9-1-2021

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Seamus P. Whelton

Paul A. McAuley

Zeina Dardari

Olusola A. Orimoloye

Erin D. Michos

See next page for additional authors

Authors

Seamus P. Whelton, Paul A. McAuley, Zeina Dardari, Olusola A. Orimoloye, Erin D. Michos, Clinton A. Brawner, Jonathan K. Ehrman, Steven J. Keteyian, Michael J. Blaha, and Mouaz H. Al-Mallah

ORIGINAL ARTICLE

Fitness and Mortality Among Persons 70 Years and Older Across the Spectrum of Cardiovascular Disease Risk Factor Burden: The FIT Project

Seamus P. Whelton, MD, MPH; Paul A. McAuley, PhD; Zeina Dardari, MS; Olusola A. Orimoloye, MD, MPH; Erin D. Michos, MD, MHS; Clinton A. Brawner, PhD; Jonathan K. Ehrman, PhD; Steven J. Keteyian, PhD; Michael J. Blaha, MD, MPH; and Mouaz H. Al-Mallah, MD, MSc

Abstract

Objective: To determine whether fitness could improve mortality risk stratification among older adults compared with cardiovascular disease (CVD) risk factors.

Methods: We examined 6509 patients 70 years of age and older without CVD from the Henry Ford ExercIse Testing Project (FIT Project) cohort. Patients performed a physician-referred treadmill stress test between 1991 and 2009. Traditional categorical CVD risk factors (hypertension, hyperlipidemia, diabetes, and smoking) were summed from 0 to 3 or more. Fitness was grouped as low, moderate, and high (<6, 6 to 9.9, and ≥10 metabolic equivalents of task). All-cause mortality was ascertained through US Social Security Death Master files. We calculated age-adjusted mortality rates, multivariable adjusted Cox proportional hazards, and Kaplan-Meier survival models.

Results: Patients had a mean age of 75±4 years, and 3385 (52%) were women; during a mean follow-up of 9.4 years, there were 2526 deaths. A higher fitness level ($P<.001$), not lower CVD risk factor burden ($P=.31$), was associated with longer survival. The age-adjusted mortality rate per 1000 person-years was 56.7 for patients with low fitness and 0 risk factors compared with 24.9 for high fitness and 3 or more risk factors. Among patients with 3 or more risk factors, the adjusted mortality hazard was 0.68 (95% CI, 0.61 to 0.76) for moderate and 0.51 (95% CI, 0.44 to 0.60) for high fitness compared with the least fit.

Conclusion: Among persons aged 70 years and older, there was no significant difference in survival of patients with 0 vs 3 or more risk factors, but a higher fitness level identified older persons with good long-term survival regardless of CVD risk factor burden.

 ■ Mayo Clin Proc. 2021;96(9):2376-2385

From the Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD (S.P.W., Z.D., O.A.O., E.D.M., M.J.B.); the Department of Health, Physical Education, and Sport Studies, Winston-Salem

Affiliations continued at the end of this article.

Risk stratification in persons 70 years of age and older presents a significant challenge because with increasing age, there is both an increased prevalence of cardiovascular disease (CVD) risk factors and a reduction in their predictive strength.[1-3] There is also a higher absolute rate of both CVD and non-CVD morbidity and mortality in older age, which contributes to an increase in competing risks.[4-6] Accordingly, for older persons, age functions as the dominant predictor in most of the commonly used risk prediction models, leading to nearly all individuals 70 years and older being classified as high risk, whether they have 0 or multiple CVD risk factors.[7-9] Whereas CVD risk factors are most strongly associated with CVD outcomes, they are notably also associated with an increased risk for total mortality, an especially important outcome to consider among older persons.[10-14] Therefore, additional variables are needed to improve risk stratification among older individuals.

Although fitness is not included in commonly used risk scores, it is one of the strongest predictors for the risk of both CVD and total mortality in the general population, and among middle-aged persons, treadmill exercise testing abnormalities significantly improve risk stratification beyond traditional CVD risk factors.[15-22] However, fitness decreases with age, and its utility for risk stratification is less well defined among older individuals.[23] It is uncertain whether older individuals have differences in their mean fitness level across a low vs high CVD risk factor burden. In addition, it is unknown whether the association between fitness and mortality differs by risk factor burden. Therefore, we sought to determine the association between fitness and mortality among persons 70 years of age and older across the spectrum of CVD risk factor burden.

METHODS

The Henry Ford ExercIse Testing Project (FIT Project) is composed of 69,885 patients who performed a physician-referred exercise treadmill stress test between January 2, 1991, and May 27, 2009, at the Henry Ford Hospital (Detroit, Michigan) and affiliated medical centers. A detailed description of the study design, methods, follow-up, and mortality ascertainment has been previously reported.[24] For this analysis, we excluded patients who were younger than 70 years (n=60,488), those with prior CVD (n=2776), and those missing data on fitness (n=112), for a total of 6509 persons 70 years of age and older who were included in this study.

Treadmill stress testing was performed using a standard Bruce protocol per the American Heart Association/American College of Cardiology guideline recommended methodology.[25,26] The test was stopped if the patient had exercise-limiting symptoms as determined by the supervising clinician (clinical exercise physiologist or nurse) or if the patient requested that the test be stopped. The test was also stopped if the patient had an abnormal blood pressure response (eg, a decrease in systolic blood pressure of >10 mm Hg despite an increased workload, systolic blood pressure >250 mm Hg, or diastolic blood pressure >115 mm Hg), significant ST-segment changes, clinically significant arrhythmia, or exercise-limiting chest pain. The patients' peak exercise workload (peak treadmill speed and peak incline) was used to calculate their maximal exercise capacity (eg, fitness), which was reported as metabolic equivalents of task (METs). Fitness was categorized as low (<6 METs), moderate (6-9 METs), and high (≥10 METs).[27] We chose 10 METs and higher as the high-fitness group because older persons have a lower mean fitness level and few patients in this study achieved 12 METs or more (n=74). We used physician referral information to group the stress test indications into common categories, such as chest pain and dyspnea.[24]

Immediately preceding the treadmill stress test, a trained nurse or clinical exercise physiologist obtained a medical history including the patient's demographic characteristics, CVD risk factors, current smoking status, current medication use, and past medical history. This self-reported information was supplemented by a retrospective search of the administrative databases or pharmacy claims files for patients who were enrolled in the Henry Ford Health System integrated health plan to augment the information on medication use and past medical history. For an electronic medical record (EMR) diagnosis to be coded as such in our database, it must have been present on at least 3 separate clinical encounters.[24] We used these data combining patient self-report, use of a disease-specific medication, or an EMR database—verified diagnosis to classify hypertension, dyslipidemia, diabetes, and current smoking as present or absent.

The reported resting systolic and diastolic blood pressures were measured immediately before the stress test, but these values were not used to define hypertension for this study because a diagnosis of hypertension must be based on 2 separate measurements on at least 2 separate visits, patients may have had higher than typical blood pressures on the day of their stress test because of withholding of medications for the stress test, and it was not recorded whether the blood pressure readings were measured with the patient in the standing or supine position. A family history of coronary artery disease was defined as the presence of a first-degree relative with a prior clinical coronary artery disease event. For patients 80 years and older, an age of 79 years was used to calculate the pooled cohort equations (PCEs) as recommended by the American College of Cardiology/American Heart Association because the PCEs were developed using individuals aged 40 to 79 years. We performed a retrospective search of the EMR and associated laboratory databases to identify laboratory values obtained within 90 days of the stress test. There were 614 participants missing laboratory data for total cholesterol concentration, but EMR data for a diagnosis of hyperlipidemia or lipid-lowering medication use were available for these patients. All-cause mortality was obtained by linkage to the Social Security Death Master File through April 2013.[24]

Each patient's traditional CVD risk factor (hypertension, dyslipidemia, diabetes, and smoking) burden was summed from 0 to 3 or more, and the proportion of individuals within each risk factor group was stratified by fitness categories. The age-adjusted mortality rate was calculated per 1000 person-years of follow-up stratified by METs and fitness groups. Kaplan-Meier survival analysis was performed on the basis of the number of CVD risk factors and fitness categories.[28] The primary outcome was all-cause mortality. Follow-up was calculated as the days between the exercise stress test date and the date of death or the end date for death matching (April 30, 2013). In addition, we performed multivariable adjusted Cox proportional hazards modeling to examine the risk of mortality based on the number of traditional CVD risk factors and fitness.[29] In our adjusted analyses, model 1 included age, sex, race, and reason for the stress test; model 2 additionally included resting systolic and diastolic blood pressure, total cholesterol concentration, high-density lipoprotein cholesterol concentration, use of hypertension medication, use of lipid-lowering medication, diabetes, and smoking status. We performed sensitivity analyses excluding patients with a diagnosis of cancer at baseline (n=777; defined as an EMR-listed diagnosis), stratified by sex, and excluding patients who died within the first year of follow-up (n=107).

RESULTS

Patients ranged in age from 70 to 96 years, with a mean age of 75 years (SD 4.2 years); 3385 (52%) were women, and 4603 (70.7%) were White (Table 1). Medication treatment for the risk factors occurred among 4269 (79%) patients with hypertension, 1766 (54%) patients with dyslipidemia, and 714 (43%) patients with diabetes (71 (10%) of whom were prescribed insulin). Patients who reported current smoking received smoking cessation advice per their referring physician's standard practice. The proportion of patients with CVD risk factors was lower with higher fitness levels (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). There were 2526 deaths during a mean follow-up of 9.4 years. The mean 10-year PCE risk score was 35.3%, and only 0.2% (n=10) had a 10-year PCE score below 7.5%. The CVD risk factor burden was similar for patients across fitness levels; 6125 (94.1%) patients had at least 1 CVD risk factor, whereas 1868 (28.7%) patients had 3 or more CVD risk factors (Figure 1). Regardless of the number of CVD risk factors, individuals in the low-fitness group had the highest age-adjusted mortality rate (56.7 per 1000 person-years), whereas patients in the highest fitness group had the lowest age-adjusted mortality rate (25.1 per 1000 person-years). In addition, within each fitness group, the age-adjusted mortality rate did not increase with a higher CVD risk factor burden (Figure 2). During 15 years of follow-up, there was no significant difference in survival for patients with 0 CVD risk factors compared with those

TABLE 1. Participant Characteristics Stratified by Number of Risk Factors[a,b,c]

No. of risk factors	0 (n=384)	1 (n=1743)	2 (n=2512)	≥3 (n=1870)	*P* for trend
Age (y)	75.6 (4.3)	75.7 (4.5)	75.5 (4.2)	75.0 (3.8)	<.01
Women	182 (47.4)	906 (52.0)	1392 (55.4)	905 (48.4)	.37
Ethnicity					
White	303 (78.9)	1249 (71.7)	1781 (70.9)	1270 (67.9)	<.001
African American	61 (15.9)	423 (24.3)	634 (25.2)	(27.8)	<.001
Systolic blood pressure (mm Hg)	138.0 (19.5)	141.2 (19.7)	142.6 (19.7)	141.7 (19.1)	.01
Diastolic blood pressure (mm Hg)	79.4 (10.1)	90.7 (10.3)	80.7 (10.1)	79.6 (10.0)	.17
Hypertension	0 (0)	1253 (71.9)	2304 (91.7)	1849 (98.9)	<.001
Hypertension medication	0 (0)	971 (55.7)	1792 (71.3)	1506 (80.5)	<.001
Total cholesterol (mg/dL)	204.9 (39.7)	203.1 (39.1)	206.5 (41.4)	198.2 (42.2)	<.001
HDL-C (mg/dL)	56.3 (17.5)	54.8 (16.9)	53.8 (15.7)	50.5 (15.0)	<.001
Dyslipidemia	0 (0)	217 (12.5)	1415 (56.3)	1636 (87.5)	<.001
Statin	0 (0)	72 (4.1)	696 (27.7)	998 (53.4)	<.001
Diabetes	0 (0)	49 (2.8)	470 (18.7)	1138 (60.9)	<.001
Current smoking	0 (0)	224 (12.9)	835 (33.2)	1288 (68.9)	<.001
Reason for stress test					
Chest pain	162 (42.2)	761 (43.7)	1052 (41.9)	716 (38.3)	<.001
Shortness of breath	37 (9.6)	189 (10.8)	318 (12.6)	252 (13.5)	<.001
Rule out ischemia	59 (15.4)	227 (13.0)	334 (13.3)	254 (13.6)	.94
Other	25 (32.8)	116 (32.5)	169 (32.2)	126 (34.6)	.47
10-year ASCVD risk[d]	24.7 (12.2)	28.9 (13.6)	34.2 (15.3)	44.7 (15.9)	<.001
METs achieved	6.4 (2.5)	6.2 (2.5)	6.2 (2.4)	6.3 (2.2)	.48
Achieving >10 METS	82 (21.4)	301 (17.2)	425 (16.7)	265 (14.1)	<.001

[a]ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; METs, metabolic equivalents of task.
[b]To convert cholesterol values to mmol/L, multiply by 0.0259.
[c]Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation).
[d]ASCVD risk estimated using the 2013 American Heart Association/American College of Cardiology pooled cohort equations.

with 3 or more CVD risk factors (*P*=.31; Figure 3A). However, higher fitness levels were associated with significantly longer survival, and during 15 years of follow-up, 669 (62.3%) patients in the highest fitness group were still alive compared with 1023 (35.4%) patients in the lowest fitness group (*P*<.001; Figure 3B).

On multivariable adjusted Cox proportional hazards modeling (Table 2), there was no significant difference in the hazard of death for patients with 3 or more CVD risk factors compared with those with 0 CVD risk factors (hazard ratio [HR], 1.18; 95% CI, 0.97 to 1.43; *P*=.10). Compared with patients in the lowest fitness group, those with moderate fitness had a 37% lower hazard of death (HR, 0.63; 95% CI, 0.57 to 0.68), and those with high fitness had a 56% lower hazard of death (HR, 0.44; 95%, CI, 0.38 to 0.50). Within each CVD risk factor group, there was approximately a 35% reduction in hazard of death for those with moderate fitness and a more than 50% reduction in hazard of death for those with high fitness compared with patients in the lowest fitness group (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). In addition, within each CVD risk factor group, there was approximately a 15% lower hazard of death for every 1 MET higher fitness achieved (*P*<.001). In sensitivity analyses, we found no significant difference in the results after excluding patients with a diagnosis of cancer at baseline, between women and men, or after excluding patients who died within the first year of follow-up.

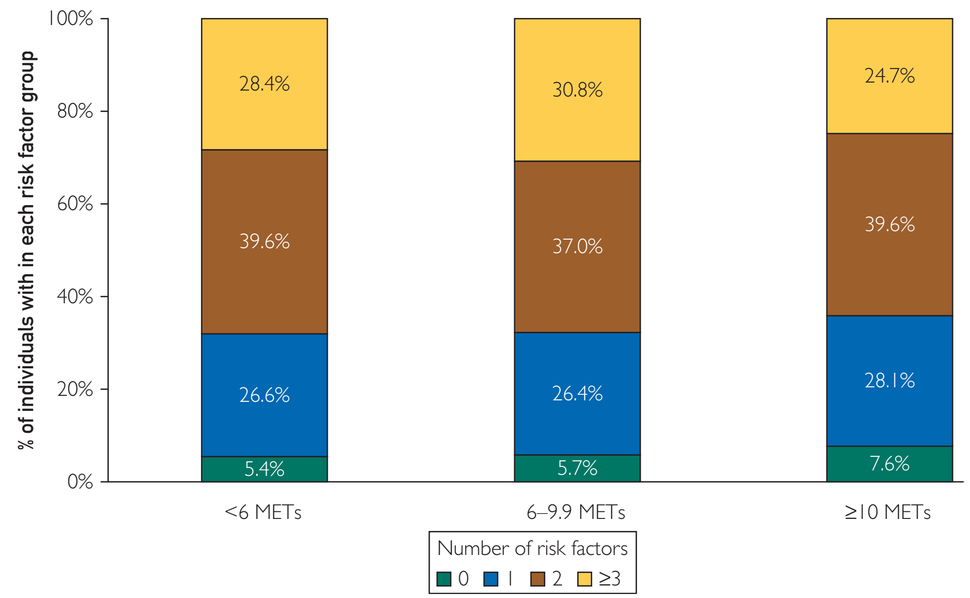

FIGURE 1. Proportion of risk factors by metabolic equivalents of task (METs) group.

DISCUSSION

Among patients aged 70 years and older who were free of known CVD, we found no significant difference in long-term survival by the number of traditional CVD risk factors, but a higher fitness level was strongly associated with a considerably lower mortality rate across the spectrum of CVD risk factor burden. These results highlight the utility of fitness as a risk stratification tool among older individuals, a group in whom risk stratification by traditional risk factors is especially challenging. In addition, our findings add further evidence supporting the importance of fitness as a leading modifiable risk factor among older persons.[30,31]

CVD risk stratification based on traditional CVD risk factors is likely to be the most commonly performed type of risk assessment in routine clinical practice. It may parenthetically also serve as a marker of overall long-term prognosis, particularly among older individuals, in whom CVD is the leading cause of death. Commonly used risk equations were derived using data from predominantly middle-aged individuals and are applied to older individuals, but this pragmatic approach overlooks meaningful physiologic differences between younger, middle-aged, and older persons.[32-34] For instance, whereas age is heavily weighted in the PCE and serves as a surrogate for CVD risk factor duration, the relative strength of the association between CVD risk factors and outcomes significantly declines with increasing age.[35-37] This is largely attributable to an increased prevalence of CVD risk factors with increasing age, consistent with our finding that 94% of individuals in this study had at least 1 CVD risk factor. In addition, higher absolute event rates for both CVD and non-CVD outcomes lead to increased competing risks.[2,38] Therefore, variables that provide a measure of physiologic age rather than of chronologic age are imperative for accurate risk stratification among older persons.[39,40]

Whereas the absence of CVD risk factors among older patients is typically considered a healthy phenotype, nearly no men older than 65 years or women older than 70 years are deemed low risk (10-year risk, <7.5%) by the PCE, even in the absence of traditional CVD risk factors.[41] Consequently, this limited ability to identify healthy older individuals is a weakness of commonly used risk scores that are based on traditional CVD risk factors.[40] In contrast, our results demonstrate that higher fitness identifies older patients with good long-term survival regardless of their CVD risk factor burden. Indeed, we found that patients with a high fitness level and 3 or more CVD risk factors had a nearly 60% lower mortality rate compared with patients without any CVD risk factors but a low fitness level.

The ability of higher fitness to identify older persons with good long-term survival is an equally important strength compared with the identification of older persons with poor long-term survival based on a low fitness level. This robustness to identify both low- and high-risk older persons is attributable to the dependence of fitness on the global cardiovascular health of an individual. Accordingly, fitness indirectly integrates measures of an individual's myocardial function, coronary and peripheral atherosclerotic burden, vascular endothelial function, and pulmonary function in addition to other important risk predictors, such as large-muscle strength and frailty.[42-46] The measurement of traditional CVD risk factors does not cohesively integrate these physiologic measures, which is at least partly responsible for the near absence of older individuals who are classified as low risk by commonly used risk prediction models.

Previous attempts to improve risk stratification in the elderly have shown only a limited improvement compared with traditional risk scores. For example, Koller et al[47] used data from the Cardiovascular Health Study and Rotterdam Study to develop a coronary heart disease risk prediction model in persons 65 years of age and older. Unfortunately, the risk score derived from the elderly population showed only a small improvement in risk prediction even after the addition of novel risk factors, such as ankle-brachial index, carotid intimal thickness, and C-reactive protein level. Vliegenthart et al,[48] also using data from the Rotterdam Study, investigated the utility of coronary artery calcium (CAC) scoring for risk prediction among individuals aged 70 years and older. Whereas they found a highly significant relative association between CAC and adverse outcomes, the addition of CAC to a multivariate model showed an increase in the area under the curve of only 0.013 for CVD and 0.006 for mortality.

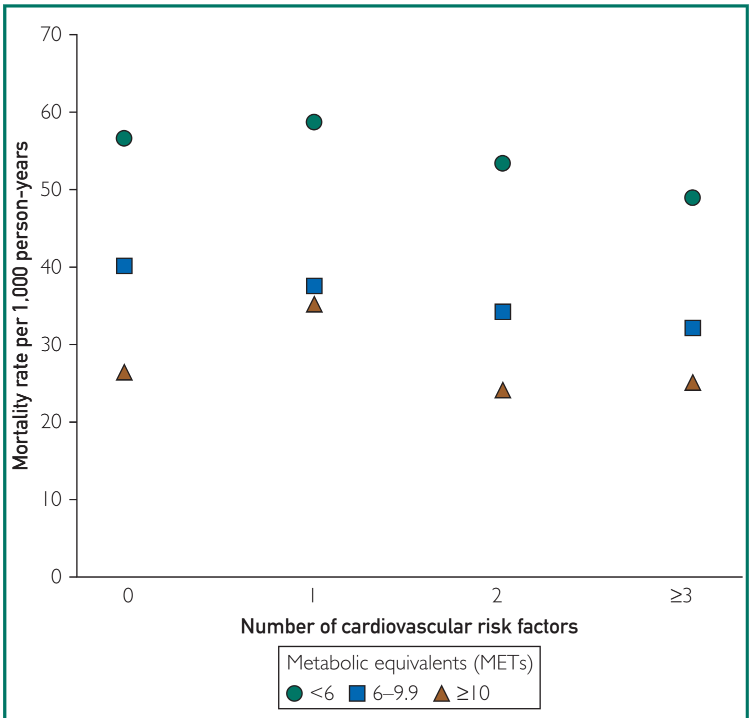

FIGURE 2. Age-adjusted mortality rate per 1000 person-years of follow-up stratified by metabolic equivalents of task (METs) groups and number of risk factors.

Although traditional CVD risk factors are most strongly associated with CVD mortality, this study's primary outcome of all-cause mortality remains an important and relevant outcome to examine. A better understanding of one's long-term mortality risk may be important for a patient's self-awareness of overall health, identifying the patient's priorities for health care treatment and quality of life along with identifying long-term goals of care.[49] Indeed, the National Institute for Health and Care Excellence highlighted the need to develop new methods for robust mortality risk stratification among patients with multiple chronic diseases, which is common among older persons.[50] Mortality risk prediction equations such as QMortality, Hospital-Patient One-Year Mortality Risk, and the Johns Hopkins Aggregated Diagnostic Groups predict only short-term mortality (1-2 years) and contain

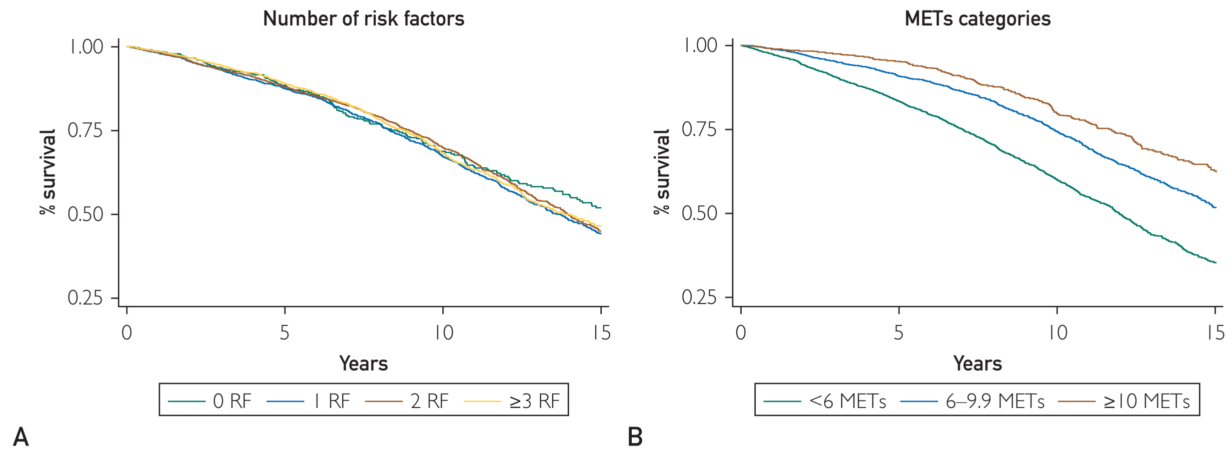

FIGURE 3. Kaplan-Meier survival stratified by (A) number of risk factors (RF) and (B) metabolic equivalents of task (METs) groups.

between 20 and 57 variables.[49,51,52] Therefore, they have a relatively narrow utility in routine patient care.

The proportion of deaths due to CVD also increases sharply above the age of 70 years and accounts for approximately one-third of all deaths in this age group (n=508,804 deaths among persons ≥75 years old in the United States in 2016).[53] Furthermore, the CVD risk factors included in this study (eg, hypertension, dyslipidemia, diabetes, and smoking) are also associated with an increased risk of cancer, Alzheimer disease, lung disease, and renal disease, which combined with CVD deaths accounts for 7 of the 10 leading causes of death in this age group.[53] Finally, all-cause mortality is an objective outcome that is not affected by misclassification bias, which is a significant concern in the determination for cause of death (especially CVD death) among older individuals who typically have multiple chronic diseases.[54,55]

Limitations of our analysis include that patients in this study may have been healthier than patients referred for a non−exercise stress test, which may limit the generalizability of our results. However, individuals deemed unsuitable for a treadmill stress test are likely to have an even lower fitness level and higher mortality rate. Submaximal cardiorespiratory fitness testing is an

TABLE 2. Hazard Ratios and 95% CIs of All-Cause Mortality by Number of Risk Factors and METs Groups

No. of risk factors	Unadjusted	*P* value	Model 1	*P* value	Model 2	*P* value
0	Reference		Reference		Reference	
1	1.16 (0.98-1.36)	.09	1.14 (0.97-1.35)	.12	1.06 (0.89-1.26)	.53
2	1.08 (0.92-1.27)	.35	1.12 (0.95-1.31)	.19	1.07 (0.90-1.28)	.46
≥3	1.10 (0.92-1.30)	.30	1.17 (0.98-1.39)	.08	1.18 (0.97-1.43)	.10
METs group	**Unadjusted**	***P* value**	**Model 1**	***P* value**	**Model 2**	***P* value**
<6	Reference		Reference		Reference	
6-9.9	0.60 (0.55-0.66)	<.001	0.61 (0.56-0.67)	<.001	0.62 (0.57-0.68)	<.001
≥10	0.43 (0.38-0.49)	<.001	0.43 (0.38-0.49)	<.001	0.44 (0.38-0.50)	<.001

METs, metabolic equivalents of task.
Model 1: age, sex, race, reason for stress test.
Model 2: model 1 plus hypertensive medication use, statin use, and diabetes medication use.

alternative measurement of fitness that improves mortality risk stratification and could be considered among individuals unable to perform a traditional treadmill stress test.[56] In our risk factor—based analyses, we did not examine how well an individual's CVD risk factors were controlled, although adjustment for risk factor treatment with medication did not significantly change the results. In addition, we did not examine change in fitness over time, although we have previously demonstrated that most individuals have a stable relative fitness level during at least 4 years of follow-up.[57] Strengths of this analysis include that more than 50% of patients were women, and patients were observed for an average of 9.4 years. Survival was determined by Social Security Death Master File, which is nearly identical to the Centers for Disease Control and Prevention methodology for calculating national death statistics in the United States during this time period. In addition, fitness was directly measured using the Bruce protocol, which is the most commonly used method for measuring fitness in clinical practice.

CONCLUSION

Among persons aged 70 years and older who performed a treadmill stress test, an individual's fitness level but not the CVD risk factor burden was significantly associated with long-term mortality risk across the spectrum of CVD risk factor burden. In addition, a high fitness level identified older patients with good long-term survival, even in the presence of a significant CVD risk factor burden. These findings provide added support for the measurement of fitness as a simple and low-cost method to improve risk stratification among older persons.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CAC,** coronary artery calcium; **CVD,** cardiovascular disease; **EMR,** electronic medical record; **HR,** hazard ratio; **METs,** metabolic equivalents of task; **PCE,** pooled cohort equation

Affiliations (Continued from the first page of this article.): State University, Winston-Salem, NC (P.A.M.); the Department of Medicine, Vanderbilt University Medical Center, Nashville, TN (O.A.O.); the Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI (C.A.B., J.K.E., S.J.K.); and the Houston Methodist DeBakey Heart & Vascular Center, Houston, TX (M.H.A.-M.).

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Seamus P. Whelton, MD, MPH, 600 North Wolfe St, Blalock 524A, Baltimore, MD 21287 (seamus.whelton@jhmi.edu; Twitter: @seamuswhelton).

ORCID

Seamus P. Whelton: https://orcid.org/0000-0001-5914-0735; Paul A. McAuley: https://orcid.org/0000-0002-9549-7202; Erin D. Michos: https://orcid.org/0000-0002-5547-5084; Clinton A. Brawner: https://orcid.org/0000-0002-1705-6620

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