Body mass index and mortality in heart failure: A meta-analysis

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Background In patients with chronic heart failure (CHF), previous studies have reported reduced mortality rates in patients with increased body mass index (BMI). The potentially protective effect of increased BMI in CHF has been termed the obesity paradox or reverse epidemiology. This meta-analysis was conducted to examine the relationship between increased BMI and mortality in patients with CHF.

Methods We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Scopus, and Web of Science to identify studies with contemporaneous control groups (cohort, case-control, or randomized controlled trials) that examined the effect of obesity on all-cause and cardiovascular mortality. Two reviewers independently assessed studies for inclusion and performed data extraction.

Results Nine observational studies met final inclusion criteria (total n = 28,209). Mean length of follow-up was 2.7 years. Compared to individuals without elevated BMI levels, both overweight (BMI \( \sim 25.0-29.9 \text{ kg/m}^2 \), RR 0.84, 95% CI 0.79-0.90) and obesity (BMI \( \sim \geq 30 \text{ kg/m}^2 \), RR 0.67, 95% CI 0.62-0.73) were associated with lower all-cause mortality. Overweight (RR 0.81, 95% CI 0.72-0.92) and obesity (RR 0.60, 95% CI 0.53-0.69) were also associated with lower cardiovascular mortality. In a risk-adjusted sensitivity analysis, both obesity (adjusted HR 0.88, 95% CI 0.83-0.93) and overweight (adjusted HR 0.93, 95% CI 0.89-0.97) remained protective against mortality.

Conclusions Overweight and obesity were associated with lower all-cause and cardiovascular mortality rates in patients with CHF and were not associated with increased mortality in any study. There is a need for prospective studies to elucidate mechanisms for this relationship. (Am Heart J 2008;156:13-22.)

Obesity is an independent risk factor for cardiovascular morbidity and mortality and doubles the risk of developing heart failure (HF).\(^1\) However, the prognostic significance of obesity in the setting of established HF is not clear. Observational data suggest a protective effect of obesity, which has been termed the obesity paradox or reverse epidemiology.\(^1\) In addition, although wasting (cachexia) appears to be a poor prognostic factor in HF,\(^3\) small observational studies have demonstrated improvements in left ventricular function and symptoms in patients with HF after intentional weight loss.\(^4,5\)

Although the updated 2008 Canadian Cardiovascular Society (CCS) Census Conference guidelines for the treatment and management of HF refer to the obesity paradox, they continue to recommend weight loss for obese patients with HF,\(^6\) even though this recommendation is not supported by evidence from clinical trials. To comprehensively synthesize the evidence pertaining to this issue, we undertook this systematic review to examine the association between increased BMI and mortality in patients with chronic HF (CHF).

Methods

Search strategy

Detailed search strategies were designed with the help of a research librarian to identify randomized control trials (RCTs) and observational studies examining the effect of overweight and obesity on total mortality in CHF. The Cochrane Central
Register of Controlled Trials (1990-June 2007), MEDLINE (1966-June 2007), EMBASE (1988-June 2007), Scopus (1966-June 2007) and Web of Science (1900-June 2007) were searched, reference lists of primary studies and review articles were scanned, and 3 experts in the field were contacted. No language or age restrictions were applied. Databases were searched using “heart failure” or “cardiac failure” and “obese$” or “body mass index” as key words, text words or MESH headings in combination with “mortality,” “survival,” “reverse epidemiology,” and “obesity paradox.”

Inclusion and exclusion criteria

Studies were included if they reported mortality in HF patients according to BMI category. The traditional World Health Organization (WHO)/National Institutes of Health (NIH) body mass index (BMI) classification scheme uses $18.5 \, \text{kg/m}^2$, $18.5-24.9 \, \text{kg/m}^2$, $25.0-29.9 \, \text{kg/m}^2$, and $\geq 30 \, \text{kg/m}^2$ to define underweight, normal BMI, overweight, and obesity, respectively. However, the lower cut point for normal is controversial and is sometimes cited as $22.5 \, \text{kg/m}^2$. We anticipated that not all studies would use the WHO/NIH BMI classification scheme; therefore, in order to avoid eliminating studies with important information, we considered BMI levels within 2 kg/m$^2$ of standard categories to be acceptable. In some instances, we collapsed the reported BMI categories into ones that most closely approximated standard WHO/NIH categories. Whenever possible, we used BMI levels of approximately $18.5$ to $24.9 \, \text{kg/m}^2$, defined as “normal” BMI, as the control group. If it was not possible to extract data for this BMI range for a given study, we used a BMI of $<25.0 \, \text{kg/m}^2$, defined as “non-elevated” BMI, as the control. Similarly, we defined “underweight” as BMI of approximately $<18.5 \, \text{kg/m}^2$; however, studies including patients with normal BMI levels of $<23.0 \, \text{kg/m}^2$ were defined as “underweight/low-normal.” Studies comparing obese vs nonobese (ie, normal plus overweight vs obese) were excluded unless outcomes in the normal BMI population alone could be ascertained.

Outcomes

The primary outcome was all-cause mortality, with a secondary outcome of cardiovascular mortality. When studies reported mortality at $\geq 2$ time intervals, the longest follow-up period was used for analysis.

Trial selection and data extraction

Two reviewers (A.O. and R.P.) independently reviewed the results of the literature search and independently performed data extraction. Cohen $\kappa$ coefficients were calculated to assess interobserver agreement for study inclusion and data extraction. Disagreements were resolved through consensus. Reviewers were not blinded to the authors’ names and institutions, journal of publication, or study results. When necessary, additional data were requested from the primary study authors. Study quality was assessed using the Ottawa-Newcastle Assessment Scale for observational studies. Maximum score on this scale is a total of 9. ‘Good’ was defined as a total score of 7 to 9; ‘fair,’ a total score of 4-6; and ‘poor,’ defined as a total score of $<4$.

Data analysis

**Primary analysis.** Unadjusted all-cause and cardiovascular mortality data were extracted and pooled to calculate relative risks (RR) and 95% CI with RevMan (version 4.2.8 for Windows; Oxford, The Cochrane Collaboration, 2003) using a random effects model. A priori, we suspected that some studies might group underweight and normal weight patients into one category. This may introduce bias, as being underweight or cachectic are known to be associated with a poorer prognosis in patients with HF and other chronic diseases. Therefore, we conducted a sensitivity analysis in which we repeated our primary analysis after excluding these studies.

**Secondary analyses.** As secondary analyses, we examined total mortality in patients with moderate to severe obesity (BMI $\geq 35 \, \text{kg/m}^2$) and underweight/low-normal-weight (BMI $<23.0 \, \text{kg/m}^2$), comparing these groups to patients with non-elevated and normal BMI levels, respectively. We also performed a baseline risk-adjusted analysis to determine if our main results were robust when quantitative pooling was limited to those studies in which we could calculate pooled adjusted all-cause mortality hazard ratios (HR). This was done because some studies have shown obesity to be associated with favourable characteristics such as younger age, higher left ventricular ejection fraction, and higher systolic blood pressure, and the presence of these favourable characteristics may potentially explain the obesity paradox.

Data pooling and heterogeneity

The generic inverse variance method was used to pool the data (log hazards and SE) using a random effects model. Heterogeneity was examined using the Higgins $I^2$ test.
Higgins $I^2$ values of 25%, 50%, and 75% can be interpreted as indicating low, moderate, and high heterogeneity.

**Results**

Of the 521 initial citations, 9 met our study eligibility criteria (Figure 1): 5 post hoc analyses of randomized controlled trial (RCT) study populations13,15-18 (all evaluated medication or device therapies in CHF and were not conducted to examine the issue of BMI and outcomes), 1 prospective cohort study in which the primary study question was the association between BMI and outcomes in CHF,11 and 3 retrospective analyses of cohort data collected for another research question10,12,19 (Table I) (total n = 28 209). Interobserver agreement was 1.0 for study inclusion and 0.8 for data extraction.

We found no RCTs that examined mortality outcomes after intentional weight loss in obese patients with HF. Six studies were excluded because the reported BMI was in an unusable format (either used BMI as a continuous variable or BMI categories with ranges that were too different from the WHO/NIH ranges); none found obesity or overweight to be a significant predictor of increased mortality.20-25 All studies were of high methodological quality (score 8-9/9) as assessed by the Ottawa-Newcastle criteria. Mean length of follow-up was 2.7 years.

**Primary analysis**

Compared to individuals without elevated BMI levels, both overweight (RR 0.84, 95% CI 0.79-0.90) (Figure 2) and obesity (RR 0.67, 95% CI 0.62-0.73) (Figure 3) were associated with lower all-cause mortality. Compared to patients with normal BMI levels, overweight (RR 0.81; 95% CI 0.72-0.92) and obesity (RR 0.60, 95% CI 0.53-0.69) were also associated with lower cardiovascular...
mortality, whereas underweight/low-normal-weight was associated with higher cardiovascular mortality (RR 1.20, 95% CI 1.04-1.38) (Figure 4). As 86% of patients in the Butler study\textsuperscript{18} had a left ventricular assist device as a bridge to transplant, we conducted a sensitivity analysis excluding this study yielding nearly identical results (data not shown).

Secondary analyses
Of the 9 included studies, 8 included additional data beyond that of obese and normal BMI groups: 3\textsuperscript{10,12,13} reported a moderate-severely obese category, and 4\textsuperscript{13,16,18} reported an underweight or underweight/low-normal-weight category. Compared to patients with nonelevated BMI, moderate-severe obesity was associated with a
lower risk of all-cause mortality (RR 0.62, 95% CI 0.55-0.69) (Figure 5), whereas underweight/low-normal BMI was associated with a significant increase in all-cause mortality (RR 1.25, 95% CI 1.19-1.31) (Figure 5), compared to patients with normal BMI.

Four studies were included in the combined risk-adjusted analysis10,13,15,17 (Figure 6). These studies used a Cox proportional hazards regression model to adjust for known baseline differences between study arms. All studies adjusted for age, sex, and New York Heart Association (NYHA) class/severity of CHF. Other covariates adjusted for included race,15 hypertension,15 cardiothoracic ratio,15 bilirubin,17 anaemia,17 C-reactive protein,17 brain natriuretic peptide,17 current angina15 ejection fraction,15,17,17 diabetes,15,17 serum creatinine,15,17 etiology of HF,15,17 presence of arrhythmia,15,17 duration of HF,15,17 current smoking,13 previous hospitalization for HF,15 medications,15,17 previous myocardial infarction,13,15 heart rate,13,15 blood pressure,13,15 clinical signs/symptoms of CHF,13,15,17 and study treatment.13,15,17 Compared to patients with nonelevated BMI, obesity and overweight were both associated with a lower risk of adjusted all-cause mortality (adjusted HR 0.88, 95% CI 0.83-0.93 and adjusted HR 0.93, 95% CI 0.89-0.97, respectively). Compared with normal BMI patients, underweight/low-normal-weight patients had a significantly higher risk-adjusted mortality (adjusted HR 1.11; 95% CI 1.01-1.23), whereas obesity significantly reduced the adjusted risk of death when compared with underweight/low-normal-weight CHF patients (adjusted HR 0.79, 95% CI 0.75-0.84). Neither the moderate-severe obesity category nor the cardiovascular mortality end point could be examined in the risk-adjusted analysis due to lack of data. Figure 7 displays a graphic summary of the differences between unadjusted and adjusted results. Although adjusting for baseline variables moved the HRs toward 1, the results of the risk-adjusted analysis remained statistically significant.

Sensitivity analysis
Exclusion of the 3 studies10-12 that included underweight individuals in their control groups did not affect the combined results for overweight vs normal BMI (HR 0.84, 95% CI 0.77-0.91) or obese vs normal BMI (HR 0.68, 95% CI 0.62-0.76) all-cause mortality comparisons.
Most studies had a mean length of follow-up between 1 and 3 years, but one study by Gustaffson et al\textsuperscript{16} had a length of follow-up of 6 years. A post hoc analysis excluding the Gustaffson paper revealed no appreciable change in the associations we found for all-cause mortality: overweight vs nonelevated BMI HR 0.83 (95% CI 0.79-0.97) and obese vs nonelevated BMI HR 0.66 (95% CI 0.59-0.73).

**Discussion**

Obese and overweight individuals with CHF exhibited lower unadjusted mortality rates compared to CHF patients with nonelevated BMI levels. Furthermore, even after adjustment for baseline risk, obesity and overweight were still associated with lower risk of mortality, and none of the identified studies reported that obesity or overweight were associated with increased mortality. In addition, the 5 studies\textsuperscript{20-24} that analyzed BMI as a continuous variable (excluded from our review) found a significant inverse relationship between increasing BMI and mortality in multivariable analyses. Although our results demonstrate an inverse relationship between BMI and survival, we could not determine if such a relationship is maintained at extreme BMI (ie, $>50$ kg/m$^2$) levels. To our knowledge, this is the first systematic review on this topic.

Our findings are consistent with evidence in other chronic disease populations demonstrating improved mortality with higher BMI levels.\textsuperscript{26} In survivors of myocardial infarction, overweight and obese patients are at lower risk for recurrent events compared with patients of normal BMI.\textsuperscript{27} A recent meta-analysis examining the effect of BMI on mortality on patients post coronary revascularization\textsuperscript{28} showed that obese patients have similar or lower short- and long-term mortality rates compared to nonelevated BMI patients. Similarly, a low baseline fat percentage and reduction in fat mass over time in are independently associated with higher mortality in chronic hemodialysis patients.\textsuperscript{29} Although the specific mechanisms may differ, the identification of an obesity paradox in such diverse clinical situations suggests a commonality that merits further investigation.

The finding of extremely high risk of death in the underweight group (likely representing patients with nonintentional weight loss) is also consistent with previous studies.\textsuperscript{3,30} The higher mortality among these patients is likely due to the presence of low protein and energy intake, malnutrition, and even cachexia that can be observed in advanced HF. Heart transplant recipients who are underweight also have a significantly higher mortality.\textsuperscript{31} These observations support the hypothesis that restoration of normal hemodynamics is not sufficient to improve prognosis of malnourished and cachectic CHF patients.

Several potential explanations for the obesity paradox exist. First, selection bias may be a contributing factor. Patients with obesity may be presenting earlier, with
less severe disease, or may have comorbidities more aggressively recognized and treated. Alternatively, only the “healthiest” of obese patients may be surviving long enough to develop HF. In addition, potential confounders such as smoking (which decreases body weight but increases mortality), unrecognized systemic illness, or unintentional weight loss may potentially account for the paradoxical results. To explore the possibility of selection bias, we determined the relative frequencies of reported baseline risk factors known to affect survival outcomes in patients with CHF (Table II). Patients with obesity were younger, had fewer current smokers and lower incidence of previous myocardial infarction, but a higher prevalence of comorbidities such as hypertension and diabetes mellitus. Other comorbidities such as duration of HF, chronic obstructive pulmonary disease and NYHA class III/IV were similar in patients with obesity compared to those with normal BMI. Use of angiotensin-converting enzyme (ACE) inhibitors and digoxin and ischemic HF were also
similar between groups, whereas ejection fraction, systolic blood pressure, and use of β-blockers were higher in the obese group. Although this descriptive analysis is not comprehensive due to the small number of studies included and because other confounders may be affecting survival, these data show that there are both favorable and unfavorable risk factors present in obese patients with CHF. Furthermore, our risk-adjusted analysis suggests a protective effect of overweight and obesity in HF.

It is also possible that excess body weight truly confers a protective effect on HF mortality. Chronic HF is a catabolic state, and the development of wasting, characterized by loss of muscle, bone, and fat, is a marker of more severe disease. Studies have demonstrated that many patients with advanced HF are malnourished, with an energy and protein intake that is inadequate to meet their energy requirements. It has been suggested that moderately obese individuals with CHF may have a higher metabolic reserve and may tolerate the metabolic stresses better than lean individuals with CHF.

Altered cytokine and neuroendocrine profiles of obese patients play a role in modulating HF progression. Tumor necrosis factor α (TNF-α) is elevated in CHF and may contribute to cardiac injury and muscle wasting through its proapoptotic and negative inotropic effects. Adipose tissue produces soluble TNF-α receptors and may play a cardioprotective role in obese patients by neutralizing the biologic effects of TNF-α. Higher B-type natriuretic peptide (BNP) and N-terminal proBNP levels are also associated with increased severity of HF and poorer outcomes. Compared with normal BMI counterparts, overweight and obese patients with acute and chronic HF have lower levels of circulating BNP and NT-proBNP. Moreover, while increased sympathetic and renin-angiotensin activity are negative prognostic factors in HF, a recent study reported attenuated sympathetic nervous system and renin-angiotensin responses to exercise in obese versus lean subjects. Alternatively, as obese patients have higher systolic blood pressure, this may permit more aggressive upward titration (or alteration of the pharmacokinetics) of disease-modifying medications including ACE inhibitors and β-blockers; previous reports have suggested that higher blood pressure confers better prognosis in patients with CHF. Finally, the interaction between obesity and higher serum lipid levels may also potentially explain the obesity paradox. There is a significant positive correlation between higher cholesterol levels and improved survival in HF. The endotoxin-lipoprotein hypothesis states that bacterial lipopolysaccharides are strong stimulators for the release of inflammatory cytokines. High circulating serum lipoproteins have the ability to bind and detoxify lipopolysaccharides, thereby potentially playing a beneficial role in HF.

Several limitations of this meta-analysis should be noted. First, not all studies reported body weight using the standard WHO/NIH BMI classification system. In particular, 3 studies grouped normal and underweight individuals together. Because underweight, malnutrition, and cachexia are associated with increased mortality in CHF, this may have resulted in an apparent relative benefit of overweight and obesity. It is notable, however, that repeating our analysis after excluding these studies demonstrated nearly identical results. Secondly, as with any systematic review, bias may occur due to selective study publication or if important studies were missed. We searched multiple databases and contacted content experts in an effort to minimize such bias. Third, although BMI is the most commonly used epidemiologic measure of obesity, it is imperfect and does not directly distinguish between adipose and lean tissue or central and peripheral

| Table II. Baseline characteristics of study population according to BMI |
|-----------------------------|-----------------------------|-----------------------------|
| **Underweight/low-normal** | **Normal** | **Overweight** | **Obese** |
| Age (y), studies = 6, n = 21821 | 69.2 | 66.5 | 62.3 |
| Women (%), studies = 6, n = 25250 | 41.5 | 22.5 | 30.6 |
| Duration of HF (mo), studies = 3, n = 19899 | 32.7 | 28.6 | 29.1 |
| NYHA class III or IV (%), studies = 4, n = 24909 | 54.3 | 42.9 | 47.7 |
| Ischemic heart disease (%), studies = 5, n = 25434 | 61.1 | 64.0 | 58.1 |
| Ejection fraction (%), studies = 2, n = 8152 | Not reported | 31.9 | 34.1 |
| COPD (%), studies = 1, n = 4700 | 35 | 21 | 24 |
| Diabetes (%), studies = 5, n = 25131 | 16.9 | 25.2 | 38.9 |
| Previous MI (%), studies = 2, n = 15199 | 53.5 | 62.6 | 50.3 |
| Hypertension (%), studies = 4, n = 20778 | 34.8 | 42.1 | 56.5 |
| Systolic blood pressure (mm Hg), studies = 3, n = 15724 | 126 | 129 | 133 |
| Current smoker (%), studies = 3, n = 12524 | 25.3 | 20.9 | 18.0 |
| β-Blockers (%), studies = 3, n = 17282 | 33.9 | 39.6 | 45.2 |
| Systolic blood pressure (mm Hg), studies = 3, n = 15724 | 126 | 129 | 133 |
| Diuretics (%), studies = 5, n = 25434 | 60.4 | 70.3 | 68.4 |
| ACE inhibitors (%), studies = 4, n = 24909 | 60.4 | 71.8 | 68.4 |
| Baseline characteristics of study population according to BMI | 69.1 | 74.1 | 77.7 |

COPD, Chronic obstructive pulmonary disease; MI, myocardial infarction.
adiposity. We were unable to determine if the apparent protective effects of obesity are due to increased fat or lean body mass. However, misclassification of body composition using BMI would be expected to bias our relative risks toward the null, thereby potentially masking a nonneutral association between BMI and mortality. Fourth, moderate statistical heterogeneity was found when quantitative pooling was performed for some outcomes. Potential explanations for heterogeneity include between-study differences in temporal and local practice patterns, patient selection, and concomitant therapies. We used a random effects model in an effort to incorporate heterogeneity between trials in our analysis but recognize that this does not eliminate the fact that heterogeneity was present. Finally, the observational nature of the studies identified provides associative, not causal, evidence and mandates caution when interpreting the results.

Conclusions

This systematic review suggests that obese and overweight individuals with CHF are at lower risk for death than CHF patients with normal body weight and we believe there is a need for prospective studies to confirm these findings and elucidate potential mechanisms. Such studies should examine body composition and fat distribution in relation to outcomes in HF and account for intentionality of weight loss and temporal weight change. Studies should also include additional outcomes such as functional status and health-related quality of life to fully explore the relationship between body weight and outcomes in this patient population. Thus, a great deal of further research is required to optimize nutritional/metabolic support for patients with CHF, with the ultimate goal of favorably impacting morbidity and mortality in this patient population.

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