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Longitudinal Algorithms to Estimate Cardiorespiratory Fitness

Associations With Nonfatal Cardiovascular Disease and Disease-Specific Mortality

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Objectives This study sought to determine the capacity of cardiorespiratory fitness (CRF) algorithms without exercise testing to predict the risk for nonfatal cardiovascular disease (CVD) events and disease-specific mortality.

Background Cardiorespiratory fitness (CRF) is not routinely measured, as it requires trained personnel and specialized equipment.

Methods Participants were 43,356 adults (21% women) from the Aerobics Center Longitudinal Study, followed up between 1974 and 2003. Estimated CRF was determined on the basis of sex, age, body mass index, waist circumference, resting heart rate, physical activity level, and smoking status. Actual CRF was measured by a maximal treadmill test. Risk reduction per 1–metabolic equivalent increase, discriminative ability (*c* statistic), and net reclassification improvement were determined.

Results During a median follow-up of 14.5 years, 1,934 deaths occurred, 627 due to CVD. In a subsample of 18,095 participants, 1,049 cases of nonfatal CVD events were ascertained. After adjustment for potential confounders, both measured and estimated CRF were inversely associated with risks for all-cause mortality, CVD-related mortality and nonfatal CVD events in men, and all-cause mortality and nonfatal CVD events in women. The risk reduction per 1–metabolic equivalent increase ranged from approximately 10% to 20%. Measured CRF had a slightly better discriminative ability (*c* statistic) than did estimated CRF, and the net reclassification improvement values in measured CRF versus estimated CRF were 12.3% in men ($p < 0.05$) and 19.8% in women ($p < 0.001$).

Conclusions These CRF algorithms utilized information routinely collected to obtain an estimate of CRF, which provides a valid indication of health status. In addition to identifying people at risk, this method can provide more appropriate exercise recommendations that reflect initial CRF levels. (J Am Coll Cardiol 2014;63:2289–96) © 2014 by the American College of Cardiology Foundation

Low cardiorespiratory fitness (CRF) is associated with increased risks for cardiovascular disease (CVD), type 2 diabetes mellitus, and all-cause and disease-specific mortality (1–4). The most valid measure of CRF is cardiopulmonary exercise testing, with maximal oxygen uptake measured by ventilatory expired gas analysis (5). The common approach, however, is to calculate maximal oxygen uptake from total test time, which has been demonstrated to be highly valid and easier to use (6,7). In a healthy, 40-year-old, 70-kg man, 1 metabolic equivalent (MET) unit is defined as 3.5 ml O_2/kg/min (8), and a 1-MET increase has been associated with 13% and 15% reductions in the

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Abbreviations and Acronyms

BMI = body mass index
CRF = cardiorespiratory fitness
CVD = cardiovascular disease
MET = metabolic equivalent
MI = myocardial infarction
RHR = resting heart rate
WC = waist circumference

risks for all-cause mortality and CVD events, respectively (9).

Unlike other important risk factors, CRF is not routinely measured. It requires trained personnel to administer an exercise test using specialized equipment. With the publication of nonexercise algorithms, it is now feasible to estimate CRF with reasonable accuracy using health indicators typically available in field and healthcare settings. Over 2 decades ago, we published the first equations (10), and many others have been developed more recently (11–15). Although they provide accurate estimates at the population level, these models were developed with cross-sectional data. Furthermore, age was included as a linear term, and recent longitudinal data have demonstrated that CRF declines nonlinearly with aging (16). To address this issue, we recently developed new longitudinal algorithms that estimate CRF changes associated with aging (17). The error estimates ranged from 1.41 to 1.69 METs (17).

Whether estimated CRF can predict health risk is yet to be determined. To the best of our knowledge, only Stamatakis et al. (18) have explored the association between estimated CRF and mortality. After a mean follow-up of 9 years, a higher level of estimated CRF was associated with lower risks for mortality from all causes and from CVD (18). Interestingly, the discriminative ability (as determined by *c* statistic) of estimated CRF was better than that of any of its modifiable components (body mass index [BMI], self-reported physical activity, and resting heart rate [RHR]) (18).

Given the underutilization of fitness testing and the potential of estimated CRF as demonstrated by Stamatakis et al. (18), the purpose of the present analyses was to examine the capacity of our new longitudinal CRF algorithms to predict incident CVD and disease-specific mortality. This study will add to the previous one (18) by comparing risk-predictive capacity with measured CRF and by adding nonfatal major CVD events, in a large established database with long-term follow-up.

Methods

Study population. The ACLS (Aerobics Center Longitudinal Study) is a prospective, observational study in adult men and women who have undergone preventive medical evaluations at the Cooper Clinic (Dallas, Texas) (1). Participants were unpaid volunteers, mostly of non-Hispanic white race, well-educated, and worked in executive or professional positions. All participants provided written informed consent and the study protocol was approved annually.

Inclusion criteria for the present analysis were: no history of or existing CVD (myocardial infarction [MI] or stroke) or cancer at baseline; achieving 85% or more of the patient's age-predicted maximal heart rate (220 − age) during treadmill exercise testing; BMI $\geq$18.5 kg/m^2; $\geq$1 year of follow-up; and complete data on CRF, mortality outcomes, covariates, and all parameters included in the CRF algorithms (17). These criteria resulted in 43,356 patients (21% women) aged 20 to 84 years who had undergone a baseline examination between 1974 and 2002.

Baseline examination. The clinical examinations were completed after an overnight fast. Height and weight were measured on a physician's scale and stadiometer, and BMI was calculated. Waist circumference (WC) was measured level with the umbilicus. Resting systolic and diastolic blood pressures were measured with a mercury sphygmomanometer using standard auscultation methods (19). Blood chemistries were analyzed with automated bioassays in the Cooper Clinic laboratory. Concentrations of total cholesterol and fasting plasma glucose were measured in accordance with the standards of the Centers for Disease Control and Prevention's Lipid Standardization Program (20).

PHYSICAL ACTIVITY. A formerly validated questionnaire was used to assess self-reported leisure-time physical activity (21). A 5-level physical activity index was created (17): no regular activity (level 0); some regular activity such as bicycling, swimming, racquet sports, and other strenuous sports, but not walking or jogging (level 1); walking or jogging <10 miles per week (level 2); walking or jogging 10 to 20 miles per week (level 3); and walking or jogging >20 miles per week (level 4). Walking and jogging were used as the basis of physical activity because they were the most common activities in this population. A second physical activity index was defined as inactive (levels 0 to 2) or active (level 3 or 4) to match as closely as possible the consensus recommendation of 150 min per week of aerobic activity (22).

MEASURED CRF. Measured CRF was quantified as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol (1,23). Patients were encouraged to give maximal effort, and the test endpoint was volitional exhaustion or termination by the physician for medical reasons. We calculated METs from the final treadmill speed and grade (24). Exercise treadmill duration on this protocol is highly correlated ($r \geq 0.92$) with measured peak oxygen uptake (6,7). Participants were classified into lower, middle, and upper groups on the basis of age- (20 to <40, 40 to <50, 50 to <60, or $\geq$60 years) and sex-specific thirds of METs distribution.

ESTIMATED CRF. Four different sex-specific algorithms were created to estimate CRF, on the basis of age, BMI (or percent body fat), WC, RHR, physical activity index (in 2 or 5 levels), and smoking status, as previously described and validated (17). For a higher applicability, the present

analyses focused on those algorithms that include BMI (rather than body fat) and physical activity in 2 levels (rather than 5):

$$\textbf{Women}: \text{Estimated CRF}_{(\text{METs})} = 14.7873 + (\text{Age} \times 0.1159) - (\text{Age}^2 \times 0.0017) - (\text{BMI} \times 0.1534) - (\text{WC} \times 0.0085) - (\text{RHR} \times 0.0364) + (\text{Active} \times 0.5987) - (\text{Smoker} \times 0.2994)$$

or

$$\textbf{Men}: \text{Estimated CRF}_{(\text{METs})} = 21.2870 + (\text{Age} \times 0.1654) - (\text{Age}^2 \times 0.0023) - (\text{BMI} \times 0.2318) - (\text{WC} \times 0.0337) - (\text{RHR} \times 0.0390) + (\text{Active} \times 0.6351) - (\text{Smoker} \times 0.4263)$$

where *active* = 1 if the participant was classified as physically active or 0 if inactive; and *smoker* = 1 if current smoker or 0 if not. Once the algorithms were implemented, participants were classified into lower, middle, and upper groups on the basis of age- (20 to <40, 40 to <50, 50 to <60, or ≥60 years) and sex-specific thirds of MET distribution.

Assessment of outcomes. Participants were followed up from the baseline examination until the date of death or December 31, 2003. Mortality surveillance was on the basis of the National Death Index. The underlying cause of death was determined from the National Death Index report or by a nosologist's review of the official death certificate. CVD-related mortality was defined by International Classification of Diseases-Ninth Revision (ICD-9) codes 390 to 449.9 before 1999 and Tenth Revision (ICD-10) codes I00 to I78 during 1999–2003 (25).

Incidence of nonfatal CVD events was ascertained in a subsample of 18,095 patients (20% women) from responses to mail-back health surveys in 1982, 1999, and 2004. The aggregate survey response rate across all survey periods in the ACLS was 65% to 75% (26). Baseline health histories and clinical measures were similar between respondents and nonrespondents and between early and late respondents (27).

Nonfatal CVD endpoints were defined as diagnosis by a physician of MI, stroke, or the need for a coronary revascularization procedure. In participants reporting multiple events, the first event was used for analysis. In a random sample of these endpoints, we applied a standard definition for defining and adjudicating MI, revascularization, and stroke (28). The percentages of agreement between reported events and participants' medical records were 88%, 100%, and 89% for MI, revascularization, and stroke, respectively (26).

Statistical analysis. Participants' baseline characteristics were summarized on the basis of sex and estimated CRF level, using analysis of the variance and chi-square tests. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) according to CRF levels (both measured and estimated). Multivariate analyses included these covariates: age (in years), examination year, alcohol intake (dichotomized as heavy drinker or not: >14 drinks per week in men and >7 drinks per week in women [29]), presence or absence of hypercholesterolemia (total cholesterol ≥240 mg/dl or previous physician's diagnosis), hypertension (resting blood pressure ≥140/≥90 mm Hg or previous physician's diagnosis), diabetes mellitus (fasting blood glucose ≥126 mg/dl, previous physician's diagnosis, or use of insulin), abnormal resting or exercise electrocardiography, and/or parental history of CVD. Sensitivity analyses compared the performance of the algorithms with 5 and 2 levels of physical activity and excluded intermediate covariates that could be on the causal pathway (hypercholesterolemia, hypertension, diabetes). Cumulative hazard plots grouped by exposure categories suggested no appreciable violations of the proportional hazards assumption.

To compare the risk-predictive capacity of measured and estimated CRF, we constructed receiver operating characteristic curves with corresponding areas under the curve (AUCs). The AUC (also known as *c* statistic) is a function of both the sensitivity and specificity of the model across all of its values, and it represents the ability of the score to discriminate future cases from noncases (30). The risk-predictive capacity of estimated CRF was also compared with its modifiable constituent components (BMI, WC, RHR, and physical activity). We used existing methods (18) to develop a continuous clustered score. After *z*-score conversion of each variable (z = [Value − Mean]/standard deviation [SD]), the 4 *z*-scores were summed, and the sum was divided by 4 to compile a score with units of SD. The continuous variable for physical activity (originally active or inactive) was calculated as MET − minutes per week (22). As it is protective, the *z*-score from physical activity was multiplied by −1. Smoking status was not included in this analysis as it was defined as a dichotomous variable (current smoker or not).

Finally, we calculated the net reclassification improvement (NRI) for all-cause mortality between estimated and measured CRF. On the basis of subsequent observed cases, this index integrates proportions of appropriate and inappropriate reclassifications between 2 risk-prediction models (30). NRI was calculated as (18,31):

$$\text{NRI} = \left[P_{(\text{up}|\text{case})} - P_{(\text{down}|\text{case})} + P_{(\text{down}|\text{noncase})} - P_{(\text{up}|\text{noncase})}\right] \times 100$$

where P is the proportion of participants moving up or down in terms of predicted risk category.

The NRI was statistically examined by an asymptotic test (31).

Data analyses were performed using SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York), and all p values are 2-sided with an alpha level of 0.05.

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Table 1 Baseline Characteristics of the Study Participants, by Sex and Estimated CRF Level, Aerobics Center Longitudinal Study (1974–2002)

Characteristic	Men (n = 34,211)			Women (n = 9,145)		
	Lower CRF Level (n = 11,402)	Middle CRF Level (n = 11,405)	Upper CRF Level (n = 11,404)	Lower CRF Level (n = 3,048)	Middle CRF Level (n = 3,049)	Upper CRF Level (n = 3,048)
Clinical						
Age, yrs	44.9 (10.0)	44.5 (9.7)	44.0 (9.5)†	44.9 (11.0)	44.5 (10.3)	44.0 (10.7)*
Body mass index, kg/m^2	30.2 (3.6)	25.9 (1.7)	23.5 (1.7)†	27.1 (4.5)	22.5 (2.0)	20.8 (1.5)†
Waist circumference, cm	103.8 (9.4)	92.4 (5.7)	84.9 (6.3)†	82.3 (11.2)	71.4 (7.0)	67.5 (5.3)†
Resting heart rate, bpm	66.6 (10.5)	60.4 (8.8)	53.6 (8.4)†	71.0 (10.3)	64.6 (7.8)	56.7 (7.5)†
Treadmill time, min	15.1 (3.9)	18.3 (3.9)	22.0 (4.3)†	11.2 (3.6)	13.7 (3.8)	16.5 (4.4)†
Blood pressure, mm Hg						
Systolic	125.2 (13.4)	120.3 (12.7)	118.0 (12.9)†	117.7 (14.9)	112.1 (14.1)	109.6 (13.8)†
Diastolic	84.7 (9.6)	80.8 (9.0)	78.2 (8.8)†	79.2 (9.6)	75.7 (9.1)	73.9 (9.1)†
Laboratory						
CRF, METs						
Measured	10.3 (1.8)	11.8 (1.9)	13.6 (2.3)†	8.5 (1.7)	9.7 (1.8)	10.9 (2.1)†
Estimated	10.7 (1.2)	12.4 (0.7)	13.8 (0.8)†	9.0 (0.9)	10.1 (0.5)	10.9 (0.6)†
Total cholesterol, mg/dl	215.6 (41.3)	210.0 (43.2)	199.4 (44.5)†	205.7 (39.5)	198.1 (45.5)	192.9 (34.7)†
Glucose, mg/dl	104.2 (22.1)	99.4 (15.2)	97.7 (86.9)†	96.5 (15.4)	96.3 (167.5)	91.9 (11.0)
History						
Physically active	645 (5.7)	1,505 (13.2)	5,157 (45.2)†	143 (4.7)	314 (10.3)	1,224 (40.2)†
Current smoker	2,766 (24.3)	1,983 (17.4)	915 (8.0)†	338 (11.1)	301 (9.9)	148 (4.9)†
Heavy drinker	986 (8.6)	981 (8.6)	797 (7.0)†	297 (9.7)	334 (11.0)	361 (11.8)*
Hypercholesterolemia	4,044 (35.5)	3,238 (28.4)	2,281 (20.0)†	888 (29.1)	616 (20.2)	468 (15.4)†
Diabetes mellitus	866 (7.6)	404 (3.5)	249 (2.2)†	169 (5.5)	101 (3.3)	85 (2.8)†
Hypertension	5,168 (45.3)	3,120 (27.4)	2,105 (18.5)†	799 (26.2)	440 (14.4)	342 (11.2)†
Abnormal ECG	957 (8.4)	804 (7.0)	714 (6.3)†	270 (8.9)	216 (7.1)	158 (5.2)†
Parental history of CVD	3,152 (27.6)	3,144 (27.6)	3,133 (27.5)	824 (27.0)	842 (27.6)	800 (26.2)

Values are mean (SD) or n (%). Analysis of the variance or chi-square test were used to test the differences between groups in each sex: *$p < 0.05$; †$p < 0.001$.
bpm = beats/min; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; ECG = electrocardiography; MET = metabolic equivalent.

Table 2 Hazard Ratios for Disease-Specific Mortality and Nonfatal CVD, by CRF Level, in Men (n = 34,211)

	Measured CRF			Estimated CRF		
		Hazard Ratio (95% CI)			Hazard Ratio (95% CI)	
	n/N	Model 1*	Model 2†	n/N	Model 1*	Model 2†
All-cause mortality						
Lower	793/11,329	1 (Ref)	1 (Ref)	642/11,402	1 (Ref)	1 (Ref)
Middle	524/12,164	0.64 (0.57–0.71)	0.68 (0.61–0.76)	557/11,405	0.74 (0.66–0.82)	0.79 (0.70–0.88)
Upper	401/10,718	0.49 (0.44–0.55)	0.56 (0.49–0.63)	519/11,404	0.59 (0.53–0.67)	0.67 (0.59–0.75)
p for linear trend		<0.001	<0.001		<0.001	<0.001
Per 1-MET increase		0.84 (0.83–0.86)	0.87 (0.85–0.89)		0.82 (0.79–0.84)	0.85 (0.82–0.88)
CVD-related mortality						
Lower	304/11,329	1 (Ref)	1 (Ref)	249/11,402	1 (Ref)	1 (Ref)
Middle	164/12,164	0.52 (0.43–0.63)	0.60 (0.49–0.72)	170/11,405	0.59 (0.48–0.71)	0.66 (0.54–0.80)
Upper	109/10,718	0.34 (0.27–0.43)	0.45 (0.36–0.57)	158/11,404	0.47 (0.38–0.57)	0.59 (0.48–0.73)
p for linear trend		<0.001	<0.001		<0.001	<0.001
Per 1-MET increase		0.78 (0.75–0.81)	0.83 (0.79–0.86)		0.76 (0.72–0.80)	0.81 (0.77–0.86)
Nonfatal CVD						
Lower	353/4,335	1 (Ref)	1 (Ref)	309/4,048	1 (Ref)	1 (Ref)
Middle	346/5,140	0.72 (0.62–0.83)	0.80 (0.69–0.93)	327/4,902	0.76 (0.65–0.89)	0.84 (0.71–0.98)
Upper	278/4,985	0.47 (0.40–0.55)	0.57 (0.48–0.67)	341/5,510	0.56 (0.48–0.65)	0.66 (0.56–0.78)
p for linear trend		<0.001	<0.001		<0.001	<0.001
Per 1-MET increase		0.87 (0.84–0.89)	0.90 (0.87–0.93)		0.84 (0.80–0.88)	0.89 (0.85–0.93)

*Adjusted for age and examination year. †Adjusted for age, examination year, alcohol intake (heavy drinker or not), hypercholesterolemia, hypertension, diabetes, abnormal resting or exercise ECG, and parental history of CVD (present or not for each).
CI = confidence interval; other abbreviations as in Table 1.

Results

Descriptive characteristics of the study population are presented in Table 1. Men and women with higher levels of estimated CRF had lower BMI, WC, RHR, total cholesterol and glucose concentrations (except in women), and systolic and diastolic blood pressures. Participants with higher levels of estimated CRF were more likely to be physically active and less likely to be smokers and heavy drinkers (except in women) and to have hypercholesterolemia, diabetes mellitus, hypertension, or an abnormal electrocardiography.

The median (25th to 75th percentiles) follow-up period for mortality was 14.5 (5.7 to 20.1) years. A total of 1,934 participants died, 627 from CVD. For incidence of nonfatal CVD events, the follow-up period was 7.7 (2.9 to 16.5) years and 1,049 cases were registered. Tables 2 and 3 show HRs (95% CI) by CRF levels. In men, both measured CRF and estimated CRF were inversely associated with the risks for all-cause mortality (HR per 1-MET increase, measured CRF: 0.87 [95% CI: 0.85 to 0.89]; estimated CRF: 0.85 [95% CI: 0.82 to 0.88]), CVD-related mortality (measured CRF: 0.83 [95% CI: 0.79 to 0.86]; estimated CRF: 0.81 [95% CI: 0.77 to 0.86]), and nonfatal CVD events (measured CRF: 0.90 [95% CI: 0.87 to 0.93]; estimated CRF: 0.89 [95% CI: 0.85 to 0.93]), after adjustments for potential confounders (Table 2). In women, both measured CRF and estimated CRF were inversely associated with risks for all-cause mortality (measured CRF: 0.91 [95% CI: 0.85 to 0.99]; estimated CRF: 0.87 [95% CI: 0.75 to 0.99]) and nonfatal CVD events (measured CRF: 0.77 [95% CI: 0.67 to 0.90]; estimated CRF: 0.76 [95% CI: 0.58 to 0.99]) (Table 3). Excluding hypercholesterolemia, hypertension and diabetes as confounders slightly strengthened some of these results (data not shown).

Table 4 presents the discrimination statistics of measured CRF and estimated CRF. The *c* statistic values (AUC) were slightly higher for measured CRF than for estimated CRF. In both cases, the discriminative ability was always higher for CVD-related mortality than for any other outcome. In general, *c* statistic values were higher in women than in men. The lowest *c* statistic value was 0.61 (estimated CRF discriminating nonfatal CVD events in men) and the highest was 0.74 (measured CRF discriminating CVD-related mortality in women). As can be observed in Table 5, the discriminative ability of estimated CRF was greater than that of any of its modifiable components, separately or together, in men and women, and for all outcomes.

Finally, Table 6 compares the reclassification statistics for all-cause mortality between both CRF methods. Compared to estimated CRF, measured CRF reclassified correctly 12.7% of men and 20.8% of women who died (i.e., they were reclassified to a higher-risk category). The overall NRI values were 12.3% in men ($p < 0.05$) and 19.8% in women ($p < 0.001$).

All of the analyses (Tables 2 to 6) were repeated using the algorithms with the 5-level physical activity variable. The results were virtually the same, with a risk-predictive capacity and discriminative ability similar to those provided by the 2-level physical activity algorithms (data not shown).

Table 3 Hazard Ratios for Disease-Specific Mortality and Nonfatal CVD, by CRF Level, in Women (n = 9,145)

	Measured CRF			Estimated CRF		
		Hazard Ratio (95% CI)			Hazard Ratio (95% CI)	
	n/N	Model 1*	Model 2†	n/N	Model 1*	Model 2†
All-cause mortality						
Lower	109/3,143	1 (Ref)	1 (Ref)	74/3,048	1 (Ref)	1 (Ref)
Middle	66/3,076	0.92 (0.68–1.25)	0.91 (0.67–1.24)	77/3,049	0.83 (0.60–1.14)	0.82 (0.59–1.13)
Upper	41/2,926	0.75 (0.52–1.07)	0.74 (0.52–1.07)	65/3,048	0.68 (0.49–0.95)	0.67 (0.48–0.94)
p for linear trend		0.281	0.275		0.079	0.068
Per 1-MET increase		0.92 (0.85–0.99)	0.91 (0.85–0.99)		0.87 (0.75–0.99)	0.87 (0.75–0.99)
CVD-related mortality						
Lower	25/3,143	1 (Ref)	1 (Ref)	21/3,048	1 (Ref)	1 (Ref)
Middle	16/3,076	1.05 (0.56–1.97)	1.08 (0.57–2.04)	15/3,049	0.63 (0.32–1.22)	0.70 (0.35–1.37)
Upper	9/2,926	0.80 (0.37–1.72)	0.89 (0.41–1.94)	14/3,048	0.58 (0.29–1.17)	0.65 (0.32–1.31)
p for linear trend		0.793	0.905		0.230	0.410
Per 1-MET increase		0.92 (0.78–1.09)	0.95 (0.81–1.13)		0.83 (0.63–1.08)	0.84 (0.64–1.12)
Nonfatal CVD						
Lower	42/1,206	1 (Ref)	1 (Ref)	27/1,024	1 (Ref)	1 (Ref)
Middle	15/1,175	0.35 (0.19–0.63)	0.36 (0.20–0.66)	27/1,239	0.64 (0.38–1.11)	0.73 (0.42–1.26)
Upper	15/1,254	0.35 (0.19–0.63)	0.38 (0.21–0.69)	18/1,372	0.34 (0.19–0.63)	0.38 (0.20–0.70)
p for linear trend		< 0.001	< 0.001		0.003	0.008
Per 1-MET increase		0.75 (0.65–0.87)	0.77 (0.67–0.90)		0.69 (0.54–0.89)	0.76 (0.58–0.99)

*Adjusted for age and examination year. †Adjusted for age, examination year, alcohol intake (heavy drinker or not), hypercholesterolemia, hypertension, diabetes, abnormal resting or exercise ECG, and parental history of CVD (present or not for each).

Abbreviations as in Tables 1 and 2.

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Table 4 Discrimination Statistics of Measured and Estimated CRF for Disease-Specific Mortality and Nonfatal CVD

	Measured CRF			Estimated CRF		
	All-Cause Mortality	CVD-Related Mortality	Nonfatal CVD	All-Cause Mortality	CVD-Related Mortality	Nonfatal CVD
Men (n = 34,211)						
Cases	1,718	577	977*	1,718	577	977*
AUC (95% CI)†	0.67 (0.66–0.69)	0.72 (0.70–0.74)	0.62 (0.60–0.64)	0.63 (0.61–0.64)	0.68 (0.66–0.70)	0.61 (0.59–0.62)
Sensitivity‡	0.46	0.53	0.36	0.37	0.43	0.32
Specificity§	0.68	0.67	0.70	0.67	0.67	0.72
Women (n = 9,145)						
Cases	216	50	72*	216	50	72*
AUC (95% CI)†	0.70 (0.66–0.73)	0.74 (0.68–0.80)	0.71 (0.64–0.77)	0.64 (0.60–0.68)	0.73 (0.66–0.81)	0.68 (0.62–0.74)
Sensitivity‡	0.50	0.50	0.58	0.34	0.42	0.38
Specificity§	0.66	0.66	0.67	0.67	0.67	0.72

*Subsample of 14,460 men and 3,635 women. †Calculated from inverted CRF (as it is protective). ‡The proportion of cases captured by lower CRF group (highest risk). §The proportion of noncases captured by combined middle and upper CRF groups.
AUC = area under the curve; other abbreviations as in Table 1.

Discussion

The purpose of the present study was to investigate the association of estimated CRF, on the basis of longitudinal algorithms, with disease-specific mortality and nonfatal CVD events in middle-aged men and women. Previous studies had shown that these (17) and other nonexercise equations (10–13,15) estimate CRF with reasonable accuracy at the population level. Now we show that estimated CRF, calculated from typically available health indicators, significantly predicted future risk for nonfatal CVD events as well as all-cause and CVD-related mortality, after adjustment for standard risk factors. However, these algorithms can still be refined for a better risk-prediction performance, as measured CRF presented a better discriminative capacity (*c* statistic) and reclassified correctly a significant proportion of cases (NRI).

Clinicians have long been aware that patients capable of high levels of physical exertion have a better prognosis than do those with limited exercise capacity. Data from the ACLS and other epidemiologic studies indicate that patients with low CRF are much more likely to develop hypertension (32), diabetes (32,33), and metabolic syndrome (32,34) and to have higher rates of death due to CVD (3,35), cancer (36), and all causes (1,3,37). Many experts have recommended CRF testing in asymptomatic and symptomatic men and women of all ages (38), and the American Heart Association recently highlighted the need for a national CRF registry (39). The present algorithms are a practical alternative for an estimate of CRF and are a useful tool for identifying persons at risk. The potential clinical implications are substantial, as this method could be applied to electronic medical record systems and easily determined in patients in clinical practice or in health maintenance plans.

The risk reduction per 1-MET increase observed in our study is consistent with previous findings using measured CRF (9), and with those from the only study so far investigating estimated CRF and mortality (18). Similar to our results, those studies suggested a 10% to 20% risk reduction per 1-MET increase, with the effect being slightly higher for CVD events than for all-cause mortality (9,18). Our findings indicate a similar protective trend in men and women, although in women there was no association with CVD-related mortality, and the linear trend for all-cause mortality did not reach statistical significance. The smaller number of cases in women likely decreased the statistical power, as suggested in previous ACLS studies (26). In the Lipid Research Clinics study (40), CRF predicted CVD-related mortality risk in women and men, whereas in the Framingham Heart Study, CRF was significantly associated with coronary heart disease events in men but not in

Table 5 AUCs (95% CI) for the Modifiable Constituent Components of the Nonexercise CRF Algorithms (Separately and Clustered) and for Estimated CRF

	Men (n = 34,211)			Women (n = 9,145)		
	All-Cause Mortality	CVD-Related Mortality	Nonfatal CVD*	All-Cause Mortality	CVD-Related Mortality	Nonfatal CVD*
Body mass index	0.49 (0.48–0.51)	0.53 (0.51–0.55)	0.53 (0.51–0.55)	0.50 (0.47–0.54)	0.51 (0.43–0.58)	0.56 (0.50–0.63)
Waist circumference	0.53 (0.52–0.55)	0.58 (0.55–0.60)	0.56 (0.55–0.58)	0.53 (0.49–0.57)	0.56 (0.49–0.63)	0.59 (0.52–0.65)
Resting heart rate	0.55 (0.53–0.56)	0.56 (0.54–0.59)	0.52 (0.50–0.54)	0.52 (0.48–0.56)	0.62 (0.55–0.69)	0.56 (0.49–0.62)
Physical activity†	0.58 (0.57–0.59)	0.57 (0.55–0.60)	0.54 (0.52–0.55)	0.61 (0.58–0.65)	0.61 (0.54–0.69)	0.59 (0.53–0.65)
Clustered score	0.55 (0.54–0.57)	0.58 (0.56–0.61)	0.56 (0.54–0.57)	0.56 (0.53–0.60)	0.61 (0.54–0.69)	0.62 (0.56–0.68)
Estimated CRF†	0.63 (0.61–0.64)	0.68 (0.66–0.70)	0.61 (0.59–0.62)	0.64 (0.60–0.68)	0.73 (0.66–0.81)	0.68 (0.62–0.74)

*Subsample of 14,460 men and 3,635 women. †Calculated from inverted physical activity and CRF (as they are protective).
Abbreviations as in Tables 1 and 5.

Table 6 Reclassification of the Predicted Risk for All-Cause Mortality in Men and Women on the Basis of Estimated CRF Versus Measured CRF

Estimated CRF	Measured CRF			Reclassified as Higher Risk	Reclassified as Lower Risk	Net Correctly Reclassified (%)
	Lower (Highest Risk)	Middle	Upper			
Men*						
Cases (n = 1,718)				468	250	12.7
Lower (highest risk)	487	132	23			
Middle	232	230	95			
Upper	74	162	283			
Noncases (n = 32,493)				6,886	6,760	−0.4
Lower (highest risk)	6,758	3,406	596			
Middle	2,964	5,126	2,758			
Upper	814	3,108	6,963			
Women†						
Cases (n = 216)				81	36	20.8
Lower (highest risk)	54	16	4			
Middle	37	24	16			
Upper	18	26	21			
Noncases (n = 8,929)				2,099	2,007	−1.0
Lower (highest risk)	1,794	874	306			
Middle	868	1277	827			
Upper	372	859	1,752			

*Net reclassification improvement: 12.3% ($p < 0.05$). †Net Reclassification improvement: 19.8% ($p < 0.001$).

women (41). The discriminative capacity (*c* statistic) of our models for CVD-related mortality (from 0.68 to 0.74) was close to that observed for the Framingham risk score and other similar prediction models (0.75 to 0.80), on the basis of the combination of multiple independent risk markers (30). The *c*-statistic values reported by Stamatakis et al. (18) for CVD deaths were also comparable (0.73 to 0.75).

The potential mechanisms for the protective role of estimated CRF could be the same as those attributed to measured CRF, achieved in most cases through healthy life-style habits: lower levels of adiposity, blood pressure, and chronic inflammation; higher insulin sensitivity and glycemic control; more favorable lipid profile; enhanced endothelial function; improved cardiac autonomic regulation; and preserved functional capacity and cognitive ability during aging, among others (22). In our study, those participants with higher levels of estimated CRF had lower BMI, WC, RHR, cholesterol and glucose concentrations, and systolic and diastolic blood pressures and were more likely to be physically active and less likely to be smokers and to have hypercholesterolemia, diabetes mellitus, or hypertension.

Strengths and limitations. Notable features make this a robust set of findings: the possibility of comparing the risk-predictive capacity between measured and estimated CRF; the large set of major outcomes studied (all-cause mortality, CVD-related mortality, and incidence of nonfatal CVD events); the large sample size and long follow-up; and the broad range of potential confounders taken into account. However, measured CRF was not directly assessed by gas analysis, but was indirectly calculated from treadmill speed and grade. Although cardiopulmonary exercise testing is considered the gold standard, both assessed and calculated METs from exercise tests have been shown to be among the strongest predictors of adverse events in a prognostic model (9). The lack of information on diet and medication use/adherence may have introduced some residual confounding. The most heavily weighted variable (physical activity) was self-reported, although any objective alternative would be less practical. And finally, participants were mostly of non-Hispanic white ethnicity, well-educated, and with professional positions; we do not know how well our algorithms would predict health risk in other populations. Cross-validation studies are needed to investigate the generalizability of these results by testing the algorithms' predictive capacity in other cohorts.

Conclusions

Our longitudinal algorithms utilize information routinely collected to obtain an estimate of CRF that provides a valid indication of health status. Although the method can still be refined, estimated CRF significantly predicted the risk for nonfatal CVD events and all-cause and disease-specific mortality. In addition to identifying people at risk, this method can potentially be utilized to provide more appropriate exercise recommendations that reflect initial CRF levels.

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Key Words: algorithms ■ cardiorespiratory fitness ■ cardiovascular disease ■ mortality.