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Association of obesity and survival in systolic heart failure after acute myocardial infarction: potential confounding by age

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Aims To determine the association between obesity and outcomes in post-acute myocardial infarction (AMI) patients with systolic heart failure (HF).

Methods and results Of the 6632 Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) participants, 6611 had data on baseline body mass index (BMI) and 6561 had BMI $\geq$ 18.5 kg/m^2. Of these, 1573 were obese (BMI $\geq$ 30 kg/m^2) and 4988 were non-obese (BMI 18.5–29.9 kg/m^2). Propensity scores for obesity, estimated for each patient, were used to assemble a cohort of 1519 pairs of obese and non-obese patients who were balanced on 65 baseline characteristics. All-cause mortality occurred in 13.7 and 13.8% of matched obese and non-obese patients, respectively, during 16 months of median follow-up [matched hazard ratio (HR) for obesity 0.98; 95% confidence interval (CI) 0.79–1.21; $P = 0.831$]. Before matching, the obese group was younger (mean age, 62 vs. 64 years; $P < 0.0001$) and had more women (37 vs. 26%; $P < 0.0001$). The paradoxical pre-match association between obesity and reduced mortality (unadjusted HR 0.82; 95% CI 0.70–0.95; $P = 0.008$) disappeared when adjusted for age alone (age-adjusted HR 0.91; 95% CI 0.78–1.06; $P = 0.206$) but not for gender alone (gender-adjusted HR 0.79; 95% CI 0.68–0.92; $P = 0.003$). Obesity had no association with mortality in 1573 pairs of age-matched obese and non-obese patients (age-adjusted HR 0.94; 95% CI 0.77–1.13; $P = 0.484$).

Conclusion In post-AMI patients with systolic HF, obesity provides no independent intrinsic survival benefit. The paradoxical unadjusted survival associated with obesity is largely explained by the younger age of obese patients.

Keywords Age • Obesity • Survival • Heart failure • Acute myocardial infarction

Introduction

Obesity is a risk factor for cardiovascular disorders such as acute myocardial infarction (AMI) and heart failure (HF).[1,2] However, the impact of obesity on outcomes in patients with cardiovascular disease is often complex.[3–13] Although obesity is associated with reduced mortality in HF,[3–5] in patients with AMI, obesity has been variably described to have a positive, neutral, or negative association with mortality.[6–13] These variations have been attributed to methodological differences of these studies and residual bias. Residual bias is a source of concern in studies using traditional regression-based multivariable risk adjustments as baseline distribution of covariate may not be balanced in these studies.[14] Further, studies using traditional regression-based risk adjustment models suffer from lack of blinding as these adjustments require access to study outcomes.[15] Studies based on propensity score matching, on the other hand, allow assembly of study populations in which exposed and unexposed groups are balanced on all measured baseline covariates.[14–16] Additionally, propensity-matched studies can mimic a key feature of randomized clinical trials, that is, investigators are blinded to study outcomes during

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the assembly of the balanced study cohorts.[15] Therefore, the objective of this study was to determine causal associations between obesity and outcomes in a propensity-matched population of post-AMI HF patients.

Methods

Source of data

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a multicenter, randomized, clinical trial of eplerenone in post-AMI patients with left ventricular systolic dysfunction (LVSD) and transient clinical HF.[17] AMI was documented by standard criteria.[17] Patients were randomized 3–14 days after their AMI to receive eplerenone ($n = 3319$) or placebo ($n = 3313$). Patients were receiving standard medical and reperfusion therapies including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers and beta-blockers. LVSD was documented by left ventricular ejection fraction $<40\%$ and HF was documented by presence of pulmonary râles, a third heart sound, or chest X-ray evidence of pulmonary venous congestion. Left ventricular systolic dysfunction and HF were required to occur after the index AMI and before randomization. Post-AMI patients with diabetes mellitus and LVSD could be enrolled even if they did not have clinical HF as they were considered to have similar cardiovascular risk as non-diabetic patients with LVSD and HF symptoms.[17,18] However, 69% (1483/2142) of patients with diabetes had clinical HF.

Baseline body mass index

Baseline body mass index (BMI) was systematically measured during standard physical exams performed during the study screening visit.[19] Of the 6632 EPHESUS participants, baseline BMI data were available for 6611 patients. For the purposes of this analysis, we excluded 50 patients who were underweight (BMI < 18.5 kg/m^2) because of the established poor prognosis associated with cachexia in HF.[20] Of the remaining 6561 patients with BMI ≥ 18.5 kg/m^2, 1573 were obese (BMI ≥ 30 kg/m^2) and 4988 were non-obese (BMI 18.5–29.9 kg/m^2). Of the 4988 non-obese patients, 2967 were overweight (BMI 25–29.9 kg/m^2) and 2021 were normal-weight (BMI 18.5–24.9 kg/m^2).

Study outcomes

The primary and co-primary end points of the EPHESUS trial, all-cause mortality and the combined end point of cardiovascular hospitalization or cardiovascular mortality, were also the primary end points for the current analysis. Secondary outcomes included other major secondary end points from EPHESUS such as cardiovascular mortality and all-cause and cardiovascular hospitalization.[17] The cause of death or the primary diagnosis leading to hospitalization was adjudicated by a blinded independent EPHESUS critical events committee.[17,19]

Assembly of a balanced study cohort

Because of the imbalances in baseline characteristics between obese and non-obese patients, we used propensity score matching to assemble a cohort in which all measured baseline characteristics between obese and non-obese patients would be balanced.[15,16] The propensity score for obesity for a patient would be that patient's probability of being obese given his or her measured baseline characteristics. We estimated propensity scores for obesity for all 6561 patients using a non-parsimonious multivariable logistic regression model based on 65 baseline characteristics displayed in *Figure 1*.[21–25] Using a greedy matching protocol, we were able to match 1519 of the 1573 obese (BMI ≥ 30 kg/m^2) patients with 1519 non-obese (BMI 18.5–29.9 kg/m^2) patients who had similar propensity scores.[21–25]

The efficacy of the regression model used to estimate propensity score is best assessed by its ability to reduce bias and achieve balance in the distribution of baseline characteristics between two groups after matching.[26,27] Because propensity score models are sample-specific adjusters and are not intended to be used for out-of-sample prediction or estimation of coefficients, measures of fitness, and discrimination are not important for the assessment of the model's effectiveness.[26,27] Therefore, we assessed pre-match imbalance and post-match balance by estimating absolute standardized differences for baseline characteristics between obese and non-obese patients and presented them as Love plots.[26,28,29] Absolute standardized differences directly quantify the bias in the means (or proportions) of covariates across the groups. These differences are expressed as a percentage of the pooled standard deviations.[28,29] Absolute standardized differences are not confounded by sample size and thus can compare balance in the initial sample with that in the matched sample.[26] An absolute standardized difference of 0% indicates no residual bias and values $<10\%$ are considered of inconsequential bias. As illustrated in *Figure 1*, the absolute standardized differences of all the baseline characteristics were $<10\%$ after matching suggesting substantial bias reduction and the efficacy of our propensity score model.

Statistical analysis

For descriptive analyses, we used Pearson χ^2 and Wilcoxon rank-sum tests for the pre-match, and McNemar's test and paired sample *t*-test for the post-match comparisons of baseline characteristics of obese and non-obese patients, as appropriate. We used Kaplan–Meier plots and matched Cox regression analyses to estimate association between obesity and outcomes during 16 months of median (maximum 30 months) follow-up. All statistical tests were evaluated using two-tailed 95% confidence levels, and data analyses were performed using SPSS 15 for Windows.[30] The authors had full access to the data and take responsibility for its integrity.

Before matching, obese patients were younger with fewer women, and had a higher prevalence of hypertension and diabetes. Therefore, we examined the effect of these covariates on the unadjusted association between obesity and mortality by separately adjusting for each of these covariates. Because of the substantial effect of age on the unadjusted association between obesity and mortality observed during preliminary analyses, we examined the association between obesity and mortality in an age-matched cohort of 1573 pairs of patients in which both groups had the *same* mean ($\pm$SD) age of 62.03 (± 10.90) years but had imbalances in the distribution of other baseline characteristics.

Sensitivity analysis

To determine if the association between BMI and mortality could be reproduced using a different cut-off of BMI, we categorized patients into overweight/obese (BMI ≥ 25 kg/m^2) and normal-weight (BMI 18.5–24.9 kg/m^2). We chose BMI 25 kg/m^2 as the cut-off as preliminary data from our pre-match patients suggest that unadjusted mortality for patients with BMI 25–29.9 and >30 kg/m^2 were similar (about 14% each) and that for those with BMI 18.5–22.5 and 22.5–24.9 kg/m^2 were also similar (about 18% each). As described above, we estimated propensity scores for being overweight/obese for each patient and then assembled a matched cohort of 1890 pairs of normal-weight and overweight/obese patients who were balanced on 65 baseline characteristics. We then used matched Cox regression analyses to

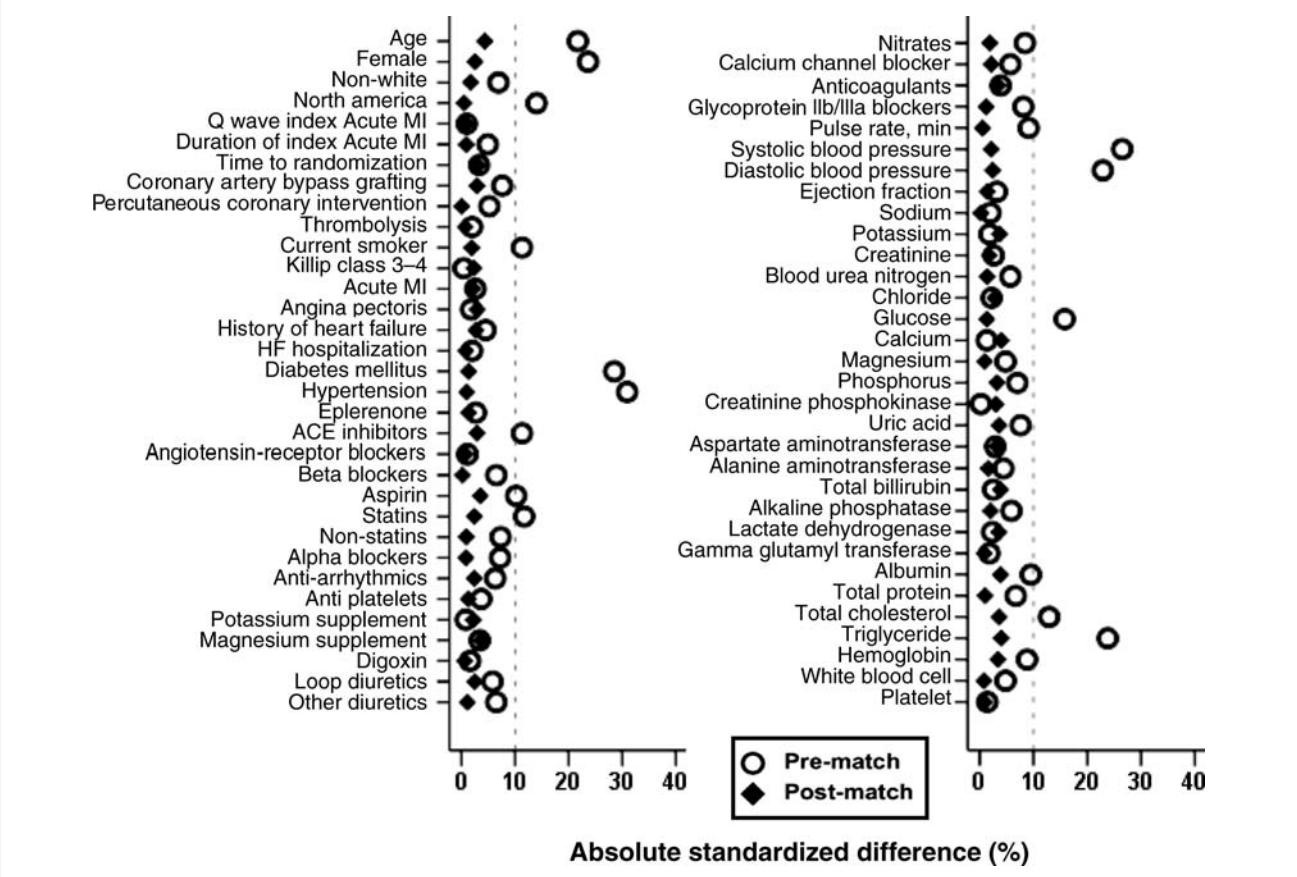

Figure 1 Love plot for absolute standardized differences before and after propensity score matching comparing covariate values between participants with body mass index 18.5–30 and $\geq$30 kg/m^2 (ACE, angiotensin-converting enzyme; MI, myocardial infarction).

estimate association between being overweight/obese and outcomes during 16 months of median (maximum 32 months) follow-up.

Results

Baseline characteristics

Matched patients had a mean ($\pm$SD) age of 62 ($\pm$11) years, 1080 (36%) were women and 249 (8%) were non-whites. Before matching, obese patients were younger (62 vs. 64 years; $P < 0.0001$) and had higher prevalence of women (37 vs. 26%; $P < 0.0001$), hypertension (72 vs. 57%; $P < 0.0001$), and diabetes mellitus (43 vs. 29%; $P < 0.0001$; *Table 1*). These and other pre-match imbalances between non-obese (BMI 18.5–29.9 kg/m^2) and obese (BMI $\geq$30 kg/m^2) patients were balanced after matching (*Tables 1* and *2*). The mean ($\pm$SD) BMI's for non-obese and obese patients before matching were 26 ($\pm$2.6) and 36 ($\pm$3.5) kg/m^2, respectively, and the respective mean BMI after matching were 26 ($\pm$2.6) vs. 33 ($\pm$3.5) kg/m^2, respectively.

Association between body mass index $\geq$30 kg/m^2 and outcomes

Overall, 418 (13.8%) matched patients died from all causes during 16 months of median follow-up. All cause mortality occurred in 13.7% (rate, 1012/10 000 person-years) and 13.8% (rate, 1053/10 000 person-years) of obese and non-obese patients, respectively (hazard ratio (HR) when obese patients were compared with non-obese patients 0.98; 95% confidence interval (CI) 0.79–1.21; $P = 0.831$; *Figure 2A* and *Table 3*). The relationship between obesity and mortality was not modified by therapy with eplerenone (data not shown).

Among 6561 pre-match patients, all-cause mortality occurred in 13.5 and 16.0% of obese and non-obese patients respectively (HR 0.82, 95% CI 0.70–0.95; $P = 0.008$; *Table 3*). However, this association lost significance when adjusted for all covariates displayed in *Figure 1* (HR 0.92; 95% CI 0.79–1.08; $P = 0.329$) and propensity scores based on all covariates displayed in *Figure 1* (HR 0.96; 95% CI 0.82–1.12; $P = 0.601$; data not shown). When we used BMI as a continuous variable, each unit increase in BMI was associated with a significant 3% decrease in mortality before matching (unadjusted HR 0.97; 95% CI 0.96–0.99; $P < 0.0001$) but had no significant association with mortality after matching (HR 0.99; 95% CI 0.97–1.01; $P = 0.372$; data not shown). Obesity had no association with the EPHESUS co-primary combined end points of cardiovascular hospitalization or cardiovascular mortality among matched patients (HR 1.02; 95% CI 0.87–1.18; $P = 0.848$; *Table 3*). Associations of BMI $\geq$ 30 kg/m^2 and the other secondary end points are displayed in *Table 3*.

Table 1 Baseline patient characterics by body mass index (BMI)

n (%) or mean (±SD)	Before propensity matching			After propensity matching		
	BMI 18.5–29.9 kg/m^2 (*n* = 4988)	BMI ≥ 30 kg/m^2 (*n* = 1573)	*P*-value	BMI 18.5–29.9 kg/m^2 (*n* = 1519)	BMI ≥ 30 kg/m^2 (*n* = 1519)	*P*-value
Age, years	64 (±12)	62 (±11)	<0.0001	62 (±12)	62 (±11)	0.220
Women	1303 (26)	582 (37)	<0.0001	531 (35)	549 (36)	0.502
Non-white race	508 (10)	129 (8)	0.021	121 (8)	128 (8)	0.692
Smoking status						
Current smokers	1599 (32)	423 (27)	<0.0001	430 (28)	417 (28)	0.926
Never smokers	1888 (38)	674 (43)		631 (42)	648 (43)	
Former smokers	1501 (30)	476 (30)		458 (30)	454 (30)	
Days of hospital stay during index AMI	15 (±10)	15 (±9)	0.103	15 (±9)	15 (±9)	0.798
ST elevation during index AMI	3542 (71)	1110 (71)	0.735	1077 (71)	1071 (71)	0.842
Past medical history						
Acute myocardial infarction	1373 (28)	415 (26)	0.375	413 (27)	399 (26)	0.594
Angina pectoris	2051 (41)	661 (42)	0.526	614 (40)	636 (42)	0.427
Hypertension	2850 (57)	1129 (72)	<0.0001	1070 (70)	1077 (71)	0.799
Diabetes mellitus	1453 (29)	671 (43)	<0.0001	635 (42)	625 (41)	0.718
Chronic kidney disease	3304 (66)	1009 (64)	0.127	995 (66)	974 (64)	0.456
Heart failure	713 (14)	250 (16)	0.118	228 (15)	243 (16)	0.478
Killip status						
I	733 (15)	314 (20)	<0.0001	261 (17)	298 (20)	0.347
II	3277 (66)	953 (61)		974 (64)	923 (61)	
III	814 (16)	266 (17)		238 (16)	260 (17)	
IV	164 (3)	40 (3)		46 (3)	38 (3)	
Blood pressure, mm Hg						
Systolic	118 (±16)	122 (±17)	<0.0001	122 (±17)	122 (±17)	0.542
Diastolic	72 (±10)	74 (±11)	<0.0001	74 (±11)	74 (±11)	0.488
Pulse, beats per minute	74 (±12)	75 (±12)	0.001	75 (±12)	75 (±12)	0.884
Creatinine, mg/dL	1.13 (±0.33)	1.12 (±0.33)	0.363	1.12 (±0.32)	1.12 (±0.33)	0.622
Glucose, mg/dL	131 (±68)	142 (±64)	<0.0001	140 (±70)	141 (±64)	0.710
Uric acid, mg/dL	6.3 (±3.2)	7.1 (±15.6)	<0.0001	6.6 (±5.0)	7.1 (±15.9)	0.151
Albumin, g/dL	3.70 (±0.60)	3.76 (±0.58)	0.001	3.78 (±0.64)	3.76 (±0.58)	0.279
Total protein, g/dL	6.87 (±1.83)	7.01 (±2.32)	0.013	7.03 (±2.45)	7.01 (±2.34)	0.779
Total cholesterol, mg/dL	192 (±48)	199 (±50)	<0.0001	200 (±50)	199 (±50)	0.302
Triglyceride, mg/dL	164 (±109)	189 (±101)	<0.0001	192 (±160)	186 (±98)	0.258
Left ventricular ejection fraction, %	33.0 (±6.1)	33.2 (±5.9)	0.272	33.3 (±6.0)	33.2 (±5.9)	0.704

Table 2 Baseline therapy by body mass index (BMI)

n (%) or mean (±SD)	Before propensity matching			After propensity matching		
	BMI 18.5–29.9 kg/m^2 (*n* = 4988)	BMI ≥ 30 kg/m^2 (*n* = 1573)	*P*-value	BMI 18.5–29.9 kg/m^2 (*n* = 1519)	BMI ≥ 30 kg/m^2 (*n* = 1519)	*P*-value
Reperfusion therapy or revascularization within 14 days[a]	2226 (45)	752 (48)	0.027	705 (46)	723 (48)	0.528
Coronary artery bypass graft	43 (1)	27 (2)	0.004	18 (1)	23 (2)	0.522
Percutaneous coronary intervention	1170 (24)	404 (26)	0.071	386 (25)	386 (25)	1.000
Thrombolysis	1322 (27)	431 (27)	0.484	409 (27)	414 (27)	0.870
Medications						
Eplerenone	2481 (50)	804 (51)	0.342	760 (50)	770 (51)	0.745
Angiotensin-converting enzyme inhibitors	4179 (84)	1380 (88)	<0.0001	1316 (87)	1331 (88)	0.448
Angiotensin-receptor blocker	161 (3)	54 (3)	0.690	55 (4)	53 (4)	0.923
Beta-blockers	3711 (74)	1214 (77)	0.026	1168 (77)	1167 (77)	1.000
Nitrates	3051 (61)	1026 (65)	0.004	1001 (66)	987 (65)	0.617
Aspirin	4381 (88)	1431 (91)	0.001	1393 (92)	1378 (91)	0.365
Anti-platelet drugs	1423 (29)	475 (30)	0.203	463 (31)	454 (30)	0.187
Anticoagulants	852 (17)	246 (16)	0.182	258 (17)	239 (16)	0.757
Statins	2262 (45)	805 (51)	<0.0001	793 (52)	775 (51)	0.531
Other lipid lowering agents	68 (1)	37 (2)	0.006	35 (2)	33 (2)	0.901
Digoxin	758 (15)	230 (15)	0.578	227 (15)	224 (15)	0.918
Loop diuretics	2716 (55)	902 (57)	0.044	841 (55)	860 (57)	0.504
Other diuretics	387 (8)	151 (10)	0.020	139 (9)	144 (10)	0.803
Potassium supplements	812 (16)	261 (17)	0.769	237 (16)	249 (16)	0.581
Magnesium supplements	188 (4)	70 (5)	0.226	58 (4)	69 (5)	0.371
Alpha-blockers	81 (2)	42 (3)	0.008	39 (3)	37 (2)	0.909
Calcium channel blockers	778 (16)	279 (18)	0.044	251 (17)	263 (17)	0.593
Anti-arrhythmic drugs	609 (12)	161 (10)	0.034	148 (10)	159 (11)	0.544
Glycoprotein IIb/IIIa blockers	36 (1)	25 (2)	0.002	18 (1)	20 (1)	0.871

[a]These numbers may not be the exact sum of the three reperfusion or revascularization procedures as some patients received more than one procedures.

Association between body mass index ≥25 kg/m^2 and outcomes

Among 1890 pairs of propensity-matched normal-weight (BMI 18.5–24.9) and overweight/obese patients (BMI ≥ 25), all-cause mortality occurred in 18.2 and 16.4% of matched normal-weight and overweight/obese patients (matched HR when overweight/obese patients were compared with normal-weight patients 0.87; 95% CI 0.74–1.03; $P = 0.104$; data not shown). Among all 6561 pre-match patients, unadjusted and propensity-adjusted HR for all-cause mortality associated with overweight/obesity were 0.74; 95% CI 0.65–0.84; $P < 0.0001$ and 0.87;95% CI 0.76–0.997; $P = 0.046$; data not shown.

Impact of age on the association between body mass index ≥30 kg/m^2 and outcomes

The significant paradoxical pre-match association between obesity and reduced mortality (unadjusted HR 0.82; 95% CI 0.70–0.95; $P = 0.008$; *Table 3*) was eliminated after adjustment for age alone (age-adjusted HR 0.91; 95% CI 0.78–1.06; $P = 0.206$; *Table 4*) but not after adjustment for gender (gender-adjusted HR 0.79; 95% CI 0.68–0.92; $P = 0.003$), hypertension (hypertension-adjusted HR 0.80; 95% CI 0.68–0.93; $P = 0.003$) or diabetes (diabetes-adjusted HR 0.77; 95% CI 0.66–0.89; $P = 0.001$; data not shown). Among the 1573 pairs of age-matched patients, obesity (BMI ≥ 30 kg/m^2) had no association with mortality (age-adjusted HR when obese patients were compared with non-obese patients 0.94; 95% CI 0.77–1.13; $P = 0.484$; *Figure 2B*). Among these patients, when BMI was used as a continuous variable, it had no significant association with all-cause mortality (unadjusted HR 0.99; 95% CI 0.97–1.01; $P = 0.165$; data not shown).

Discussion

The results of the current analysis demonstrate that obesity was associated with reduced all-cause mortality among post-AMI patients with LVSD and HF but this association was not intrinsic in nature. The unadjusted mortality reduction associated with obesity may in part be explained by imbalances in baseline

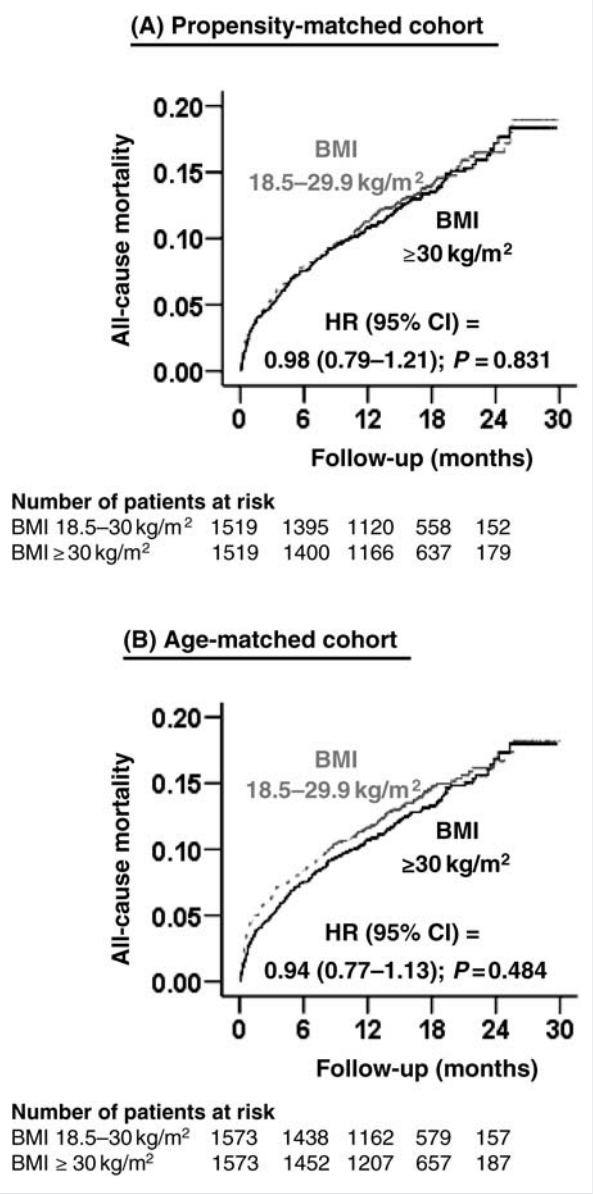

Figure 2 Kaplan–Meier plots for all-cause mortality for patients with body mass index (BMI) 18.5–30 and $\geq$30 kg/m^2. (*A*) In propensity-matched cohort and (*B*) In age-matched cohort (HR, hazard ratio; CI, confidence interval).

characteristics between obese and non-obese patients, in particular by the younger age of obese patients. However, when these imbalances were eliminated after matching or using other methodological approaches, obesity had no association with all-cause mortality, suggesting lack of a true intrinsic association. To the best of our knowledge, this is the first report of an association between obesity and outcomes in a propensity-matched cohort of post-AMI patients with LVSD and HF.

Previous findings of a paradoxical association between obesity and reduced mortality have been explained by confounding associated with higher BMI that are also obvious from pre-match baseline characteristics in our study. For example, obese patients in our study were younger and were more likely to be women, both of which may have given them a survival advantage. However, obesity was also associated with higher prevalence of hypertension and diabetes mellitus, which may have increased their mortality risk. Therefore, the unadjusted mortality reduction associated with obesity indicates that the confounding by age, gender, and other favourable baseline characteristics may have been more powerful than that by hypertension, diabetes, and other unfavourable baseline characteristics. However, in models adjusted specifically for age, either by assembling an age-matched cohort or adjusting for age alone in a regression model, BMI was no longer associated with mortality. These findings suggest that the unadjusted mortality reduction associated with obesity may in large part be explained by younger age of obese patients and that there may be no intrinsic association between obesity and mortality.

Findings from our study are consistent with a recent report that also demonstrated an unadjusted paradoxical association between obesity and mortality after AMI which was also eliminated after multivariable risk adjustment.[13] In that study, each unit increase in BMI was associated with an unadjusted but significant 5% reduction in 1-year mortality. Similar to our study, when adjusted for age alone, the association between BMI and mortality became insignificant. However, unlike the post-AMI patients with LVSD and HF in our study, patients in that study were older, had higher left ventricular ejection fraction and the vast majority had Killip class I symptoms. Further, our propensity score matching allowed us to assemble a balanced cohort and examine intrinsic associations between obesity and other outcomes.

Taken together, the findings of these studies may help dispel the notion of a true obesity paradox in patients with AMI. Adjustment for age and other covariates did attenuate the significant unadjusted association between obesity and reduced mortality and made it non-significant. Interestingly, even adjustment for all these confounder did not reverse the association to demonstrate an increased risk associated with obesity. This suggests that the association between obesity and mortality in post-AMI patients with HF and LVSD is complex and may not be completely explained by those measured covariates. However, considering the known association of obesity with traditional risk factors such as hypertension and diabetes mellitus, these conditions should be properly managed in post-AMI obese patients with LVSD and HF. The association between obesity and outcomes has also been extensively studied in patients with systolic HF.[3,5,31–34] Findings from those studies also suggest that obese patients were in general younger in age and that the association between obesity and reduced mortality did not disappear after adjustment for age and other covariates in multivariable regression-based models.[3,5,31–34] However, regression adjustments may not ensure balance in the distribution of age or other baseline characteristics.[14] Further, unlike our study, the association of BMI with mortality was not examined in a model adjusted for age alone or in an age-matched cohort. Finally, the differential confounding effect of age may also be attributed to the differences in study populations. Unlike HF patients in those studies, patients in our study were post-AMI with LVSD and HF.

Several limitations of our study must be acknowledged. Patients in our study were post-AMI with LVSD and HF and were enrolled in a

Table 3 Associations of body mass index (BMI) ≥30 kg/m^2 with outcomes in Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

	Rate, per 10 000 person-years follow-up (events/follow-up in years)		Absolute rate difference[a] (per 10 000 person-years)	Matched hazard ratio (95% confidence interval)	*P*-value
	BMI 18.5–29.9 kg/m^2	BMI ≥ 30 kg/m^2			
Before matching	*n* = 4988	*n* = 1573			
All-cause mortality	1237 (798/6450)	995 (212/2130)	−242	0.82 (0.70–0.95)	0.008
Cardiovascular hospitalization or cardiovascular mortality	2516 (1409/5600)	2339 (432/1847)	−177	0.95 (0.85–1.06)	0.342
Cardiovascular mortality	1056 (681/6450)	892 (190/2130)	−164	0.86 (0.73–1.01)	0.061
Heart failure mortality	265 (171/6450)	239 (51/2130)	−26	0.91 (0.67–1.25)	0.561
All-cause hospitalization	5359 (2238/4176)	5343 (739/1383)	−16	1.02 (0.94–1.11)	0.661
Cardiovascular hospitalization	1652 (925/5600)	1668 (308/1847)	+16	1.03 (0.91–1.17)	0.650
Heart failure hospitalization	919 (547/5954)	901 (178/1975)	−17	1.00 (0.85–1.19)	0.988
Fatal or non-fatal acute myocardial infarction	730 (450/6162)	710 (143/2014)	−20	0.99 (0.82–1.20)	0.926
After matching	*n* = 1519	*n* = 1519			
All-cause mortality	1053 (210/1994)	1012 (208/2056)	−41	0.98 (0.79–1.21)	0.831
Cardiovascular hospitalization or cardiovascular mortality	2342 (407/1738)	2327 (416/1788)	−15	1.02 (0.87–1.18)	0.848
Cardiovascular mortality	903 (180/1994)	910 (187/2056)	+7	1.02 (0.82–1.27)	0.865
Heart failure mortality	186 (37/1994)	243 (50/2056)	+58	1.09 (0.68–1.77)	0.714
All-cause hospitalization	5496 (698/1270)	5295 (709/1339)	−201	0.99 (0.88–1.13)	0.924
Cardiovascular hospitalization	1582 (275/1738)	1639 (293/1788)	+56	1.06 (0.88–1.27)	0.549
Heart failure hospitalization	837 (155/1851)	890 (170/1910)	+53	1.03 (0.81–1.30)	0.810
Fatal or non-fatal acute xmyocardial infarction	757 (144/1901)	693 (135/1947)	−64	0.95 (0.74–1.23)	0.952

[a]Absolute differences were calculated by subtracting the percentage of events in the BMI 18.5–29.9 kg/m^2 from those in the BMI ≥ 30 kg/m^2 group (before values were rounded).

Table 4 Impact of age on the associations of body mass index ≥30 kg/m^2 with all-cause mortality in Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

Outcomes	Hazard ratio (95% confidence interval)	*P*-value
Adjusted for age	0.91 (0.78–1.06)	0.206
Age-matched	0.94 (0.77–1.13)	0.484

randomized clinical trial which limits generalizability. We used BMI to define obesity. We had no data on abdominal adiposity, which is considered a better marker for cardiovascular risk associated with obesity.[35,36] However, abdominal adiposity has not been shown to have any intrinsic association with mortality.[13] We also had no data on weight changes, a potential marker of cardiac cachexia.[31] However, the prevalence of chronic cachexia is probably low as the prevalence of prior AMI and HF was low and patients with BMI < 18.5 were excluded. Concern for the loss of patients during matching is alleviated by our ability to reproduce all key results among pre-match patients using traditional regression-based analyses. Confounding by an unmeasured variable is possible. However, that concern is lessened by the neutral finding from our matched analysis that did not show any intrinsic association between obesity and mortality.

In conclusion, despite a higher prevalence of hypertension and diabetes among obese patients, obesity was associated with an unadjusted paradoxical reduction in mortality in post-AMI patients with LVSD and HF. This may be largely explained by the younger age of the obese patients and suggests the lack of an intrinsic association with BMI and mortality in these patients. A well-designed randomized control trial needs to be conducted to prospectively examine whether aggressive management of traditional cardiovascular risk factors such as hypertension and diabetes can improve outcomes in obese post-AMI patients with LVSD and HF.

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