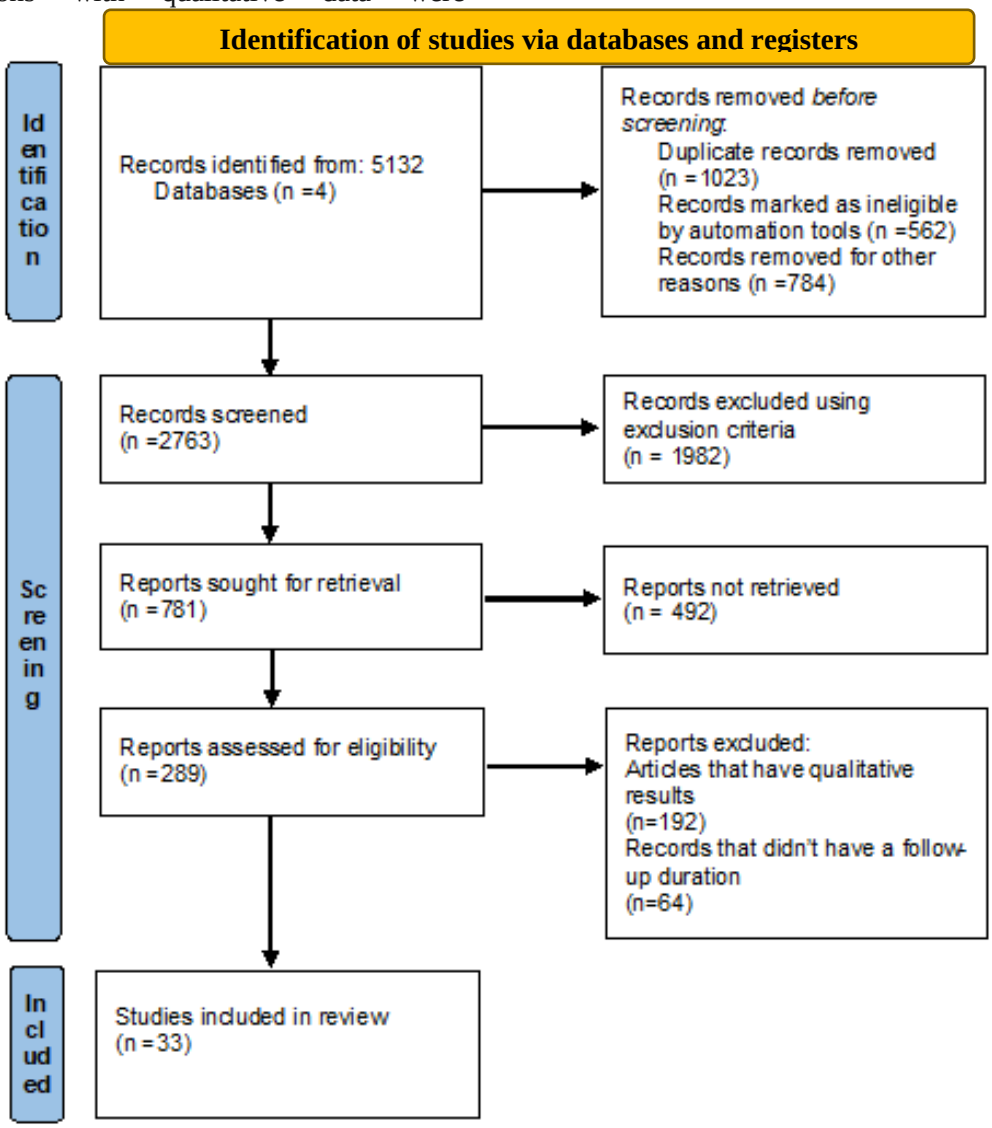

Figure 1. *A detailed flow chart diagram of study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.*

The full-text articles were scored using the Ottawa scale criteria using a standard form that was utilized for data extractions. As a methodological quality indicator, publications were ranked on a low, medium, or high scale based on a number of factors including reporting bias, performance, and selection. Preference for selection was scored using the descriptions of the inclusion and randomization criteria. Performance bias was assessed by considering descriptions of a control arm and allocation concealment. Differing scores were assigned to selective reporting, partial data management, industry sponsorship, and biased reporting. Reporting uniformity and eligibility restrictions were discussed in multiple teleconferences. Before making a decision, a third author (W T Z) looked into differences in the reviewers' scores.

3. Results

3.1. Obesity Paradox Dynamics

It is believed that obesity is a separate risk factor for the onset of chronic heart disease, which can ultimately result in heart failure. Despite the fact that obesity and elevated BMI increase a patient's risk of cardiovascular disease (CVD), new research has revealed an "obesity paradox": an inverse association between obesity and the prognosis of established CVD. Numerous

studies indicate that obese patients with heart failure do better than theirleaner counterparts(14).

Zamora et al. demonstrated that patients with HF who were overweight or obese had the best prognosis, while those with an underweight or normal BMI had the worst prognosis. When compared to individuals with lower BMI, those with higher BMI (overweight and obese patients) had lower crude and adjusted risks of all-cause mortality and death from heart failure in a cohort study included 2527 outpatients with HF who were classified using the BMI scale(15).

Higher BMI patients strangely had better 3-year survival rates, according to a retrospective analysis on 600 HF patients. A further investigation involving over 1100 patients with decompensated HF revealed a 10% reduction in mortality for every 5 units increase in BMI(1). Underweight and normal BMI patients exhibited higher mortality than overweight and obese participants in a randomized controlled trial involving 1700 symptomatic patients with HF and preserved or impaired systolic function. In comparison to individuals with normal BMI, those who were overweight or obese experienced lower rates of cardiovascular and all-cause mortality, according to an observational study involving 2,800 patients with HF(16).

Case-control research with 1200 participants showed that underweight patients with chronic heart failure had a higher risk of hospitalization and overall CVD death than did overweight persons(17).

Numerous studies have recently shown how cardiorespiratory fitness (CRF) levels affect the prognosis in heart failure(18-21). These results imply that the obesity paradox is mitigated by greater CRF levels, which dramatically alter the association between obesity and improved HF outcomes. It is noteworthy that determining elevated CRF values in patients with obesity can provide difficulties. However, given the same BMI group, patients with greater CRF levels should expect better outcomes **(Table 1).**

Table 1. *Some notable studies which has reported obesity paradox*

Author	Study Type	Patients	Year	NYHAclass	Comments
Zamora et al, 2016(15)	Cohort	2527	2016	II–IV	Underweight or low BMI in symptomatic heart failure patients with preserved or lowered LVEF is linked to higher mortality
Lopez-Delgado et al, 2019 (22)	observational study	2449	2015	I–IV	The lowest and highest BMI groups showed the highest rate of unfavorable outcomes in a U-shaped association.
Wang et al, 2021 (23)	Longitudinal	1500	2019	II–IV	Higher BMI, regardless of other clinical factors, is linked to a better prognosis
Patel et al, 2020(24)	Cohort	2000	2020	I–IV	Cachexia patients have a less favorable outcome.
Nguyen et al, 2021(25)	Observational study	3000	2021	I–III	For every 1% absolute decrease in body fat, there was a 13% increase in major clinical events. Additionally, event-free survival was independently predicted by BMI and total body fat.
Kim et al, 2019 (26)	Case-control	800	2022	II–IVI	10% decrease in risk-adjusted death for each unit increase in BMI
Tanaka et al, 2019 (27)	Cohort	1200	2018	I–IV	underlined further how obesity paradox exists even in people with extremely severe heart failure
Kaur et al, 2022 (28)	Observational study	2500	2023	I–IV	Patients with pre-morbid weights that are overweight or obese die from heart failure (HF) with a lower rate of death than patients with normal body mass index.
Nguyen et al, 2020(29)	Cohort	1500	2020	II–IV	Death rates were higher in patients with BMI<kg/m2, then in people with BMI 45 kg/m2.
Kim et al, 2021 (30)	Cross-sectional	700	2018	I–IV	Patients who were overweight or obese had decreased rates of CV and all-cause death.

3.2. Obesity paradox in HF

Studies have long demonstrated that obese people with heart failure had a reduced mortality rate, a finding known as the "obesity paradox." The obesity paradox in HF was initially reported by Horwich et al. According to another research, people who are overweight (BMI 25–29.9) or obese (BMI 30-34.9) have the best results, with the highest death rates occurring at the extremes of the range. The current meta-analysis shows a U-curve for CV mortality with the best results in

the overweight group and validates the counterintuitive drop in all-cause mortality with increasing fat(31).

Numerous factors have been proposed as causes of the obesity paradox, but the precise mechanisms are still unknown. Patients who are obese may show symptoms earlier in the course of the illness and have more functional impairment. Similarly, low BMI groups have been linked to myocardial cachexia, reduced use of ACE medications and beta-blockers, and older age. Reducing the obesity paradox has been demonstrated, albeit sporadically, when factors including age, left ventricular function, and cardiorespiratory reserve are taken into account(32).

The obesity paradox in HF has been criticized for being largely supported by data from post hoc analyses of clinical trials with different objectives, retrospective studies, or registry analysis, raising questions about statistical validity and potential selection bias-induced unmeasured confounding. Prognostic data may also be impacted by a lead time bias in the identification of heart failure (HF) in obese persons and a reduced specificity of HF diagnosis in obese patients(33). Compared to HF patients of normal weight, obese people with HF have distinct clinical and epidemiological characteristics, which may have an effect on mortality. Thus, variations in age, HF aetiology, LVEF, blood pressure, anemia, diabetes mellitus, and other factors may not be taken into consideration when comparing HF outcomes based on BMI. Renal function and nutritional status where differences are present when comparing obese versus non-obese individuals(34).

3.3. Impact of Obesity on Causes of HF

We examined eleven studies with 4019 patients, mean age 67±4 years, and follow-up of 4.8±3.4 years. For underweight, overweight, and obese people, the HRs for HF mortality (reference group: normal BMI) were 1.20 (95% CI 0.61 to 2.39, n=2 studies, p=0.6), 0.86 (95% CI 0.79 to 0.94); n=3 studies, p=0.001, and 0.97 (95% CI 0.72 to 1.33, n=4 studies, p=0.87), respectively(35, 36).

With no discernible heterogeneity, the CV mortality was lower in the overweight group than in the normal BMI population (I2 =57%; p = 0.10). The other groups under analysis did not exhibit a statistically significant difference in CV mortality. Significant heterogeneity (I2 ≥79%, p≤0.03) was noted in these groups. For the purpose of conducting a meta-analysis on CV mortality in individuals classified as severely obese, insufficient data were available(37).

In studies evaluating the effect of obesity on all-cause mortality in patients with heart failure, Table 1 presents the study design and baseline patient characteristics. With a progressive drop in mortality as BMI increased from underweight to severely obese categories, the underweight group had a considerably greater risk of all-cause mortality. For underweight, overweight, obese, and morbidly obese individuals in HF, the HRs for all-cause mortality were 1.40 (95% CI 1.25 to 1.57, n = 4 trials, p90%)(38, 39).

3.4. Quality of Study and Assessment Bias

Every study that was included had a sufficient sample size and was representative of the relevant population. In every study, the risk of detection and information biases was minimal.

4. Discussion

Obesity and heart failure have a complicated association, with multiple research projects indicating a contradictory relationship with death(40). The recent study emphasizes how the risk of HF rises with BMI in all categories. Obesity was linked to a counterintuitive drop in all-cause mortality in the presence of established HF, despite the increased incidence of HF in obesity. The association between BMI and CV mortality was shown to be U-shaped, with the overweight cohort having the lowest CV mortality. Notably, myocardial function and heart structural indicators improved in obese patients who underwent bariatric surgery to intentionally lose weight. It is unknown how weight loss therapies affect HF patients' clinical results(41).

The factors underlying heart failure in obesity are complex. Studies in both the laboratory and the clinic have shown that obesity raises cardiac output and filling pressure in the left heart. This, in turn, causes left ventricular hypertrophy and cardiac remodeling, which ultimately cause diastolic dysfunction. Subclinical myocardial dysfunction, characterized by lower systolic mitral annulus velocities and reduced longitudinal strain, is well-described in obesity investigations, despite the fact that overt systolic dysfunction is uncommon in the absence of additional CV illness(42). The clustering of incident CV risk factors that lead to the development of ischemic heart disease is also

associated with obesity, and this factor alone accounts for a sizable portion of the HF etiological load.Moreover, biventricular failure may result from unfavorable left ventricular loading, dilatation and hypertrophy, pulmonary hypertension, and the metabolic syndrome and obstructive sleep apnea that are commonly found in obese people(42).

Epicardial adipose tissue has been demonstrated to invade the underlying cardiac muscle and release profibrotic and proinflammatory cytokines, which results in cardiac remodeling, in addition to aberrant loading conditions. After ten years of extreme obesity, these alterations take many years to manifest, resulting in a sharp rise in the risk of heart failure(43).

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4.1. Clinical Implications

According to the current study, morbid obesity in obese people results in positive cardiac remodeling. Obesity is also linked to heart failure. Additionally, it shows that the overweight group has the lowest CV mortality in HF. Therefore, theoretical information about the possible predictive benefit of purposeful weight loss in obese individuals with HF is provided by this meta-analysis. When planning studies to assess the impact of purposeful weight loss in this type of group, this information can be quite important.

5. Conclusion

There is a link between obesity and a higher chance of heart failure. There is a counterintuitive drop in all-cause mortality observed despite the greater risk. Similar to this, there is a U-shaped curve for CV mortality, with the overweight group showing the greatest results. In obese people without heart failure, purposeful weight loss improves cardiac structure and function markers. There is an urgent need for sufficiently powered and appropriately planned trials to evaluate the impact of purposeful weight loss in obese patients with heart failure (HF), given the rising incidence of HF in the population.

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