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

Running title: Kokkinos et al.; Exercise capacity threshold, mortality

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Abstract

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 <50; 50-59; 60-69; ≥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=4,646); Fit (2.1-4 METs above Threshold; n=1,874) and High-Fit (>4 METs above Threshold; n=1,301). Multivariable Cox models were used to estimate hazard ratios and 95% confidence interval [CI] for mortality across fitness categories. During follow-up (median=10.8 years) 5,102 died. Mortality risk for the cohort and each age category increased for the Least-Fit and Low-Fit (hazard ratios, 1.51; 95% CI, 1.37 to 1.66), and 1.21; 95% CI, 1.12 to1.30, respectively), and decreased for the Moderate-Fit; Fit and High-Fit categories (hazard ratios, 0.71; 95% CI, 0.65 to 0.78; 0.63; 95% CI, 0.56 to 0.78; and 0.49; 95% CI, 0.41 to 0.58, respectively). The trends were similar for five and 10-year mortality risk.

Conclusions—We defined age-specific exercise capacity thresholds to guide assessment of mortality risk in individuals undergoing a clinical exercise test.

Key words: exercise capacity, mortality, risk prediction
Introduction

Findings from large epidemiologic studies and diverse populations support a robust, inverse, and independent association between cardiorespiratory (CR) fitness of an individual (as estimated by a symptom-limited exercise stress test) and cardiovascular and overall mortality risk regardless of age, race, gender, documented cardiovascular disease (CVD), 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 5-6 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 5-6 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 approximately 6 METs and 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 current study was to develop age-specific peak exercise capacity thresholds to assess mortality risk across age categories.

Methods

Study Population

Symptom-limited exercise tolerance tests (ETT) were performed on over 20,000 veterans.
between 1986 and 2011 at two VAMCs (Washington, DC; n=10,507 and Palo Alto, California; n=7,595), either as part of a routine evaluations, clearance to participate in exercise or to assess exercise-induced ischemia. To minimize the potential impact of low body mass index (BMI) on mortality due to cachexia, we excluded those with BMI<18.5 kg/m² and those with exercise capacity <2 METs. We also excluded those with: 1) implanted pacemaker; 2) left bundle branch block; 3) chronic obstructive pulmonary disease; 4) those with chronic failure NYHA class II or higher; and 5) those unable to complete the test (reach volitional fatigue) as a result of musculoskeletal reasons; and 5) those required emergent intervention. After these exclusions, the cohort comprised a total of 18,102 male subjects (mean age 58.4±11.4 years). Of those, 8,305 (45.9%) were African-American (mean age 57.7±11.2 years); 8,746 (48.3%) were Caucasian (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 prior to their ETT.

Assessments of Covariables

Detailed information on relevant demographic, clinical and medication information, risk factors and co-morbidities as defined by ICD coding for all participants were obtained from electronic medical records at the time of the ETT. Body weight and height were assessed using a standardized scale and recorded prior to the test. BMI was calculated as weight (kg) divided by height² (m²). Additionally, risk factors and co-morbidities were recorded from the electronic medical records.

Assessments of Exercise Capacity

Exercise capacity was assessed by a standard treadmill test utilizing the Bruce protocol at the VAMC, Washington DC, and an individualized ramp protocol as described elsewhere¹⁷ for
subjects assessed at the VAMC, Palo Alto CA. Peak exercise capacity (METs) was estimated using standardized equations. One MET is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 ml O\textsubscript{2} per kg body weight per minute. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping. The use of handrails was allowed only if necessary for balance and safety. Medications were not altered before testing.

**Fitness Categories**

We stratified the cohort into four age-groups (<50; 50-59; 60-69; and ≥70 years). We then used the proportional hazards model with the B-spline\textsuperscript{20} for each age category to define the MET level associated with no increase in mortality risk (hazard ratio =1.0) and formed the Threshold category (Threshold; n=3,705). We used this category to form five additional age-specific fitness categories based on METs achieved above and below the threshold (Table 1): Low-Fit (Threshold-2 METs; n=4,884); Least-Fit; (Threshold->2 METs; n=1,692); Moderate-Fit (Threshold+2 METs; n=4,646); Fit (Threshold+ 2-4 METs; n=1,874) and High-Fit (Threshold+>4 METs (n=1,301).

**Ascertainment of Deaths**

The study endpoint was death from any cause. Dates of death were verified from the Veterans Affairs Beneficiary Identification and the Record Locator System File. This system is used to determine benefits to survivors of veterans and has been shown to be 95% complete and accurate regarding mortality.\textsuperscript{21} Vital status was determined as of December 2012.

**Statistical Analysis**

Follow-up time was calculated from the ETT date to the death date for decedents and to 12/31/2012 for survivors and 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 values ± SD and categorical variables as relative frequencies (%). Baseline associations between categorical variables were tested using chi-square. 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 of categorical variables between fitness categories.

The proportional hazard model was used to depict hazard ratios associated with exercise capacity (METs) for the entire cohort and for each age category. In the fully adjusted model, the covariates were age in years, BMI, race, CVD (myocardial infarction, cardiac bypass surgery, percutaneous interventions, stroke, peripheral vascular disease), risk factors (hypertension (HTN), type 2 diabetes mellitus (DM), dyslipidemia and smoking at the time of the test), muscle-wasting diseases (cancer, HIV/AIDS, and renal failure), cardiac/anti-hypertensive medications (β-blockers, calcium-channel blockers; diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers), lipid-lowering and hypoglycemic agents. All variables included in the models were based on the rationale of their clinical role on the outcome and the main factors of interest. Cox proportional hazard models were then used to compare risks between the fitness categories using the threshold category as the reference group. The model was adjusted for the aforementioned covariates. The assumption of proportionality for the Cox proportional hazard models was graphically tested by plotting the logarithm of the cumulative hazards with time for each covariate; the proportionality assumption was fulfilled for each model. All hypotheses were two sided and p-values <0.05 were considered statistically significant. The prediction of five and ten year all-cause mortality (1-survival probability) is based on the proportional hazards model for the entire cohort. For each age group, the population mean was
used in the Cox Proportional hazard model in predicting mortality. Finally, we estimated the
death burden attributable to low fitness while accounting for the aforementioned covariates. For
this, we dichotomized the cohort to 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, USA).

Results

Study Population

For the 18,102 male participants included in the analysis, the mean age at the time of the exercise
stress test was 58.4±11.4 years. The follow-up time ranged from 0.5-25 years (mean 11.5±6.7).
The median was 10.8 years (6.5 and 15.8 for 25th and 75th percentiles respectively); comprising a
total of 208,108 person-years. There were 5,103 deaths (28.2%) with an average annual mortality
rate of 24.5 events per 1,000 person-years. There were no interactions between site-by-fitness
(p=0.31) or race-by-fitness (p=0.08) therefore, the data were not stratified by site or race. A
significant interaction was noted between age and MET levels (p<0.001).

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 within the highest fitness category. They
were also heavier, had higher BMI, higher blood pressure, and a relatively less favorable lipid
profile. In general, the prevalence of HTN, CV disease, muscle-wasting diseases, smoking,
alcohol/drug abuse and the use of all medications was progressively lower with increased fitness
(when moving from the Least-Fit to the High-Fit category), while the prevalence of
dyslipidemia and diabetes mellitus was progressively higher (p<0.001 for trend).

The MET thresholds for four age categories were: 8-9 METs; 7-8 METs; 6-7 and 5-6
METs for <50 years, 50-59; 60-69 yrs; and ≥70 yrs, 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 (hazard ratio, 0.88, 95% confidence interval [CI], 0.86-0.89,
p<0.001) for the entire cohort, 15% (hazard ratio, 0.85; 95% CI, 0.83-0.87, p<0.001) for those
<60, and 11% (hazard ratio, 0.89; 95% CI 0.88-0.91, p<0.001) for those ≥60 years of age.
Additional predictors of mortality risk were CVD (hazard ratio, 1.20; 95% CI, 1.13-1.27,
p<0.001), smoking (hazard ratio, 1.29; 95% CI, 1.21-1.37, p<0.001), DM (hazard ratio, 1.20;
95% CI, 1.12-1.28, p<0.001), muscle-wasting diseases (hazard ratio, 1.66; 95% CI, 1.54-1.78
(p<0.001); age in years (hazard ratio per year, 1.05; 95% CI, 1.03-1.06, p<0.001), drug/alcohol abuse (hazard ratio, 1.22; 95% CI, 1.06-1.39, p<0.001), and lipid-lowering medications (hazard ratio, 0.50; 95% CI, 0.46-0.55, p<0.001).

When considering fitness categories, mortality risk was progressively higher in the two
fitness categories comprised of individuals with a peak MET level below the threshold.
Specifically, the hazard ratio for individuals in the Low-Fit category was 1.21; 95% CI, 1.12 to
1.31 and 1.52; 95% CI, 1.39 to 1.67 for those in the Least-Fit category. Conversely, mortality
risk was progressively lower for the fitness categories with a peak MET level above the
threshold. Specifically, the hazard ratio for was 0.71; 95% CI, 0.65 to 0.78 for Moderate-Fit;
0.62; 95% CI, 0.54 to 0.70 for Fit; and 0.46; 95% CI, 0.39 to 0.55 for High-Fit individuals. The
trend was similar for each age category (Table 3).

Cardiac medications, especially β-blockers, may influence exercise capacity. In our cohort, peak MET level of participants treated with β-blockers was 1 MET lower compared to those not treated with β-blockers (6.8±2.3 versus 7.8±3.0, respectively). To account for this, we excluded those treated with β-blockers and re-analyzed 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 five and 10-year mortality risk across fitness categories and for the different age groups is presented in Table 4. In general, the five and 10-year mortality risk was 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 five and 10-year mortality risk for individuals in the lowest fitness category (Least-Fit) across age groups is approximately 3 times higher when compared to those in the highest fitness category (High-Fit).

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 (PAR) based on the formula Pc (1-1/HR-adjusted), where Pc is the prevalence of low fitness among deceased and HR-adjusted is the multivariable-adjusted HR for death associated with low fitness. The adjusted HR for the Unfit group was 1.79 (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 current 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 approximately 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). Based on these findings, we calculated the five and 10-year mortality risk for the aforementioned age categories. As evident in Table 4, both five and 10-year risk 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 for individuals with an exercise capacity >4 METs above 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 studies²⁻⁷,¹¹⁻¹⁶ and individuals achieving the lowest quintile of fitness (usually <5 METs) demonstrate a particularly high risk for mortality.²,⁴,¹¹⁻¹⁵ However, because exercise capacity declines with age, absolute cutoffs to delineate risk for different age groups in men remain unclear.

The current study is the only one to our knowledge 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 findings are derived from a large clinically-referred cohort (n=18,106), roughly 46% of
whom were African-American, with a follow-up time of 208,108 person-years. In addition, the equal access to care independent of a patient’s financial status provided by the Veterans Health Administration, a unique feature of this study, permits epidemiologic evaluations while minimizing the influence of disparities in medical care. This, along with the existence of electronic health records within the VA Healthcare System, enables detailed observation of prior history, medications, co-morbidities 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 current study and reported by previous studies strengthens the concept that increased fitness plays an integral role in survival regardless of age. However, a unique aspect of the current study is that the impact of fitness was assessed across a broad age range (25-92 years). In this regard, low fitness may be more detrimental for individuals <60 years than those ≥60 years of age. Specifically, while the favorable impact of increased fitness on mortality risk was similar across the age categories, when compared to the reference group, mortality risk for individuals <50 years of age in the two lowest fitness categories was 40% to 82% higher and 41% to 79% higher for those 50-59 years old. For those 60-69 years of age, in the same fitness categories, mortality risk ranged from 30% to 48%. Finally, for those ≥70 years, 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 to those ≥60 years (11%). An explanation for this is not readily available and beyond the scope of the current study. It is likely that the higher prevalence of co-morbidities 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 approximately 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, 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.\textsuperscript{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 adequate number of participants to assess mortality risk in those <30 years of age. However, the fitness threshold for the age category <50 years did not change significantly when individuals <30 years of age were excluded from the analysis. We only had information on all-cause mortality, and did not have data on cardiovascular interventions and mortality. The onset of chronic diseases, their severity, and duration of therapy were not evaluated. Dietary information
was also not available in our records. The history of smoking, length of smoking and amount were not available. The two 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.\(^2,17\) However, separate analyses from the two locations yielded similar results, suggesting that the differences in protocols had minimal impact.\(^2,4\) Fitness levels were based on one 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.

In conclusion, the current 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 easily used 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.

**Conflict of Interest Disclosures:** None.

**References:**


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

<table>
<thead>
<tr>
<th>Mean age/Range</th>
<th>&gt;2 METs Below Threshold (Least-Fit)</th>
<th>2 METs Below Threshold (Low-Fit)</th>
<th>Threshold Group</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 yrs (n=4,086)</td>
<td>43 6.0-7.9</td>
<td>&lt;6.0 8.0-9.0</td>
<td>9.1-11.0 11.1-13.0</td>
<td>&gt;13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 yrs (n=5,547)</td>
<td>55 5.0-6.9</td>
<td>&lt;5.0 7.0-8.0</td>
<td>8.1-10.0 10.1-12.0</td>
<td>&gt;12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69 yrs (n=5,424)</td>
<td>64 4.0-5.9</td>
<td>&lt;4.0 6.0-7.0</td>
<td>7.1-9.0 9.1-11.0</td>
<td>&gt;11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 yrs (n=3,045)</td>
<td>75 3.0-4.9</td>
<td>&lt;3.0 5.0-6.0</td>
<td>6.1-8.0 8.1-10.0</td>
<td>&gt;10.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Demographic and Clinical Characteristics According to Fitness Categories

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>&gt;2 METs Below Threshold (Least-Fit)</th>
<th>&gt;2 METs Below Threshold (Low-Fit)</th>
<th>Threshold Group</th>
<th>&gt;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>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18,102</td>
<td>1,692</td>
<td>4,884</td>
<td>3,705</td>
<td>4,646</td>
<td>n=1,874</td>
<td>1,301</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No of Events (%)</td>
<td>1,506 (28.2)</td>
<td>750 (44.3)</td>
<td>1,845 (37.8)</td>
<td>1,102 (29.7)</td>
<td>899 (19.3)</td>
<td>331 (17.7)</td>
<td>179 (13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.4±11</td>
<td>57±10</td>
<td>60±11</td>
<td>59±12</td>
<td>58±11</td>
<td>58±11</td>
<td>53±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89±17</td>
<td>93±22</td>
<td>92±19</td>
<td>91±17</td>
<td>88±15</td>
<td>86±15</td>
<td>83±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29±5</td>
<td>30±6</td>
<td>30±6</td>
<td>29±5</td>
<td>28±5</td>
<td>28±4</td>
<td>27±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>73±14</td>
<td>77±15</td>
<td>75±14</td>
<td>73±14</td>
<td>71±13</td>
<td>72±13</td>
<td>74±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting systolic BP (mm Hg)</td>
<td>131±20</td>
<td>133±22</td>
<td>134±21</td>
<td>132±20</td>
<td>129±19</td>
<td>129±18</td>
<td>130±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting diastolic BP (mm Hg)</td>
<td>80±11</td>
<td>81±12</td>
<td>80±12</td>
<td>79±11</td>
<td>80±11</td>
<td>82±11</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Peak exercise capacity (METs)</td>
<td>7.6±2.9</td>
<td>3.8±1.5</td>
<td>5.4±3.0</td>
<td>7.0±5.0</td>
<td>8.6±6.0</td>
<td>10.6±8.0</td>
<td>14.2±10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>197±45</td>
<td>197±52</td>
<td>191±46</td>
<td>192±45</td>
<td>196±44</td>
<td>204±42</td>
<td>204±42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>108±62</td>
<td>110±58</td>
<td>112±63</td>
<td>112±59</td>
<td>109±69</td>
<td>94±49</td>
<td>101±47</td>
<td>0.005</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>136±47</td>
<td>142±56</td>
<td>131±49</td>
<td>131±46</td>
<td>134±46</td>
<td>146±45</td>
<td>147±45</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>44±13</td>
<td>41±11</td>
<td>42±12</td>
<td>42±11</td>
<td>45±13</td>
<td>45±12</td>
<td>48±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>10,555 (58.3%)</td>
<td>994 (58.7%)</td>
<td>3,102 (63.5%)</td>
<td>2,232 (60.2%)</td>
<td>2,560 (55.1%)</td>
<td>996 (53.1%)</td>
<td>671 (51.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>8,204 (45.3%)</td>
<td>763 (45.1%)</td>
<td>2,250 (46.1%)</td>
<td>1,673 (45.2%)</td>
<td>1,877 (40.4%)</td>
<td>884 (47.2%)</td>
<td>757 (58.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>4,621 (25.5%)</td>
<td>554 (32.7%)</td>
<td>1,514 (31.0%)</td>
<td>966 (26.1%)</td>
<td>1,096 (23.6%)</td>
<td>311 (16.6%)</td>
<td>180 (13.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (n)</td>
<td>8,038 (44.4%)</td>
<td>629 (37.2%)</td>
<td>1,964 (40.2%)</td>
<td>1,563 (42.2%)</td>
<td>2,121 (45.7%)</td>
<td>974 (52.0%)</td>
<td>787 (60.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV disease (n)</td>
<td>5,734 (31.7%)</td>
<td>756 (44.7%)</td>
<td>1,952 (40.0%)</td>
<td>1,191 (32.1%)</td>
<td>1,253 (27.0%)</td>
<td>382 (20.4%)</td>
<td>200 (15.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medications† (n)</td>
<td>12,200 (67.4%)</td>
<td>1,235 (73.0%)</td>
<td>3,693 (75.6%)</td>
<td>2,648 (71.5%)</td>
<td>3,148 (67.8%)</td>
<td>1,007 (53.7%)</td>
<td>469 (36.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle-wasting illness (n)</td>
<td>2,521 (13.9%)</td>
<td>223 (13.2%)</td>
<td>981 (20.1%)</td>
<td>562 (15.2%)</td>
<td>630 (13.6%)</td>
<td>119 (6.4%)</td>
<td>6 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol/Drug abuse</td>
<td>941 (5.2%)</td>
<td>101 (6.0%)</td>
<td>299 (6.1%)</td>
<td>222 (6.0%)</td>
<td>273 (5.9%)</td>
<td>44 (2.3%)</td>
<td>2 (0.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P-values for linear trend
† Medications included cardiovascular, antihypertensive, lipid-lowering, and hypoglycemic agents
Table 3. Adjusted Mortality Risk According to Fitness Categories.

<table>
<thead>
<tr>
<th>Categories (no of events/n)</th>
<th>&gt;2 METs Below Threshold (Least-Fit)</th>
<th>2 METs Below Threshold (Low-Fit)</th>
<th>Threshold Group</th>
<th>&gt;2-4 METs Above Threshold (Moderate-Fit)</th>
<th>&gt;4 METs Above Threshold (Fit)</th>
<th>&gt;4 METs Above Threshold (High-Fit)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Cohort (5,106/18,102)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.52 (1.39-1.67)</td>
<td>1.21 (1.12-1.31)</td>
<td>1</td>
<td>0.71 (0.65-0.78)</td>
<td>0.62 (0.54-0.70)</td>
<td>0.46 (0.39-0.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;50 yrs (533/4,095)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.82 (1.40-2.37)</td>
<td>1.40 (1.09-1.80)</td>
<td>1</td>
<td>0.60 (0.44-0.81)</td>
<td>0.75 (0.51-1.11)</td>
<td>0.50 (0.33-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50-59 yrs (1,093/5,553)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.79 (1.48-2.16)</td>
<td>1.41 (1.19-1.68)</td>
<td>1</td>
<td>0.68 (0.55-0.83)</td>
<td>0.40 (0.29-0.56)</td>
<td>0.44 (0.31-0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-69 yrs (1,953/5,420)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.48 (1.26-1.74)</td>
<td>1.30 (1.15-1.47)</td>
<td>1</td>
<td>0.72 (0.62-0.83)</td>
<td>0.60 (0.48-0.74)</td>
<td>0.46 (0.35-0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥70 yrs (1,527/3,034)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.30 (1.05-1.59)</td>
<td>1.02 (0.89-1.16)</td>
<td>1</td>
<td>0.76 (0.66-0.89)</td>
<td>0.71 (0.58-0.86)</td>
<td>0.46 (0.32-0.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, blood pressure, race, site, beta-blockers, calcium channel blockers, ACE-I, ARBs, aspirin, diuretics, lipid-lowering agents, hypoglycemic agents, history of smoking, history of CV disease, type 2 diabetes mellitus, muscle wasting diseases, alcohol/drug abuse, dyslipidemia, hypertension and year of entry in the study.
Table 4. Average 5-year and 10-year mortality risk across fitness categories for the different age groups

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>&gt;2 METs Below Threshold (Least-Fit)</th>
<th>2 METs Below Threshold (Low-Fit)</th>
<th>Threshold Category</th>
<th>&gt;2-4 METs Above Threshold (Moderate-Fit)</th>
<th>&gt;4 METs Above Threshold (Fit)</th>
<th>&gt;4 METs Above Threshold (High-Fit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-yr</td>
<td>10-yr</td>
<td>5-yr</td>
<td>10-yr</td>
<td>5-yr</td>
<td>10-yr</td>
</tr>
<tr>
<td>&lt;50</td>
<td>6.0%</td>
<td>13.2%</td>
<td>4.8%</td>
<td>10.7%</td>
<td>4.0%</td>
<td>8.9%</td>
</tr>
<tr>
<td>50-59</td>
<td>10.2%</td>
<td>22%</td>
<td>8.3%</td>
<td>18%</td>
<td>6.9%</td>
<td>15.2%</td>
</tr>
<tr>
<td>60-69</td>
<td>15.6%</td>
<td>32.3%</td>
<td>12.7%</td>
<td>26.8%</td>
<td>10.7%</td>
<td>22.8%</td>
</tr>
<tr>
<td>≥70</td>
<td>24.8%</td>
<td>48.1%</td>
<td>20.4%</td>
<td>40.7%</td>
<td>17.2%</td>
<td>35.2%</td>
</tr>
</tbody>
</table>
Age-Specific Exercise Capacity Threshold for Mortality Risk Assessment in Male Veterans
Peter Kokkinos, Charles Faselis, Jonathan Myers, Xuemei Sui, Jiajia Zhang and Steven N. Blair

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