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

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Abstract

In patients with prevalent coronary heart disease (CHD), studies have found a paradoxical relationship in that patients with higher body mass index (BMI) have lower mortality. One possibility is that individuals with higher BMI have greater muscle mass; and higher BMI may be a marker of better overall health status. We evaluated whether the paradoxical association of BMI with mortality in CHD patients 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 designed to investigate the influence of psychosocial factors on the progression of CHD. Outpatient 24-hour timed urine collections were obtained. Participants were followed up for death for 5.9 ($\pm$ 1.9) years. Cox proportional hazards models evaluate the association between sex-specific BMI quintiles and mortality. There were 886 participants in our study population. Participants in higher quintiles of BMI were younger, 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 relationship. 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, however low muscle mass does not appear to explain why CHD patients with low BMI have worse survival.

Keywords

muscle; BMI; mortality; CHD

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INTRODUCTION

Using urinary creatinine excretion rate as an indirect measure of muscle mass, we demonstrated in a prior 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 among patients with coronary heart disease (CHD).¹ Thus, both low creatinine excretion rate and low body mass index (BMI) are markers of greater risk of death in persons with CHD. What is unknown, however, is whether the association of low BMI with mortality in patients with CHD²⁻⁴ is explained by low muscle mass. To that end, we evaluate 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 one of the following inclusion criteria: history of myocardial infarction or coronary revascularization, angiographic evidence of > 50% stenosis in ≥ 1 coronary vessels, 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. Between September 2000 and December 2002, 1024 participants enrolled and underwent a baseline study appointment that included a medical history, physical examination, and health status questionnaire. Outpatient 24-hour 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 (87%) participants.

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 appointment and to begin the collection from that point forward. Research personnel arrived at the patient's home 24 hours after the timed collection was initiated. If patients reported missing any urine or collections were < 1 or > 3 liters, collections were repeated. If participants were unable to collect all urine, no data were recorded. Urine volume was recorded (mL), and creatinine was measured by the rate Jaffe method. Urinary creatinine excretion was calculated in milligrams per day (urine volume [mL] times urine creatinine [mg/dL] divided by 100).

Between the baseline examination and May 1, 2009 annual telephone interviews were conducted with study participants (or their proxy) 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 not to 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 with a particle-enhanced immunonephelometric assay⁷ (N Latex Cystatin-C, Dade Behring, Inc, Deerfield, Ill) and used to calculate estimated GFR (eGFR_{cys}) with the following formula: $eGFR_{cys} = 76.7 \times \text{cystatin C}^{-1.19}$. This formula, which has been validated with comparison with iothalamate-measured GFR 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-density lipoprotein (HDL) cholesterol were measured with standard clinical chemistry analyzers. High sensitivity C-reactive protein (CRP) was measured with the Roche (Indianapolis, Ind) and the Beckman Extended Range (Galway, Ireland) assays.⁹ Fasting glucose was measured by a standard clinical analyzer, and fasting insulin was measured by ELISA (Linco Research, St Charles, Mo). 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 method¹¹ and indexed to body surface area. Left ventricular ejection fraction was determined by biplane method of disks.¹² Exercise treadmill test by the modified Bruce protocol was performed and the maximum number of metabolic equivalents (METs) and heart rate achieved were recorded.

We began by exploring the association of sex-specific BMI quintiles in men (24.0 kg/m², 26.3 kg/m², 28.7 kg/m², 31.6 kg/m²) and women (24.6 kg/m², 27.4 kg/m², 30.0 kg/m², 34.6 kg/m²) with mortality. 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 were compared across BMI quintiles using ANOVA tests for continuous variables and the 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 sex-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. Prior analyses have demonstrated a linear relationship of urine creatinine excretion rate with 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 mL/min), an estimate of GFR. eGFR_{cys} provided another estimate of GFR that was independent of the quality of timed urine collections and of creatinine kinetics. Because the eGFR_{cys} estimate is given as GFR normalized to body surface area, to compare the two renal function estimates, measured creatinine clearance was divided by body surface area and multiplied by 1.73.

We also explored whether measures of subclinical cardiovascular disease might attenuate the associations of BMI with mortality in our population. We stratified the outcome of mortality into early (< 3 years from enrollment) versus late mortality ($\geq$ 3 years from enrollment). This cut-point was chosen as the half-way point of the median follow-up in our study (6 years). Additional analyses evaluated whether adjustment for self-reported overall health (on a 5-point Likert 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, NC, USA). P-values < 0.05 were considered statistically significant.

RESULTS

The mean age of the 886 participant study population was 66.8 ($\pm$ 10.9) years. 82% were male, reflecting heavy sampling from a VA medical center. The mean BMI was 28.4 ($\pm$ 5.3) kg/m². Mean follow-up time was 5.9 ($\pm$ 1.9) years, during which time 273 participants died, 22 of whom were women. Baseline characteristics of the study population by sex-specific BMI quintiles are shown in Table 1.

BMI and urinary creatinine excretion rate were directly correlated (Pearson correlation coefficient 0.35, $P < .0001$). 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/m² greater BMI was associated with a 21% lower risk of death (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.68–0.91). Adjustment for major demographic variables, cardiovascular risk factors and kidney function did not attenuate the relationship (HR per 5 kg/m² greater 0.80; 95% CI 0.68–0.94). Additional adjustment for urinary creatinine excretion rate did not change the association between BMI and all-cause mortality (HR 0.82; 95% CI 0.69–0.96; Figure 1).

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

We also evaluated whether the association of BMI with mortality was similar among individuals who died within < 3 years from enrollment versus later. In this analysis, the inverse association between BMI and all-cause mortality appeared stronger among individuals who died early compared with 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).

As low BMI in persons 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 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 relationship between low BMI and mortality observed among CHD patients. We found that while 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 (ESRD).^{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 Our study took a similar approach in persons with stable CHD. Unlike findings in ESRD patients, our results demonstrate that the inverse association between BMI and mortality was not explained by muscle mass in persons 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 individuals who died < 3 years from enrollment. This suggests the possibility of reverse causality; individuals 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 U.S. population, risk of mortality among those with lower BMI was substantially reduced when the first five years of follow-up were excluded.²² Among 99,000 male physicians, the relative risk for death was lower in men with BMI < 20 kg/m² after excluding those who died within the first two 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, where 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 relationship 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 relationship between BMI and mortality. Self-reported overall health,^{25,26} METS achieved on the modified Bruce protocol treadmill test²⁷ and elevated left ventricular mass index have been found to be associated with worse outcomes.^{28,29} Thus, while 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 CHD patients with low BMI at greatest risk of death.

Our study had several strengths. It evaluated a large, well-characterized CHD cohort with a median 5.9 years of follow-up for mortality. Our study is one of a few that contains 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 echocardiograms. Our study also had some limitations. Subjects were older, mostly male, 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 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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References

1. Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: the Heart and Soul Study. *Circulation*. 2010; 121:1295–1303. [PubMed: 20212276]
2. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006; 368:666–678. [PubMed: 16920472]
3. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005; 366:1640–1649. [PubMed: 16271645]
4. Galal W, van Domburg RT, Feringa HH, Schouten O, Elhendy A, Bax JJ, Awara AM, Klein J, Poldermans D. Relation of body mass index to outcome in patients with known or suspected coronary artery disease. *Am J Cardiol*. 2007; 99:1485–1490. [PubMed: 17531566]
5. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008; 300:2379–2388. [PubMed: 19033588]
6. Ix JH, Shlipak MG, Liu HH, Schiller NB, Whooley MA. Association between renal insufficiency and inducible ischemia in patients with coronary artery disease: the heart and soul study. *J Am Soc Nephrol*. 2003; 14:3233–3238. [PubMed: 14638921]
7. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest*. 1999; 59:1–8. [PubMed: 10206092]
8. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008; 51:395–406. [PubMed: 18295055]
9. Whooley MA, Caska CM, Hendrickson BE, Rourke MA, Ho J, Ali S. Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. *Biol Psychiatry*. 2007; 62:314–320. [PubMed: 17434456]
10. Ix JH, Shlipak MG, Chertow GM, Ali S, Schiller NB, Whooley MA, Cystatin C. left ventricular hypertrophy, and diastolic dysfunction: data from the Heart and Soul Study. *J Card Fail*. 2006; 12:601–607. [PubMed: 17045178]
11. Byrd BF 3rd, Wahr D, Wang YS, Bouchard A, Schiller NB. Left ventricular mass and volume/mass ratio determined by two-dimensional echocardiography in normal adults. *J Am Coll Cardiol*. 1985; 6:1021–1025. [PubMed: 2931468]
12. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989; 2:358–367. [PubMed: 2698218]
13. Hallin R, Gudmundsson G, Suppli Ulrik C, Nieminen MM, Gislason T, Lindberg E, Brondum E, Aine T, Bakke P, Janson C. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). *Respir Med*. 2007; 101:1954–1960. [PubMed: 17532198]
14. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1999; 160:1856–1861. [PubMed: 10588597]

15. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. *Eur Respir J*. 2002; 20:539–544. [PubMed: 12358326]
16. Gonzalez-Reimers E, Garcia-Valdecasas-Campelo E, Santolaria-Fernandez F, Sanchez-Perez MJ, Rodriguez-Rodriguez E, Gomez-Rodriguez MA, Vina-Rodriguez J. Prognostic value of nutritional status in alcoholics, assessed by double-energy X-ray absorptiometry. *Alcohol Alcohol*. 2008; 43:314–319. [PubMed: 18310599]
17. Mendenhall CL, Tosch T, Weesner RE, Garcia-Pont P, Goldberg SJ, Kiernan T, Seeff LB, Sorell M, Tamburro C, Zetterman R. VA cooperative study on alcoholic hepatitis. II: Prognostic significance of protein-calorie malnutrition. *Am J Clin Nutr*. 1986; 43:213–218. [PubMed: 3080866]
18. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr*. 2004; 80:324–332. [PubMed: 15277152]
19. Kakiya R, Shoji T, Tsujimoto Y, Tatsumi N, Hatsuda S, Shinohara K, Kimoto E, Tahara H, Koyama H, Emoto M, Ishimura E, Miki T, Tabata T, Nishizawa Y. Body fat mass and lean mass as predictors of survival in hemodialysis patients. *Kidney Int*. 2006; 70:549–556. [PubMed: 16788699]
20. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW. Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2001; 16:2386–2394. [PubMed: 11733631]
21. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. *J Am Soc Nephrol*. 2003; 14:2366–2372. [PubMed: 12937315]
22. Freedman DM, Ron E, Ballard-Barbash R, Doody MM, Linet MS. Body mass index and all-cause mortality in a nationwide US cohort. *Int J Obes (Lond)*. 2006; 30:822–829. [PubMed: 16404410]
23. Gelber RP, Kurth T, Manson JE, Buring JE, Gaziano JM. Body mass index and mortality in men: evaluating the shape of the association. *Int J Obes (Lond)*. 2007; 31:1240–1247. [PubMed: 17342077]
24. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010; 363:2211–2219. [PubMed: 21121834]
25. Norekval TM, Fridlund B, Rokne B, Segadal L, Wentzel-Larsen T, Nordrehaug JE. Patient-reported outcomes as predictors of 10-year survival in women after acute myocardial infarction. *Health Qual Life Outcomes*. 2010; 8:140. [PubMed: 21108810]
26. Heidrich J, Liese AD, Lowel H, Keil U. Self-rated health and its relation to all-cause and cardiovascular mortality in southern Germany. Results from the MONICA Augsburg cohort study 1984–1995. *Ann Epidemiol*. 2002; 12:338–345. [PubMed: 12062922]
27. Johnson NP, Wu E, Bonow RO, Holly TA. Relation of exercise capacity and body mass index to mortality in patients with intermediate to high risk of coronary artery disease. *Am J Cardiol*. 2008; 102:1028–1033. [PubMed: 18929704]
28. Burchfiel CM, Skelton TN, Andrew ME, Garrison RJ, Arnett DK, Jones DW, Taylor HA Jr. Metabolic syndrome and echocardiographic left ventricular mass in blacks: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2005; 112:819–827. [PubMed: 16061739]
29. Quinones MA, Greenberg BH, Kopelen HA, Koilpillai C, Limacher MC, Shindler DM, Shelton BJ, Weiner DH. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. *Studies of Left Ventricular Dysfunction*. *J Am Coll Cardiol*. 2000; 35:1237–1244. [PubMed: 10758966]

Figure 1.
Hazard Ratio for Mortality by Sex-Specific Body Mass Index (BMI) Quintiles

Table 1

Characteristics of the study cohort (N=886)

BMI sex-specific quintiles	Q1 (N=177)	Q2 (N=177)	Q3 (N=177)	Q4 (N=178)	Q5 (N=177)	P-value
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
BMI (kg/m ²), 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	<0.001
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
Prior myocardial infarction	61%	53%	49%	57%	52%	0.2
Prior stroke/TIA	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
HDL cholesterol (mg/dL)	51 ± 17	48 ± 16	46 ± 12	43 ± 13	41 ± 10	<0.001
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	<0.001
eGFR _{MDRD} (ml/min/1.73m ²)*	77 ± 26	76 ± 23	75 ± 20	76 ± 23	79 ± 21	0.4
eGFR _{Cys} (ml/min/1.73m 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 hours)	1110 ± 331	1282 ± 354	1313 ± 372	1422 ± 393	1624 ± 484	<0.001
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	<0.001
Maximum heart rate achieved on Bruce treadmill testing (bpm)	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

* $eGFR_{MDRD} = \text{estimated glomerular filtration rate by the MDRD equation } [186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})]$

[†] $eGFR_{CYS} = \text{estimated glomerular filtration rate by Cystatin C equation } (76.7 \times \text{cystatin C}^{-1.19})$

Table 2

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

Body mass index in sex-specific quintiles	Q1	Q2	Q3	Q4	Q5	Per 5 kg/m ² increase
All-cause mortality N (% per person years)	60 (6.13)	51 (5.07)	43 (4.07)	48 (4.51)	35 (3.24)	
Unadjusted model HR (95% CI)	1.0 (ref)	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 (ref)	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 (ref)	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)

* P<0.05

[†] Patient characteristics: age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack years, CRP, eGFR/CYS, total cholesterol, HDL cholesterol, serum albumin, urine albumin concentration

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)

Body mass index by sex-specific quintiles	Q1	Q2	Q3	Q4	Q5	Per 5 kg/m ² increase
All-cause mortality N (% per person years)	26 (6.52)	17 (5.32)	12 (3.74)	14 (5.72)	5 (2.28)	
Unadjusted model	1.0 (ref)	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)
HR (95% CI)						
Adjusted for patient characteristics [†]	1.0 (ref)	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)
HR (95% CI)						
Additional adjustment for urinary creatinine excretion	1.0 (ref)	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)
HR (95% CI)						

* P<0.05

[†] Patient characteristics: age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack years, CRP, eGFR, CYS, total cholesterol, HDL cholesterol, serum albumin, urine albumin concentration

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*

Body mass index in sex specific quintiles	Q1	Q2	Q3	Q4	Q5	Per 5 kg/m ² increase
EARLY DEATH (<3 years from enrollment)[‡]	1.0 (ref)	0.83 (0.45–1.51)	0.54 (0.27–1.07)	0.45 [‡] (0.22–0.91)	0.39 [‡] (0.18–0.85)	0.66 [‡] (0.46–0.96)
N=80	N= 24	N= 21	N= 13	N= 12	N= 10	
LATE DEATH (≥ 3 years from enrollment)[‡]	1.0 (ref)	0.91 (0.55–1.52)	0.85 (0.50–1.43)	0.97 (0.58–1.61)	0.73 (0.41–1.28)	0.91 (0.75–1.12)
N=157	N= 36	N= 31	N= 29	N= 37	N= 24	

* Adjusted for patient characteristics: age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack years, CRP, eGFR/CYS, total cholesterol, HDL cholesterol, serum albumin, urine albumin concentration

[‡] P<0.05

Table 5

Association between body mass index (per 1kg/m² increase) and all-cause mortality adjusted for select patient variables

	HR with 95% CI	P-value
Adjusted for patient characteristics only*	0.96 (0.93 – 0.99)	<0.001
Patient characteristics + adjustment for urinary creatinine excretion	0.96 (0.94 – 0.99)	0.018
Patient characteristics + self-reported overall health	0.96 (0.93 – 0.99)	<0.001
Patient characteristics + METS achieved on Bruce Protocol	0.94 (0.91 – 0.97)	<0.001
Patient characteristics + left ventricular mass index	0.96 (0.93 – 0.99)	<0.001
Patient characteristics + all variables above	0.94 (0.92 – 0.97)	<0.001

* Patient characteristics: age, race, gender, family history of CHD, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, tobacco use, tobacco pack years, CRP, eGFR_{CYS}, total cholesterol, HDL cholesterol, serum albumin, urine albumin concentration