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CLINICAL RESEARCH STUDY

Body Mass, Fitness and Survival in Veteran Patients: Another Obesity Paradox?

Paul McAuley, PhD, Jonathan Myers, PhD, Joshua Abella, MD, Victor Froelicher, MD

Cardiology Division, VA Palo Alto Health Care System/Stanford University, Palo Alto, Calif.

ABSTRACT

PURPOSE: The paradox of obesity in patients with heart failure (HF) also has been observed in non-HF veteran patients. Veterans had to have met military fitness requirements at the time of their enlistment. Therefore, we assessed the relation of body mass index (BMI) to mortality in a clinical cohort of non-HF veterans, adjusting for fitness.

METHODS: After excluding HF patients (n = 580), the study population comprised 6876 consecutive patients (mean age 58 [±11] years) referred for exercise testing. Patients were classified by BMI category: normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), or obese (BMI ≥30.0 kg/m^2). The association between BMI, fitness, other clinical variables, and all-cause mortality was assessed by Cox proportional hazards analysis.

RESULTS: During a mean (±SD) follow-up of 7.5 ± 4.5 years, a total of 1571 (23%) patients died. In a multivariate analysis including clinical, risk factor, and exercise test data, higher BMI was associated with better survival. Expressing the data by BMI category, obese patients were 22% less likely to die (relative risk [RR] = 0.78, 95% confidence interval [CI], 0.69-0.90, $P < .001$) than patients of normal weight. After further adjustment for cardiorespiratory fitness (CRF), this relationship strengthened such that mortality risk for the obese category was 35% lower (RR = 0.65, 95% CI, 0.57-0.76, $P < .001$), versus the normal weight category.

CONCLUSIONS: As has been observed in HF patients, obesity was associated with a substantially lower mortality risk in a clinical population of non-HF veterans. Higher CRF and obesity in later life may account for an obesity paradox in this population.

KEYWORDS: Cardiorespiratory fitness; Exercise testing; Mortality; Obesity

Obesity is associated with an increased risk of adverse outcomes in the general population.[1] Paradoxically, in patients with heart failure (HF), an inverse relationship between body mass index (BMI) and mortality has been observed,[2-4] including our population of veterans.[5] A similar phenomenon has been reported in dialysis patients,[6] and to a lesser degree in acute myocardial infarction,[7] and patients undergoing coronary artery interventions.[8-10] Some have speculated that such an "obesity paradox" is little more than basic protection against the wasting from HF and other cachectic disease states.[11] Others have suggested that obesity is protective because it is associated with larger coronary arteries[10] or increased muscle mass.[12]

A recent, large-scale epidemiological study in a general population found lower relative risks of mortality with obesity than previously observed.[13] This resulted from a more rigorous analysis involving more appropriate adjustment of confounding factors.[14] Because cardiorespiratory fitness is such a powerful predictor of mortality,[15,16] we hypothesized that its inclusion as a potential confounder might further affect relative risk estimates associated with obesity, especially in veterans, all of whom must meet fitness criteria in order to qualify for military service.

Although a selected group, veterans referred for exercise testing for clinical reasons provide objective measurements of exercise capacity, along with a wealth of other clinical

Requests for reprints should be addressed to Jonathan Myers, PhD, Cardiology Division, 111C, VA Palo Alto Health Care System, 3801 Miranda Ave., Palo Alto CA 94304.

E-mail address: drj993@aol.com

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findings. The aim of the present study was to determine the association between BMI and all-cause mortality in a clinical population of veterans without HF, adjusting for cardiorespiratory fitness.

METHODS

Population

We studied 6876 consecutive veteran patients (mean age 58 ± 11 years) referred for exercise testing for clinical reasons between 1988 and 2004. Study participants were followed from their baseline examination until their death or until January 2004. Patients were excluded if their BMI was <18.5 kg/m^2 (n = 58), if they had HF (n = 580), or if there was missing information (n = 145). The presence or absence of HF was coded at the time of the test and was defined by clinical history and an ejection fraction <40%. After exclusions, patients were grouped into 1 of 3 BMI categories using World Health Organization (WHO) criteria:[17] normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), or obese (BMI ≥30.0 kg/m^2).

CLINICAL SIGNIFICANCE

- Although obesity is associated with numerous health conditions, including a higher risk of cardiovascular disease, obesity has not been uniformly associated with mortality.
- In this study, higher BMI was associated with better survival (3% per BMI unit). Adjustment for fitness strengthened this association.

Body Mass Index

Before exercise testing, height and weight were measured using standard procedures. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

Exercise Testing

All patients underwent maximal exercise testing with the use of an individualized ramp treadmill protocol.[18] This test individualizes both warm-up and peak walking speeds (on the basis of a given patient's height, fitness, and familiarity with treadmill walking) and ramp rate (rate of change in speed and grade) to yield a test duration between 8 and 12 minutes.[19-21] A microcomputer automatically increased workload after an individualized walking speed and predicted values for maximal exercise capacity were entered. Standardized equations were used to determine the calculated peak metabolic equivalents (METs) on the basis of treadmill speed and grade.[20]

Blood pressure was recorded on alternate minutes throughout the test, and a 12-lead electrocardiogram was recorded each minute. The patient's subjective level of exertion was assessed by the Borg 6-20 scale.[22] Standard clinical criteria for terminating the tests (eg, fall in systolic blood pressure, ST-segment depression >2 mm, dangerous arrhythmias) were followed,[19,20] but no heart rate or time limit was imposed and a maximal effort was encouraged. Patients were discouraged from holding onto the handrails for support.

Statistical Analysis

Total (all-cause) mortality was used as the endpoint for survival analysis with cardiovascular disease (CVD) mortality as a secondary endpoint. Survival analysis was performed using Kaplan-Meier curves to compare variables and cut-points, and a Cox proportional hazards model was used to determine which variables were significantly associated with time to death and to develop relative risks for BMI categories (Number Crunching Statistical Software, Kayesville, Utah). We developed 3 proportional hazards models—first adjusting only for age, sex, and BMI category; second by adding CVD and CVD risk factors; and lastly, including METs in the final adjustment model. The Armitage test for trends in proportions was used to test the significance of relative risks for BMI category.

Death status was determined as of January 2004. The California Health Department Service and Social Security death indices were used to ascertain the vital status of each patient. Accuracy of deaths was reviewed by 2 clinicians blinded to exercise test results and confirmed using the Veterans Affairs computerized medical records. Deaths due to CVD included myocardial infarction, sudden cardiac death (arrhythmic deaths), and stroke.

In order to compare our results with those of previous studies, we used criteria from the WHO consultation on obesity,[17] which classifies all subjects, irrespective of age or sex, by BMI. The normal weight category (BMI 18.5-24.9 kg/m^2) was considered the reference group, and relative risks (RR) were calculated for the other groups (BMI 25.0-29.9 kg/m^2; and BMI ≥30.0 kg/m^2).

RESULTS

Baseline demographic and clinical characteristics of the study group, by BMI category, are listed in Table 1. Obesity prevalence in our population was 30.4%; 44.4% of the population was overweight; and the remaining 25.2% were of normal weight. Compared with normal weight subjects, obese subjects were younger, had higher incidences of hypercholesterolemia, hypertension, and diabetes and a lower prevalence of "high" fitness (≥10 METs).

Exercise Responses

Exercise test results are listed in Table 2. The mean (±SD) peak heart rate was 138 ± 24 beats/min, corresponding to 85% of the age-predicted maximum heart rate. The mean

Table 1 Baseline Demographic and Clinical Characteristics

Variable	Normal BMI 18.5-24.9 kg/m² (n = 1733)	Overweight BMI 25.0-29.9 kg/m² (n = 3050)	Obese BMI ≥30.0 kg/m² (n = 2093)	*P* Value*
Demographic characteristics				
Women	86 (5%)	72 (2%)	69 (3%)	<.001
Ethnicity (non-white)	436 (25%)	844 (28%)	586 (28%)	.34
Age (mean [±SD], years)	60 (±12)	59 (±11)	56 (±11)	<.001
Height (mean [±SD], inches)	69 (±3)	69 (±3)	69 (±3)	.41
Weight (mean [±SD], lbs)	156 (±17)	186 (±18)	233 (±32)	<.001
BMI (mean [±SD], kg/m²)	23.0 (±1.5)	27.3 (±1.4)	34.2 (±4.0)	<.001
Low fitness (<5 METs)†	264 (15%)	465 (15%)	338 (16%)	.62
High fitness (≥10 METs)†	682 (39%)	1145 (38%)	511 (24%)	<.001
Medications				
Calcium antagonist	375 (22%)	700 (23%)	546 (26%)	.003
Beta-blocker	267 (15%)	609 (20%)	490 (23%)	<.001
Antihypertensive agent	272 (16%)	600 (20%)	491 (23%)	<.001
Medical history				
Hypertension	650 (38%)	1437 (47%)	1241 (59%)	<.001
Hypercholesterolemia (>220 mg/dL)	456 (26%)	959 (31%)	728 (35%)	<.001
Smoking (current)	635 (37%)	894 (29%)	518 (25%)	<.001
Myocardial infarction	341 (20%)	552 (18%)	350 (17%)	.06
Typical angina‡	270 (16%)	480 (16%)	337 (16%)	.89
Diabetes	122 (7%)	335 (11%)	334 (16%)	<.001
Pulmonary disease	140 (8%)	158 (5%)	152 (7%)	<.001
Claudication‡	100 (6%)	124 (4%)	81 (4%)	.007
Stroke	48 (3%)	92 (3%)	51 (2%)	.46
Atrial fibrillation‡	21 (1%)	48 (2%)	38 (2%)	.32
Interventions				
Coronary bypass surgery	168 (10%)	268 (9%)	182 (9%)	.49
Percutaneous transluminal coronary angioplasty	119 (7%)	236 (7%)	151 (7%)	.52

Values are number of participants (%) unless otherwise stated.

*Trend for associations with BMI category obtained by modeling the median of each BMI category as a continuous variable (*P* value represents main effect across BMI groups).

†METs = metabolic equivalents (calculated from treadmill speed and grade); 1 MET = 3.5 mL/kg/min.

‡Defined by history, by their occurrence during the exercise test, or both, using standard clinical criteria.

(±SD) peak rating of perceived exertion was 17 ± 2, which did not differ significantly across BMI categories, suggesting that a maximal effort was achieved by most patients.

Peak METs were similar for normal weight and overweight categories (8.8 and 8.6, respectively), but 11% lower (7.8) for the obese category. Additionally, 39% of normal patients and 38% of overweight patients registered "high" fitness (≥10 METs); whereas only 24% of obese patients achieved this level (Table 1). Nevertheless, a low correlation between BMI and peak METs was observed (r = −0.12). Similarly, this association persisted across BMI categories: 0.07, −0.05, and −0.14 for normal weight, overweight, and obese, respectively.

Survival

During a mean 7.5 ± 4.5 years of follow-up, 1571 (23%) patients died. Death occurred in 31% of the normal weight group, 22% of the overweight group, and 18% of the obese group.

Hazard ratios according to clinical variables, BMI, and cardiorespiratory fitness are shown in Table 3. After adjustments for age, sex, and BMI category, presence of CVD and CVD risk factors, a 13% lower risk of death occurred (*P* <.001). After further adjustment for cardiorespiratory fitness, mortality risk was 20% lower per BMI category (*P* <.001).

Associations of clinical variables and cardiorespiratory fitness to risk of death according to BMI category were then assessed (Table 4). All models were adjusted for age and sex. In this analysis, including CVD and CVD risk factors, a 22% lower risk of death was observed (*P* <.001) among obese patients as compared with patients of normal weight. After further adjustment for cardiorespiratory fitness, this association strengthened such that morality risk for the obese category was 35% lower (*P* <.001) than the normal weight category.

Additionally, we entered BMI as a continuous variable in our fully-adjusted multivariate model and found a 3% reduction in mortality per BMI unit (RR = 0.97, 95% confidence interval [CI], 0.96-0.98, *P* <.001).

Kaplan-Meier survival curves by BMI category demonstrated that the 2 higher BMI categories were associated with better survival versus the normal weight category (*P* <.001, Figure 1). Moreover, when the obesity category was divided according to WHO obesity class, the trend

Table 2 Exercise Test Responses

Variable	Normal BMI 18.5-24.9 kg/m^2 (n = 1733)	Overweight BMI 25.0-29.9 kg/m^2 (n = 3050)	Obese BMI ≥30.0 kg/m^2 (n = 2093)	*P* Value*
Rest				
Heart rate (beats/min)	75 (±14)	76 (±14)	78 (±14)	<.001
Systolic blood pressure (mm Hg)	130 (±21)	133 (±20)	135 (±19)	<.001
Diastolic blood pressure (mm Hg)	79 (±11)	82 (±11)	84 (±12)	<.001
Peak exercise				
Metabolic equivalents (METs)†	8.8 (±4.0)	8.6 (±3.6)	7.8 (±3.1)	<.001
Heart rate (beats/min)	138 (±25)	139 (±25)	138 (±24)	.39
Systolic blood pressure (mm Hg)	173 (±28)	179 (±28)	182 (±29)	<.001
Diastolic blood pressure (mm Hg)	82 (±15)	85 (±15)	87 (±15)	<.001
Perceived exertion (Borg scale)	17 (±2)	17 (±2)	17 (±2)	.63

Values are mean (±SD).

*Trend for associations with BMI category obtained by modeling the median of each BMI category as a continuous variable (*p* value represents main effect across BMI groups).

†METs = metabolic equivalents (calculated from treadmill speed and grade); 1 MET = 3.5 mL/kg/min.

continued. Similar patterns were observed for CVD mortality (Figure 2).

DISCUSSION

In contrast to the well-established relationship between obesity and mortality observed in numerous general population studies,[1,23,24] we found that mortality was lower in veteran patients with higher BMI. Our findings therefore confirm that an "obesity paradox" exists in patients other than those with HF, those undergoing coronary artery interventions, or those undergoing dialysis.[2-12] Our study has several strengths: all subjects underwent an extensive physical examination, which provides thorough information on the presence or absence of baseline disease; cardiorespiratory fitness was determined by maximal exercise testing; and a large sample size of nearly 7000 patients with an average follow-up of more than 7 years (>50,000 person-years).

There are other noteworthy findings from the present study. Importantly, the lower prevalence of high fitness in the obese category versus the normal weight category identifies a potential confounder often missing from previous analyses. After we adjusted for cardiorespiratory fitness, multivariate mortality risk for the obese category fell substantially (from 22% to 35%). This confirms our original hypothesis that adjusting for fitness would amplify the obesity paradox and indicates that among the potential confounders of the obesity-mortality relationship, cardiorespiratory fitness is an independent risk factor at least as important as traditional CVD risk factors or pre-existing conditions. The mechanism responsible for such marked reduction in mortality risk after adjusting for cardiorespiratory fitness remains unclear. Perhaps cardiorespiratory fitness is a proxy for physical activity[15] and other positive lifestyle practices.

Previous Studies Observing an Obesity Paradox

Although obesity is associated with numerous health conditions, including a higher risk of cardiovascular disease,[1,23,24] in particular populations, obesity has not been associated with mortality. For example, obesity was not associated with mortality risk in Pima Indian women[1] or African-American women.[23] However, in neither case was any *protective* effect of obesity found. Only in certain clinical populations has an obesity paradox been observed thus far.

In 1996, Ellis and co-workers[25] were among the first to identify higher BMI as a predictor of survival in a clinically referred population. In patients undergoing percutaneous coronary intervention (PCI), the mortality rate in the "mildly obese" group (BMI 26-34 kg/m^2; n = 2566) was one-fourth that of the "low-normal" group (BMI ≤25 kg/m^2; n = 614). Paradoxically, the lowest risk of in-hospital death (0%) was observed in the heaviest patients (>120 kg; n = 82).

Horwich and colleagues[26] found no significant increase in 5-year mortality in overweight and obese HF patients, and elevated BMI was an independent predictor of improved survival at 1 and 2 years. Gurm et al[8] were the first

Table 3 Multivariate Predictors of All-cause Mortality

Adjustments	Hazard Ratio	95% CI
Age + sex + BMI category	0.88	(0.82-0.94)
Above + CVD* + CVD risk factors†	0.87	(0.81-0.93)
Above + METs	0.80	(0.75-0.86)

BMI = body mass index; MET = metabolic equivalent (3.5 mL of oxygen/kg per minute); CVD = cardiovascular diseases.

*History of myocardial infarction, stroke or surgery for CVD.

†CVD risk factors include smoking, hypertension and hypercholesterolemia.

Table 4 Multivariate Relative Risk (RR) of All-cause Mortality by BMI Category

	Normal BMI 18.5-24.9 kg/m^2 (n = 1733)	Overweight BMI 25.0-29.9 kg/m^2 (n = 3050)	Obese BMI ≥30.0 kg/m^2 (n = 2093)
Deaths (all-cause)	530 (31%)	671 (22%)	370 (18%)
Deaths (CVD)	169 (10%)	239 (8%)	134 (6%)
Adjustments		RR (95% CI)	RR (95% CI)
Age + sex	1.0	0.73 (0.65-0.82)	0.80 (0.75-0.92)
Above + CVD* + CVD risk factors†	1.0	0.73 (0.65-0.82)	0.78 (0.69-0.90)
Above + METs	1.0	0.70 (0.63-0.79)	0.65 (0.57-0.76)

BMI = body mass index; MET = metabolic equivalent (3.5 mL of oxygen/kg per minute); CVD = cardiovascular diseases.
*History of myocardial infarction, stroke or surgery for CVD.
†CVD risk factors include smoking, hypertension and hypercholesterolemia.

to report a paradoxic protective effect of obesity on outcome. They followed 11,300 patients after PCI and found that obesity was associated with a 20% reduction in 30-day mortality risk with a trend favoring lower mortality at 1 year. Gruberg et al[9] published similar findings in 9633 patients undergoing PCI. In the latter study, each 1-unit increase in BMI conferred a 4% survival benefit.

These reports were followed by several studies documenting the existence of an obesity paradox in HF,[2-5] dialysis patients,[6] and a recently published randomized trial in patients with multivessel disease undergoing either coronary artery bypass grafting (CABG) or stenting.[10]

Fitness and Mortality in Obesity

Within the body of obesity-mortality literature, comparatively little attention has focused on the role of fitness in survival. For example, the Aerobics Center Longitudinal Study[24] of over 25,000 men (with a mean follow-up of over 10 years) found no increased mortality risk with obesity as long as subjects had a moderate or high age-adjusted fitness level. Fitness was therefore a more important marker of mortality risk than obesity. These data suggest that when a minimum age-related criterion fitness level was reached, obesity had no impact on mortality.

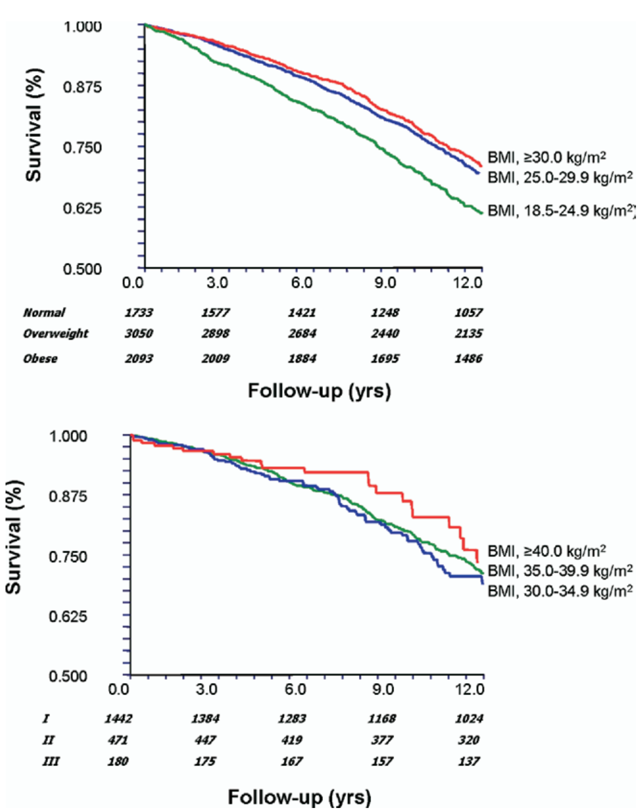

Figure 1 Kaplan-Meier survival curves of all-cause mortality by BMI category (top) and BMI obesity class (bottom).

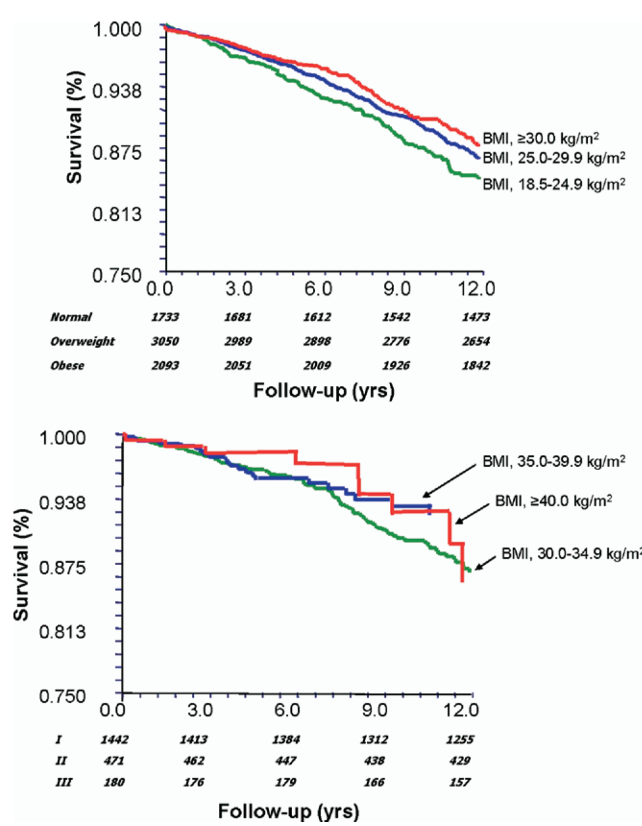

Figure 2 Kaplan-Meier survival curves for CVD mortality by BMI category (top) and BMI obesity class (bottom).

Likewise, cardiovascular fitness was a strong independent predictor of mortality in the present study. However, our findings differed from those of the Aerobics Center Longitudinal Study in that obesity significantly reduced mortality in our population of veteran patients. Differences in the baseline characteristics of the study populations (eg, subjects in our study were older, referred to exercise testing for clinical reasons, and had prior military service) may account for this.

The Veteran Effect

Prevalence of obesity (30.4%) in our population mirrors that recently reported for the general population; however, severe (class III) obesity was lower in our population (2.6%), as compared with the general population (4.9%).[27] Veterans differ from other populations of patients in several other respects. One of the most prominent differences is the meeting of selection criteria at the time of enlistment. These criteria include, among other things, minimum height requirements, maximum weight requirements, and exclusion of recruits having certain preexisting health problems. Consequently, individuals having obesity in early life are excluded from our population. Pediatric obesity has been shown to have a greater impact on disease outcomes than obesity that develops in later life. For example, Barker et al[28] recently examined the effects of birth weight and childhood growth rates on subsequent disease risk in Finnish men and women. They reported that the rate of childhood gain in BMI between 2 years and 11 years of age was strongly related to the risk of coronary events and insulin resistance in later life. It is therefore possible that many such individuals are excluded from the veteran population by reason of weight. Finally, the influence of self-selection in our population must be considered. Individuals volunteering and qualifying for military service may be more likely to be predisposed toward physical fitness or have other health attributes than those avoiding military service.

Limitations

A limitation of our study is that it included a predominantly male population, all of whom had prior military service and were referred for exercise testing for clinical reasons. Thus, we evaluated survival in the context of a clinical population, many of whom were limited by symptoms, medications, and other factors related to CVD. Any effort to predict mortality by using BMI, clinical, or demographic data should be considered population-specific. Therefore, our results may not apply to more general or healthier populations. Although BMI is the most commonly used method to determine obesity status, it is not the optimal measure; other methods (eg, waist to hip ratio and lean body weight) are suggested to be superior. Finally, because we only have baseline data on weight, cardiorespiratory fitness, and other exposures, we do not know if changes in any of these variables occurred during follow-up or how this might have influenced the results.

Summary

BMI was protective for mortality in a heterogeneous clinically referred male veteran population. Further adjustment for cardiorespiratory fitness strengthened this association; each 1-unit increase in BMI conferred a 3% survival benefit. Our results reveal that the "obesity paradox" previously observed in specific clinical populations occurs over a broader spectrum of veteran patients. The interactions among obesity, fitness, and mortality are complex and the underlying mechanisms responsible for this phenomenon require further elucidation. Therefore, future studies of the obesity paradox phenomenon should be directed toward both the extent of its occurrence and the nature of its existence. The present findings concur with previous studies in particular clinical populations and suggest that obesity can confer survival benefits in certain conditions. A combination of factors such as self-selection, meeting recruitment standards for and maintaining physical fitness during military service, obesity in later life, and even psychosocial factors might explain this phenomenon.

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