Cardiorespiratory Fitness and Mortality Risk Across the Spectra of Age, Race, and Sex

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Cardiorespiratory Fitness and Mortality Risk Across the Spectra of Age, Race, and Sex

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ABSTRACT

BACKGROUND Cardiorespiratory fitness (CRF) is inversely associated with all-cause mortality. However, the association of CRF and mortality risk for different races, women, and elderly individuals has not been fully assessed.

OBJECTIVES The aim of this study was to evaluate the association of CRF and mortality risk across the spectra of age, race, and sex.

METHODS A total of 750,302 U.S. veterans aged 30 to 95 years (mean age 61.3 ± 9.8 years) were studied, including septuagenarians (n = 110,637), octogenarians (n = 26,989), African Americans (n = 142,798), Hispanics (n = 35,197), Native Americans (n = 16,050), and women (n = 45,232). Age- and sex-specific CRF categories (quintiles and 98th percentile) were established objectively on the basis of peak METs achieved during a standardized exercise treadmill test. Multivariable Cox models were used to estimate HRs and 95% CIs for mortality across the CRF categories.

RESULTS During follow-up (median 10.2 years, 7,803,861 person-years of observation), 174,807 subjects died, averaging 22.4 events per 1,000 person-years. The adjusted association of CRF and mortality risk was inverse and graded across the age spectrum, sex, and race. The lowest mortality risk was observed at approximately 14.0 METs for men (HR: 0.24; 95% CI: 0.23-0.25) and women (HR: 0.23; 95% CI: 0.17-0.29), with no evidence of an increase in risk with extremely high CRF. The risk for least fit individuals (20th percentile) was 4-fold higher (HR: 4.09; 95% CI: 3.90-4.20) compared with extremely fit individuals.

CONCLUSIONS The association of CRF and mortality risk across the age spectrum (including septuagenarians and octogenarians), men, women, and all races was inverse, independent, and graded. No increased risk was observed with extreme fitness. Being unfit carried a greater risk than any of the cardiac risk factors examined.
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Epidemiologic evidence strongly supports an inverse and independent association between all-cause mortality and cardiorespiratory fitness (CRF), assessed objectively using a standardized exercise treadmill test (ETT) and expressed in METs.[1-7] Compared with least fit individuals (<5.0 METs), lower risk is most evident and proportionally greater in those with moderate exercise capacity, often in the order of 5 to 7 METs. Relatively smaller declines in risk continue with further increases in

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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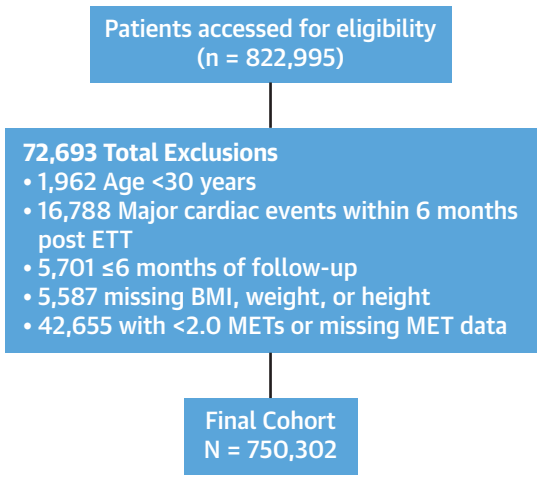
FIGURE 1 Flowchart for Cohort Selection



Flowchart depicts exclusions of subjects on the basis of predetermined criteria and the final cohort. BMI = body mass index; ETT = exercise treadmill test.

CRF, reaching optimal risk reduction at approximately 10 METs.[3-8] The amount of physical activity (PA) necessary to achieve a certain level of CRF has not been clearly defined. However, most middle-aged individuals who meet the current recommendations of ≥150 min/wk of moderate-intensity PA[9] are likely to achieve at least a moderate level of CRF.[5-9] Less is known about the association of CRF and mortality risk in elderly individuals, particularly septuagenarians and octogenarians.[2,10-17] As more adults now survive into old age,[18] and the impact of CRF on health outcomes for elderly individuals is recognized, there is a need for better understanding of the association of CRF and mortality risk in this population.[19]

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A potential risk associated with excessive PA has been reported by some[20-22] but not all[2,23,24] studies. Excessive PA is relative to the fitness status of the individual,[25,26] and its potential detrimental effects are likely greater in older populations.[20-24] However, to our knowledge, no studies have examined the risk associated with extreme CRF assessed objectively by ETT across the age spectrum, particularly in those ≥70 years of age. Finally, most of the available evidence in this area is based on studies conducted among predominantly White populations,[2-4,6,7,9] with limited information available for other races, especially Native Americans.[5,6,27,28]

The Veterans Affairs health care system is unique in that it ensures equal access to medical care independently of a patient's financial status.[29-31] In addition, the electronic health care database facilitates risk-adjustment models, thereby increasing the accuracy in determining health outcomes.[32] In the present study, the unprecedentedly large sample of >750,000 U.S. veterans nationally permitted a more accurate assessment of the association of CRF and mortality risk and a focus on gaps in the published research while minimizing the influence of medical care disparities.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
CHF = chronic heart failure
CRF = cardiorespiratory fitness
CVD = cardiovascular disease
DM2 = type 2 diabetes mellitus
ETT = exercise treadmill test
MI = myocardial infarction
PA = physical activity
PCI = percutaneous coronary intervention

METHODS

STUDY POPULATION. The cohort was derived from the ETHOS (Exercise Testing and Health Outcomes Study) based at the Veterans Affairs Medical Center in Washington, DC. We identified 822,995 U.S. veterans who underwent ETTs performed within Veterans Affairs hospitals across the United States between October 1, 1999, and September 3, 2020, using the Bruce protocol. Of those, we excluded 72,693 subjects (**Figure 1**) who met the following criteria: 1) <30 years of age at the time of the ETT (n = 1,962); 2) inability to achieve maximal effort (the ETT was deemed incomplete as stated in the medical notes), achievement of <2.0 METs (n = 24,014), or MET values that exceeded physiological criteria (n = 18,641); 3) body mass index (BMI) <18.5 kg/m^2 or missing BMI (n = 5,587); and 4) follow-up period <6 months (n = 5,701).

To lower the likelihood of including individuals with overt heart disease, we also excluded those who met the following conditions within 6 months post-ETT: 1) coronary artery bypass grafting (n = 2,296); 2) percutaneous coronary intervention (PCI) (n = 6,238); and 3) myocardial infarction (MI) (n = 2,370) or diagnosis of chronic heart failure (CHF) (n = 5,884).

After these exclusions, the final cohort consisted of 750,302 subjects (705,163 men and 45,139 women). Of those, 552,922 (73.7%) were White; 142,798 (19.0%) African American; 35,197 (4.7%) Hispanic; and 16,050 (2.1%) Native American, Asian, or Hawaiian; 3,335 subjects (0.4%) declined to report. The study was approved by the Veterans Affairs Medical Center in Washington, DC Institutional Review Board.

Detailed information on relevant demographic, clinical, and medication information, risk factors, and comorbidities as defined by International Classification of Diseases-9th Revision and International Classification of Diseases-10th Revision coding, with at least 2 recordings at least 6 months apart, was obtained for all participants from the Veterans Affairs

TABLE 1 Clinical Characteristics of Participants According to Fitness Categories

	All (N = 750,302)	Least Fit (n = 133,741)	Low Fit (n = 208,073)	Moderately Fit (n = 156,685)	Fit (n = 130,382)	Highly Fit (n = 89,850)	Extremely Fit (n = 31,571)
Age, y	61.3 ± 9.8	61.6 ± 9.3	62.7 ± 10.3	60.0 ± 8.2	60.7 ± 10.0	60.7 ± 10.7	60.6 ± 10.7
Peak METs achieved	8.5 ± 3.0	4.7 ± 1.5	7.0 ± 1.4	9.0 ± 1.3	10.4 ± 1.4	12.0 ± 1.6	14.5 ± 2.1
Men	705,070 (94.0)	125,277 (93.7)	194,604 (93.5)	149,905 (95.7)	121,266 (93.0)	84,534 (94.1)	29,481 (93.4)
Women	45,232 (6.0)	8,464 (6.3)	13,466 (6.5)	6,780 (4.3)	9,116 (7.0)	5,316 (5.9)	2,090 (6.0)
Weight, kg	92.1 ± 17.6	95.5 ± 20.2	93.6 ± 18.0	93.0 ± 17.0	89.9 ± 15.5	87.7 ± 14.5	84.2 ± 13.2
BMI, kg/m^2	29.6 ± 4.7	30.6 ± 5.9	30.0 ± 4.8	29.7 ± 4.4	29.0 ± 4.0	28.5 ± 3.7	27.7 ± 3.4
Smoking status	176,719 (23.6)	42,544 (31.8)	51,115 (24.6)	36,678 (23.4)	26,335 (20.2)	15,605 (17.4)	4,442 (14.1)
Hypertension	405,598 (54.1)	90,078 (67.4)	123,537 (59.4)	81,745 (52.2)	61,469 (47.1)	37,689 (41.9)	11,080 (35.1)
DM2	158,039 (21.1)	42,167 (31.5)	51,895 (24.9)	30,662 (19.6)	20,393 (15.6)	10,433 (11.6)	2,489 (7.9)
CVD	225,945 (30.1)	57,816 (43.2)	69,099 (33.2)	41,598 (26.5)	31,813 (24.4)	19,813 (22.1)	5,806 (18.4)
Atrial fibrillation	28,635 (3.8)	8,774 (6.6)	8,813 (4.2)	4,544 (2.9)	3,465 (2.7)	2,377 (2.6)	662 (2.1)
Dyslipidemia	385,990 (51.4)	77,583 (58.0)	112,890 (54.3)	78,641 (50.2)	62,847 (48.2)	40,890 (15.5)	13,139 (41.6)
CKD	28,563 (3.8)	9,048 (6.8)	9,093 (4.4)	4,606 (2.9)	3,303 (2.5)	2,005 (2.2)	508 (1.6)
All cancer	31,796 (4.2)	6,647 (5.0)	10,042 (4.8)	5,496 (3.5)	5,008 (3.8)	3,509 (39)	1,094 (3.5)
Statins	333,334 (44.4)	70,093 (52.4)	100,510 (48.3)	66,405 (42.4)	52,828 (40.3)	33,253 (37.0)	10,245 (32.5)
Hypoglycemics	134,548 (19.9)	36,803 (27.5)	44,890 (21.6)	25,794 (16.5)	16,993 (13.0)	8,260 (9.2)	1,808 (5.7)
Cardiac/antihypertensive medications	430,124 (57.3)	95,449 (71.4)	131,012 (63.0)	87,053 (55.6)	65,125 (49.9)	40,001 (44.4)	11,484 (36.4)

Values are mean ± SD or n (%).
BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; DM2 = type 2 diabetes mellitus.

Computerized Patient Record System at the time of the ETT. The Veterans Affairs records have high sensitivity for the incidence of chronic conditions.[33,34] Historical information included onset of previous MI, cardiac procedures, CHF, hypertension, type 2 diabetes mellitus (DM2), hypercholesterolemia, cancer (all), renal disease, stroke, smoking status (current and past), aspirin, and cardiac or antihypertensive medications. Data and analyses are presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies.[35]

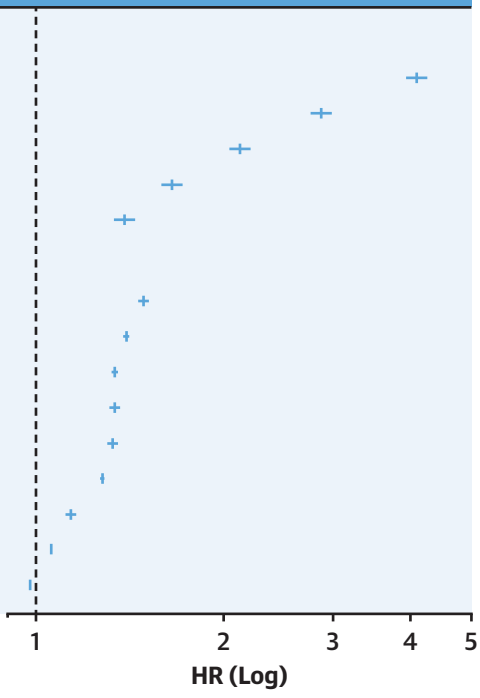
MET EXTRACTION. We randomly selected 3,000 samples of physician clinical notes on exercise capacity from the data set and identified METs manually. This annotated data set was further preprocessed and then used to train the natural language processing models. In the preprocessing phase, we removed special characters ($, &, etc) and restricted the note to 30 characters before and after the word "METs" or "MET." These words were then replaced with a special character to identify their location within the notes. Spacy software was then used to convert the resulting string into word tokens and then to vector of numbers. The corresponding labels were created such that 1 meant that the corresponding token contained the MET value and 0 that it did not. We used a 2-layer convolutional neural network using the TensorFlow software library to predict the probable location of METs in the note. The model was trained over 100 epochs. Once METs were extracted, the MET data were randomly and manually checked for errors. The model accuracy on the test data set was 97%.

CRF CATEGORIES. Peak MET levels were calculated for each participant by standardized American College of Sports Medicine equations on the basis of treadmill speed and grade.[36] To determine the age-specific CRF categories, we first stratified the cohort into 5 age groups (30-49, 50-59, 60-69, 70-79, and 80-95 years). Then, we established 6 CRF categories within each age group using methods described in our previous work.[37] Briefly, we identified those with a sex-specific MET level that corresponded to the 20th, 40th, 60th, 80th, 97th, and ≥98th percentiles within their respective age categories and stratified the cohort accordingly. We then combined the respective percentiles to form the following CRF categories: least fit (n = 133,741, 4.7 ± 1.5 METs), low fit (n = 208,073, 7.1 ± 1.4 METs), moderately fit (n = 156,685, 9.0 ± 1.3 METs), fit (n = 130,382, 10.4 ± 1.4 METs), highly fit (n = 91,680, 12.1 ± 1.8 METs), and extremely fit (n = 29,741, 14.3 ± 2.1 METs)

ASCERTAINMENT OF DEATHS. The primary outcome was all-cause mortality. Dates of death were verified from the Veterans Affairs Beneficiary Identification Records Locator Subsystem. This system, used to determine benefits to survivors of veterans, has been shown to be 95% complete, accurate, and comparable with the Social Security Administration.[38,39] Vital status was determined as of September 30, 2021.

FIGURE 2 Relative Mortality Risk Associated With Select Clinical Characteristics

Variable	HR (95% CI)	*P* Value
Extremely Fit (Referrent)		
Least	4.09 (3.94-4.24)	<0.001
Low	2.88 (2.78-2.99)	<0.001
Moderate	2.13 (2.05-2.21)	<0.001
Fit	1.66 (1.60-1.73)	<0.001
High	1.39 (1.34-1.45)	<0.001
Comorbidities		
Chronic Kidney Disease	1.49 (1.46-1.52)	<0.001
Smoking	1.40 (1.39-1.42)	<0.001
Diabetes	1.34 (1.33-1.36)	<0.001
Atrial Fibrillation	1.34 (1.31-1.36)	<0.001
Cancer (all)	1.33 (1.30-1.35)	<0.001
Cardiovascular Disease	1.28 (1.27-1.29)	<0.001
Hypertension	1.14 (1.13-1.16)	<0.001
Age	1.06 (1.06-1.06)	<0.001
Body Mass Index	0.98 (0.97-0.98)	<0.001



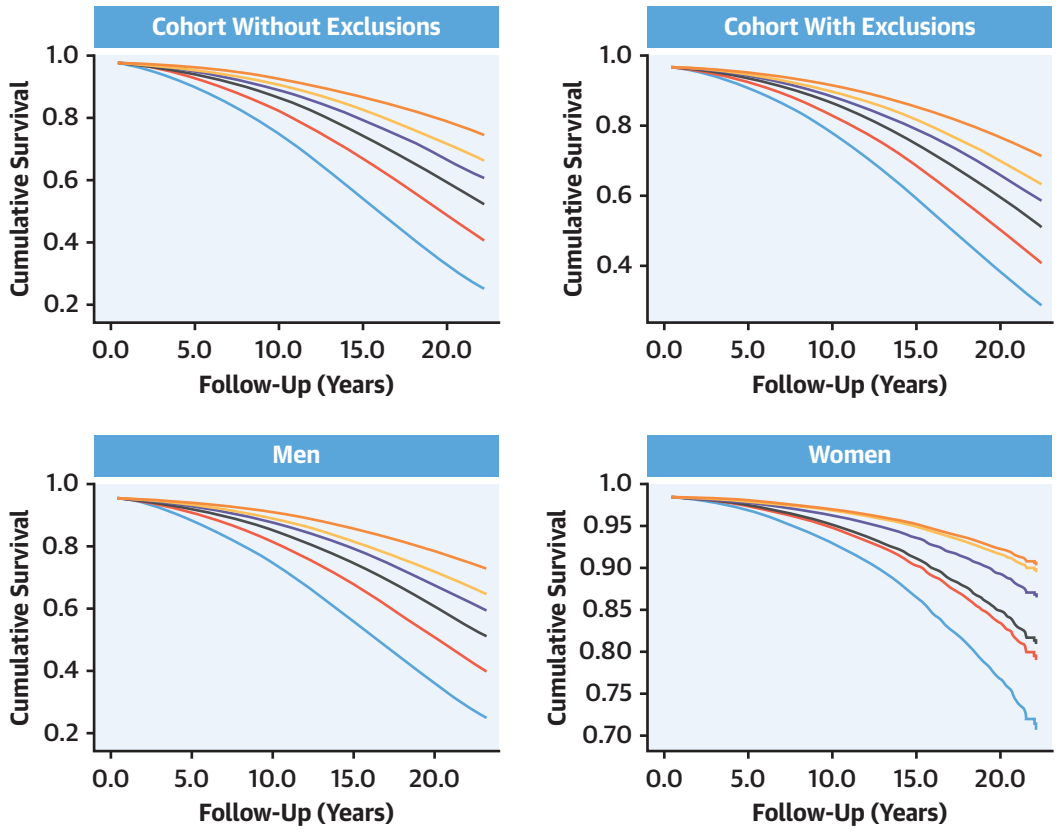
Forest plot of HRs and 95% CIs from multivariable Cox regression analysis examining the association between cardiorespiratory fitness categories and select comorbidities.

STATISTICAL ANALYSIS. Follow-up time was calculated from the ETT date to the death date for decedents and to September 30, 2021, for survivors and is presented as median and mean ± SD. Follow-up time is presented as median and IQR. We calculated mortality rate as the ratio of deaths to person-years of observation. Continuous variables are presented as mean ± SD and categorical variables as relative frequency (percentage). We tested baseline mean differences of normally distributed variables between individuals within CRF categories using 1-way analysis of variance and associations between categorical variables with chi-square or *z* tests. The assumption of equality of variances between groups was tested using the Levene test and the assumption of normality using probability-probability plots.

The proportional hazards model was used to depict HRs associated with exercise capacity (METs) for all-cause mortality across the CRF categories. In addition, we stratified the cohort on the basis of sex, race, and age groups and calculated HRs for CRF categories within each of these subgroups. For these models, we used the least fit CRF category (20th percentile) as the reference group. We also used the 98th percentile group (extremely fit) as the referent to express the incremental increase in risk with decline in CRF. All analyses were adjusted for the following covariates assessed at the time of the ETT: age, BMI, race, sex, history of cardiovascular disease (CVD) and risk factors (hypertension, DM2, dyslipidemia, and smoking), chronic kidney disease, cancer (all), and use of cardiac or antihypertensive medications (β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretic medications), insulin, metformin, sulfonylureas, and statins.

The assumption of proportionality for all Cox proportional hazards analyses was tested graphically by plotting the logarithm of cumulative hazards with respect to each covariate separately. The proportionality assumption was fulfilled for each model. All hypotheses were 2 sided, and P values < 0.05 were deemed to indicate statistical significance. All statistical procedures were performed using SPSS version 26.0 (SPSS).

FIGURE 3 Survival Curves According to Cardiorespiratory Fitness Categories



Blue, least fit; **red**, low fit; **gray**, moderately fit; **purple**, fit; **yellow**, highly fit; **orange**, extremely fit.

RESULTS

Baseline demographic and clinical characteristics across CRF categories are presented in Table 1. We observed significant differences among the 6 CRF categories among all variables examined. In general, body weight, BMI, CVD risk factors, and overall disease burden were progressively more unfavorable for those in the lowest compared with the highest CRF categories. Conversely, lower CRF levels were associated with progressively higher use of all medications ($P < 0.001$).

PREDICTORS OF ALL-CAUSE MORTALITY. The median follow-up duration was 10.2 years (IQR: 6.1-14.4 years), providing 7,803,861 person-years of observation. Age was significantly greater in Whites (61.7 ± 9.9 years) compared with African Americans (58.4 ± 9.2 years), Hispanics (58.5 ± 10.8 years), and Native Americans (58.4 ± 10.2 years).

A total of 174,807 participants died (23.3%) in the entire cohort, with an average annual mortality rate of 22.4 events per 1,000 person-years. There were 171,396 deaths in men (24.3%) and 7,350,766 person-years, for an average annual mortality rate of 23.3 events per 1,000 person-years. In women, there were 3,411 deaths (7.5%) and 453,095 person-years, for an average annual mortality rate of 7.5 events per 1,000 person-years.

Death rates for the different ethnic groups were as follows: 139,498 deaths in Whites (28.0 per 1,000 person-years), 26,147 in African Americans (20.1 per 1,000 person-years), 5,514 in Hispanics (18.9 per 1,000 person-years), and 2,738 in Native Americans (19.1 per 1,000 person-years).

COX PROPORTIONAL HAZARDS REGRESSION. In the fully adjusted model, significant predictors of all-cause mortality were age (HR: 1.06; 95% CI: 1.07-1.08; $P < 0.001$), BMI (HR: 0.97; 95% CI: 0.97-0.99; $P < 0.001$), chronic kidney disease (HR: 1.49; 95% CI: 1.46-1.52; $P < 0.001$), smoking (HR: 1.40; 95% CI: 1.39-1.42; $P < 0.001$), atrial fibrillation (HR: 1.34; 95% CI: 1.31-1.36; $P < 0.001$), CVD (HR: 1.28; 95% CI: 1.27-1.29;

TABLE 2 Mortality Risk Across Fitness Categories According to Age Groups

	Age Categories									
	30-49 y (n = 69,754)		50-59 y (n = 243,313)		60-69 y (n = 299,609)		70-79 y (n = 110,637)		80-95 y (n = 26,989)	
	No. of Deaths	3,324 (4.8%)	43,220 (17.8%)		66,766 (22.3%)		44,318 (40.1%)		17,179 (63.7%)	
Least fit	1,396 (10.8)	1.00	13,854 (33.4)	1.00	22,118 (37.9)	1.00	9,372 (57.4)	1.00	3,357 (75.7)	1.00
Low fit	1,004 (4.9)	0.57 (0.52-0.61)	13,217 (22.2)	0.69 (0.67-0.70)	17,797 (25.8)	0.68 (0.67-0.69)	22,678 (44.2)	0.76 (0.75-0.78)	5,343 (70.7)	0.73 (0.70-0.76)
Moderately fit	269 (3.5)	0.41 (0.36-0.47)	10,537 (14.2)	0.47 (0.46-0.48)	11,890 (20.1)	0.52 (0.51-0.53)	3,896 (34.5)	0.61 (0.58-0.63)	2,820 (63.7)	0.62 (0.59-0.65)
Fit	435 (2.8)	0.36 (0.32-0.40)	2,909 (9.6)	0.34 (0.33-0.36)	10,260 (14.8)	0.39 (0.38-0.40)	3,128 (32.9)	0.56 (0.54-0.59)	3,363 (57.8)	0.54 (0.51-0.56)
Highly fit	210 (1.8)	0.26 (0.22-0.30)	2,136 (7.6)	0.28 (0.27-0.30)	3,668 (11.8)	0.28 (0.27-0.29)	4,315 (24.8)	0.47 (0.45-0.49)	1,690 (51.7)	0.42 (0.40-0.45)
Extremely fit	10 (0.8)	0.16 (0.15-0.30	567 (5.9)	0.22 (0.20-0.24)	963 (7.7)	0.20 (0.19-0.22)	929 (19.3)	0.34 (0.32-0.37)	606 (40.6)	0.27 (0.24-0.29)

Values are n (%) or HR (95% CI). The model was adjusted for age, body mass index, sex, race, history of hypertension, cardiovascular disease, smoking, type 2 diabetes mellitus, dyslipidemia, chronic kidney disease, cancer (all), use of cardiac or antihypertensive medications, insulin, metformin, sulfonylureas, and statins.

$P < 0.001$), all cancers (HR: 1.33; 95% CI: 1.30-1.36; $P < 0.001$), hypertension (HR: 1.15; 95% CI: 1.13-1.16; $P < 0.001$), and DM2 (HR: 1.34; 95% CI: 1.33-1.33; $P < 0.001$).

In addition, higher exercise capacity was inversely related to mortality risk for the entire cohort and for each age category. For every increase of 1 MET in exercise capacity, the adjusted HR for mortality was 0.86 (95% CI: 0.85-0.87; $P < 0.001$) for the entire cohort and was similar for men, women, and racial groups.

Adjusted HRs and CIs for CRF categories and select clinical comorbidities with the extremely fit CRF category as the referent are presented in Figure 2. The adjusted all-cause mortality risk increased progressively with reduced CRF and was highest in the least fit individuals (HR: 4.09; 95% CI: 3.94-4.24; $P < 0.001$), followed by low fit (HR: 2.88; 95% CI: 2.78-2.99; $P < 0.001$).

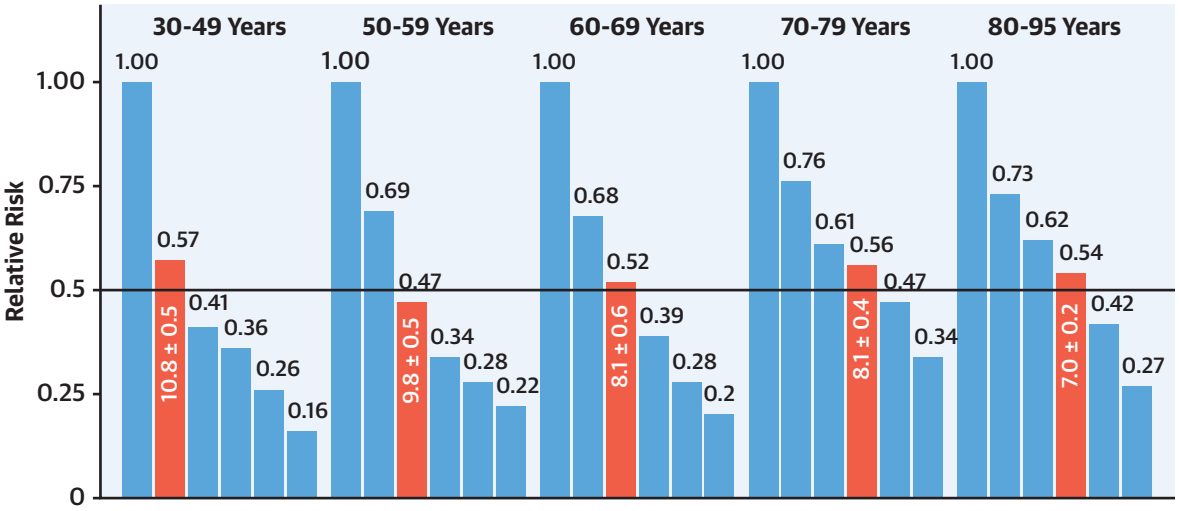
CRF AND MORTALITY RISK ACROSS THE SPECTRUM OF AGE, SEX, AND ETHNICITY. Survival curves are presented in Figure 3. After multivariate adjustment, incrementally higher survival rates were evident with higher CRF for the entire cohort and for men and women. Approximately 80% of men and 95% of women in the highest CRF category (98th percentile) were alive at 20 years of follow-up, compared with <40% of men and approximately 75% of women in the least fit CRF category (20th percentile).

HRs and CIs for the association of CRF and mortality risk within age categories are presented in Table 2 and the Central Illustration. We observed a progressively lower mortality risk with increased CRF in all age groups. For an approximate 50% reduction in mortality risk, the peak MET level requirements were approximately 11.0 METs for those aged 30-49 years, 10.0 METs for those aged 50-59 years, 8.0 METs for those aged 60-79 years, and 7.0 METs for octogenarians. Similar trends were noted in the association of CRF and risk for the 4 race groups (Figure 4).

We observed no erosion of the association of CRF and risk with extreme fitness for the entire cohort (Figure 5), men and women (Figure 6), and across the spectra of age (Central Illustration) and race (Figure 4). The lowest mortality risk was observed at approximately 14.0 METs for both men (HR: 0.24; 95% CI: 0.23-0.25) and women (HR: 0.23; 95% CI: 0.17-0.29). Men with peak exercise capacity of approximately 10.0 to 12.0 METs (fit and highly fit) lived 4.5 years longer compared with those in the 20th percentile (age at death 77.7 years vs 73.2 years, respectively). Those classified as extremely fit (≥98th percentile) lived 6.0 years longer (age at death 79.2 years vs 73.2 years, respectively). Similarly, women with peak CRF of approximately 10.0 to 11.5 METs (fit and highly fit) lived 2.5 years longer (age at death 71.5 years vs 69.0 years) compared with those in the 20th percentile and were 6.7 years older at the time of death (75.7 years vs 69.0 years) for those in the ≥98th percentile (approximately 14.0 METs). Those ≥70.0 years of age with CRF ≥7.0 METs lived 2.7 years longer compared with those with CRF in the ≤20th percentile (4.7 METs; age at death 87.3 ± 6.9 years vs 84.6 ± 6.6 years, respectively).

SENSITIVITY ANALYSIS. Because patients referred for ETTs may have higher incidences of clinical pathologic findings that influence CRF, higher mortality rates observed in the low-fitness categories may be the result of underlying disease and not low fitness per se (reverse causality). To attenuate the probability of reverse causality, those who experienced major coronary events or underwent PCI within 6 months

CENTRAL ILLUSTRATION **Relative Risk According to Cardiorespiratory Fitness Categories Across the Age Spectrum**



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Bars from **left** to **right** within each age group represent the cardiorespiratory fitness (CRF) categories on the basis of the percentile of age-specific peak METs achieved (≤20%, 21%-40%, 41%-60%, 61%-80%, 81%-97%, and ≥98%). The mortality risk associated with CRF within each age category is depicted by the HRs (numbers) above each **bar**. **Red bars** represent the CRF category for each age group and the peak METs required for approximately 50% lower mortality risk.

post-ETT were excluded from the initial cohort. We also excluded those who had MIs, strokes, CHF, PCI, or coronary artery bypass grafting or were diagnosed with cancer 1 year prior to their ETTs and those who died within the initial 1 year (n = 99,687) and 2 years (n = 105,532) of follow-up and repeated the analyses. The association of CRF and mortality risk remained robust, and the risk reduction did not deviate substantially from that observed in the entire cohort (Table 3).

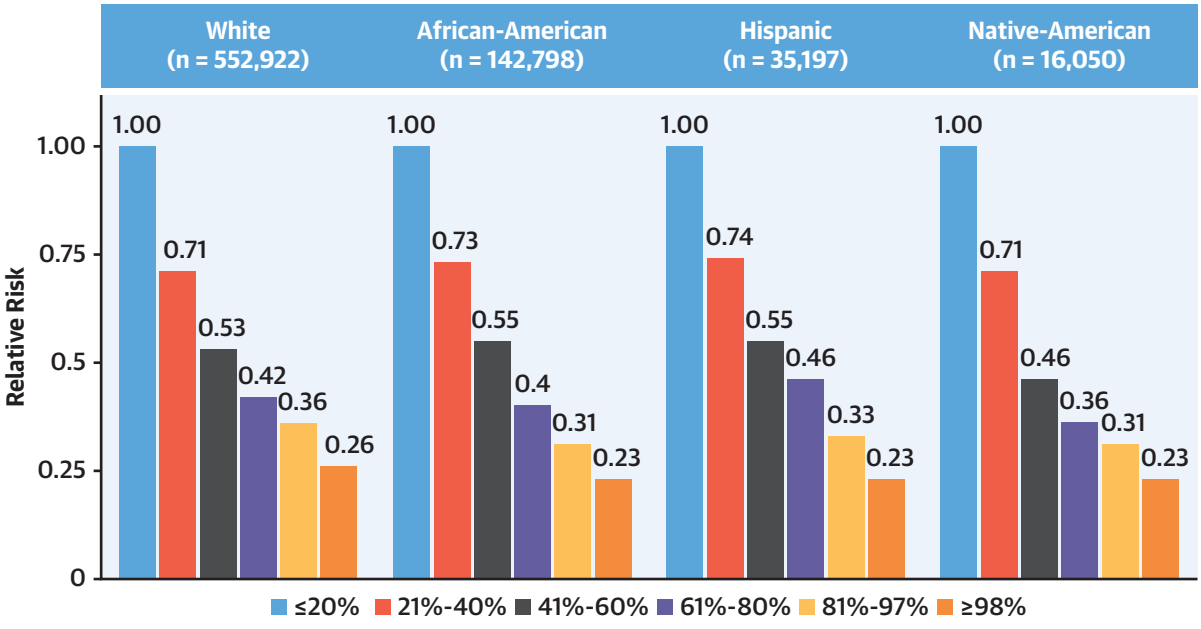
DISCUSSION

Our findings support an inverse, independent, and graded association between CRF and all-cause mortality across the spectra of age, race, and sex. Mortality risk for individuals classified as least fit (20th percentile; peak METs 4.7 ± 1.5) was >4-fold higher compared with individuals classified as extremely fit (≥98th percentile; peak METs 14.5 ± 2.1). This risk was higher than the risks associated with any of traditional cardiac risk factors examined (Figure 2).

To our knowledge, this was the largest cohort of its type with CRF assessed objectively using a standardized ETT. This allowed us to better define the association of CRF and mortality risk across the age spectrum, including septuagenarians (n = 110,637) and octogenarians (n = 26,989), and different racial groups, especially Native Americans, data that were previously either limited or not available.[2,5,11-17] Our findings reveal that CRF has a strikingly similar impact regardless of age or race (Central Illustration, Figure 4). Additionally, the large cohort of women (n = 45,232) contributes to the limited information on the association of CRF and mortality risk in women with CRF assessed objectively using an ETT.[40,41]

Finally, our cohort consisted of a relatively large number of individuals with exercise capacity ≥50% greater than expected by age and sex.[40,42] We found no evidence of increased risk in these extremely fit individuals, across all age groups, race, and sex. This is in accordance with finding of a relatively large study reported recently[2] and refutes some previous reports of increased risk among those who reported engaging in inordinately high levels of PA.[19-22] Although we do not know the PA status of our cohort, and genetic factors cannot be excluded, it is

FIGURE 4 Relative Mortality Risk Across Fitness Categories According to Race



Bar colors represent respective cardiorespiratory fitness categories on the basis of percentiles of peak METs achieved.

likely that CRF of this magnitude was largely the outcome of substantial and consistent engagement in aerobic activities.[43,44]

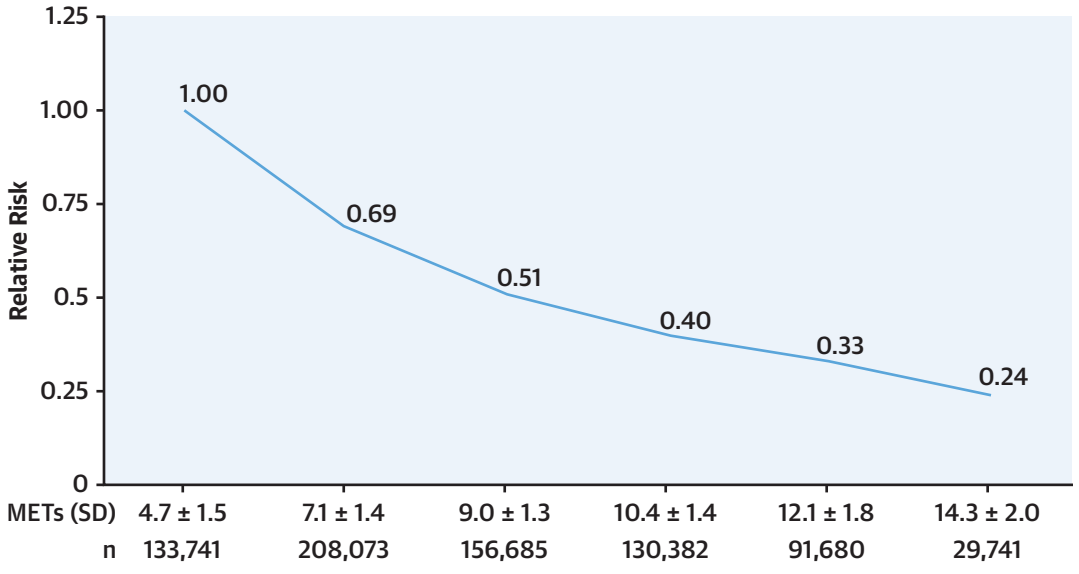
Our observation of no increased risk in those with extremely high exercise capacities, along with those of others,[2] suggests that appropriate exercise is relatively safe even at high exercise volumes and may extend life. Consistent with this, the mean age at the time of death was significantly higher for each CRF category compared with the least fit individuals (20th percentile). Men and women in the ≥98th percentile of peak exercise capacities of approximately 14.0 METs lived 6.0 and 6.7 years longer, respectively, compared with those in the ≤20th percentile of CRF. This is consistent with previous findings suggesting that elite athletes live longer than the general population.[45,46]

However, evidence of potential cardiac maladaptation, cardiac microdamage, myocardial fibrosis, coronary exercise-induced cardiac biomarker release, artery calcification, and myocardial fibrosis has been reported after high-volume and/or high-intensity exercise bouts.[47,48] This is especially true in overzealous, relatively low-fit individuals[47,49] and those with a genetic predisposition to cardiac disease or previous cardiac injury.[50,51] Accordingly, the potentially injurious impact of excessive exercise may not be manifested exclusively in highly fit individuals. Rather, this may occur in anyone engaging in exercise practices excessive relative to their fitness status and without adequate recovery time. In this regard, detection of exercise-related adverse outcomes may be obscured. This may explain in part why the present study and that of Mandsager et al,[2] the 2 largest studies with CRF assessed objectively, demonstrated no risk associated with extreme CRF, in contrast to the findings of studies based on PA status.[19-21] Future studies that combine objective assessments of exercise capacity and PA status may be better suited to address this issue.

Of special interest also is the impact of CRF on longevity, particularly for elderly individuals. For those ≥70.0 years of age with exercise capacity of approximately ≥7.0 METs, the life expectancy was approximately 2.7 years longer compared with those with CRF in the ≤20th percentile (87.3 ± 6.9 years vs 84.6 ± 6.6 years, respectively). These findings suggest the potential for extended longevity through CRF levels achievable by most middle-aged and older individuals by meeting the current recommendations of ≥150 min/wk of moderate-intensity PA.[5-9]

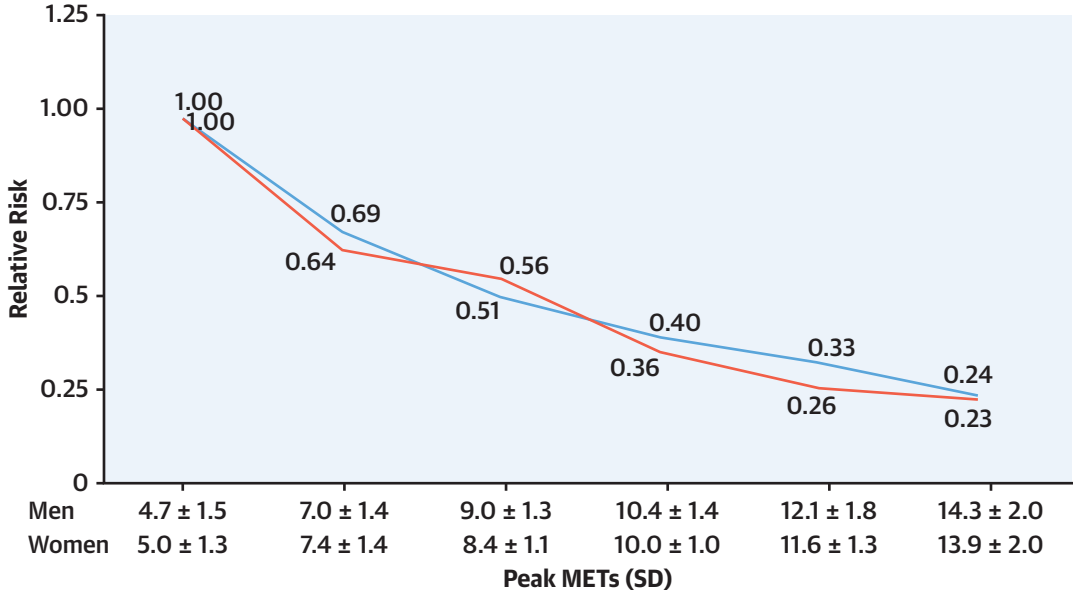
STUDY LIMITATIONS. The retrospective nature of the study does not demonstrate causation, regardless of

FIGURE 5 Mortality Risk for the Entire Cohort According to Peak METs Achieved



Values along the **curve** are HRs from multivariable Cox regression analysis examining the association between cardiorespiratory fitness categories (peak METs achieved) and mortality risk for the entire cohort.

FIGURE 6 Mortality Risk for Men and Women According to Peak METs Achieved



Values along the curve are HRs from multivariable Cox regression analysis examining the association between cardiorespiratory fitness categories (peak METs achieved) and mortality risk for men **(blue line)** and women **(red line)**.

the strong association of CRF and mortality risk. Accordingly, we cannot discern whether increased mortality risk was the outcome of poor CRF or subclinical disease that underlies low CRF (reverse causality). To minimize the probability of reverse causality we excluded individuals who experienced major coronary events or underwent percutaneous transluminal coronary angioplasty within 6 months post-ETT. In addition, in our sensitivity analyses, we excluded individuals diagnosed with CVD or cancer 1 year prior to their ETTs and those who died within the initial 1 and 2 years of follow-up. The association of CRF and mortality risk did not change substantially from that of the entire cohort in either instance (**Table 3**). These findings suggest that the probability of reverse causality was minimal.

We also recognize that CRF was based on a participant's performance on a single ETT, and we cannot account for changes in CRF during the follow-up period and their association with mortality. Nevertheless, changes in CRF are not likely to invalidate the association of CRF and mortality risk.[12] Also, we acknowledge that veterans referred for ETT may have clinical indications that make them distinct from the general population.

In addition, individuals ≥80 years of age completing ETTs may not be representative of a community cohort, as the ability to perform a Bruce protocol at that age may indicate a select group of individuals.

Finally, we assumed that a high CRF status of a given individual was the outcome of increased PA. However, we recognize that CRF is also determined by genetic factors[52] and that the independent or synergistic effects of genetic factors and CRF on mortality risk are beyond the scope of the present study.

CONCLUSIONS

The salient message from present study is that relatively poor CRF is a stronger predictor of mortality than any of the traditional risk factors examined regardless of age, sex, or race. Notably, at least a 50% reduction in risk can be achieved by most individuals with moderate CRF for their respective age categories (**Central Illustration**). This CRF level is likely to be achieved by meeting the current PA recommendations of 150 min/wk.[9] These findings have public health significance, particularly for septuagenarians and octogenarians, considering the limited information on the association of CRF and mortality risk in this growing segment of the population. Thus, it is prudent that CRF status be included in routine clinical practice, as advocated by public health professionals and recent scientific statements.[9,43,44]

TABLE 3 Mortality Risk Across Fitness Categories After Exclusions

	Model 1 (n = 750,302)	Model 2 (n = 650,615)	Model 3 (n = 644,770)
Least fit	1.00	1.00	1.00
Low fit	0.71 (0.70-72)	0.71 (0.70-0.72)	0.72 (0.71-0.73)
Moderately fit	0.53 (0.52-0.54)	0.54 (0.53-0.55)	0.54 (0.53-0.55)
Fit	0.42 (0.41-0.43)	0.42 (0.41-0.43)	0.42 (0.40-0.43)
Highly fit	0.35 (0.34-0.36)	0.35 (0.34-0.36)	0.35 (0.34-0.36)
Extremely fit	0.25 (0.24-0.26)	0.26 (0.25-0.27)	0.26 (0.25-0.27)

Values are HR (95% CI). Model 1 includes the entire cohort. Model 2 excludes those who were diagnosed with or had at least one of the following 1 year prior to ETT: MI, stroke, CHF, CABG, percutaneous transluminal coronary angioplasty or percutaneous coronary intervention, cancer (all), and death within 1-year post-ETT (n = 99,687). Model 3 excludes those who were diagnosed with who or had at least one of the following within 1 year prior to ETT: MI, stroke, CHF, CABG, percutaneous transluminal coronary angioplasty or percutaneous coronary intervention, cancer (all), and death within 2 years post-ETT (n = 105,532).

CABG = coronary artery bypass graft; CHF = chronic heart failure; ETT = exercise treadmill test; MI = myocardial infarction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Increased CRF attained by performing moderate intensity PA for ≥150 minutes weekly reduces mortality by ≥50% across all age groups, races, and sex, independent of comorbidities, and extremely high fitness does not increase mortality.

TRANSLATIONAL OUTLOOK: Studies that measure peak work load achieved on exercise testing are needed to determine whether very high levels of exercise affect mortality in individuals without cardiovascular risk factors.

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