The Obesity Paradox, Cardiorespiratory Fitness, and Coronary Heart Disease

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Abstract

Objective: To investigate associations of cardiorespiratory fitness (CRF) and different measures of adiposity with cardiovascular disease (CVD) and all-cause mortality in men with known or suspected coronary heart disease (CHD).

Patients and Methods: We analyzed data from 9563 men (mean age, 47.4 years) with documented or suspected CHD in the Aerobics Center Longitudinal Study (August 13, 1977, to December 30, 2002) using baseline body mass index (BMI) and CRF (quantified as the duration of a symptom-limited maximal treadmill exercise test). Waist circumference (WC) and percent body fat (BF) were measured using standard procedures.

Results: There were 733 deaths (348 of CVD) during a mean follow-up of 13.4 years. After adjustment for age, examination year, and multiple baseline risk factors, men with low fitness had a higher risk of all-cause mortality in the BMI categories of normal weight (hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.24-2.05), obese class I (HR, 1.38; 95% CI, 1.04-1.82), and obese class II/III (HR, 2.43; 95% CI, 1.55-3.80) but not overweight (HR, 1.09; 95% CI, 0.88-1.36) compared with the normal-weight and high-fitness reference group. We observed a similar pattern for WC and percent BF tertiles and for CVD mortality. Among men with high fitness, there were no significant differences in CVD and all-cause mortality risk across BMI, WC, and percent BF categories.

Conclusion: In men with documented or suspected CHD, CRF greatly modifies the relation of adiposity to mortality. Using adiposity to assess mortality risk in patients with CHD may be misleading unless fitness is considered.

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A decade ago, Gruberg and colleagues¹ coined the term *obesity paradox* to describe their unexpected finding that overweight and obese patients undergoing percutaneous coronary intervention had lower mortality rates than their normal-weight counterparts. Since then, this counterintuitive phenomenon has been observed in a range of cardiovascular disease (CVD) pathologies and in several patient groups without CVD,² suggesting that the obesity paradox is less population-specific than originally thought. Moreover, the spectrum of patients in whom the obesity paradox occurs is not well defined. For example, one recent report³ observed the obesity paradox in patients without coronary heart disease (CHD) as determined by stress single-photon emission computed tomography myocardial perfusion imaging. Nevertheless, the most consistent evidence for the obesity paradox to date is in patients with known or suspected CHD. For example, in their large meta-analysis of 40 studies with more than 250,000 patients with CHD, Romero-Corral and colleagues⁴ found no increased total mortality even among patients with body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) greater than or equal to 35 kg/m².

Although higher levels of adiposity are associated with increased mortality risk in men in the Aerobics Center Longitudinal Study (ACLS), higher levels of cardiorespiratory fitness (CRF) attenuate this association.⁵ To our knowledge, only 2 studies have specifically addressed this issue in patients with known or suspected CHD.^{6,7} In both studies, when stratified by fitness, the inverse association of BMI with mortality was nullified among patients with high fitness but persisted among those with low fitness. Although these findings demonstrate that CRF modifies associations of BMI with total mortality in patients with CHD, neither study included measures of subcutaneous body fat (BF) or examined CVD mortality. Therefore, our aim was to evaluate the relationship of different measures of adiposity, including BMI, waist circumference (WC), and percent BF, and CRF with CVD and all-cause mortality in men with documented or suspected CHD from the ACLS.

PATIENTS AND METHODS

Data Description

Data for the present study are from the ACLS, a prospective epidemiological study of patients who underwent extensive health examinations at the Cooper Clinic in Dallas, Texas. Between 1977 and

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2002, 10,363 men with documented myocardial infarction or suspected (chest pain or abnormal exercise electrocardiogram [ECG]) CHD received a comprehensive medical examination that included a maximal treadmill exercise test. Patients were unpaid volunteers, sent by their employers or doctors or self-referred, and gave informed consent to participate in the study. The Cooper Institute Institutional Review Board reviewed and approved the study protocol annually.

Participants were excluded from the current analysis if they were underweight (BMI <18.5 kg/m²) (n=361), had a history of stroke (n=43) or cancer (n=75), died during the first year of follow-up (n=96), or had missing data on any one of the 3 adiposity measures (n=225). These criteria resulted in 9563 men, aged 20 to 84 years, who were followed up until date of death or December 31, 2003. Participants were predominantly white, well-educated, and within the middle-to-upper socioeconomic strata.

Data on clinical examinations, as well as measures of adiposity and CRF, are described elsewhere.⁸⁻¹⁰ Blood pressure was measured with standard auscultatory methods after the participant had been seated for 5 minutes. Systolic and diastolic blood pressures were recorded as the first and fifth Korotkoff sounds, respectively. Hypertension (HTN) was defined as systolic blood pressure greater than or equal to 140 mm Hg and/or diastolic blood pressure greater than or equal to 90 mm Hg, or a physician diagnosis. Abnormal exercise ECG responses included rhythm and conduction disturbances and ischemic ST-T wave abnormalities, as described in detail elsewhere.¹¹ Previously, we found 90% agreement between the ECG interpretation recorded in our database and a group of 3 physicians who read a random sample of 357 patient records.¹¹ Fasting plasma glucose and total cholesterol levels were determined in the Cooper Clinic clinical chemistry laboratory, which participates in and meets the quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. Diabetes mellitus (DM) was defined as a fasting glucose concentration of greater than or equal to 126 mg/dL (to convert mg/dL to mmol/L, multiply by 0.0555), previous physician diagnosis, or use of insulin. Hypercholesterolemia was defined as a total cholesterol concentration of greater than or equal to 240 mg/dL (to convert mg/dL to mmol/L, multiply by 0.0259) or previous physician diagnosis. Personal history of myocardial infarction, stroke, HTN, DM, and cancer; family history of CVD; smoking habits; alcohol intake; and physical activity habits were obtained from a standardized questionnaire.

Cardiorespiratory Fitness

We determined CRF by a maximal treadmill exercise test using a modified Balke protocol¹² as previously described.⁸⁻¹⁰ The test end point was volitional exhaustion or termination by the physician for medical reasons. Total test time correlates highly ($r=0.92$) with directly measured maximal oxygen uptake in men.¹³ To standardize interpretation of exercise test performance, maximal metabolic equivalents (METs; 1 MET = 3.5 mL O₂ uptake/kg per min) were estimated on the basis of the final treadmill speed and grade.¹⁴ Cardiorespiratory fitness results were grouped for our primary analysis using age-specific tertiles of the maximal exercise duration.

Adiposity Measures

Body mass index was computed from measured weight and height. Percent BF was assessed with hydrostatic weighing, with the sum of 7 skinfold measures, or with both assessments, following standardized protocols.¹⁵ A detailed description of our hydrodensitometry procedures has been published elsewhere.⁵ Waist circumference was measured level with the umbilicus. Body mass index exposure groups were based on standard clinical definitions: normal-weight BMI (18.5-24.9), overweight (25.0-29.9), moderately obese (class I) (30.0-34.9), and severely obese (class II/III) (≥ 35.0). For groups based on percent BF and WC, we used specific tertiles from this population.

Vital Status

All participants were followed up from the date of their baseline examination until their date of death or until December 31, 2003. We used the National Death Index as the primary data source for mortality surveillance, augmented with official death certificates obtained from the department of vital records within the decedent's state of residence. The National Death Index has been shown to be an accurate method of ascertaining deaths in observational studies, having high sensitivity (96%) and specificity (100%).¹⁶

Statistical Analyses

Descriptive analyses summarized baseline characteristics of all participants by BMI groups. The mean levels of continuous variables were compared using the Jonckheere-Terpstra test; to account for the ordered nature of the categories, the χ^2 test for linear trend was used to compare the distribution of categorical variable values. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), according to exposure categories: CRF, BMI, percent BF, or WC.

TABLE 1. Baseline Characteristics of Participants With Documented or Suspected Coronary Heart Disease, by Body Mass Index Groups

Characteristic	Body mass index groups ^a				P for linear trend
	Normal (n=3286)	Overweight (n=4648)	Obese I (n=1317)	Obese II/III (n=312)	
Age (y)	46.9±11.7	47.8±10.2	47.4±9.7	45.7±9.6	.011
Body mass index (kg/m ²)	23.2±1.3	27.2±1.4	31.9±1.3	38.7±3.7	<.001
Waist circumference (cm)	86.0±5.8	96.0±6.4	107.6±6.4	122.6±11.7	<.001
Body fat (%)	17.8±4.7	23.3±4.3	28.4±4.0	34.0±4.0	<.001
Treadmill time (min)	19.3±5.0	16.5±4.4	13.9±4.0	10.4±3.5	<.001
Maximal metabolic equivalents	12.3±2.5	10.9±2.1	9.8±1.8	8.1±1.6	<.001
Total cholesterol (mg/dL) ^b	203.9±38.9	215.0±42.1	217.4±42.4	211.6±38.9	<.001
Fasting blood glucose (mg/dL) ^c	98.0±13.3	101.9±18.5	106.8±26.1	115.7±39.1	<.001
Blood pressure (mm Hg)					
Systolic	119.8±14.4	122.7±14.0	126.7±14.0	131.7±15.1	<.001
Diastolic	78.9±9.0	82.1±9.2	85.4±9.5	87.7±10.0	<.001
Physically inactive, ^d No. (%)	652 (19.8)	1277 (27.5)	439 (33.3)	130 (41.7)	<.001
Current smokers, No. (%)	497 (15.1)	813 (17.5)	252 (19.1)	63 (20.2)	<.001
Heavy drinkers, ^e No. (%)	282 (8.6)	526 (11.3)	137 (10.4)	29 (9.3)	.028
Baseline medical conditions, No (%)					
Hypercholesterolemia	866 (26.4)	1788 (38.5)	558 (42.4)	122 (39.1)	<.001
Diabetes mellitus	93 (2.8)	249 (5.4)	144 (10.9)	51 (16.3)	<.001
Hypertension	827 (25.2)	1743 (37.5)	717 (54.4)	202 (64.7)	<.001

^aValues are mean ± SD unless otherwise indicated.^bTo convert mg/dL to mmol/L, multiply by 0.0259.^cTo convert mg/dL to mmol/L, multiply by 0.0555.^dDefined as reporting no physical activity during leisure time in the 3 mo before the examination.^eDefined as >14 drinks/wk.

In multivariable analyses, we adjusted for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/wk or not), hypercholesterolemia, HTN and DM (present or not for each), and family history of CVD (model 1). Then, we additionally adjusted for BMI, WC, and percent BF when CRF was the exposure, or for CRF (treadmill test duration in minutes) when BMI, WC, or percent BF was the exposure (model 2).

To determine whether the association between adiposity and mortality in CHD patients differed by age, we used BMI categories as the exposure and examined the association in younger men (<55 years) and older men (≥55 years). We also examined whether this association varied by follow-up time, analyzing separately CHD patients who were followed up for less than 10 years and for 10 or more years. The joint impact of adiposity and CRF was examined by using combined groups. We created 8 categories based on categories of BMI (normal-weight BMI, overweight, moderately obese [class I], and severely obese [class II/III]) and dichotomized these into low fitness (lower tertile) and high fitness (middle and upper tertiles). We created 6 categories

based on tertiles of WC and percent BF and also dichotomized these into low and high fitness. Reference groups were high fitness-normal BMI, -lower WC tertile, and -lower percent BF tertile, respectively. Cumulative hazard plots grouped by exposures suggested no appreciable violations of the proportional hazards assumption. Data analyses were performed using PASW statistical package version 18.0 (SPSS Inc, Chicago, IL), and all P values are 2-sided with an α level of .05.

RESULTS

During a mean follow-up of 13.4 years (range, 1.0-26.4 years), there were 733 deaths (348 due to CVD), resulting in 57.2 all-cause and 27.2 CVD deaths per 10,000 man-years of follow-up. Overall, the mean (SD) age of men participating in this study was 47.4 (10.7) years at baseline. Compared with the normal-weight group, significant trends across ascending BMI groups included decreasing age ($P=.011$); decreasing maximal METs ($P<.001$); and higher prevalence of physical inactivity ($P<.001$), current smokers ($P<.001$), hypercholesterolemia

TABLE 2. Hazard Ratios for All-Cause and Cardiovascular Disease Mortality in Men With Documented or Suspected Coronary Heart Disease^a

Characteristic	No. of patients	No. of deaths		All-cause mortality		CVD mortality	
		All-cause	CVD	Model 1 ^b	Model 2 ^c	Model 1 ^b	Model 2 ^c
CRF							
Low	3193	354	190	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Middle	3170	209	88	0.72 (0.60-0.86)	0.69 (0.58-0.83)	0.59 (0.46-0.77)	0.58 (0.45-0.76)
Upper	3200	170	70	0.65 (0.54-0.80)	0.60 (0.48-0.74)	0.54 (0.40-0.73)	0.51 (0.37-0.70)
BMI (kg/m ²)							
18.5-24.9	3286	303	131	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25-29.9	4648	314	159	0.82 (0.70-0.97)	0.73 (0.61-0.86)	0.96 (0.76-1.22)	0.80 (0.63-1.03)
30-34.9	1317	91	42	0.99 (0.78-1.27)	0.80 (0.62-1.03)	1.03 (0.72-1.47)	0.76 (0.52-1.10)
≥35	312	25	16	2.07 (1.36-3.16)	1.42 (0.91-2.21)	3.31 (1.92-5.72)	1.93 (1.08-3.45)
Body fat (%)							
Low (<20)	3228	240	101	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Middle (20-25)	3115	222	113	0.86 (0.72-1.03)	0.76 (0.63-0.92)	1.03 (0.78-1.35)	0.87 (0.66-1.14)
Upper (>25)	3220	271	134	0.97 (0.81-1.16)	0.77 (0.63-0.93)	1.08 (0.83-1.42)	0.78 (0.58-1.03)
Waist circumference (cm)							
Low (<90)	3341	264	114	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Middle (90-98)	3073	218	105	0.82 (0.68-0.98)	0.74 (0.61-0.89)	0.91 (0.69-1.19)	0.79 (0.60-1.04)
Upper (>98)	3149	251	129	0.95 (0.79-1.14)	0.76 (0.63-0.93)	1.11 (0.85-1.45)	0.81 (0.61-1.08)

^aBMI = body mass index; CHD = coronary heart disease; CRF = cardiorespiratory fitness; CVD = cardiovascular disease.

^bAdjusted for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/wk or not), hypercholesterolemia, hypertension and diabetes (present or not for each), and family history of CVD.

^cAll variables in model 1 plus BMI, body fat, and waist circumference (as continuous variables) for CRF, or CRF (as a continuous variable) for BMI, body fat, and waist circumference.

($P<.001$), DM ($P<.001$), and HTN ($P<.001$) (Table 1).

Hazard ratios for all-cause and CVD mortality according to CRF and adiposity categories are shown in Table 2. After adjustment for age, baseline examination year, physical activity, smoking, alcohol intake, hypercholesterolemia, HTN, DM, and family history of CVD (model 1), men in the middle and upper thirds of CRF had 28% and 35% lower risks of total mortality compared with men in the lower third of CRF. Additional adjustment for BMI, WC, and percent BF (model 2) did not appreciably alter these results. We also modeled each adiposity measure separately, and the results were nearly identical. Similar inverse associations were observed between CRF and CVD death. Across the adiposity categories, in the fully adjusted model (model 2), there were between 24% and 27% lower risks of total mortality at the next higher levels of adiposity (BMI of 25.0-29.9 kg/m² and the middle thirds of percent BF and WC) than in the normal-weight and lower-third counterparts, respectively. There was a similar lower all-cause mortality risk among the upper thirds of percent BF and WC, but not for BMI of 30.0-34.9 kg/m² (moderately obese) or greater than

or equal to 35.0 kg/m² (severely obese), in which risks of total mortality did not differ significantly from those of the normal-weight group. Except for the severely obese group, which was associated with 93% higher risk of CVD mortality, higher levels of adiposity neither provided protection against nor contributed to CVD mortality.

Hazard ratios of all-cause and CVD mortality according to BMI group stratified by age and follow-up time are presented in Table 3. Among men younger than 55 years, all-cause mortality risk in the overweight and obese groups did not differ significantly from that in the normal-weight reference group. Only the severely obese group had a higher risk for CVD mortality (HR, 2.78; 95% CI, 1.25-6.16). In contrast, among men older than 55 years, overweight men remained at lower risk for all-cause mortality (HR, 0.61; 95% CI, 0.49-0.77) and CVD mortality (HR, 0.58; 95% CI, 0.42-0.80); moderately obese men had no higher risk of all-cause mortality and a lower CVD mortality risk (HR, 0.59; 95% CI, 0.35-0.99); and severely obese men had no higher risk for all-cause mortality or CVD mortality. Stratification for follow-up of less than 10 years and 10 or more years had little effect on our findings,

TABLE 3. Hazard Ratios for All-Cause and Cardiovascular Disease Mortality According to Body Mass Index and Stratified by Age or Follow-up Time^a

	No. of patients	No. of deaths		HR (95% CI) ^b	
		All-cause	CVD	All-cause mortality	CVD mortality
Age <55 y	7389	326	145		
18.5-24.9	2517	111	33	1.00 (reference)	1.00 (reference)
25.0-29.9	3560	157	78	0.91 (0.70-1.17)	1.36 (0.89-2.08)
30.0-34.9	1044	41	23	0.77 (0.52-1.15)	1.16 (0.65-2.09)
≥35	268	17	11	1.61 (0.90-2.88)	2.78 (1.25-6.16)
Age ≥55 y	2174	407	203		
18.5-24.9	769	192	98	1.00 (reference)	1.00 (reference)
25.0-29.9	1088	157	81	0.61 (0.49-0.77)	0.58 (0.42-0.80)
30.0-34.9	273	50	19	0.87 (0.63-1.22)	0.59 (0.35-0.99)
≥35	44	8	5	1.33 (0.63-2.80)	1.54 (0.59-4.04)
Follow-up <10 y	3353	287	142		
18.5-24.9	848	118	52	1.00 (reference)	1.00 (reference)
25.0-29.9	1710	127	71	0.99 (0.75-1.31)	1.24 (0.83-1.86)
30.0-34.9	611	30	13	1.07 (0.68-1.67)	1.04 (0.53-2.04)
≥35	184	12	6	2.33 (1.19-4.59)	2.38 (0.90-6.26)
Follow-up ≥10 y	6210	446	206		
18.5-24.9	2438	185	79	1.00 (reference)	1.00 (reference)
25.0-29.9	2938	187	88	0.72 (0.58-0.89)	0.72 (0.52-1.00)
30.0-34.9	706	61	29	0.96 (0.70-1.32)	0.91 (0.57-1.44)
≥35	128	13	10	1.58 (0.87-2.88)	2.59 (1.25-5.37)

^aCI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.

^bMultivariable analysis adjusted for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/wk or not), hypercholesterolemia, hypertension and diabetes (present or not for each), family history of CVD, and cardiorespiratory fitness (treadmill test duration).

except in the severely obese group, in which CVD mortality risk was higher for follow-up of 10 or more years (HR, 2.59; 95% CI, 1.25-5.37) but failed to reach significance for follow-up of less than 10 years.

Finally, we evaluated the influence of joint associations of CRF and adiposity measure on all-cause mortality (Figure 1) and CVD mortality (Figure 2) in multivariate analysis. Among men with high fitness, all-cause and CVD mortality risks across BMI categories of overweight, moderately obese, and severely obese did not differ significantly from risks in the normal-weight and high-fitness reference group. In contrast, among men with low fitness, a higher risk of all-cause mortality was found across BMI categories of normal weight (HR, 1.60; 95% CI, 1.24-2.05), moderately obese (HR, 1.38; 95% CI, 1.04-1.82), and severely obese (HR, 2.43; 95% CI, 1.55-3.80), but not overweight (HR, 1.09; 95% CI, 0.88-1.36). A similar pattern was observed among men with low fitness for CVD mortality, except that overweight

men had a higher risk (HR, 1.46; 95% CI, 1.07-2.00). Similar patterns among men with low and high fitness for all-cause and CVD mortality were seen for WC and percent BF.

DISCUSSION

Previous studies of patients with established CHD have consistently demonstrated that individuals with higher BMI have a lower mortality risk than their normal-weight counterparts,^{1,2,4} and recent evidence suggests that this extends to patients with only suspected CHD.³ In contrast to results of previous studies from the broad population of ACLS participants, in the current study of ACLS men with known or suspected CHD, overweight men had a lower risk for all-cause mortality compared with their normal-weight counterparts, and the pattern of association was similar whether WC or percent BF was used as the adiposity exposure. Furthermore, men with higher levels of WC, percent BF, or BMI up to 35.0 kg/m² had CVD mortality risks that did

FIGURE 1. Joint effects of cardiorespiratory fitness and body mass index (BMI) (A), waist circumference (WC) (B), and percent body fat (BF) (C), on all-cause mortality. Hazard ratios (boxes) and 95% confidence intervals (error bars represent values) after adjusting for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/wk or not), hypercholesterolemia, hypertension and diabetes (present or not for each), and family history of cardiovascular disease.

not differ significantly from those of their respective reference groups. Only men who were severely obese (BMI, ≥ 35.0 kg/m²) and younger than 55 years had a higher CVD mortality risk; the CVD mortality risk for severely obese men aged 55 years and older did not differ significantly from that of their normal-weight counterparts.

Our results on associations of BMI with all-cause and CVD mortality were nearly identical to the main findings of the large systematic review and meta-analysis of 40 studies with more than 250,000 coronary artery disease patients by Romero-Corral et al.⁴ Specifically, we found that (1) overweight men had approximately 25% lower, and obese men had no higher, all-cause mortality risk than their normal-weight counterparts and (2) CVD mortality

risk was higher (by nearly 2-fold) only for men who were severely obese. However, when data were stratified by age, we found that the higher CVD mortality risk only applied to men who were younger than 55 years.

Comparatively few studies of the obesity paradox have used measures of adiposity other than BMI. Two recent reports in CHD patients showed that the obesity paradox was not present if central obesity was considered,^{6,17} a finding that was not supported by our data with WC. However, in their recent studies of 529 and 581 patients, respectively, with CHD, Lavie et al^{18,19} found that both higher BMI and higher percent BF were independently associated with a lower mortality risk; in fact, those with combined low BMI and low BF had markedly higher mortality during 3-year fol-

FIGURE 2. Joint effects of cardiorespiratory fitness and body mass index (BMI) (A), waist circumference (WC) (B), and percent body fat (BF) (C), on cardiovascular disease (CVD) mortality. Hazard ratios (boxes) and 95% confidence intervals (error bars represent values) after adjusting for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/wk or not), hypercholesterolemia, hypertension and diabetes (present or not for each), and family history of CVD. Obese categories (I/II/III) were joined because of the small number of cases.

low-up compared with other CHD patients. The current analysis of a large patient cohort, using percent BF with 13-year mortality, confirms the results of these smaller studies. Taken together, these findings demonstrate that the obesity paradox should not be dismissed as an anomaly due to the limitations of BMI, as some have urged.²⁰

Several theories have been advanced in an attempt to explain the obesity paradox, including the finding that in most studies the obese population is younger²¹ and the observed protective effect may be limited to the relatively short follow-up period of most studies.²² Although these factors at least partially may explain the obesity paradox in some prospective studies, the patients in our study were homogeneous with respect to age and were followed for mortality for 13 years. Others have suggested that obese patients may receive better medical care

sooner,²³ a possibility that cannot be ruled out in the present study. Finally, it has been suggested that the obesity paradox may be due in part to unintentional weight loss before study entry, leading to a worse prognosis in the normal-weight group during follow-up.^{24,25} For example, Strandberg et al,²⁶ in a long-term follow-up study in 1114 Finnish men, found that subsequent weight decrease among overweight patients and high CVD risk in midlife (mean age, 47 years) predicted the worst prognosis in late life (mean age, 73 years). However, Lavie et al¹⁸ evaluated purposeful weight loss in 529 overweight and obese CHD patients and found that although 3-year mortality risk only trended lower for those who lost weight, several CVD risk factors and behavioral factors were markedly improved. Several other recent studies support the beneficial effects of purposeful weight loss in overweight and obese CHD

patients.²⁷ Taken together, these studies raise important questions about the potential benefits of purposeful vs unintentional weight loss for overweight and obese CHD patients.

In 2 landmark ACLS reports, Lee et al⁵ and Wei et al²⁸ found that although obese men had a higher all-cause and CVD mortality risk than lean men, obese men who were fit were no more likely to die than lean men who were fit. These findings, as well as subsequent findings from the ACLS and several other studies included in a recent systematic review by Fogelholm,²⁹ provide ample evidence that CRF greatly modifies the association of adiposity with mortality. Given such strong evidence for CRF as an effect modifier in the general population, it is surprising that there are such limited data on the influence of CRF on the obesity paradox. To our knowledge, only 2 studies have specifically addressed this issue,^{6,7} and both studies found that the obesity paradox was neutralized in fit patients but persisted among those who were unfit. The findings of the current study accord with these studies with respect to fit, but not unfit, men. For example, overweight and unfit men had a 46% higher CVD mortality risk than normal-weight and fit men. This difference may be due to the younger and potentially healthier reference group of fit and normal-weight men in our study than the older participants in the aforementioned studies.

This study has several limitations. First, because we included men who were predominantly white and from middle-to-upper socioeconomic strata, our results may not extend to other patient populations. Second, CRF is a variable that is influenced by genetics and other factors, such as age and physical activity level.¹⁴ Third, because all exposure variables in this study were obtained from baseline measures only, we were unable to account for the influence of longitudinal changes on the results. Fourth, we lacked information on medication use (types, dosages, duration and efficacy of treatment). However, it is unlikely that this would be a meaningful confounder in this well-educated population of men receiving excellent medical care. Finally, because of limitations of the body composition techniques employed in this study, we were unable to evaluate the independent effect of muscle mass vs CRF.

CONCLUSION

These findings demonstrate that BMI and other standard measures of adiposity exert much less influence on survival in CHD patients than previously thought. Rather, it appears that CRF is more closely linked to mortality risk in populations exhibiting an obesity paradox. Our findings also suggest that strategies to reduce mortality risk in such populations should emphasize preserving or increasing CRF over weight loss.

Future studies should focus on the extent to which changes in fitness level and/or body weight affect mortality and other health outcomes.

Abbreviations and Acronyms: ACLS = Aerobics Center Longitudinal Study; BF = body fat; BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio; HTN = hypertension; WC = waist circumference

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