

Cardiorespiratory Fitness and Incidence of Major Adverse Cardiovascular Events in US Veterans: A Cohort Study

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Abstract

Objective: To assess the association between exercise capacity and the risk of major adverse cardiovascular events (MACEs).

Patients and Methods: A symptom-limited exercise tolerance test was performed to assess exercise capacity in 20,590 US veterans (12,975 blacks and 7615 whites; mean \pm SD age, 58.2 \pm 11.0 years) from the Veterans Affairs medical centers in Washington, District of Columbia, and Palo Alto, California. None had a history of MACE or evidence of ischemia at the time of or before their exercise tolerance test. We established quintiles of cardiorespiratory fitness (CRF) categories based on age-specific peak metabolic equivalents (METs) achieved. We also defined the age-specific MET level associated with no risk for MACE (hazard ratio [HR], 1.0) and formed 4 additional CRF categories based on METs achieved below (least fit and low fit) and above (moderately fit and highly fit) that level. Multivariate Cox models were used to estimate HR and 95% CIs for mortality across fitness categories.

Results: During follow-up (median, 11.3 years; range, 0.3-33.0 years), 2846 individuals experienced MACEs. The CRF-MACE association was inverse and graded. The risk for MACE declined precipitously for those with a CRF level of 6.0 METs or higher. When considering CFR categories based on the age-specific MET threshold, the risk increased for those in the 2 CFR categories below that threshold (HR, 1.95; 95% CI, 1.73-2.21 and HR, 1.41; 95% CI, 1.27-1.56 for the least-fit and low-fit individuals, respectively) and decreased for those above it (HR, 0.77; 95% CI, 0.68-0.87 and HR, 0.57; 95% CI, 0.48-0.67 for moderately fit and highly fit, respectively).

Conclusion: Increased CRF is inversely and independently associated with the risk for MACE. When an age-specific MET threshold was defined, the risk for MACE increased significantly for those below that threshold and decreased for those above it ($P < .001$).

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The findings of large epidemiological studies overwhelmingly support an inverse and graded association between mortality risk and exercise capacity or cardiorespiratory fitness (CRF) estimated from a standardized exercise test. This association is independent of age,^{1,2} race,³ sex,⁴⁻⁸ documented cardiovascular disease,⁹ or comorbidities.¹⁰⁻¹⁵ Health benefits are generally observed at a relatively low exercise capacity (below approximately 5-6 metabolic equivalents [METs]) and increase thereafter with higher CRF in a dose-response fashion.^{1-4,9-16} Exercise capacity declines with age. Thus, in

our previous work we defined a specific MET threshold for different age categories. We noted a graded decline in overall risk for all-cause mortality for individuals with an exercise capacity 2, 4, and more than 4 METs higher than their respective age-specific MET threshold and an incremental increase in risk for those with a peak exercise capacity 2 METs and 4 METs below the threshold.¹⁷ This approach delineates the risk for different age groups and can assist clinicians in estimating mortality risk below and above an age-specific MET threshold for individuals undergoing an exercise test.

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We have also determined that increased CRF protects against the development of certain chronic illnesses such as hypertension¹⁸ and chronic kidney disease (CKD).¹⁹ Others have reported an inverse association between CRF and the incidence of heart failure,^{20,21} myocardial infarction (MI), and revascularization.²¹⁻²⁴ These findings suggest that increased CRF may protect against the development of a cardiovascular event. Thus, in the current study, we sought to evaluate the association between CRF and the risk for major adverse cardiovascular events (MACEs) in US veterans using CRF categories based on age-specific quintiles of peak exercise capacity thresholds. We defined MACE as the initial occurrence of MI (fatal and nonfatal), congestive heart failure (CHF), cerebrovascular accident (fatal and nonfatal), or coronary artery bypass graft (CABG).

PATIENTS AND METHODS

Study Design and Population

This prospective cohort study included individuals from the Exercise Testing and Health Outcomes Study at the Veterans Affairs Medical Center in Washington, District of Columbia, and the Veterans Exercise Testing Study at the Veterans Hospital in Palo Alto, California. Both are prospective observational studies designed to address the impact of exercise capacity and clinical and lifestyle factors and their association with disease states and health outcomes. All participants underwent a symptom-limited exercise tolerance test (ETT) between January 15, 1986, and December 31, 2014, at the Veterans Affairs medical centers (12,073 in Washington and 9817 in Palo Alto) as part of a routine evaluation, clearance to participate in exercise, or assessment of suspected coronary artery disease. To minimize the potential confounding impact of low body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) resulting from muscle wasting conditions on CRF and other health outcomes, we excluded individuals with a BMI of less than 18.5 kg/m² and those with an exercise capacity of less than 2 METs. We also excluded participants with an implanted pacemaker, left bundle branch block, chronic obstructive pulmonary disease, and inability

to complete the test as a result of musculoskeletal factors, those requiring emergent intervention, and participants with missing medical data. After these exclusions, the cohort comprised a total of 20,590 participants (mean \pm SD age, 58.2 \pm 11.3 years) with no evidence of MACE at the time of the exercise test. Of those, 12,975 (63.0%) were black (mean \pm SD age, 58.0 \pm 11.3 years), and 7615 (37.0%) were white or other races (mean \pm SD age, 58.5 \pm 11.3 years). The study was approved by the institutional review board at each institution, and all participants gave written informed consent before their ETT.

Assessments of Covariates

For all participants, detailed information on relevant demographic characteristics, medical history, concurrent medications, and risk factors as defined by *International Classification of Diseases, Ninth Revision* coding was obtained from the computerized patient record system at the time of the ETT. The onset of MACE subsequent to the baseline ETT was recorded from computerized patient records, which were coded based on the *International Classification of Diseases, Ninth Revision*. Body weight and height were assessed with a standardized scale and recorded before ETT.

Exercise-Related Assessments

Cardiorespiratory fitness was assessed by a standard ETT using the Bruce protocol at the Veterans Affairs Medical Center in Washington and by an individualized ramp protocol as described elsewhere²⁵ for participants assessed at the VA Health Care System facility in Palo Alto. Peak exercise capacity (METs) was estimated with use of standardized equations.^{25,26} One MET is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 mL per kilogram of body weight per minute. Participants were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.²⁷ The use of handrails was allowed only if necessary for balance and safety and not for support. Medications were not altered before testing.

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