

# Use of Functional Aerobic Capacity Based on Stress Testing to Predict Outcomes in Normal, Overweight, and Obese Patients

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## Abstract

**Objective:** To determine the poorly studied relationship between functional aerobic capacity (FAC) as measured by treadmill stress testing and mortality in normal, overweight, and obese patients.

**Patients and Methods:** Patients were identified retrospectively from the stress testing database at Mayo Clinic in Rochester, Minnesota. We selected 5328 male nonsmokers (mean  $\pm$  SD age, 51.8 $\pm$ 11.5 years) without baseline cardiovascular disease who were referred for treadmill exercise testing between January 1, 1986, and December 31, 1991, and classified them by body mass index (BMI) into normal-weight (18.5-24.9 kg/m<sup>2</sup>), overweight (25.0-29.9 kg/m<sup>2</sup>), and obese ( $\geq$ 30 kg/m<sup>2</sup>) categories. Functional aerobic capacity was assessed by maximal exercise test results based on age- and sex-specific metabolic equivalents, and patients were stratified into fitness quintiles. Cox proportional hazards analysis was used to determine the relationship of all-cause mortality to fitness in each BMI category.

**Results:** There were 322 deaths during 14 years of follow-up. After adjustment for age and exercise confounders, FAC predicted mortality in the 3 BMI groups. Hazard ratios for FAC less than 80% of predicted vs a reference group with normal BMI and fitness (FAC  $\geq$ 100%) were 1.754 (95% CI, 0.874-3.522), 1.962 (1.356-2.837), and 1.518 (1.056-2.182) for the normal, overweight, and obese groups, respectively. The CIs of the hazard ratios overlapped with no statistically significant differences ( $P>.05$ ).

**Conclusion:** A significant increase in mortality occurs with FAC below 80% of predicted for overweight and obese subjects and below 70% for normal weight subjects. Our results suggest that clinicians need not adjust the standard for low fitness in obese patients.

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 Obesity represents a growing health crisis in the United States. Over two-thirds of Americans are either overweight or obese,<sup>1</sup> and obesity rates have increased more than 3-fold since 1980 in many areas worldwide, including North America.<sup>2</sup> As the prevalence of overweight and obesity increases, so too does the prevalence of cardiovascular risk factors such as diabetes, atherosclerosis, and hypertension.<sup>3</sup> It is well established (with few paradoxical exceptions in special conditions<sup>4,5</sup>) that obesity correlates with decreased life expectancy.<sup>6,7</sup> Obese patients also have a reduced ability to exercise as defined by low functional aerobic capacity (FAC) during exercise treadmill testing.<sup>8</sup> Functional aerobic capacity is a strong predictor of all-cause and cardiovascular mortality.<sup>9</sup> However, reduced functional capacity in obese patients may be solely related to carrying

excess weight up the treadmill grade, whereas poor performance in a normal-weight individual would more likely be attributable to underlying cardiovascular disease (CVD) or other organic limitation such as pulmonary disease. Stated differently, an obese patient who is exercising according to current recommendations might attain the same performance on the treadmill (as measured by FAC) as a normal-weight patient who is sedentary. Therefore, the validity of FAC as a predictor of mortality in obese patients is less clear. Whether separate cut points for increased risk based on FAC are needed for patients in different weight categories is also unknown.

A literature search was conducted using various permutations of the MeSH terms *exercise test*, *physical fitness*, *mortality*, and *obesity*. Nine pertinent studies were found. Most (6) of these studies examined the same cohort from a

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research facility in Dallas, Texas. These articles generally concluded that fitness is a better predictor of mortality than body mass index (BMI) and that higher cardiorespiratory fitness is associated with reduced mortality in the overweight/obese population.<sup>10-15</sup> Few studies found that low FAC is an independent predictor of mortality in all BMI groups.<sup>14-18</sup> However, no available literature addressed whether fitness cutoffs need to be adjusted for obese patients.

Previous studies have used BMI as a measure of adiposity, with data revealing that—when used alone—other metrics fail to predict mortality.<sup>18</sup> The operant belief has been that better FAC improves mortality outcomes irrespective of BMI.<sup>15</sup> The purpose of this study was to reevaluate the validity of FAC as a predictor of mortality in overweight and obese individuals. We additionally assessed the hypothesis that obese patients require a more liberal cutoff for low FAC than their nonobese counterparts for accurate prognostication of mortality.

## PATIENTS AND METHODS

The study protocol was reviewed and approved by the Institutional Review Board of the Mayo Clinic.

### Study Population

The study population consisted of adult males older than 18 years who underwent treadmill exercise testing without imaging to screen for ischemic heart disease between January 1, 1986, and December 31, 1991. Exercise tests were performed for the evaluation of symptoms of chest pain, dyspnea, fatigue, or dizziness or for screening before exercise prescription in sedentary patients with multiple coronary disease risk factors.<sup>19</sup> Patients were identified retrospectively from the stress testing database at the Mayo Clinic in Rochester, Minnesota. We selected 5328 male nonsmokers (median  $\pm$  SD age, 51.8 $\pm$ 11.5 years) without baseline CVD referred for treadmill exercise testing between 1986 and 1991. Females were excluded because obesity in females may not be equivalent to obesity in males given the variance in weight distribution. Cardiovascular disease (with the exception of systemic hypertension) was an exclusion criterion because its presence would require considerable multivariate analysis, result in the concentration of patients with CVD in the low fitness groups, and potentially confound

the analyses by way of the obesity paradox.<sup>4,5</sup> Patients with diabetes were also excluded because it was considered a CVD equivalent.

### Clinical Data and Anthropometric Determinations

All patients underwent anthropometry, electrocardiography (ECG), and blood pressure measurements (by sphygmomanometry in the sitting position after 5 minutes of rest) before the test. Information regarding exclusion based on CVD and smoking history was obtained through a combination of medical record review and patient interview. Cardiovascular disease was defined as a history of myocardial infarction, coronary artery bypass operation, angina with angiographically documented coronary artery disease with or without angioplasty, or ischemic cardiomyopathy. Body mass index was calculated as weight in kilograms divided by height in meters squared. Per the World Health Organization classification system,<sup>20</sup> patients were divided into 3 weight groups: (1) normal weight (BMI, 18.5-24.9 kg/m<sup>2</sup>), (2) overweight (BMI, 25.0-29.9 kg/m<sup>2</sup>), and (3) obese (BMI,  $\geq$ 30.0 kg/m<sup>2</sup>).

Weight groups were then further adjusted for inconsistency with percent body fat estimated from skinfold caliper measurements. These measurements were obtained by vertical fold according to the recommendations of Jackson and Pollock at the chest, abdomen, and thigh.<sup>21</sup> In general, only 15% to 40% of body mass is due to adipose tissue, and patients with so-called normal weight obesity characterized by high central adiposity with low overall muscle mass and normal BMI are at increased mortality risk.<sup>22</sup> Combination of other metrics such as skinfold measurement with BMI has been shown to better assess obesity.<sup>22</sup> Thus, when pertinent, patients with body fat percentage greater than the average of the higher weight group were shifted to that group. Similarly, patients with body fat less than the average of the lower weight group were shifted down to that group. This adjustment for body fat variation also increased confidence in the accuracy of weight group assignments.

### Treadmill Exercise Testing

Symptom-limited maximal treadmill exercise tests were performed using the standard Bruce protocol<sup>23</sup> on a motor-driven treadmill (Quinton

Instrument Company or Marquette Electronics). The end point of the test was usually fatigue, as indicated by a rating on the standard Borg perceived exertion scale<sup>24</sup> or inability to keep pace with the treadmill, unless another indication for test termination was met first.<sup>19</sup> Fewer than 2% of tests were terminated because of arrhythmia or angina. Active use of the treadmill handrails was not permitted. A 12-lead ECG was obtained every minute during exercise, at peak exercise, and every minute during a 3-minute cooldown at 1.7 mph and 0% grade with a 3-minute seated recovery. Exercise workload was estimated in metabolic equivalents (METs), where 1 MET = 3.5 mL/kg per minute of oxygen consumption. Fitness was quantified as FAC, a term that is interchangeable for this purpose with aerobic capacity and functional capacity. Functional aerobic capacity was calculated as achieved METs/predicted METs based on age and sex.<sup>25</sup> This method of testing has been consistently found to serve as a reliable predictor of mortality (with a tighter correlation than other established risk factors for CVD).<sup>26,27</sup> On the basis of performance, patients were stratified into fitness quintiles. Normal fitness was considered an FAC of 100% or more of age- and sex-predicted METs (approximately equivalent to the highest quintile in the study population before application of exclusion criteria). Low fitness was considered an FAC of less than 80% predicted (approximately equivalent to the lowest quintile). A reference group with normal fitness (FAC  $\geq$ 100%) and normal BMI was used for comparisons. This cutoff has often been used for stratifying fitness and, as with the categorization system for BMI, allows for more straightforward comparison of a continuous variable.

### Study End Point

Follow-up through 14 years after exercise testing was available for all patients. Therefore, the primary end point of the study was all-cause 14-year mortality. All-cause mortality is considered an unbiased and objective end point, which is therefore often superior to cardiovascular mortality.<sup>27,28</sup> Mortality was determined by examination of the National Death Index up to August 2005.

### Statistical Analyses

All analyses were performed using SAS software version 9.1 (SAS Institute Inc). Continuous

variables are reported as mean  $\pm$  SD. The Student *t* test and 2-way analysis of variance were used to test continuous variables. A Pearson  $\chi^2$  contingency test was used to compare categorical variables. The 14-year mortality was initially determined for quintile of FAC and weight group. The lowest quintile of FAC was split into first and second deciles because of a rapid increase in mortality with declining fitness at this end of the fitness spectrum. Cox proportional hazards regression was then used to estimate the true impact of fitness and weight on total mortality. Age adjustment was indicated because FAC is specific to age group and thus is not age-dependent as METs would be. We also performed multivariate analysis and adjustment for systemic hypertension and exercise confounders including  $\beta$ -blocker therapy and chronotropic incompetence. In addition, we adjusted for BMI because there was a small but significant residual variation in BMI within each weight group. Adjustment was made for  $\beta$ -blocker therapy because it may limit exercise while reducing cardiovascular mortality. Chronotropic incompetence was defined as failure to achieve 85% or more of age-predicted maximal heart rate (220 beats/min – age [years]).

We determined the hazard ratios (HRs) for mortality for specific groups of patients by weight and fitness using normal-weight patients in the highest quintile of fitness as the reference group. Kaplan-Meier curves were used for survival analysis.  $P < .05$  was considered statistically significant. Data are reported with a 95% CI estimate, and all reported *P* values are 2-sided.

### RESULTS

The demographic profile of the patients included in the study is presented in Table 1. All patients were male nonsmokers, and more than 90% of the study population was white. Of the 5328 patients evaluated in this study, 1370 (26%) had a normal BMI, 2333 (44%) were overweight, and 1625 (30%) were classified as obese (BMI  $\geq$ 30 kg/m<sup>2</sup>). These percentages are comparable to national averages in the United States.<sup>29</sup> The distribution of obese subjects based on World Health Organization class was 75% (1218), 20% (325), and 5% (82) for classes I through III, respectively. The range of BMI in the study population was 13 to 65 kg/m<sup>2</sup>. With increasing BMI, there was a higher incidence of

**TABLE 1. Demographic and Clinical Characteristics of the Study Patients<sup>a,b</sup>**

Variable	Normal weight (BMI, 18.5-24.9 kg/m <sup>2</sup> ) (n=1370)	Overweight (BMI, 25.0-29.9 kg/m <sup>2</sup> ) (n=2333)	Obese (BMI, ≥30.0 kg/m <sup>2</sup> ) (n=1625)	P value
Age (y)	49.2±12.8	53.0±11.0	53.4±10.5	.001
Height (cm)	178.0±7.1	177.5±7.1	177.8±7.1	.78
Weight (kg)	76.2±8.3	86.1±8.8	102.0±13.8	.001
BMI (kg/m <sup>2</sup> )	24.0±1.9	27.3±2.1	32.3±3.8	.001
Body fat (%)	17.9±3.5	23.9±2.5	29.4±2.6	.001
Hypertension	575 (42.0)	1250 (53.6)	1047 (64.4)	.001
β-Blocker use	75 (5.5)	194 (8.3)	184 (11.3)	.001
Death	55 (4.0)	136 (5.8)	131 (8.1)	.001

<sup>a</sup>BMI = body mass index.

<sup>b</sup>Data are presented as No. (percentage) of patients for categorical variables and mean ± SD for continuous variables.

hypertension, chronotropic incompetence, and β-blocker use (Table 1). Obese patients were also more likely to have higher resting heart rate and blood pressure. Exercise testing data are summarized in Table 2.

There were 322 deaths within the 14-year mortality window after the exercise test. Adjusting BMI groups based on skinfold body fat measurement improved the association of obesity groups with mortality. For instance, the 14-year mortality for patients who did not require adjustment for body fat (n=4310) was 7.9% compared with 5.6% for the group moved to a lower weight group (n=428). The group adjusted upward (n=590) had the highest mortality (10.4%). Comparisons for mortality among all 3 groups were significant ( $P < .001$ ).

Figure 1 displays the Kaplan-Meier curve of survival based on fitness quintile. As shown, the lowest quintile of FAC portended significantly worse survival compared with the 4 higher FAC quintiles with only a slight increase in mortality from quintile 5 down to quintile 2. The FAC averages for each quintile (5 through 1) were 127%±11% (minimum, ≥100%), 109%±3%, 99%±3%, 88%±3%, and 77%±3%.

In Figure 2, mortality for each FAC and weight group has been converted to HRs, after multivariate analysis, with patients with normal weight and fifth quintile of FAC being the reference group (HR, 1.0). The relationship between mortality and FAC was of the form  $f(x) = 1/x$  overall and for each weight group. As was also seen in the Kaplan-Meier curve (Figure 1), there was a rapid increase in mortality as FAC decreased below 80%: HRs were 1.754 (95% CI, 0.874-3.522), 1.962 (1.356-2.837), and 1.518 (1.056-2.182) for the normal-weight, overweight, and obese groups, respectively. The CIs of the HRs overlapped with no statistically significant differences ( $P > .05$ ). At any FAC less than 100%, there was no evidence that reduced FAC was associated with lower mortality in the overweight or obese patients vs the normal-weight patients. At levels of FAC below 100%, adjusted mortality at any given FAC tended to be slightly higher for overweight or obese patients vs normal-weight patients, although none of these differences were statistically significant. There seems to be

**TABLE 2. Treadmill Exercise Testing Characteristics of the Study Patients<sup>a,b</sup>**

Variable	Normal weight (BMI, 18.5-24.9 kg/m <sup>2</sup> ) (n=1370)	Overweight (BMI, 25.0-29.9 kg/m <sup>2</sup> ) (n=2333)	Obese (BMI, ≥30.0 kg/m <sup>2</sup> ) (n=1625)	P value
Resting systolic BP, mm Hg	128.3±17.6	131.3±17.3	135.4±17.6	.001
Resting diastolic BP, mm Hg	83.4±9.8	85.5±9.7	87.6±9.9	.001
Resting HR, beats/min	71.3±12.2	73.2±12.1	75.7±12.1	.001
Peak HR, beats/min	170.6±20.4	165.2±20.2	160.8±20.2	.001
Abnormal ECG <sup>c</sup>	234 (17.1)	417 (17.9)	309 (19.0)	.38
Inadequate HR	90 (6.6)	216 (9.3)	219 (13.5)	.001
METs	12.7±3.0	11.2±2.5	9.7±2.3	.001
FAC (%) <sup>d</sup>	109±22	100±19	87±18	.001

<sup>a</sup>BMI = body mass index; BP = blood pressure; ECG = electrocardiographic results; FAC = functional aerobic capacity; HR = heart rate; METs = metabolic equivalents.

<sup>b</sup>Data are presented as No. (percentage) of patients for categorical variables and mean ± SD for continuous variables.

<sup>c</sup>Defined as findings concerning for ischemia (ie, >1-mm ST-segment deviation from normal baseline).

<sup>d</sup>Percent of predicted FAC based on age and sex.

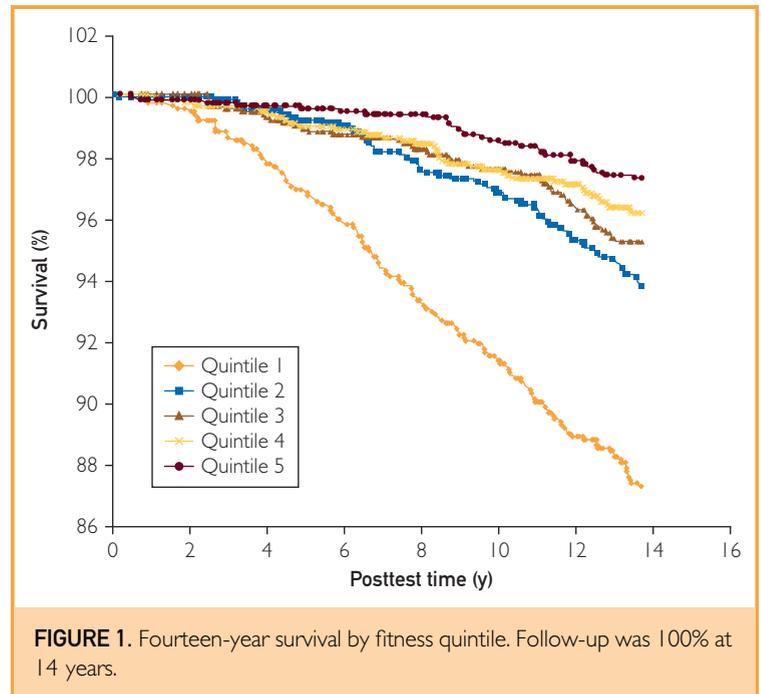
no indication that a more liberal allowance for FAC should be given to overweight or obese patients in interpreting the prognostic significance of the stress test performance. However, compared with the reference group of normal weight and highest quintile of FAC, mortality was significantly increased in normal-weight patients with an FAC below 70%, in overweight patients with an FAC below 80%, and in obese patients with an FAC below 90%.

## DISCUSSION

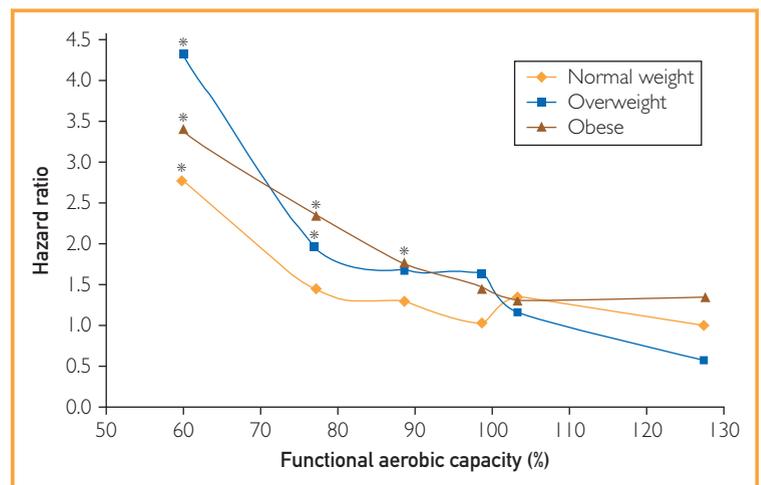
The main findings of this study can be summarized as follows: (1) patients in the lowest fitness quintile had much worse survival compared with those in the highest 4 fitness quintiles; (2) a significant increase in mortality occurred at low FAC for all weight groups—the cut point at which low FAC predicted higher mortality increased from 70% in normal-weight to 80% in overweight and 90% in obese patients; (3) there appears to be no need to adjust the standards for FAC in stress test interpretation on the basis of weight group.

In terms of multivariate analysis, we kept adjustment to a minimum to avoid overfitting our Cox regression models and to keep the results straightforward and applicable to clinical practice. We did adjust the HRs in the Cox regression for age because FAC is calculated for a specific age group and thus is minimally age dependent, unlike an absolute measure of exercise capacity such as METs. There were minimal differences in the frequency of abnormal ECG results across the 3 weight groups, so adjustment for that factor was not necessary.  $\beta$ -Blockade is known to reduce FAC while possibly reducing cardiovascular mortality.

The study groups as divided by BMI were relatively well matched, other than a higher rate of hypertension in the overweight and obese groups. However, this is an expected finding because obesity is independently associated with hypertension.<sup>30</sup> Adjustment was made for hypertension because although this variable does not impact functional capacity, it is related to the outcome of interest (mortality). Overweight and obese patients also had higher rates of  $\beta$ -blocker use, and we adjusted for this as described previously. Our results confirm the well-established concepts that increased adiposity decreases FAC and is associated with increased all-cause mortality.<sup>31</sup>



Interestingly, we found that low FAC, as determined by treadmill exercise testing, predicted mortality in obese patients with no further adjustment necessary. The relationship of mortality to FAC appears to follow a  $1/x$  function, which is consistent with findings in previous studies using both physical activity and physical fitness as independent variables.<sup>11,32</sup> Compared with the reference group with good fitness (highest quintile of FAC), the cut point at which reduced FAC is a concern seems to



vary by weight group. In normal-weight patients, only the lowest decile of FAC is at a statistically higher risk for mortality; for overweight patients, it is the lowest quintile, and for obese patients, it is the lowest 2 quintiles. Although the relationship between FAC and mortality was relatively flat for normal-weight patients with the exception of the lowest decile of FAC, overweight and especially obese patients had additional mortality benefit with each transition to a superior fitness group up to 100% of FAC.

A question might be raised as to whether differences in mortality between normal-weight and overweight or obese patients might have been compromised by inclusion of patients with a very low BMI because no minimum cutoff was used. As such, low BMI in some patients may represent a manifestation of illness or failure to thrive.<sup>33</sup> However, exclusion of patients with a BMI of less than 20 did not significantly impact results because few patients met this condition (n=26).

We hypothesized that adiposity would impact performance on treadmill stress testing such that results would fail to accurately predict mortality. This is an important notion to assess because it could influence clinician judgment and potentially change management. Our results, however, suggest that this is not the case and that clinicians need not adjust the standard for low fitness in obese patients. Fitness predicts mortality irrespective of, and across, weight groups. Variation, if any, is in favor of higher, not lower, risk due to poor fitness in overweight and obese patients. In addition, obesity appears to predict mortality independent of fitness. Therefore, we conclude that not all of the mortality associated with obesity can be ascribed to poor cardiorespiratory fitness. Poorer performance on the treadmill due to excess weight appears to be balanced by increased mortality associated with obesity.<sup>7</sup> That is, while overweight or obese patients may have poor treadmill results due to extra load (ie, weight), the clinical implication of the results remains valid. It should not be dismissed as an artifact of mechanical (weight-based) disadvantage. This is an important and clinically relevant finding because low cardiorespiratory fitness is as robust a predictor of mortality as traditional cardiac risk factors such as diabetes mellitus, hyperlipidemia, and cigarette smoking.<sup>15</sup>

Overall, our results confirm previous findings by other investigators that poor functional capacity is an independent predictor of all-cause mortality in obese individuals. The relative risk of poor fitness in obese men reported by Lee et al<sup>14</sup> (1.92 for all-cause mortality) is comparable to the finding in the present study. Both Wei et al<sup>15</sup> and Stevens et al<sup>17</sup> also reported a higher risk of all-cause mortality in unfit obese patients. However, the obese group assessed by Sui et al<sup>18</sup> exhibited no higher mortality risk based on fitness. This may be due to a small sample size in their obese group with an inadequate number of deaths (50) to power a significant difference. Our finding that overweight and obese patients have greater reductions in risk with improved fitness is consistent with work by Kokkinos et al.<sup>16</sup> Their cohort, however, was limited to diabetic males. All prior studies have used the lowest quintile to define low fitness for comparisons. To our knowledge, however, our study is the first careful examination of the specific cutoff for fitness across BMI groups.

There are several identifiable limitations to this study. Ours is an observational, single-center experience limited only to men. More than 90% of the study population was white. Current smokers were excluded because smoking has been reported to reduce body weight,<sup>34</sup> decrease FAC,<sup>15</sup> and increase mortality.<sup>35</sup> Inclusion of current smokers, who comprised less than 10% of the patients in the stress test database overall, would unnecessarily complicate the analysis. Females were excluded because obesity in females may not be equivalent to obesity in males given the variance in weight distribution; the relationship between BMI and mortality appears to hold true for android obesity (or the so-called apple-shaped body type) and less so for gynecoid obesity (pear-shaped body type).<sup>36</sup> Therefore, these findings may not be applicable to other patient populations. Further, statistical analysis was limited to the primary end point of all-cause mortality. All-cause mortality was chosen as a hard end point because it is considered a better indicator than cardiovascular mortality and is less susceptible to ascertainment bias.<sup>27,28,37</sup> Disease-specific mortality may provide additional, customizable information. Although adjustments were attempted, BMI as a measure of obesity has limitations with respect to body fat estimation. Finally, there may be some referral bias

because obese patients may be less likely to be referred for treadmill testing than nonobese patients.

## CONCLUSION

Treadmill exercise testing is a commonly available, noninvasive, and relatively cost-effective risk stratification tool. Our study found that a significant increase in mortality occurs with FAC below 80% of predicted for overweight and obese subjects and below 70% for normal weight subjects. Our results further suggest that standard techniques need not be adjusted or interpreted differently for obese patients. Obese patients with poor fitness have increased mortality irrespective of the cause of low exercise capacity (whether this is due to excess weight or deconditioning). Poor fitness as ascertained by treadmill testing often dictates aggressiveness of therapy and referral for interventions. This clinical tool remains valuable for patients of all BMI classes. Practitioners should continue to use treadmill testing for prognostication and to encourage their obese and overweight patients to increase physical activity and lose weight.

**Abbreviations and Acronyms:** BMI = body mass index; CVD = cardiovascular disease; ECG = electrocardiography; FAC = functional aerobic capacity; HR = hazard ratio; MET = metabolic equivalent

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