Age-Specific Exercise Capacity Threshold for Mortality Risk Assessment in Male Veterans

Peter Kokkinos, PhD; Charles Faselis, MD; Jonathan Myers, PhD; Xuemei Sui, MD, PhD, MPH; Jiajia Zhang, PhD; Steven N. Blair, PED

Background—Mortality risk decreases beyond a certain fitness level. However, precise definition of this threshold is elusive and varies with age. Thus, fitness-related mortality risk assessment is difficult.

Methods and Results—We studied 18,102 male veterans (8,305 blacks and 8,746 whites). All completed an exercise test between 1986 and 2011 with no evidence of ischemia. We defined the peak metabolic equivalents (METs) level associated with no increase in all-cause mortality risk (hazard ratio, 1.0) for the age categories of <50, 50 to 59, 60 to 69, and ≥70 years. We used this as the threshold group to form additional age-specific fitness categories based on METs achieved below and above it: least-fit (>2 METs below threshold; n=1,692), low-fit (2 METs below threshold; n=4,884), moderate-fit (2 METs above threshold; n=4,464), fit (2.1–4 METs above threshold; n=1,874), and high-fit (>4 METs above threshold; n=1,301) categories. Multivariable Cox models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality across fitness categories. During follow-up (median=10.8 years), 5,102 individuals died. Mortality risk for the cohort and each age category increased for the least-fit and low-fit categories (HR, 1.51; 95% CI, 1.37–1.66; and HR, 1.21; 95% CI, 1.12–1.30, respectively) and decreased for the moderate-fit; fit and high-fit categories (HR, 0.71; 95% CI, 0.65–0.78; HR, 0.63; 95% CI, 0.56–0.78; and HR, 0.49; 95% CI, 0.41–0.58, respectively). The trends were similar for 5- and 10-year mortality risk.

Conclusion—We defined age-specific exercise capacity thresholds to guide assessment of mortality risk in individuals undergoing a clinical exercise test. (Circulation. 2014;130:653-658.)

Key Words: exercise test ■ exercise tolerance ■ metabolic equivalent ■ mortality

Findings from large epidemiological studies and diverse populations support a robust, inverse, and independent association between the cardiorespiratory fitness of an individual (as estimated by a symptom-limited exercise stress test) and cardiovascular and overall mortality risk regardless of age, race, sex, documented cardiovascular disease, or comorbidities. These health benefits are generally achieved beyond a certain threshold and increase thereafter with higher fitness status in a dose-response fashion. This threshold is influenced by several factors, including age, but its precise definition is elusive. When assessing the exercise capacity-mortality risk relationship, we and others estimated the exercise threshold to be the lowest quartile or quintile of the entire cohort, which typically translates to roughly 5 to 6 metabolic equivalents (METs). Statistical adjustments are then applied to account for the strong influence of age on exercise capacity. Although this approach allows adequate assessment of the exercise–mortality risk association, using 5 to 6 METs as a reference point to predict mortality risk in a clinical setting may be misleading. For example, most middle-aged individuals can perform well above the exercise threshold of ≥6 METs; therefore, mortality for these individuals will be underestimated. Conversely, the risk in the elderly will be overestimated. Therefore, an age-specific standardized exercise capacity threshold is necessary to guide clinical assessment of mortality risk. Thus, the aim of the present study was to develop age-specific peak exercise capacity thresholds to assess mortality risk across age categories.

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Study Population
Symptom-limited exercise tolerance tests were performed on ≥20,000 veterans between 1986 and 2011 at 2 Veterans Affairs Medical Centers (Washington, DC [n=10,507], and Palo Alto, CA [n=7,595]), as part of a routine evaluations, clearance to participate in exercise, or assessment of exercise-induced ischemia. To minimize the potential impact of low body mass index (BMI) resulting from cachexia on mortality, we excluded those with BMI <18.5 kg/m² and those with exercise capacity <2 METs. We also excluded those with an implanted pacemaker, left bundle-branch block, chronic obstructive pulmonary disease, chronic failure New York Heart Association class II or higher, and an inability to complete the test (reach volitional fatigue) as a result of musculoskeletal reasons, as well as those requiring emergent intervention. After these exclusions, the cohort comprised a total of operations related to musculoskeletal reasons, as well as those requiring emergent intervention. After these exclusions, the cohort comprised a total of operations related to musculoskeletal reasons, as well as those requiring emergent intervention.
18,102 male subjects (mean age, 58.4±11.4 years). Of those, 8,305 (45.9%) were black (mean age, 57.7±11.2 years), 8,746 (48.3%) were white (mean age, 59.3±11.4 years), and 1,051 (5.8%) were other races (mean age, 57.3±12.2 years). The study was approved by the Institutional Review Board at each institution, and all subjects gave written informed consent before their exercise tolerance test.

Assessments of Covariables
Detailed information on relevant demographic, clinical, and medication information; risk factors; and comorbidities as defined by International Classification of Diseases coding for all participants was obtained from electronic medical records at the time of the exercise tolerance test. Body weight and height were assessed with a standardized scale and recorded before the test. BMI was calculated as weight in kilograms divided by height squared in meters squared. Additionally, risk factors and comorbidities were recorded from the electronic medical records.

Assessments of Exercise Capacity
Exercise capacity was assessed by a standard treadmill test using the Bruce protocol at the Veterans Affairs Medical Center in Washington, DC, and an individualized ramp protocol as described elsewhere for subjects assessed at the Veterans Affairs Medical Center in Palo Alto, CA. Peak exercise capacity (METs) was estimated by use of standardized equations. One MET is defined as the energy expended at rest, converting for all participants. Threshold (Least-Fit), METs (n) = 2 METs Below Threshold (Low-Fit), METs (n) = 2 METs Above Threshold (High-Fit), METs (n)

Fitness Categories
We stratified the cohort into 4 age groups (<50, 50–59, 60–69, and ≥70 years). We then used the proportional hazards model with the B spline for each age category to define the MET level associated with no increase in mortality risk (hazard ratio [HR], 1.0) and formed the threshold category (n=3705). We used this category to form 5 fitness categories.

Ascertainment of Deaths
The study endpoint was death resulting from any cause. Dates of death were verified from the Veterans Affairs Beneficiary Identification and the Record Locator System File. This system, used to determine benefits to survivors of veterans, has been shown to be 95% complete and accurate in terms of mortality. Vital status was determined as of December 2012.

Statistical Analysis
Follow-up time was calculated from the exercise tolerance test date to the death date for decedents and to December 31, 2012, for survivors and is presented as median and mean±SD. Mortality rate was calculated as the ratio of deaths by the person-years of observation. Continuous variables are presented as mean±SD and categorical variables as relative frequencies (percent). Baseline associations between categorical variables were tested with the chi-square test. Univariate analysis, adjusted for age, BMI, and race, was applied to evaluate mean differences of normally distributed variables between fitness categories. Logistic regression, adjusted for age, BMI, and race, was applied to evaluate differences in categorical variables between fitness categories.

Assessments of Covariables
Detailed information on relevant demographic, clinical, and medication information; risk factors; and comorbidities as defined by International Classification of Diseases coding for all participants was obtained from electronic medical records at the time of the exercise tolerance test. Body weight and height were assessed with a standardized scale and recorded before the test. BMI was calculated as weight in kilograms divided by height squared in meters squared. Additionally, risk factors and comorbidities were recorded from the electronic medical records.

The results were presented as mean±SD and test statistics (t-test) were calculated for normally distributed variables between fitness categories. The distribution of the remaining variables was nonparametric and were tested using the Wilcoxon rank-sum test. Finally, we estimated the death burden attributable to low fitness while controlling for the aforementioned covariates. For this, we dichotomized the cohort as those with an exercise capacity at or below the threshold and those above it. All statistical analyses were performed using R and SPSS software version 19.0 (SPSS Inc, Chicago, IL).

Table 1. Exercise Threshold and Fitness Categories for the Different Age Groups

<table>
<thead>
<tr>
<th>Age Group, y (n)</th>
<th>Mean Age/Range, y</th>
<th>&gt;2 METs Below Threshold (Least-Fit), METs (n)</th>
<th>2 METs Below Threshold (Low-Fit), METs (n)</th>
<th>Threshold Group, METs (n)</th>
<th>2 METs Above Threshold (Moderate-Fit), METs (n)</th>
<th>&gt;2–4 METs Above Threshold (Fit), METs (n)</th>
<th>&gt;4 METs Above Threshold (High-Fit), METs (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 (4086)</td>
<td>43 (24–49)</td>
<td>&lt;6.0 (472)</td>
<td>6.0–7.9 (868)</td>
<td>8.0–9.0 (805)</td>
<td>9.1–11.0 (1053)</td>
<td>11.1–13.0 (408)</td>
<td>&gt;13.0 (480)</td>
</tr>
<tr>
<td>50–59 (5547)</td>
<td>55 (50–59)</td>
<td>&lt;5.0 (620)</td>
<td>5.0–6.9 (1368)</td>
<td>7.0–8.0 (1095)</td>
<td>8.1–10.0 (1485)</td>
<td>10.1–12.0 (607)</td>
<td>&gt;12.0 (372)</td>
</tr>
<tr>
<td>60–69 (5424)</td>
<td>64 (60–69)</td>
<td>&lt;4.0 (421)</td>
<td>4.0–5.9 (1718)</td>
<td>6.0–7.0 (1044)</td>
<td>7.1–9.0 (1356)</td>
<td>9.1–11.0 (556)</td>
<td>&gt;11.0 (329)</td>
</tr>
<tr>
<td>≥70 (3045)</td>
<td>75 (70–92)</td>
<td>&lt;3.0 (n=179)</td>
<td>3.0–4.9 (930)</td>
<td>5.0–6.0 (761)</td>
<td>6.1–8.0 (752)</td>
<td>8.1–10.0 (303)</td>
<td>&gt;10.0 (120)</td>
</tr>
</tbody>
</table>

MET indicates metabolic equivalent.
Demographic and clinical characteristics across fitness categories are presented in Table 2. In general, significant differences were observed between fitness categories among all variables examined. The differences tended to be more pronounced between the least-fit and high-fit individuals. Specifically, participants in the lowest fitness category were younger than those within the reference group but older than those in the highest fitness category. They were also heavier and had higher BMIs, higher blood pressures, and relatively less favorable lipid profiles. In general, the prevalence of hypertension, cardiovascular disease, muscle-wasting diseases, smoking, and alcohol/drug abuse and the use of all medications were progressively lower with increased fitness (moving from the least-fit to the high-fit category), whereas the prevalence of dyslipidemia and diabetes mellitus was progressively higher ($P<0.001$ for trend).

The MET thresholds for 4 age categories were 8 to 9, 7 to 8, 6 to 7, and 5 to 6 METs for <50, 50 to 59, 60 to 69, and ≥70 years, respectively (Table 1).

### Predictors of All-Cause Mortality

In the fully adjusted model, higher exercise capacity was inversely related to mortality risk for the entire cohort and each age category. For every 1-MET increase in exercise capacity, mortality risk was 12% lower (HR, 0.88; 95% confidence interval [CI], 0.86–0.89; $P<0.001$) for the entire cohort, and had higher BMIs, higher blood pressures, and relatively lower triglycerides and HDL cholesterol but higher prevalence of dyslipidemia and diabetes mellitus as progressively higher ($P<0.001$ for trend).

The MET thresholds for 4 age categories were 8 to 9, 7 to 8, 6 to 7, and 5 to 6 METs for <50, 50 to 59, 60 to 69, and ≥70 years, respectively (Table 1).

#### Table 2. Demographic and Clinical Characteristics According to Fitness Categories

| Fitness Category | Entire Cohort | >2 METs Below Threshold (Low-Fit) | 2 METs Below Threshold (High-Fit) | Threshold Group | 2 METs Above Threshold (Moderate-Fit) | >2–4 METs Above Threshold (Fit) | >4 METs Above Threshold (High-Fit) | $P$ Value*
|------------------|---------------|-----------------------------------|-----------------------------------|----------------|--------------------------------------|-------------------------------|-------------------------------|----------------
| Value*           | n             | Events, n (%)                      | Age, y                            | Weight, kg     | BMI, kg/m²                            | Resting heart rate, bpm       | Resting systolic BP, mm Hg | Resting diastolic BP, mm Hg | Peak exercise capacity, METs | Total cholesterol, mg/dL | Triglycerides, mg/dL | LDL cholesterol, mg/dL | HDL cholesterol, mg/dL | Hypertension, n (%) | Diabetes mellitus, n (%) | Smoking, n (%) | Dyslipidemia, n (%) | CV disease, n (%) | Medications, n (%)† | Muscle-wasting illness, n (%) | Alcohol/drug abuse, n (%) |
|------------------|---------------|-----------------------------------|-----------------------------------|----------------|--------------------------------------|-------------------------------|----------------------------|----------------------------|--------------------------|----------------------|--------------------|---------------------|----------------------|--------------------|------------------|----------------------|----------------------|------------------|---------------------|-----------------------|
| Value*           | n             | Events, n (%)                      | Age, y                            | Weight, kg     | BMI, kg/m²                            | Resting heart rate, bpm       | Resting systolic BP, mm Hg | Resting diastolic BP, mm Hg | Peak exercise capacity, METs | Total cholesterol, mg/dL | Triglycerides, mg/dL | LDL cholesterol, mg/dL | HDL cholesterol, mg/dL | Hypertension, n (%) | Diabetes mellitus, n (%) | Smoking, n (%) | Dyslipidemia, n (%) | CV disease, n (%) | Medications, n (%)† | Muscle-wasting illness, n (%) | Alcohol/drug abuse, n (%) |
| Value*           | n             | Events, n (%)                      | Age, y                            | Weight, kg     | BMI, kg/m²                            | Resting heart rate, bpm       | Resting systolic BP, mm Hg | Resting diastolic BP, mm Hg | Peak exercise capacity, METs | Total cholesterol, mg/dL | Triglycerides, mg/dL | LDL cholesterol, mg/dL | HDL cholesterol, mg/dL | Hypertension, n (%) | Diabetes mellitus, n (%) | Smoking, n (%) | Dyslipidemia, n (%) | CV disease, n (%) | Medications, n (%)† | Muscle-wasting illness, n (%) | Alcohol/drug abuse, n (%) |
To account for this, we excluded those treated with β-blockers and reanalyzed the remaining cohort. We also analyzed those treated with β-blockers. The findings in trend and magnitude of risk were very similar to those observed for the entire cohort.

The 5- and 10-year mortality risks across fitness categories and for the different age groups are given in Table 4. In general, the 5- and 10-year mortality risks were progressively higher for individuals with a fitness level below the age-specific threshold and progressively lower for those with a fitness level above the age-specific threshold. This is evident for all age groups. Notably, the 5- and 10-year mortality risks for individuals in the lowest fitness category (least-fit group) across age groups are ≈3 times higher than those in the highest fitness category (high-fit group).

To estimate the death burden attributable to low fitness, we dichotomized the cohort to those at or below (unfit) and above (fit) the MET threshold. We estimated the population-attributable risk from the following formula: \( \text{PA} = \frac{p_c(1-1/\text{adjusted HR})}{\text{adjusted HR}} \), where \( p_c \) is the prevalence of low fitness among deceased and adjusted HR is the multivariable-adjusted HR for death associated with low fitness. The adjusted HR for the unfit group was 1.79 (95% CI, 1.68–1.91; \( P < 0.001 \)), and the death prevalence was 72.5%. We found that 32% of deaths attributable to low fitness may be avoided if individuals with an exercise capacity at or below the threshold improve their fitness status to above the threshold.

**Discussion**

The findings of the present study support the existence of an age-specific exercise threshold (MET level) beyond which mortality risk is altered in a graded fashion. Specifically, mortality risk was progressively higher for those with a peak MET level below the age-specific threshold. The increase in mortality risk varied across the age categories, ranging from ≈30% to 80%. Conversely, mortality risk was progressively lower for those with a peak MET level above the age-specific threshold. The risk reduction varied across age categories, with an approximate range of 25% to 50% (Table 3). From these findings, we calculated the 5- and 10-year mortality risks for the aforementioned age categories. As evident in Table 4, both the 5- and 10-year risks increased with lower fitness and decreased with higher fitness in a graded fashion. This trend was evident in all age categories. It is also noteworthy that the 5-year mortality risk for individuals ≥60 years of age with an exercise capacity >4 METs above the threshold is similar to that of individuals <50 years of age with an exercise capacity ≥2 METs below the threshold.

The concept that exercise capacity strongly predicts mortality has been reported by numerous cohort studies, and individuals achieving the lowest quintile of fitness (usually <5 METs) demonstrate a particularly high risk for mortality. However, because exercise capacity declines with age, absolute cutoffs to delineate risk for different age groups in men remain unclear.

The present study is, to the best of our knowledge, the only one to identify an age-specific exercise capacity threshold. This much-needed information can assist clinicians in estimating mortality risk below and above an age-specific MET threshold for individuals undergoing an exercise test. These

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### Table 4. Average 5- and 10-Year Mortality Risks Across Fitness Categories for the Different Age Groups

<table>
<thead>
<tr>
<th>Age, y</th>
<th>&gt;2 METs Below Threshold (Least-Fit), %</th>
<th>2 METs Below Threshold (Low-Fit), %</th>
<th>Threshold Category, %</th>
<th>2 METs Above Threshold (Moderate-Fit), %</th>
<th>&gt;2–4 METs Above Threshold (Fit), %</th>
<th>&gt;4 METs Above Threshold (High-Fit), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>6.0</td>
<td>13.2</td>
<td>4.8</td>
<td>8.9</td>
<td>6.5</td>
<td>5.7</td>
</tr>
<tr>
<td>50–59</td>
<td>10.2</td>
<td>22.2</td>
<td>8.3</td>
<td>18</td>
<td>15.2</td>
<td>11.1</td>
</tr>
<tr>
<td>60–69</td>
<td>15.6</td>
<td>32.3</td>
<td>12.7</td>
<td>26.8</td>
<td>22.8</td>
<td>16.9</td>
</tr>
<tr>
<td>≥70</td>
<td>24.8</td>
<td>48.1</td>
<td>20.4</td>
<td>40.7</td>
<td>35.2</td>
<td>26.7</td>
</tr>
</tbody>
</table>

MET indicates metabolic equivalent.
findings are derived from a large clinically referred cohort (n=18 106), roughly 46% of whom were black, with a follow-up time of 208 108 person-years. In addition, the equal access to care independently of a patient’s financial status provided by the Veterans Health Administration, a unique feature of this study, permits epidemiological evaluations while minimizing the influence of disparities in medical care.23,24 This, along with the existence of electronic health records within the Veterans Affairs Healthcare System, enables detailed observation of prior history, medications, comorbidities, and alterations in health status. These attributes, coupled with the consideration for individuals diagnosed with muscle-wasting disease, minimize the likelihood of reverse causality and support the validity of the fitness–mortality risk association for all ages and the age-specific exercise thresholds for risk assessment.

The exercise-mortality risk association observed in the present study and reported by previous studies2–7,11–16 strengthens the concept that increased fitness plays an integral role in survival regardless of age. However, a unique aspect of the present study is that the impact of fitness was assessed across a broad age range (age, 25–92 years). In this regard, low fitness may be more detrimental for individuals <60 years of age than those ≥60 years of age. Specifically, although the favorable impact of increased fitness on mortality risk was similar across the age categories, compared with the reference group, the mortality risk was 40% to 82% higher for individuals <50 years of age in the 2 lowest fitness categories and 41% to 79% higher for those 50 to 59 years old. For those 60 to 69 years of age in the same fitness categories, mortality risk ranged from 30% to 48%. Finally, for those ≥70 years of age, mortality risk ranged from 2% to 30% higher. This was also reflected by the degree of change in mortality risk per 1-MET increase in those <60 years of age (15%) compared with those ≥60 years (11%). An explanation for this is not readily available and is beyond the scope of the present study. It is likely that the higher prevalence of comorbidities in older individuals explains a significant portion of the mortality risk, obscuring the deleterious effects of low fitness. Nevertheless, the salient message of our findings is that increased fitness is beneficial regardless of age.

Other aspects of the study are also noteworthy. For example, it is of interest that mortality risk was ≥25% to 30% lower in all age categories for individuals achieving just 2 METs beyond the fitness threshold and 30% to 50% lower for those with an exercise capacity ≥2 METs beyond the threshold. Meeting these relatively modest fitness thresholds is likely achievable by moderate-intensity physical activity, ranging from a brisk walk for those ≥60 years of age to a slow jog for younger individuals 30 minutes per day on most days of the week. From a public health perspective, the implementation of strategies to promote physical activity can have profound and positive health consequences nationwide.25–27

We also estimated the percent of deaths that could be avoided if individuals with a peak exercise capacity at or below the threshold were to improve their fitness status above the threshold. We found that 32% of deaths attributable to low fitness may be avoided if individuals with an exercise capacity at or below the threshold improve their fitness status to above the threshold.

Limitations
This study has several limitations inherent in prospective follow-up evaluations. We did not have an adequate number of participants to assess mortality risk in those <30 years of age. However, the fitness threshold for the age category of <50 years did not change significantly when individuals <30 years of age were excluded from the analysis. We had information only on all-cause mortality and did not have data on cardiovascular interventions and mortality. The onset of chronic diseases, their severity, and the duration of therapy were not evaluated. Dietary information was also not available in our records. The history of smoking, length of smoking, and number of cigarettes were not available. The use of 2 different exercise protocols used to assess fitness is also a potential limitation. Our previous work suggests that the ramp protocol is somewhat more accurate in predicting measured METs.2,37 However, separate analyses from the 2 locations yielded similar results, suggesting that the differences in protocols had minimal impact.24 Fitness levels were based on 1 assessment, and follow-up data on the fitness status of the participants were not available. Finally, only male veterans were included, which limits the ability to generalize the findings to women and other populations. Therefore, future studies are needed to validate our findings.

Conclusions
The present findings provide age-specific fitness thresholds and mortality risks associated with subjects who achieve fitness levels below and above this threshold for different age categories. This information can then be used easily by clinicians to assess mortality risk for individuals undergoing an exercise test. Therapeutic interventions can then be pursued more aggressively for high-risk individuals.

The relatively low exercise capacity of ≥2 METs beyond the exercise threshold necessary to realize these health benefits is achievable by most middle-aged and older adults. Thus, the concept of promoting fitness merits increased efforts to promote physical activity nationwide.

Disclosures
None.

References
The cardiorespiratory fitness–mortality risk association is robust and inverse, regardless of age, race, sex, documented cardiovascular disease, or comorbidities. These health benefits are generally achieved beyond a certain threshold and increase thereafter with higher fitness status in a dose–response fashion. This threshold is influenced by several factors, including age, but its precise definition is elusive. In the present study, we identify an age-specific exercise capacity threshold (metabolic equivalent [MET] level) that can be used to guide clinical assessment of mortality risk across age categories. This threshold was between 8 to 9 METs for individuals <50 years, 7 to 8 METs for those aged 50 to 59 years, 6 to 7 METs for those 60 to 69 years, and 5 to 6 METs for those ≥70 years. The mortality risk increased progressively for all age categories in those with a peak exercise capacity of 2 and >2 METs below the threshold and decreased for those with a peak exercise capacity of 2, 4, and >4 METs above the threshold.

**CLINICAL PERSPECTIVE**

The cardiorespiratory fitness–mortality risk association is robust and inverse, regardless of age, race, sex, documented cardiovascular disease, or comorbidities. These health benefits are generally achieved beyond a certain threshold and increase thereafter with higher fitness status in a dose–response fashion. This threshold is influenced by several factors, including age, but its precise definition is elusive. In the present study, we identify an age-specific exercise capacity threshold (metabolic equivalent [MET] level) that can be used to guide clinical assessment of mortality risk across age categories. This threshold was between 8 to 9 METs for individuals <50 years, 7 to 8 METs for those aged 50 to 59 years, 6 to 7 METs for those 60 to 69 years, and 5 to 6 METs for those ≥70 years. The mortality risk increased progressively for all age categories in those with a peak exercise capacity of 2 and >2 METs below the threshold and decreased for those with a peak exercise capacity of 2, 4, and >4 METs above the threshold.