

Obesity Paradox and Cardiorespiratory Fitness in 12,417 Male Veterans Aged 40 to 70 Years

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OBJECTIVE: To evaluate the influence of cardiorespiratory fitness (fitness) on the obesity paradox in middle-aged men with known or suspected coronary artery disease.

PATIENTS AND METHODS: This study consists of 12,417 men aged 40 to 70 years (44% African American) who were referred for exercise testing at the Veterans Affairs Medical Centers in Washington, DC, or Palo Alto, CA (between January 1, 1983, and June 30, 2007). Fitness was quantified as metabolic equivalents achieved during a maximal exercise test and was categorized for analysis as low, moderate, and high (defined as <5, 5-10, and >10 metabolic equivalents, respectively). Adiposity was defined by body mass index (BMI) according to standard clinical guidelines. Separate and combined associations of fitness and adiposity with all-cause mortality were assessed by Cox proportional hazards analyses.

RESULTS: We recorded 2801 deaths during a mean \pm SD follow-up of 7.7 \pm 5.3 years. Multivariate hazard ratios (95% confidence interval) for all-cause mortality, with normal weight (BMI, 18.5-24.9 kg/m²) used as the reference group, were 1.9 (1.5-2.3), 0.7 (0.7-0.8), 0.7 (0.6-0.7), and 1.0 (0.8-1.1) for BMIs of less than 18.5, 25.0 to 29.9, 30.0 to 34.9, and 35.0 or more kg/m², respectively. Compared with highly fit normal-weight men, underweight men with low fitness had the highest (4.5 [3.1-6.6]) and highly fit overweight men the lowest (0.4 [0.3-0.6]) mortality risk of any subgroup. Overweight and obese men with moderate fitness had mortality rates similar to those of the highly fit normal-weight reference group.

CONCLUSION: Fitness altered the obesity paradox. Overweight and obese men had increased longevity only if they registered high fitness.

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BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MET = metabolic equivalent; VETS = Veterans Exercise Testing Study

Body mass index (BMI) has been widely used to evaluate the mortality risk associated with obesity. Although many large epidemiological studies of the general population report a positive association between BMI and mortality,¹⁻³ consistent inverse associations (the so-called obesity paradox) have been observed among patients with heart failure,⁴ coronary heart disease,^{5,6} hypertension,⁷ peripheral artery disease,⁸ type 2 diabetes,⁹ and chronic kidney disease.¹⁰ An obesity paradox has also been observed in healthier populations as diverse as San Francisco longshoremen,¹¹ Native American women of the Pima tribe,¹² men from rural Scotland,¹³ Nauruan men,¹⁴ and the elderly.¹⁵

Although substantial evidence for an obesity paradox has accumulated during the past decade,¹⁶ including a re-

cent examination of the influence of weight loss,¹⁷ the influence of cardiorespiratory fitness (fitness) has not been adequately explored. Objective measures of fitness from clinical exercise testing are not readily available. Consequently, few studies have examined the combined effects of fitness and BMI on mortality, and these data come from only 2 cohorts: the Lipid Research Clinics Study^{18,19} and the Aerobics Center Longitudinal Study.²⁰⁻²⁶ Collectively, these reports provide convincing evidence that fitness is a more powerful predictor of mortality than BMI. However, these findings are from populations without an obesity paradox.

The Veterans Exercise Testing Study (VETS) affords a unique opportunity to study simultaneous measures of fitness and adiposity in a large patient population exhibiting an obesity paradox. A previous report from our group provided compelling evidence that higher levels of fitness, as well as higher BMI, reduced mortality risk in men referred for exercise testing.²⁷ However, this report did not examine the combined effects of fitness and BMI on mortality. Such joint analyses may identify associations obscured in independent analyses alone. To avoid bias associated with age,²⁸ we confined our investigation to men aged 40 to 70 years. The purpose of the current study was to examine the influence of fitness on the obesity paradox in middle-aged men with known or suspected cardiovascular disease (CVD).

PATIENTS AND METHODS

VETS is an ongoing, prospective epidemiological investigation of veteran patients that began in 1983. All patients are referred for exercise testing either as a routine evaluation or as an evaluation for exercise-induced ischemia.

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Participants in the current study were drawn from a cohort of 15,660 male veterans (excluding patients with a history of implanted pacemaker, those who developed left bundle-branch block during the test, and those who were clinically unstable or required emergent intervention) at the Veterans Affairs Medical Center, Washington, DC (n=9042) and the Veterans Affairs Palo Alto (CA) Health Care System (n=6618) who completed an exercise tolerance test at least once during 1983-2007. After patients younger than 40 (n=711) and older than 70 (n=2532) years were excluded, 12,417 patients were included in the analysis.

The 12,417 participants were either African American (n=5435) or white (n=6982) men who ranged in age from 40 to 70 years (mean \pm SD, 57 \pm 8 years). Ethnicity was determined by electronic records and self-reports at the time of exercise testing. All patients gave written consent before the exercise tolerance test. The study was approved by the institutional review board at each site.

Additional information on study methods and characteristics of this cohort has been previously published.²⁹

CLINICAL EVALUATION AND EXERCISE TESTING

A standardized medical examination by a physician, including personal and family histories, was completed for all participants before exercise testing. All demographic, clinical, and medication information was obtained from patients' computerized medical records just before the exercise tolerance test. Each participant also was asked to verify the computerized information with regard to history of chronic disease, current medications, and cigarette smoking habits. Medications were not changed or stopped before testing. Body weight and height were recorded before the test. Body mass index was calculated as weight in kilograms divided by height in meters squared.

The exercise capacity of the participants at the Veterans Affairs Medical Center (Washington, DC) was assessed by the standard Bruce protocol.³⁰ For participants at the Veterans Affairs Palo Alto Health Care System, an individualized ramp protocol was used, as described previously.³¹ Peak exercise time was recorded in minutes. Peak workload was estimated as metabolic equivalents (METs). One MET is defined as the energy expended at rest, which is equivalent to an oxygen consumption of 3.5 mL \cdot kg⁻¹ \cdot min⁻¹.³² Exercise capacity (in METs) was estimated on the basis of American College of Sports Medicine equations.³² Participants were encouraged to exercise until volitional fatigue in the absence of symptoms or other indicators of ischemia. Supine resting heart rate and blood pressure (BP) were assessed after 5 minutes of rest. Exercise BP was recorded every 2 minutes, at peak exercise, and during recovery. Indirect arm-cuff sphygmomanometry was used for all BP assessments. ST-segment

depression was measured visually. ST depression of 1.0 mm or greater, horizontal or downsloping, was considered suggestive of ischemia.

Patients were classified according to 5 predetermined BMI groups: less than 18.5 (underweight), 18.5 to 24.9 (normal weight), 25.0 to 29.9 (overweight), 30.0 to 34.9 (obese I), and 35.0 or more (obese II or III). They were also classified according to 3 predetermined fitness groups: less than 5.0 (low), 5.0 to 10.0 (moderate), and more than 10.0 (high) METs. We used this approach to maintain consistency in our study methods and because a widely accepted clinical categorization of fitness does not exist. The normal-weight group (BMI, 18.5-24.9) and high-fitness group (>10.0 METs) were used as the reference groups. To evaluate the joint effects of BMI and fitness on mortality, we further classified patients within fitness strata according to BMI group.

MORTALITY SURVEILLANCE

We recorded death dates from the Veterans Affairs Beneficiary Identification and Record Locator System File. The Social Security Death Index was used to match all patients to their records according to Social Security number. Accuracy of deaths was reviewed by 2 clinicians blinded to exercise test results and was confirmed using the Veterans Affairs computerized medical records. Vital status was determined as of June 30, 2007.

STATISTICAL ANALYSES

Continuous variables are presented as mean \pm SD, and categorical variables as absolute and relative frequencies (percent). Descriptive statistics summarized baseline characteristics by BMI category.

Cox proportional hazards analyses were used to determine separate and combined associations of fitness and BMI with time to death. Continuous variables (age, BMI, and METs) were tested using analysis of variance, and categorical variables (fitness, BMI, and fitness-BMI groups) were tested using χ^2 tests. We tested models for potential interactions of BMI and race, and BMI and fitness, with all-cause mortality.

Independent effects of fitness were examined by 1 proportional hazards model, adjusting for age in years, ethnicity, examination year, test site, CVD (history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease), CVD risk factors (hypertension, dyslipidemia, diabetes mellitus, and/or current smoking), CVD medications (aspirin, angiotensin-converting enzyme inhibitors, β -blockers, calcium channel blockers, vasodilators, and/or statins), and BMI (entered as a continuous variable). In-

TABLE 1. Baseline Characteristics of Study Participants^a

Variable	BMI group					
	Underweight <18.5 (n=137)	Normal weight 18.5-24.9 (n=2885)	Overweight 25.0-29.9 (n=5187)	Obese (class) 30.0-34.9 (I) (n=2893)	35.0-39.9 (II) (n=947)	≥40.0 (III) (n=368)
Follow-up (y)	6.9±5.9	8.1±5.4	8.0±5.3	7.3±5.2	6.7±4.9	7.3±5.0
Demographics						
Age (y)	61.2±7.1	57.6±8.1	57.5±8.0	56.8±8.1	56.1±7.8	54.4±7.6
White	63 (46.0)	1636 (56.7)	2988 (57.6)	1584 (54.8)	498 (52.6)	213 (57.9)
African American	74 (54.0)	1249 (43.3)	2199 (42.4)	1309 (45.2)	449 (47.4)	155 (42.1)
BMI (kg/m ²)	17.3±1.0	22.8±1.6	27.4±1.4	32.1±1.4	37.0±1.4	44.1±4.3
Medical history						
CVD ^b	41 (29.9)	905 (31.4)	1715 (33.1)	1002 (34.6)	340 (35.9)	130 (35.3)
Hypertension	38 (27.7)	1103 (38.2)	2419 (46.6)	1684 (58.2)	616 (65.0)	231 (62.8)
Diabetes mellitus	14 (10.2)	325 (11.3)	820 (15.8)	653 (22.6)	291 (30.7)	116 (31.5)
Current smoker	62 (45.3)	1067 (37.0)	1646 (31.7)	849 (29.3)	223 (23.5)	111 (30.2)
Medications						
ACEI	8 (5.8)	248 (8.6)	639 (12.3)	494 (17.1)	202 (21.3)	88 (23.9)
β-blocker	9 (6.6)	356 (12.3)	792 (15.3)	543 (18.8)	195 (20.6)	70 (19.0)
Diuretic	9 (6.6)	190 (6.6)	391 (7.5)	307 (10.6)	130 (13.7)	68 (18.5)
Nitrate	27 (19.7)	395 (13.7)	593 (11.4)	313 (10.8)	102 (10.8)	44 (12.0)
Statin	2 (1.5)	82 (2.8)	269 (5.2)	199 (6.9)	75 (7.9)	23 (6.3)
Clinical						
SBP (mm Hg)	122.4±23.8	126.4±21.8	129.8±20.4	132.2±20.1	133.9±20.6	132.4±18.1
METs ^c	6.0±2.3	7.7±3.2	7.7±2.9	7.2±2.5	6.7±2.2	6.2±2.1
Fitness category (METs)						
Low (<5.0)	48 (35.0)	543 (18.8)	800 (15.4)	489 (16.9)	179 (18.9)	108 (29.3)
Moderate (5.0-10.0)	83 (60.6)	1779 (61.7)	3471 (66.9)	2088 (72.2)	714 (75.4)	240 (65.2)
High (>10.0)	6 (4.4)	563 (19.5)	916 (17.7)	316 (10.9)	54 (5.7)	20 (5.4)

^a Data are presented as mean ± SD or number (percentage). ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; CVD = cardiovascular disease; MET = metabolic equivalent; SBP = systolic blood pressure.

^b CVD included history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease.

^c Calculated from final treadmill speed and grade achieved on the exercise test (1 MET = 3.5 mL/kg/min).

dependent effects of BMI were assessed using 2 proportional hazards models—first, adjusting for age, ethnicity, examination year, test site, CVD, CVD risk factors, and CVD medications; second, by adding fitness entered as a continuous variable. This second model was also used to assess independent effects of hypertension, diabetes, and current smoking (except CVD risk factors were mutually adjusted). Cox proportional hazards analyses were repeated after excluding current smokers and patients who died in the first 2 years of follow-up.

Follow-up was calculated from the date of a patient's baseline exercise test and examination until the date of death or June 30, 2007. Statistical tests were 2-sided, and values of $P < .05$ were considered statistically significant. All statistical analyses were performed using NCSS 2007 software (NCSS, Kaysville, UT).

RESULTS

During a mean ± SD follow-up of 7.7±5.3 years (range, 0.08-22.92 years), 2801 deaths were recorded. Baseline characteristics grouped according to BMI category are presented in Table 1. The study population consisted of 6982

(56.2%) white and 5435 (43.8%) African American men who ranged in age from 40 to 70 years. There were 137 underweight patients (1.1%), 2885 normal-weight (23.2%), 5187 overweight (41.8%), and 4208 obese (33.9%) (2893 obese I [23.3%], 947 obese II [7.6%], and 368 obese III [3.0%]) patients. Median BMI was 28.0 (range, 13.2-65.6); ranges for quartiles 1 through 4 were 13.2 to 25.1, 25.2 to 27.9, 28.0 to 31.3, and 31.4 to 65.6, respectively. Testing of interaction models revealed a significant interaction between BMI and fitness ($P = .001$), but not BMI and race ($P = .79$).

Multivariate adjusted hazard ratio (HR) (95% confidence interval [CI]) for hypertension, diabetes mellitus, and current smoking was 1.1 (1.0-1.2), 1.3 (1.2-1.4), and 1.4 (1.3-1.5), respectively (data not shown).

Multivariate BMI-adjusted HR (95% CI) for low and moderate fitness, compared with the high-fitness reference group, was 3.6 (2.9-4.4) and 2.3 (1.9-2.8), respectively (Table 2). Multivariate fitness-adjusted HR (95% CI) for all-cause mortality associated with BMI categories of underweight, normal weight, overweight, obese I, and obese II or III was 1.9 (1.5-2.3), 1.0 (reference), 0.7 (0.7-0.8), 0.7 (0.6-0.7), and 1.0 (0.8-1.1), respectively (Table 3). These

TABLE 2. **Multivariate Proportional Mortality Hazard Ratios (HRs) by Fitness Category in Study Participants^a**

Fitness category (METs) ^b	No. of men	No. (%) of deaths	HR (95% CI) ^c	P value
High (>10.0)	1875	153 (8)	1 (Reference)	
Moderate (5.0-10.0)	8375	1750 (21)	2.31 (1.90-2.82)	<.001
Low (<5.0)	2167	898 (41)	3.56 (2.88-4.40)	<.001

^a CI = confidence interval; MET = metabolic equivalent.
^b 1 MET = 3.5 mL/kg/min.
^c Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD) (history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease), hypertension, dyslipidemia, diabetes mellitus, current smoking, CVD medications (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates, vasodilators, and/or statins), and body mass index (entered as a continuous variable in kg/m²).

TABLE 3. **Multivariate Proportional Mortality Hazard Ratios (HRs) by Body Mass Index (BMI) Category in Study Participants^a**

BMI category (kg/m ²)	No. of men	No. (%) of deaths	Model 1, HR (95% CI) ^b	Model 2, HR (95% CI) ^c
<18.5	137	83 (61)	2.02 (1.61-2.54)	1.86 (1.48-2.33)
18.5-24.9	2885	854 (30)	1 (Reference)	1 (Reference)
25.0-29.9	5187	1114 (22)	0.73 (0.67-0.80)	0.74 (0.68-0.81)
30.0-34.9	2893	526 (18)	0.70 (0.62-0.78)	0.65 (0.59-0.72)
≥35.0	1315	224 (17)	1.04 (0.89-1.22)	0.96 (0.82-1.12)

^a CI = confidence interval.
^b Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD), hypertension, dyslipidemia, diabetes mellitus, current smoking, and CVD medications.
^c Adjusted for covariates listed in model 1 plus fitness (entered as a continuous variable in metabolic equivalents (METs); 1 MET = 3.5 mL/kg/min).

analyses were repeated for nonsmokers, and no substantial differences were found when compared with the entire cohort. Body mass index mortality curves, extended further in 5-unit increments from 35.0 to 50.0 or greater, with and without adjustment for fitness, are presented in the Figure.

Results of the joint effects of fitness and BMI on all-cause mortality are presented in Table 4. Compared with findings for highly fit normal-weight men, adjusted HR (95% CI) for all-cause mortality was lower for highly fit overweight men (0.4 [0.3-0.6]) and highly fit obese men

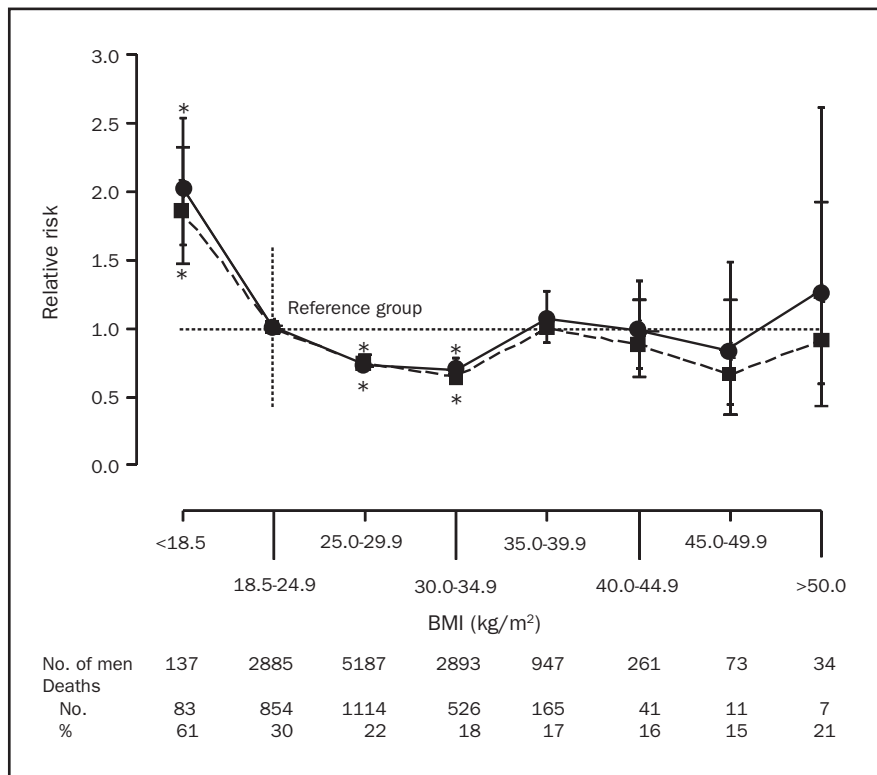


FIGURE. Multivariate hazard ratios for all-cause mortality by body mass index (BMI), adjusted for age, ethnicity, examination year, test site, cardiovascular disease, diabetes, hypertension, dyslipidemia, smoking status, and cardiovascular disease medications (solid line), and with additional adjustment for fitness, entered as a continuous variable (dashed line). Error bars are 95% confidence intervals. Number of men and number and percentage of deaths are given below each BMI category. *Differs significantly from reference group (P<.001).

TABLE 4. Multivariate Proportional Mortality Hazard Ratios (HRs) by Body Mass Index (BMI) and Fitness in Study Participants^{a,b}

Fitness category	No. of men	No. (%) of deaths	HR (95% CI) ^c
BMI <18.5 (kg/m ²)			
Low fitness	48	37 (77)	4.48 (3.06-6.57)
Moderate fitness	83	46 (55)	3.09 (2.17-4.38)
High fitness ^d	6	0 (0)	...
BMI 18.5-24.9 (kg/m ²)			
Low fitness	543	259 (48)	2.03 (1.60-2.58)
Moderate fitness	1779	526 (30)	1.65 (1.34-2.04)
High fitness	563	69 (12)	1 [Reference]
BMI 25.0-29.9 (kg/m ²)			
Low fitness	800	330 (41)	1.79 (1.43-2.25)
Moderate fitness	3471	724 (21)	1.15 (0.93-1.42)
High fitness	916	60 (7)	0.43 (0.32-0.59)
BMI ≥30.0 (kg/m ²)			
Low fitness	776	272 (35)	1.61 (1.27-2.03)
Moderate fitness	3042	454 (15)	0.99 (0.80-1.23)
High fitness	390	24 (6)	0.52 (0.34-0.82)

^a CI = confidence interval.

^b Fitness defined as peak metabolic equivalents (METs) achieved on a maximal exercise test: low (<5.0); moderate (5.0-10.0); high (>10.0). 1 MET = 3.5 mL/kg/min.

^c Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD), hypertension, dyslipidemia, diabetes mellitus, current smoking, and CVD medications.

^d Too few participants for stratified analysis.

(0.5 [0.3-0.8]) and higher for the following groups: low-fitness underweight (4.5 [3.1-6.6]), moderately fit underweight (3.1 [2.2-4.4]), low-fitness normal-weight (2.0 [1.6-2.6]), moderately fit normal-weight (1.7 [1.3-2.0]), low-fitness overweight (1.8 [1.4-2.3]), and low-fitness obese (1.6 [1.3-2.0]). No significant differences were found for the moderately fit overweight ($P=.19$) and moderately fit obese ($P=.96$) groups compared with the reference group. Removing current smokers and patients who died during the first 2 years of follow-up from the analysis did not appreciably alter the results.

DISCUSSION

In multivariate analyses, both fitness and BMI were independently and inversely associated with mortality risk. To ascertain whether low BMI resulted from undetected illness at baseline, we excluded all patients who died during the first 2 years of follow-up and current smokers, but this did not substantially change the primary findings. In joint analyses, elevated BMI generally reduced mortality risk within each fitness category, and higher levels of fitness decreased mortality risk within each BMI category. Highly fit overweight men ($n=916$) had the lowest mortality risk of any fitness-BMI combination and were 57% less likely to die (HR, 0.43 [95% CI, 0.32-0.59]) as highly fit normal-weight men. Fitness altered the obesity paradox in

that overweight and obese men with low fitness were less likely to survive than normal-weight men with high fitness. However, an obesity paradox persisted within fitness group strata.

Our findings that BMI and fitness are inversely associated with all-cause mortality are consistent with earlier results from the VETS²⁷ and extend them to joint analyses of fitness and BMI in a larger cohort of middle-aged men. Explanations for better survival with higher BMI in the current study include the following: (1) reverse causation in clinically referred patients,³³ (2) increased coronary artery size,³⁴ (3) the “veteran effect,”²⁷ (4) healthy obesity,³⁵ and (5) the survival effect.³⁶

Several previous studies have reported an obesity paradox in specific patient populations.⁴⁻¹⁰ First, in patient populations similar to ours, Galal et al³³ and Johnson et al³⁷ found significantly lower mortality in overweight and obese patients with known or suspected coronary artery disease compared with patients with normal BMI; this finding was consistent with our results.

Second, greater coronary artery size among patients with higher BMI has been proposed as a possible mechanism for the obesity paradox.³⁴ This may also be a factor in the favorable survival outcomes we observed among overweight and obese men in the current study of clinically referred patients, one third of whom had documented CVD.

Third, a related issue that might further explain our counterintuitive findings is the veteran effect, which we have previously noted.²⁷ Veterans differ from other populations in that they all must meet selection criteria at the time of enlistment. These criteria include minimum height requirements and maximum weight requirements, which must be maintained for the duration of military service. Specifically, maximum allowable weights for different branches of the service correspond to BMI of 25.9 to 29.9 for men.³⁸ Hence, obesity, when present in our population, must have developed after discharge from the service in later life. Some investigators have suggested that adult-onset obesity is less hazardous than obesity developing in childhood or adolescence.³⁹ In addition, men qualifying for military service may have greater than average muscle mass. This might explain the inverse associations between BMI and mortality found in other self-selected populations with physical attributes similar to veterans, such as longshoremen.¹¹

Fourth, in the larger population of obese adults, some experience good health. This is illustrated in some of the findings from the Framingham Heart Study.¹ Participants who had a normal BMI at 40 years of age but developed obesity during 20 years of follow-up had no increased mortality risk. Moreover, in healthy obese mice, preferential storage of triglycerides in adipose tissue and reduced levels

in the liver⁴⁰ may result in improved insulin sensitivity, preventing diabetes and heart disease in such animals. A similar mechanism has been proposed for obese humans,⁴¹ and a metabolically benign form of obesity has been recently identified.³⁵

Fifth, our findings may be explained in part by the well-known survival effect,³⁶ which has particular relevance in epidemiological studies of older adults. Although our study patients were middle-aged, those in the upper range of this age group were possibly less susceptible to the negative effects of overweight.

Because objective measures of fitness (maximal exercise testing on a treadmill) are often unavailable, data on the joint effects of BMI and fitness on mortality are sparse. We know of 9 published studies that have specifically assessed the joint effects of fitness (as measured from standard exercise testing) and BMI on mortality.¹⁸⁻²⁶ Two studies^{18,19} examined this issue by using data from the Lipid Research Clinics Study. All 7 of the remaining published studies used data from the Aerobics Center Longitudinal Study.²⁰⁻²⁶ Collectively, these studies demonstrated that fitness was a stronger predictor of mortality than BMI and that higher fitness eliminated the mortality risk of elevated BMI (the fat-but-fit hypothesis). Our results differ from these studies in that both high fitness and higher BMI independently reduced mortality risk. The effect of higher BMI on fitness in our cohort was that it generally reduced mortality risk across fitness categories. When highly fit patients were compared by BMI category, those who were overweight and obese experienced dramatic reductions in mortality risk (HR [95% CI], 0.43 [0.32-0.59] and 0.52 [0.34-0.82], respectively). However, only 916 overweight and 390 obese men registered high fitness at baseline, which represents only 7% and 3% of our cohort, respectively. Further study of individuals having this rare phenotype is needed to confirm our findings.

Our study has several strengths. First, all participants underwent an extensive physical examination, and detailed information on medication use was obtained, providing thorough information on the presence or absence of baseline disease. Second, fitness level was determined objectively by maximal exercise testing. Third, the study had a large sample size of more than 12,000 men and an average follow-up of nearly 8 years. Fourth, when smokers and patients who died during the first 2 years of follow-up were excluded, the results were not meaningfully altered.

Our study also has limitations. First, because waist circumference measures were not obtained, we were unable to evaluate body fat distribution characteristics. Second, we included only men who had prior military service and were referred for exercise testing for clinical reasons. Any effort to predict mortality by using fitness, BMI, or clinical or de-

mographic data should be considered population-specific. Although most men were free of CVD, all patients were referred for exercise testing for clinical reasons. Third, fitness is a single measure that is influenced by many factors, including age, heredity, and recent and lifelong activity patterns.^{32,42} The extent of fitness improvement in adults, or the influence this may have on mortality, cannot be determined from the current investigation. Fourth, we had insufficient information about diet or physical activity patterns to study these factors. Fifth, because we have only baseline data on weight, exercise capacity, and other exposures, we do not know if changes in any of these variables occurred during follow-up and how this might have influenced the results.

CONCLUSION

Both higher BMI and higher fitness were protective for all-cause mortality in this cohort of white and African American middle-aged male veterans with known or suspected CVD. Fitness altered the obesity paradox such that overweight and obese men had increased longevity only if they registered high fitness. Future studies should focus on the influence of fitness and BMI on mortality in diverse populations and whether changes in fitness level and/or body weight affect health outcomes.

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