Relation of Body Mass Index to Urinary Creatinine Excretion Rate in Patients With Coronary Heart Disease

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In patients with prevalent coronary heart disease (CHD), studies have found a paradoxical relation in that patients with higher body mass indexes (BMIs) have lower mortality. One possibility is that patients with higher BMIs have greater muscle mass, and higher BMI may be a marker of better overall health status. The aim of this study was to evaluate whether the paradoxical association of BMI with mortality in patients with CHD is attenuated when accounting for urinary creatinine excretion, a marker of muscle mass. The Heart and Soul Study is an observational study of outpatients with stable CHD. Outpatient 24-hour timed urine collections were obtained. Participants were followed up for death for 5.9 ± 1.9 years. Cox proportional-hazards models were used to evaluate the association between gender-specific BMI quintiles and mortality. There were 886 participants in the study population. Participants in higher quintiles of BMI were younger, were more likely to have diabetes mellitus and hypertension, and had higher urinary creatinine excretion rate. Compared to the lowest BMI quintile, subjects in higher BMI quintiles were less likely to die during follow-up. Adjustment for major demographic variables, traditional cardiovascular risk factors, and kidney function did not attenuate the relation. Additional adjustment for urinary creatinine excretion rate did not materially change the association between BMI and all-cause mortality. In conclusion, low muscle mass and low BMI are each associated with greater all-cause mortality, but low muscle mass does not appear to explain why CHD patients with low BMIs have worse prognosis. **(Am J Cardiol 2011;108:179–184)**

Using urinary creatinine excretion rate as an indirect measure of muscle mass, we demonstrated in a previous study that lower urinary creatinine excretion rate was strongly associated with mortality independent of conventional measures of body composition, kidney function, and traditional cardiovascular risk factors in patients with coronary heart disease (CHD).[1] Thus, low creatinine excretion rate and low body mass index (BMI) are markers of greater risk for death in patients with CHD. What is unknown, however, is whether the association of low BMI with mortality in patients with CHD[2–4] is explained by low muscle mass. To that end, we evaluated the association of BMI with mortality in outpatients with stable CHD to determine whether the association is attenuated when accounting for urinary creatinine excretion, a marker of muscle mass.

Methods

The Heart and Soul Study is an observational study designed to investigate the influence of psychosocial factors on the progression of CHD. Methods have been described previously.[5] Briefly, participants were recruited from outpatient clinics in the San Francisco Bay area if they met 1 of the following inclusion criteria: history of myocardial infarction or coronary revascularization, angiographic evidence of >50% stenosis in ≥1 coronary vessel, exercise-induced ischemia by treadmill or nuclear testing, or documented diagnosis of CHD. Participants were excluded if they were unable to walk 1 block, experienced myocardial infarction in the past 6 months, or were likely to move out of the area within 3 years. The study protocol was approved by the institutional review boards of participating institutions, and all participants provided written informed consent. From September 2000 to December 2002, 1,024 participants enrolled and underwent a baseline study appointment that included a medical history, physical examination, and health status questionnaire. Outpatient 24-hour

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Table 1
Characteristics of the study cohort (n = 886)

Variable	Gender-Specific BMI Quintile					p Value
	Quintile 1 (n = 177)	Quintile 2 (n = 177)	Quintile 3 (n = 177)	Quintile 4 (n = 178)	Quintile 5 (n = 177)	
BMI (kg/m^2)						
Men	22.2 ± 1.8	25.3 ± 0.7	27.4 ± 0.7	30 ± 0.9	36.1 ± 4.4	<0.001
Women	21.7 ± 2.1	26 ± 0.7	28.9 ± 0.7	31.8 ± 1.3	37.2 ± 4.4	<0.001
Age (years)	66.9 ± 12.3	68.0 ± 10.9	68.3 ± 9.9	67.0 ± 10.3	63.3 ± 10.8	<0.0001
Female	18%	18%	18%	18%	18%	1.0
African American	15%	15%	17%	13%	15%	0.8
White	58%	60%	59%	63%	66%	0.8
Diabetes mellitus	19%	24%	20%	32%	37%	<0.001
Hypertension	68%	63%	68%	74%	80%	<0.01
Previous myocardial infarction	61%	53%	49%	57%	52%	0.2
Previous stroke/transient ischemic attack	10%	17%	18%	16%	11%	0.1
Current tobacco use	29%	21%	15%	16%	18%	<0.01
Systolic blood pressure (mm Hg)	131 ± 21	132 ± 21	134 ± 24	135 ± 22	133 ± 18	0.3
Diastolic blood pressure (mm Hg)	73 ± 10	74 ± 11	75 ± 13	76 ± 11	75 ± 11	0.3
Total cholesterol (mg/dl)	178 ± 40	177 ± 41	178 ± 45	176 ± 46	179 ± 41	0.9
High-density lipoprotein cholesterol (mg/dl)	51 ± 17	48 ± 16	46 ± 12	43 ± 13	41 ± 10	<0.0001
Serum albumin (g/dl)	3.88 ± 0.37	3.94 ± 0.31	3.93 ± 0.31	3.91 ± 0.32	3.91 ± 0.29	0.3
C-reactive protein (mg/L)	0.4 ± 1.4	0.6 ± 1.3	0.7 ± 1.3	0.7 ± 1.2	1.1 ± 1.2	<0.0001
$eGFR_{MDRD}$ (ml/min/1.73 m^2)*	77 ± 26	76 ± 23	75 ± 20	76 ± 23	79 ± 21	0.4
$eGFR_{CYS}$ (ml/min/1.73 m^2)†	71 ± 25	71 ± 20	71 ± 21	70 ± 21	72 ± 25	1.00
Urine albumin (mg/dl)	6 ± 20	5 ± 18	3 ± 14	4 ± 20	5 ± 16	0.8
Urine creatinine excretion (mg/24 h)	1,110 ± 331	1,282 ± 354	1,313 ± 372	1,422 ± 393	1,624 ± 484	<0.0001
Left ventricular mass index (g/m^2)	102 ± 57	100 ± 29	95 ± 24	102 ± 26	101 ± 26	0.5
METs achieved on Bruce treadmill testing	7.90 ± 3.85	7.83 ± 3.62	7.45 ± 3.07	7.35 ± 2.91	6.13 ± 2.86	<0.0001
Maximum heart rate achieved on Bruce treadmill testing (beats/min)	131 ± 24	131 ± 26	129 ± 24	131 ± 24	127 ± 23	0.4
Self-reported "excellent" or "very good" overall health	57 (32)	70 (39)	54 (30)	51 (28)	33 (19)	<0.001

* Estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation ($186 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742$ [if female] $\times$ 1.212 [if African American]).

† Estimated glomerular filtration rate by cystatin C equation ($76.7 \times [\text{cystatin C}]^{-1.19}$).

timed urine collections and fasting (12-hour) morning venous blood samples were obtained. Participants were followed through June 30, 2009. For the present analysis, we excluded participants with missing urine collections (n = 57) or missing covariate data (n = 81), providing a final analytic sample of 886 participants (87%).

The protocol for timed urine collection has been described previously.[6] In brief, participants received instructions on urine collection and specimen refrigeration. They were asked to void at the end of their study appointments and to begin the collection from that point forward. Research personnel arrived at patients' homes 24 hours after the timed collection was initiated. If patients reported missing any urine or collections were <1 or >3 L, collections were repeated. If participants were unable to collect all urine, no data were recorded. Urine volume (milliliters) was recorded, and creatinine was measured by the rate Jaffe method. Urinary creatinine excretion was calculated in milligrams per day (urine volume [milliliters] times urine creatinine [milligrams per deciliter] divided by 100).

Between the baseline examination and May 1, 2009, annual telephone interviews were conducted with study participants or their proxies for vital status. For any reported event, medical records, death certificates, and coroner's reports were retrieved. Date of death was recorded to provide time-to-event data from the baseline examination.

Patient demographics and co-morbid diseases were determined by questionnaire. Systolic and diastolic blood pressures were measured after 5 minutes of rest in subjects in the supine position by trained research personnel. Participants were instructed to take their blood pressure medications on the morning of the intake appointment and to not smoke or consume caffeine 5 hours before the visit. Weight and height were measured in participants wearing light clothing and no shoes. BMI was calculated as weight in kilograms divided by height in meters squared.

Serum cystatin C concentrations were measured using a particle-enhanced immunonephelometric assay[7] (N Latex Cystatin C; Dade Behring, Inc., Deerfield, Illinois) and used to calculate estimated glomerular filtration rate ($eGFR_{CYS}$) using the following formula: $eGFR_{CYS} = 76.7 \times (\text{cystatin C})^{-1.19}$. This formula, which has been validated with comparison to iothalamate-measured glomerular filtration rate in a pooled cohort of kidney disease studies, showed little bias and provided a non-creatinine-based method to adjust for kidney function for this study.[8] Total cholesterol and high-

Table 2
Association of body mass index with all-cause mortality in outpatients with stable coronary heart disease (n = 886)

Variable	Gender-Specific BMI Quintile					Per 5 kg/m^2 Increase
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
All-cause mortality, n (% per patient-years)	60 (6.13%)	51 (5.07%)	43 (4.07%)	48 (4.51%)	35 (3.24%)	
Unadjusted model, HR (95% CI)	1.0 (reference)	0.83 (0.57–1.20)	0.65† (0.44–0.97)	0.72 (0.49–1.05)	0.51† (0.34–0.78)	0.79† (0.68–0.91)
Adjusted for patient characteristics,* HR (95% CI)	1.0 (reference)	0.90 (0.61–1.32)	0.72 (0.48–1.08)	0.75 (0.50–1.12)	0.58† (0.37–0.90)	0.80† (0.68–0.94)
Additional adjustment for urinary creatinine excretion, HR (95% CI)	1.0 (reference)	0.92 (0.62–1.35)	0.73 (0.49–1.11)	0.77 (0.51–1.16)	0.61† (0.39–0.96)	0.82† (0.69–0.96)

* Age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack-years, C-reactive protein, $eGFR_{CYS}$, total cholesterol, high-density lipoprotein cholesterol, serum albumin, and urine albumin concentration.
† $p < 0.05$.
CI = confidence interval; HR = hazard ratio.

density lipoprotein cholesterol were measured using standard clinical chemistry analyzers. High sensitivity C-reactive protein was measured using the Roche (Indianapolis, Indiana) and the Beckman Extended Range (Galway, Ireland) assays.[9] Fasting glucose was measured using a standard clinical analyzer, and fasting insulin was measured using enzyme-linked immunosorbent assay (Linco Research, St. Charles, Missouri). Participants provided rest transthoracic echocardiograms that were read by a single expert cardiologist blinded to all clinical data, as described previously.[10] Left ventricular mass was calculated with the truncated ellipsoid method[11] and indexed to body surface area. The left ventricular ejection fraction was determined using the biplane method of disks.[12] Exercise treadmill testing using the modified Bruce protocol was performed, and the maximum number of METs and heart rate achieved were recorded.

We began by exploring the association of gender-specific BMI quintiles in men and women with mortality (cut points between quintiles in men were 24.0, 26.3, 28.7, and 31.6 kg/m^2 and in women were 24.6, 27.4, 30.0, and 34.6 kg/m^2). We verified the linearity of the association between BMI and mortality to maximize statistical power. The distribution of demographic variables and standard CHD risk factors was compared across BMI quintiles using analyses of variance for continuous variables and chi-square tests for categorical variables, as appropriate. We performed Cox proportional-hazards regression to examine the association between BMI and all-cause mortality, using the lowest gender-specific BMI quintile as the referent category. Patient demographics, co-morbid diseases, physical measurements, and laboratory values were added to the Cox proportional-hazards regression models. Previous analyses have demonstrated a linear relation of urine creatinine excretion rate to mortality in this cohort.[1] Urinary creatinine excretion rate was included in the final model as a continuous covariate to evaluate whether it attenuated the association of BMI with all-cause mortality.

We performed a sensitivity analyses to investigate whether over- or under-urine collections may have introduced bias. We excluded participants whose measured 24-hour urinary creatinine clearance was >30% different from their $eGFR_{CYS}$. This takes advantage of the fact that urinary creatinine excretion rate divided by serum creatinine equals creatinine clearance (in milliliters per minute), an estimate of glomerular filtration rate. The $eGFR_{CYS}$ value provided another estimate of glomerular filtration rate that was independent of the quality of timed urine collections and of creatinine kinetics. Because the $eGFR_{CYS}$ estimate is given as glomerular filtration rate normalized to body surface area, to compare the 2 renal function estimates, measured creatinine clearance was divided by body surface area and multiplied by 1.73.

We stratified the outcome of mortality into early (<3 years from enrollment) versus late (≥3 years from enrollment) mortality. This cut point was chosen as the halfway point of the median follow-up period in our study (6 years). Additional analyses evaluated whether adjustment for self-reported overall health (on a 5-point, Likert-type scale), total METs achieved on the modified Bruce protocol treadmill test, and left ventricular mass index attenuated the association of BMI with mortality in Cox models.

All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina), and p values <0.05 were considered statistically significant.

Results

The mean age of the 886 participant study population was 66.8 ± 10.9 years. Eighty-two percent were men, reflecting heavy sampling from a Veterans Affairs medical center. The mean BMI was 28.4 ± 5.3 kg/m^2. The mean follow-up time was 5.9 ± 1.9 years, during which time 273 participants died, 22 of whom were women. Baseline characteristics of the study population by gender-specific BMI quintiles are listed in Table 1.

BMI and urinary creatinine excretion rate were directly correlated (Pearson's correlation coefficient = 0.35, $p < 0.0001$). Compared to the lowest BMI quintile, those in higher BMI quintiles were less likely to die during follow-up (Table 2). This association was fairly monotonic with increasing BMI quintiles. When BMI was evaluated as a continuous risk factor, each 5 kg/m^2 greater BMI was associated with a 21% lower risk for death (hazard ratio 0.79, 95% confidence interval 0.68 to 0.91). Adjustment for major demographic variables, cardiovascular risk factors,

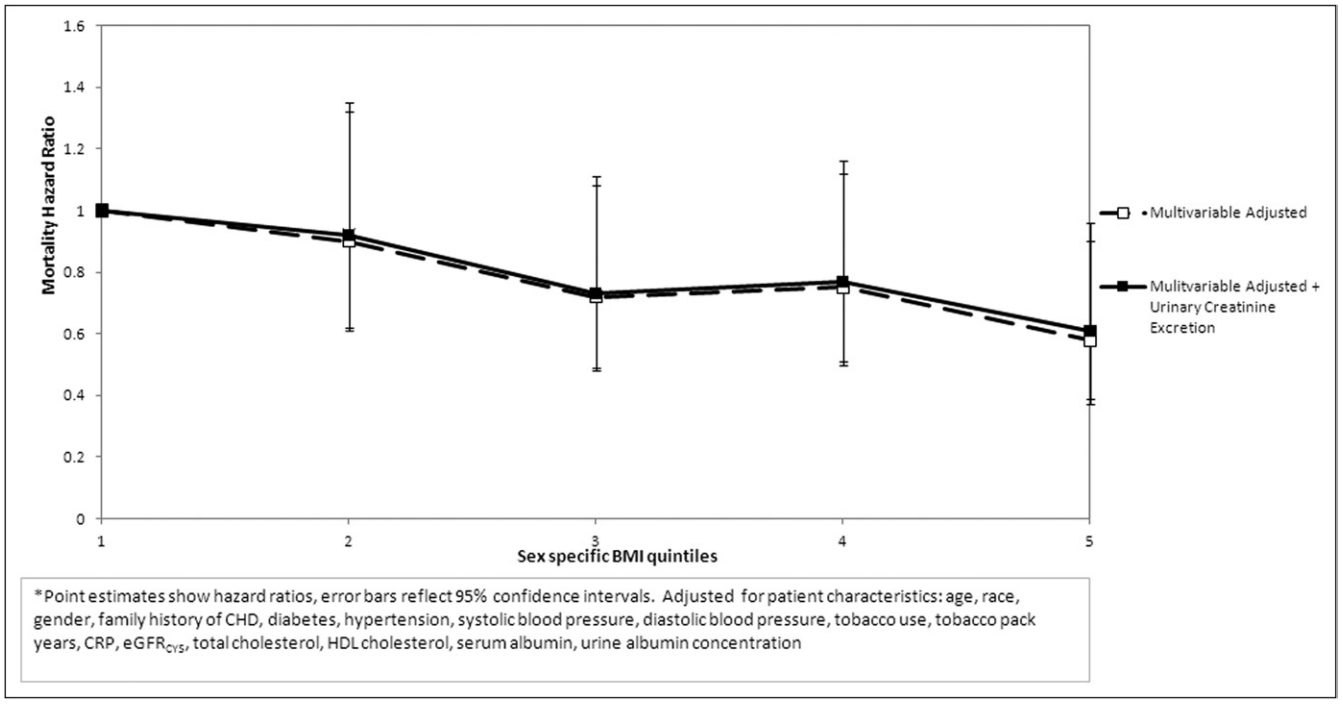

Figure 1. Hazard ratio for mortality by gender-specific BMI quintiles.

Table 3
Association of body mass index and all-cause mortality in outpatients with stable coronary heart disease: sensitivity analysis testing validity of urine collection (n = 628)

Variable	Gender-Specific BMI Quintile					Per 5 kg/m^2 Increase
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
All-cause mortality, n (% per patient-years)	26 (6.52%)	17 (5.32%)	12 (3.74%)	14 (5.72%)	5 (2.28%)	
Unadjusted model, HR (95% CI)	1.0 (reference)	0.82 (0.45–1.51)	0.57 (0.29–1.12)	0.86 (0.45–1.65)	0.35† (0.13–0.90)	0.73† (0.55–0.98)
Adjusted for patient characteristics,* HR (95% CI)	1.0 (reference)	1.11 (0.57–2.17)	0.58 (0.27–1.26)	0.80 (0.39–1.65)	0.45 (0.16–1.23)	0.79 (0.57–1.11)
Additional adjustment for urinary creatinine excretion, HR (95% CI)	1.0 (reference)	1.15 (0.59–2.24)	0.60 (0.27–1.30)	0.84 (0.41–1.74)	0.48 (0.17–1.33)	0.81 (0.58–1.14)

* Age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack-years, C-reactive protein, eGFR$_{CYS}$, total cholesterol, high-density lipoprotein cholesterol, serum albumin, and urine albumin concentration.
† $p < 0.05$.
Abbreviations as in Table 2.

and kidney function did not attenuate the relation (hazard ratio per 5 kg/m^2 greater BMI 0.80, 95% confidence interval 0.68 to 0.94). Additional adjustment for urinary creatinine excretion rate did not materially change the association between BMI and all-cause mortality (hazard ratio 0.82, 95% confidence interval 0.69 to 0.96; Figure 1).

We performed a sensitivity analysis in which we excluded participants whose measured 24-hour urinary creatinine clearance was >30% different from their eGFR$_{CYS}$ to evaluate potential bias introduced by potentially inaccurately collected urine specimens. A total of 258 participants (29%) were excluded for disparate collections by this criteria for this analysis. Among the remaining subjects, the results did not differ significantly from those observed in all participants (Table 3).

We also evaluated whether the association of BMI with mortality was similar between patients who died <3 years after enrollment compared to those who died later. In this analysis, the inverse association between BMI and all-cause mortality appeared stronger in patients who died early compared to those who died later (Table 4). Adjustment for creatinine excretion rate in addition to traditional cardiovascular risk factors did little to change the nature of the association of BMI with mortality (results not shown).

Because low BMI in patients with CHD may reflect poorer global health status or poorer physical fitness, we performed additional analyses evaluating variables that could attenuate the association between BMI and mortality, including self-reported overall health, METs achieved on the modified Bruce treadmill test, and left ventricular mass

Table 4
Hazard ratios between body mass index and all-cause mortality in patients with stable coronary heart disease, stratified by early versus late death*

Variable	Gender-Specific BMI Quintile					Per 5 kg/m^2 Increase
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Early death (<3 years from enrollment) (n = 80)	1.0 (reference) (n = 24)	0.83 (0.45–1.51) (n = 21)	0.54 (0.27–1.07) (n = 13)	0.45† (0.22–0.91) (n = 12)	0.39† (0.18–0.85) (n = 10)	0.66† (0.46–0.96)
Late death (≥3 years from enrollment) (n = 157)	1.0 (reference) (n = 36)	0.91 (0.55–1.52) (n = 31)	0.85 (0.50–1.43) (n = 29)	0.97 (0.58–1.61) (n = 37)	0.73 (0.41–1.28) (n = 24)	0.91 (0.75–1.12)

* Adjusted for age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack-years, C-reactive protein, $eGFR_{CYS}$, total cholesterol, high-density lipoprotein cholesterol, serum albumin, and urine albumin concentration.
† $p < 0.05$.

Table 5
Association between body mass index (per 1 kg/m^2 increase) and all-cause mortality adjusted for select patient variables

Variable	HR (95% CI)	p Value
Adjusted for patient characteristics only*	0.96 (0.93–0.99)	<0.001
Patient characteristics plus adjustment for urinary creatinine excretion	0.96 (0.94–0.99)	0.018
Patient characteristics plus self-reported overall health	0.96 (0.93–0.99)	<0.001
Patient characteristics plus METs achieved on Bruce protocol	0.94 (0.91–0.97)	<0.001
Patient characteristics plus left ventricular mass index	0.96 (0.93–0.99)	<0.001
Patient characteristics plus all variables above	0.94 (0.92–0.97)	<0.001

* Age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack-years, C-reactive protein, $eGFR_{CYS}$, total cholesterol, high-density lipoprotein cholesterol, serum albumin, and urine albumin concentration.
Abbreviations as in Table 2.

index. Adjusting for these variables either individually or jointly did not materially alter the hazard ratio between BMI and mortality (Table 5).

Discussion

The purpose of our study was to evaluate whether low urinary creatinine excretion rate, a marker of low muscle mass, may explain the paradoxical relation between low BMI and mortality observed in patients with CHD. We found that although low creatinine excretion and low BMI were associated with greater mortality, controlling for creatinine excretion did not explain why patients with low BMI have worse survival.

Low BMI and low lean mass have been associated with higher mortality in other populations, including those with chronic obstructive pulmonary disease,[13–15] end-stage liver disease,[16,17] and end-stage renal disease.[18–20] However, it remains unclear whether low muscle mass accounts for the paradoxical association between BMI and mortality in these populations. A study of hemodialysis patients also used urinary creatinine excretion rate to estimate muscle mass and found that the protective effect of higher BMI was limited to patients with normal or high muscle mass.[21] We took a similar approach in patients with stable CHD. Unlike findings in patients with end-stage renal disease, our results demonstrate that the inverse association between BMI and mortality was not explained by muscle mass in patients with CHD. This suggests that varying mechanisms may account for the BMI-mortality paradox in different patient populations.

The inverse association between BMI and mortality was stronger in patients who died <3 years from enrollment. This suggests the possibility of reverse causality; patients with a greater burden of subclinical diseases may have been prone to weight loss and early mortality. Other studies have examined the association between BMI and early mortality in the general population and found similar results. In a study of the general United States population, risk for mortality in those with lower BMI was substantially reduced when the first 5 years of follow-up were excluded.[22] Among 99,000 male physicians, the relative risk for death was lower in men with BMIs <20 kg/m^2 after excluding those who died within the first 2 years of follow-up.[23] In a large study of 1.46 million white adults, the increased hazard ratio for death with low BMI was no longer seen after ≥15 years of follow-up.[24] To our knowledge, our study is the first to extend these observations to those with preexisting CHD. If confirmed with other larger longitudinal studies, loss of body mass may be a useful indicator of greater death risk, and closer surveillance and investigation of subclinical diseases may ultimately prove useful for delaying death if appropriate corrective measures can be identified.

We also explored other potential mechanisms to explain the paradoxical relation between BMI and mortality, such as self-reported overall health, METs achieved on a treadmill test, and left ventricular mass index. Adjustment for these additional variables did not attenuate the relation between BMI and mortality. Self-reported overall health,[25,26] METs achieved on the modified Bruce protocol treadmill test,[27] and elevated left ventricular mass index have been found to be associated with worse outcomes.[28,29] Thus, although the mechanisms responsible for the BMI-mortality paradox remain unclear, these data suggest that measurement of muscle mass, self-reported health status, evaluation of physical fitness, and left ventricular mass may not be useful to identify patients with CHD with low BMIs at greatest risk for death.

Our study had several strengths. It evaluated a large, well-characterized CHD cohort with a median of 5.9 years of follow-up for mortality. Our study is one of a few that contain data on 24-hour urine creatinine excretion, providing a standardized method to estimate muscle mass. All participants provided physical performance measurements on Bruce treadmill protocol and transthoracic echocardiography.

Our study also had some limitations. Subjects were older, mostly men, and had stable CHD. Results may differ in other populations. Other measures of muscle mass, such as dual energy x-ray absorptiometry, were not available. Larger sample sizes may have allowed the detection of subtle differences in the association of BMI with mortality when adjusted for creatinine excretion rate. However, the very modest or altogether absent effect of adjustment observed in this study suggests that any such an effect would likely be modest.

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