The Obesity Paradox

Body Mass Index and Outcomes in Patients With Heart Failure

Jeptha P. Curtis, MD; Jared G. Selter, MD; Yongfei Wang, MS; Saif S. Rathore, MPH; Ion S. Jovin, MD; Farid Jadbabaie, MD; Mikhail Kosiborod, MD; Edward L. Portnay, MD; Seth I. Sokol, MD; Feras Bader, MD; Harlan M. Krumholz, MD

Background: In the general population, obesity is associated with increased risk of adverse outcomes. However, studies of patients with chronic disease suggest that overweight and obese patients may paradoxically have better outcomes than lean patients. We sought to examine the association of body mass index (BMI) and outcomes in stable outpatients with heart failure (HF).

Methods: We analyzed data from 7767 patients with stable HF enrolled in the Digitalis Investigation Group trial. Patients were categorized using baseline BMI (calculated as weight in kilograms divided by the square of height in meters) as underweight (BMI <18.5), healthy weight (BMI, 18.5-24.9, overweight (BMI, 25.0-29.9), and obese (BMI ≥30.0). Risks associated with BMI groups were evaluated using multivariable Cox proportional hazards models over a mean follow-up of 37 months.

Results: Crude all-cause mortality rates decreased in a near linear fashion across successively higher BMI groups, from 45.0% in the underweight group to 28.4% in the obese group (*P* for trend <.001). After multivariable adjustment, overweight and obese patients were at lower risk for death (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.80-0.96, and HR, 0.81; 95% CI, 0.72-0.92, respectively), compared with patients at a healthy weight (referent). In contrast, underweight patients with stable HF were at increased risk for death (HR 1.21; 95% CI, 0.95-1.53).

Conclusions: In a cohort of outpatients with established HF, higher BMIs were associated with lower mortality risks; overweight and obese patients had lower risk of death compared with those at a healthy weight. Understanding the mechanisms and impact of the "obesity paradox" in patients with HF is necessary before recommendations are made concerning weight and weight control in this population.

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Author Affiliations: Department of Medicine, Section of Cardiovascular Medicine (Drs Curtis, Selter, Jovin, Jadbabaie, Kosiborod, Portnay, Sokol, Bader, and Krumholz and Messrs Wang and Rathore); Department of Epidemiology and Public Health, Section of Health Policy and Administration, The Robert Wood Johnson Clinical Scholars Program, Yale University School of Medicine, and The Center for Outcomes Research and Evaluation (Dr Krumholz), Yale-New Haven Hospital, New Haven, Conn.
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In the general population, excess weight is associated with a significantly increased risk of coronary artery disease, heart failure (HF), and death.[1-5] National guidelines strongly endorse weight loss for patients who are overweight or obese, and a major goal of *Healthy People 2010* is to reduce the proportion of obese adults in the United States from 23% to 15%.[6,7] These initiatives, however, do not distinguish between healthy individuals and those with chronic diseases such as HF and atherosclerotic coronary artery disease. Making the distinction between these populations may be important as there is evidence that among patients with chronic disease excess weight is paradoxically associated with a decreased risk of adverse outcomes.[8-12]

Previous studies of patients with established HF suggest that individuals with higher body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) are at decreased risk for death and hospitalization compared with patients with a "healthy" BMI.[13-18] These studies, however, may not be generalizable because they are small,[14-18] conducted at single centers,[13-18] and limited to patients with severe HF and left ventricular dysfunction.[13-15] Thus, it is unclear if these findings are applicable to the larger population of outpatients with stable HF or preserved systolic function.

Current guidelines for the management of HF provide conflicting directions regarding the prognosis and management of BMI.[19-21] American College of Cardiology/American Heart Association (ACC/AHA)

Table 1. Baseline Characteristics of a Cohort of Patients With Stable HF According to BMI*

Characteristic	Total (N = 7767)	Underweight: BMI <18.5† (n = 160)	Healthy Weight: BMI, 18.5-24.9† (n = 2583)	Overweight: BMI, 25.0-29.9† (n = 3084)	Obese: BMI ≥30.0† (n = 1940)	*P* for Difference	*P* for Trend
Age, mean ± SD, y	63.9 ± 10.9	69.2 ± 11.6	65.9 ± 11.0	64.1 ± 9.9	60.5 ± 11.2	<.001	<.001
Sex, female	24.6	50.0	27.0	19.8	26.9	<.001	.001
Race, black	14.4	13.8	14.4	12.2	17.9	<.001	.005
Disease history							
Myocardial infarction	63.2	52.5	62.3	68.6	56.5	<.001	.04
Diabetes mellitus	28.4	18.1	19.7	28.6	40.5	<.001	<.001
Hypertension	47.1	40.0	39.5	46.1	59.3	<.001	<.001
Signs/symptoms at enrollment							
Rales	16.7	25.0	18.6	14.9	16.3	<.001	.002
Elevated JVP	13.1	15.0	14.5	11.9	13.0	.04	.07
Peripheral edema	20.9	11.3	14.7	18.5	33.5	<.001	<.001
Dyspnea at rest/orthopnea	21.8	26.9	20.8	19.7	26.1	<.001	.002
Dyspnea on exertion	75.2	76.3	73.4	74.2	79.3	<.001	<.001
Limitation of activity	75.8	81.9	75.0	74.7	78.0	.01	.15
S3 Heart sound	23.7	28.8	27.6	22.3	20.4	<.001	<.001
Pulmonary congestion	14.2	21.9	15.4	13.0	14.0	.002	.02
Angina	27.2	21.3	25.2	28.3	28.4	.01	.003
Heart rate, bpm	78.4 ± 12.6	80.7 ± 12.8	78.3 ± 12.6	77.5 ± 12.6	79.7 ± 12.4	<.001	.02
Systolic BP, mm HG	127.5 ± 20.4	123.9 ± 22.5	124.3 ± 20.4	127.1 ± 19.9	131.7 ± 20.4	<.001	<.001
HF duration	29.7 ± 36.4	27.8 ± 36.5	29.9 ± 37.5	30.2 ± 36.4	28.9 ± 35.0	.56	.45
NYHA functional class							
Class I	14.3	10.6	14.2	14.9	13.5	<.001	
Class II	54.5	37.5	53.0	57.1	53.7		
Class III/IV	31.3	51.9	32.8	28.0	32.8		
Ischemic etiology	68.9	61.3	67.9	73.8	63.2	<.001	.07
Laboratory findings							
LVEF	31.9 ± 12.5	30.8 ± 13.1	30.6 ± 12.0	31.9 ± 12.2	33.9 ± 13.2	<.001	<.001
Cardiothoracic ratio	53.1 ± 7.4	54.6 ± 9.0	53.2 ± 7.3	52.7 ± 7.2	53.7 ± 7.7	<.001	.03
Creatinine, mg/dL (mmol/L)	1.28 ± 0.4 (113.15 ± 35.36)	1.2 ± 0.5 (106.08 ± 44.20)	1.3 ± 0.4 (114.92 ± 35.36)	1.3 ± 0.4 (114.92 ± 35.36)	1.2 ± 0.3 (106.08 ± 26.52)	<.001	.01
Potassium, mEq/L	4.4 ± 5.2	4.4 ± 0.4	4.3 ± 0.5	4.3 ± 0.5	4.6 ± 10.4	.43	.36
Medication on admission							
Prior use of digoxin	43.3	53.1	50.2	41.6	35.9	<.001	<.001
Potassium-sparing diuretics	7.6	11.3	7.7	7.4	7.6	.36	.42
All other diuretics	78.0	82.5	77.3	76.5	81.0	.001	.03
ACE inhibitor	93.4	95.6	93.1	93.2	93.9	.48	.63
Nitrates	42.2	41.9	40.7	42.7	43.5	.28	.07
Hydralazine	2.0	2.5	2.2	1.8	2.1	.56	.58
Other vasodilators	1.2	0.6	1.4	0.9	1.5	.21	.54
Randomized to digoxin	49.9	44.4	52.8	48.5	48.8	.003	.02

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; bpm, beats per minute; HF, heart failure; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

*Values are given as mean ± SD or as percentage of patients.

†BMI was calculated as weight in kilograms divided by the square of height in meters.

HF clinical practice guidelines for adults do not directly address the issue of BMI. However, ACC/AHA guidelines for the secondary prevention of coronary artery disease, a condition that is highly represented among patients with HF, recommend weight loss for all overweight and obese patients.[19] In addition, the European Society of Cardiology recommends weight loss for overweight and obese patients with HF even though this recommendation is not supported by data from clinical trials.[21]

Given the uncertain role of BMI in the clinical management of patients with HF, we examined the relationship of weight and outcomes among outpatients with stable disease enrolled in the Digitalis Investigation Group (DIG) trial. Specifically, we examined the association of accepted BMI categories with hospitalization and mortality.

METHODS

PATIENT POPULATION

We obtained a public-use copy of the DIG trial database by submitting a written request to the National Heart, Lung, and Blood Institute. None of the authors were involved in the conduct of the DIG trial.

In the DIG trial, 7788 patients with stable HF in sinus rhythm were randomized to digoxin or placebo at 302 centers in the United States and Canada between February 1991 and August 1993.[22,23] Those with a left ventricular ejection fraction (LVEF) of 45% or less were were enrolled in the main trial (n=6800) and those with an LVEF greater than 45% were enrolled in a parallel ancillary trial (n=988). Left ventricular ejection frac-

tion was measured in all patients prior to enrollment by equilibrium radionuclide angiography (n=5074 [65.2%]), left ventricular contrast angiography (n=428 [5.5%]), or 2-dimensional echocardiography (n=2296 [29.4%]). Because eligibility criteria were otherwise identical, we combined data from the main and ancillary trials. A total of 21 patients (0.3%) were excluded from the analysis because their BMI was unavailable or the recorded value exceeded our predefined range of plausible values (10-50).

BMI CATEGORIES AND OUTCOMES

We grouped patients according to BMI at enrollment into the 4 categories endorsed by the National Institutes of Health: underweight (<18.5), healthy weight (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0).[24]

The primary end point of the DIG trial was all-cause death within 37 months of randomization (range, 24-48 months). We also examined 3 prespecified secondary outcomes from the DIG trial (death due to cardiovascular causes, death due to worsening HF, and hospitalization for worsening HF) as well as all-cause hospitalization.[22] Local investigators assigned cause of death and hospitalization based on medical chart review and interview of relatives.[22]

STATISTICAL ANALYSIS

We first compared baseline characteristics of patients in each BMI group using χ^2 and Cochran-Armitage trend analyses for categorical variables and the Wilcoxon test for trend for continuous variables. To evaluate the crude association of BMI and patient outcomes, we compared crude rates of all-cause death, death due to cardiovascular causes, death due to worsening HF, all-cause hospitalization, and hospitalization due to worsening HF across BMI groups using global and test for trend χ^2 analyses. Kaplan-Meier survival curves were plotted for each BMI group and compared using a log-rank test.

Multivariable Cox proportional hazards analysis was conducted to determine the independent association of BMI and all-cause mortality. Variables were entered into the model on the basis of statistical significance and clinical relevance. Patient characteristics included age; sex; LVEF; New York Heart Association class; history of myocardial infarction; dyspnea; duration of HF symptoms; diabetes; hypertension; HF etiology; blood pressure; heart rate; rales; elevated jugular venous pressure; peripheral edema; presence of an S3 heart sound; radiologic evidence of pulmonary congestion; prior use of digoxin, potassium-sparing diuretics, all other diuretics, angiotensin-converting enzyme inhibitors, nitrates, and/or hydralazine; randomization to digoxin; and creatinine levels. Because the relationship of LVEF and outcomes was not linear, LVEF was entered into the analysis as a continuous variable, with all measures of LVEF greater than 45% set to 45%. Multivariable analyses were repeated for the separate end points of cardiovascular death, death due to worsening HF, all-cause hospitalization, and hospitalization due to worsening HF.

We conducted additional analyses to examine the robustness of the association of BMI and patient outcomes. First, to further define the association of BMI and outcomes, analyses were repeated modeling BMI as a single continuous variable using fractional polynomial logistic regression.[25] Second, we stratified crude outcomes by LVEF, sex, HF etiology, and duration of HF symptoms to confirm that the association of BMI and outcomes was comparable across these subgroups. Statistical analyses were performed using software packages SAS, version 8.02 (SAS Institute Inc, Cary, NC), and Stata, version 7.0 (Stata Corp, College Station, TX).

RESULTS

STUDY SAMPLE

More than half of the patients in the DIG trial were overweight or obese (median BMI, 26.6; interquartile range, 23.7-30.0). Patients with lower BMIs were, on average, older, and a higher proportion were women. Higher proportions of patients in lower BMI groups had signs and symptoms of HF, including rales, elevated jugular venous pressure, limitation of activity, S3 gallop, and radiological evidence of pulmonary congestion, but had a lower rate of peripheral edema compared with patients in higher BMI groups. In addition, patients in lower BMI groups had lower systolic and diastolic blood pressure, and lower proportions of patients had diabetes, hypertension, or a history of prior myocardial infarction compared with patients in higher BMI groups (**Table 1**).

BMI AND OUTCOMES

Over a mean follow-up of 37 months, there were 2597 total deaths (33.4%). Kaplan-Meier survival curves differed by BMI group (**Figure 1**). Examining BMI as a continuous variable demonstrated a near linear decrease in all-cause death in patients with higher BMI, with evidence of either a plateau or perhaps increased risk observed among patients with a BMI greater than 35 (**Figure 2**). A smaller proportion of overweight and obese patients died during follow-up compared with underweight or healthy-weight patients. Patients in higher BMI groups were at lower risk of all-cause mortality (overweight, 32.4%; obese, 28.4%; *P* for trend <.001), cardiovascular death (overweight, 27.0%; obese, 24.4%; *P* for trend <.001), and death due to worsening HF (overweight, 10.3%; obese, 9.5%; *P* for trend <.001) compared with patients at a healthy weight. Although underweight patients had a higher all-cause mortality than patients at a healthy weight (45.0% vs 37.8%; P=.07), underweight patients had similar rates of cardiovascular mortality (28.1% vs 32.5%; *P*=.25) and death due to worsening HF (13.8% vs 14.6%; *P*=.76) (**Table 2**).

In multivariable analysis, overweight and obese patients remained at lower risk of all-cause mortality (overweight hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.80-0.96; obese HR, 0.81; 95% CI, 0.72-0.92) compared with patients at a healthy weight (**Table 3**). Findings were similar for death due to cardiovascular causes and death due to worsening HF. In contrast, underweight patients had a higher risk of all-cause mortality (HR, 1.21; 95% CI, 0.95-1.53) compared with patients at a healthy weight, although this did not reach statistical significance. Risks of death and death due to worsening HF were comparable in underweight and healthy-weight patients.

BMI AND HOSPITALIZATION

Rates of all-cause hospitalization and hospitalization due to worsening HF were similar across BMI groups (*P*=.25 for all-cause hospitalization and *P*=.18 for hospitaliza-

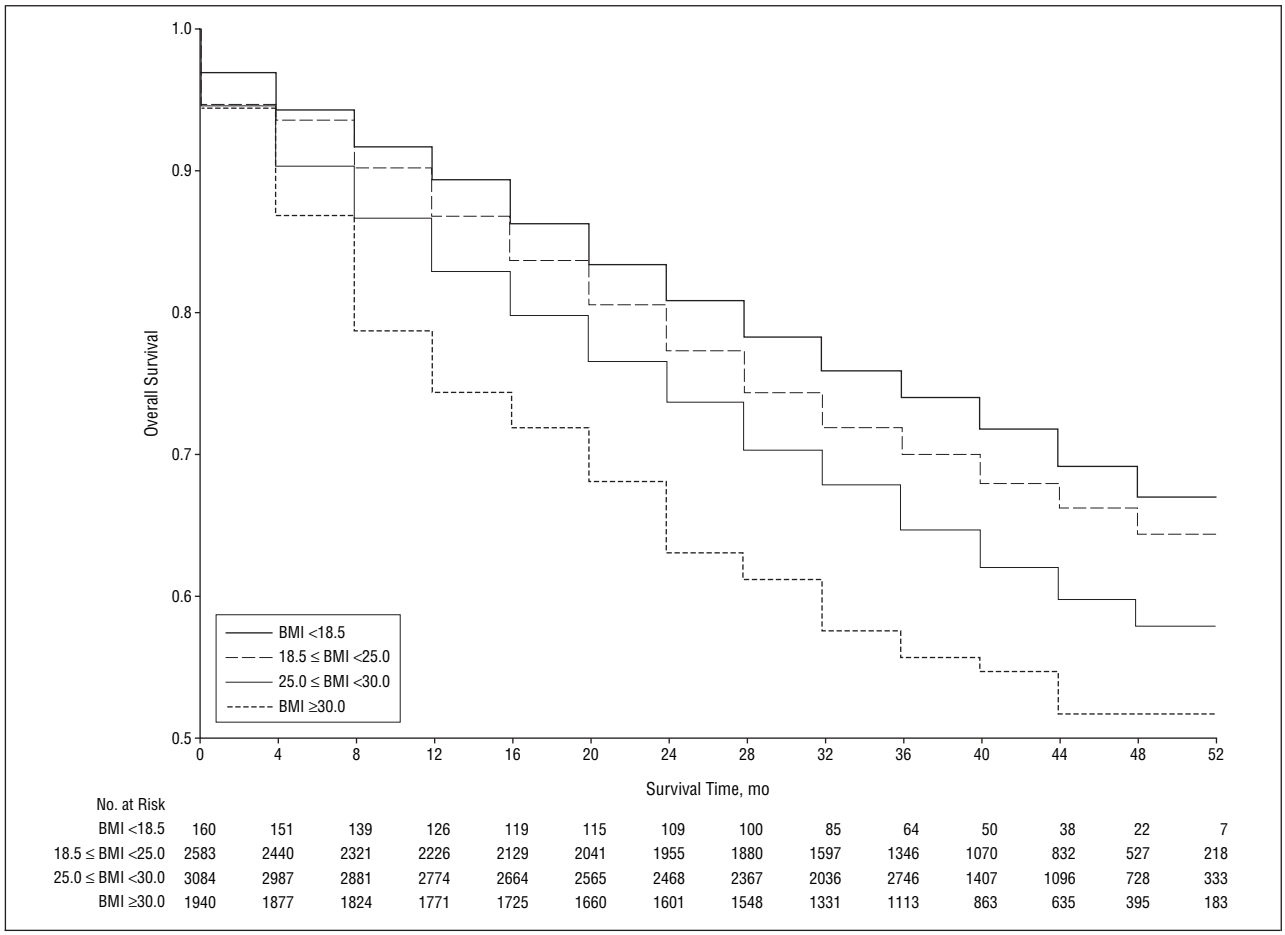

Figure 1. Kaplan-Meier survival curves stratified by body mass index (BMI) groups and showing numbers of patients at risk according to month since study initiation. Body mass index is calculated as weight in kilograms divided by the square of height in meters.

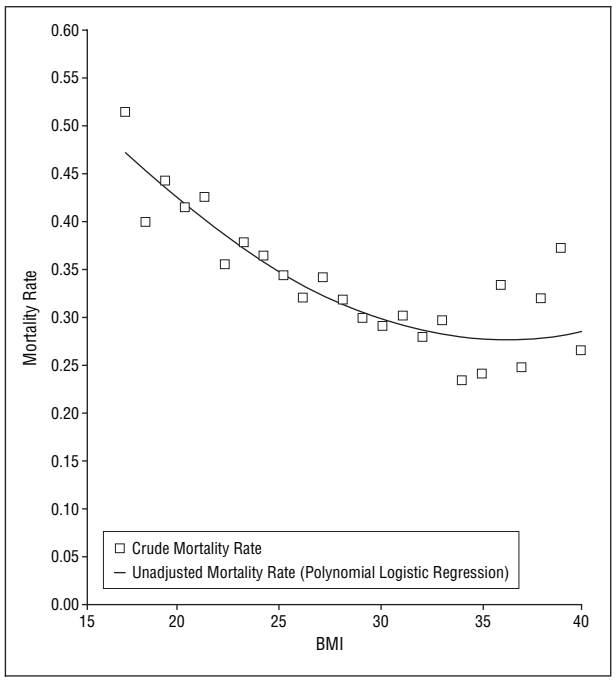

Figure 2. Association of body mass index (BMI) as a continuous variable and unadjusted all-cause mortality using polynomial logistic regression. Each point represents the mortality rate associated with a BMI integer.

tion due to worsening HF) (Table 2). Findings were similar after multivariable adjustment (Table 3).

The association of BMI with the outcomes of death and hospitalization was similar when analyses were repeated stratifying by LVEF, HF etiology, sex, and duration of HF symptoms (**Table 4**).

COMMENT

In contrast to observations from the general population, we found that overweight and obese patients with HF have lower crude and adjusted risks of all-cause mortality and death owing to worsening HF compared with patients who are at a healthy weight. Our findings confirm the existence of an "obesity paradox" among patients with established HF. Given the higher survival rates observed among patients with higher BMI in our cohort, recommendations for weight management derived from the general population may not be appropriate for patients with HF.

Our analysis of a large multicenter study of outpatients with stable HF confirms the results of smaller, less generalizable studies.[13-16] Taken together, the current literature provides a clear and consistent finding of an association of higher BMI with lower mortality in patients with HF.

Table 2. Crude Outcomes for a Cohort of Patients With Stable Heart Failure According to Body Mass Index (BMI)*

No. of Patients	Total (N = 7767)	Underweight: BMI <18.5† (n = 160)	Healthy Weight: BMI, 18.5-24.9† (n = 2583)	Overweight: BMI, 25.0-29.9† (n = 3084)	Obese: BMI ≥30.0† (n = 1940)	*P* for Difference	*P* for Trend
Cause of death							
All-cause	2597 (33.4)	72 (45.0)	977 (37.8)	998 (32.4)	550 (28.4)	<.001	<.001
Worsening heart failure	903 (11.6)	22 (13.8)	378 (14.6)	319 (10.3)	184 (9.5)	<.001	<.001
Cardiovascular	2191 (28.2)	45 (28.1)	840 (32.5)	833 (27.0)	473 (24.4)	<.001	<.001
Cause of hospitalization							
All-cause	5112 (65.8)	113 (70.6)	1672 (64.7)	2024 (65.6)	1303 (67.2)	.20	.25
Worsening heart failure	2278 (29.3)	60 (37.5)	779 (30.2)	866 (28.1)	573 (29.5)	.04	.18

*Values are given as number (percentage).
†BMI was calculated as weight in kilograms divided by the square of height in meters.

Table 3. Unadjusted and Adjusted Risk of Adverse Outcomes for a Cohort of Patients With Stable Heart Failure According to Body Mass Index (BMI)*

	Hazard Ratio			
Variable	Underweight: BMI <18.5 (n = 160)	Healthy Weight: BMI, 18.5-24.9 (Referent)	Overweight: BMI, 25.0-29.9 (n = 3084)	Obese: BMI ≥30.0 (n = 1940)
Death				
All-cause				
Unadjusted	1.33 (1.05-1.69)	1.00	0.81 (0.74-0.88)	0.70 (0.62-0.78)
Adjusted	1.21 (0.95-1.53)	1.00	0.88 (0.80-0.96)	0.81 (0.72-0.92)
Cardiovascular				
Unadjusted	0.97 (0.72-1.30)	1.00	0.79 (0.71-0.87)	0.70 (0.63-0.79)
Adjusted	0.88 (0.65-1.19)	1.00	0.86 (0.78-0.95)	0.82 (0.72-0.94)
Worsening heart failure				
Unadjusted	1.06 (0.69-1.63)	1.00	0.67 (0.58-0.78)	0.61 (0.51-0.72)
Adjusted	0.86 (0.56-1.32)	1.00	0.79 (0.68-0.92)	0.82 (0.66-1.01)
Hospitalization				
All-cause				
Unadjusted	1.20 (0.99-1.45)	1.00	0.99 (0.93-1.06)	1.03 (0.96-1.11)
Adjusted	1.13 (0.93-1.37)	1.00	1.00 (0.93-1.07)	0.99 (0.91-1.08)
Worsening heart failure				
Unadjusted	1.32 (1.02-1.72)	1.00	0.91 (0.82-1.00)	0.95 (0.86-1.06)
Adjusted	1.12 (0.86-1.46)	1.00	0.97 (0.88-1.07)	1.03 (0.90-1.17)

*Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Table 4. All-Cause Mortality of 7767 Patients According to BMI Stratified by LVEF, HF Etiology, Sex, and HF Duration*

Variable	Total No. (%) (N = 7767)	Underweight: BMI <18.5 (n = 160)	Healthy Weight: BMI, 18.5-24.9 (n = 2583)	Overweight: BMI, 25.0-29.9 (n = 3084)	Obese: BMI ≥30.0 (n = 1940)	*P* for Trend
LVEF≤45%	34.9	46.9	38.8	33.6	30.3	<.001
LVEF>45%	23.4	33.3	28.9	23.2	18.7	.002
HF etiology						
Ischemic	33.7	45.9	37.8	32.8	28.7	<.001
Nonischemic	32.8	43.6	37.9	31.2	27.8	<.001
Sex						
Male	34.7	48.8	39.3	33.6	29.7	<.001
Female	29.5	41.3	33.7	27.2	24.6	<.001
HF duration ≤24 mo	31.7	40.2	37.1	31.2	24.6	<.001
HF duration >24 mo	36.3	53.5	39.0	34.3	34.6	.005

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HF, heart failure; LVEF, left ventricular ejection fraction.
*Values are given as percentage unless otherwise indicated.

The underlying pathophysiology of the obesity paradox, however, is not known. One possibility is that the increased cardiac output and myocardial demands, in combination with the higher prevalence of endothelial dysfunction,[26,27] may cause overweight and obese patients to be diagnosed with HF at an earlier stage of their disease than patients in lower BMI categories. This may explain the discordance between the risks of death and hospitalization observed in the present study. Overweight and obese patients with HF may have less severe myocardial dysfunction than patients at a healthy weight, and thus be at lower risk of death, yet be equally vulnerable to developing decompensated HF. However, in cardiopulmonary testing, the peak oxygen uptake of overweight patients is similar to that of patients at a healthy weight both before and after adjustment for lean body mass, suggesting that disease severity is comparable across BMI groups.[16,17]

Another potential explanation is the presence of cardiac cachexia, a wasting syndrome observed in patients with advanced HF that has no accepted definition but is characterized by significant weight loss in the absence of peripheral edema.[28-30] Studies have demonstrated that many patients with advanced HF are malnourished, with a calorie and protein intake that is inadequate to meet their energy requirements.[31,32] In addition, patients with HF have low levels of insulinlike growth factor 1[33-35] and elevated levels of circulating renin, catecholamines, transforming factor β, and inflammatory cytokines such as tumor necrosis factor, interleukins 1 and 6, and interferon γ.[36-42] These factors are associated with the anorexia and muscle wasting that are a hallmark of cardiac cachexia and have been associated with an increased risk of adverse outcomes.[43] In the DIG trial, it seems likely that there was a higher proportion of cachectic patients in the healthy-weight and underweight groups than in the group with a higher BMI, and this may have contributed to the higher mortality observed in these groups. It is unlikely, however, that cachexia entirely explains the association of lower BMI and higher mortality, as other investigators have demonstrated that noncachectic HF patients with lower BMIs are at increased risk of adverse outcomes compared with heavier patients.[16]

Our findings are consistent with other evidence showing that higher BMIs are associated with better outcomes among patients with a variety of conditions.[44] In studies of survivors of myocardial infarction, overweight and obese patients were at lower risk of recurrent events compared with patients at a healthy weight.[8,9] Similarly, patients with lower BMIs were at increased risk of complications after percutaneous interventions.[10-12] Although the specific mechanisms may differ, the identification of an obesity paradox in such diverse clinical situations suggests a commonality that merits further investigation.

Our analysis considers only a patient's BMI at the time of enrollment, and we do not have information on changes in BMI over time. Accordingly, although our analysis establishes the fact that patients with HF who are overweight or obese have better outcomes than those at a healthy weight, it does not address the effect of weight gain or loss in this population. Nevertheless, our study, coupled with other studies showing that patients with HF who lose weight are at higher risk of adverse outcomes,[43,45] emphasizes the need for additional research into the obesity paradox in patients with HF. It is evident that the association of weight and outcomes in patients with HF is strikingly different from the association observed in the general population. As such, well-designed clinical trials are needed to determine whether weight loss is an appropriate recommendation for overweight and obese patients with HF. Patients with HF may, in fact, be better served by the identification and prevention of malnutrition and cardiac cachexia rather than by focusing on weight categories derived from healthy populations.

Several aspects of our analysis merit further consideration. First, the DIG trial was conducted before the routine use of β-blockers. Although we would not expect this to have an impact on the general nature of the association between BMI and outcomes that we describe, additional research would be necessary to confirm the existence of this association in patients receiving contemporary HF treatment. Second, it is possible that important unmeasured markers of HF severity between BMI categories, as might be indicated by plasma norepinephrine and brain natriuretic peptide concentrations, may have confounded the association of BMI and outcomes. Similarly, the DIG investigators did not obtain measures of nutritional status and caloric intake. Accordingly, we are unable to examine the contribution of malnutrition to the obesity paradox. Finally, patients enrolled in the DIG trial had clinically stable, established HF, and it is not known if our findings would apply to patients with new HF, treated outside the setting of a controlled clinical trial, or followed for longer periods.

CONCLUSIONS

Among outpatients with stable HF, higher BMI values are independently associated with a lower risk of death and death due to worsening HF, such that overweight and obese patients have better survival rates compared with patients at a healthy weight. Developing a clearer understanding of the underlying mechanisms and impact of the obesity paradox in patients with HF is necessary before definitive recommendations concerning weight and weight control can be made for this population.

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Correspondence: Harlan M. Krumholz, MD, Yale University School of Medicine, 333 Cedar St, PO Box 208088, New Haven, CT 06520-8088 (harlan.krumholz@yale.edu).

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