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Longitudinal Algorithms to Estimate Cardiorespiratory Fitness: Associations with Non-fatal Cardiovascular Disease and Disease-Specific Mortality

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Running title: Estimated fitness and health

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ABSTRACT

Objective: To predict risk for non-fatal cardiovascular disease (CVD) and disease-specific mortality using CRF algorithms that do not involve exercise testing.

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 between 1974 and 2003. Estimated CRF was based on 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.

Results: During a median follow-up of 14.5 years, 1,934 deaths occurred, 627 due to CVD. In a sub-sample of 18,095 participants, 1,049 cases of non-fatal CVD events were ascertained. After adjusting for potential confounders, both measured CRF and estimated CRF were inversely associated with risk of all-cause mortality, CVD mortality and non-fatal CVD incidence in men, and with all-cause mortality and non-fatal CVD in women. The risk reduction per 1-metabolic equivalent (MET) increase ranged approximately from 10 to 20 %. Measured CRF had a slightly better discriminative ability (c-statistic) than estimated CRF, and the net reclassification improvement (NRI) of measured CRF vs. estimated CRF was 12.3% in men ($p<0.05$) and 19.8% in women ($p<0.001$).

Conclusions: These algorithms utilize information routinely collected to obtain an estimate of CRF that 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.

KEY WORDS: cardiorespiratory fitness, mortality, cardiovascular disease, algorithms

ABBREVIATIONS LIST

ACLS = Aerobics Center Longitudinal Study.
BMI = body mass index.
CRF = cardiorespiratory fitness.
CVD = cardiovascular disease.
MET = metabolic equivalent.
NRI = net reclassification improvement.
RHR = resting heart rate.
VO_2max = maximal oxygen uptake.
WC = waist circumference.

INTRODUCTION

Low cardiorespiratory fitness (CRF) is associated with increased risk of cardiovascular disease (CVD), type 2 diabetes, and all-cause and disease-specific mortality (1-4). The most valid measure of CRF is cardiopulmonary exercise testing (CPX) with maximal oxygen uptake (VO_2max) measured by ventilatory expired gas analysis (5). The common approach, however, is to calculate VO_2max from total test time, which has demonstrated to be highly valid and easier to use widely (6,7). In a healthy 40 year-old, 70 kg man, 1 metabolic equivalent (MET) unit is defined as 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (8), and every 1-MET increase has been associated with a 13% and 15% risk reduction of 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 non-exercise algorithms, it is now feasible to estimate CRF with reasonable accuracy using health indicators typically available in field and healthcare settings. Over two 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 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 a lower risk of mortality from all causes and CVD (18). Interestingly, estimated CRF had a

better discriminative ability (as judged by c-statistic) than 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 is 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 non-fatal major CVD events, in a large established database with long follow-up.

METHODS

Study population

The Aerobics Center Longitudinal Study (ACLS) is a prospective observational study of adult men and women who underwent preventive medical evaluations at the Cooper Clinic (Dallas, TX) (1). Participants were unpaid volunteers, mostly non-Hispanic whites, 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 existing CVD (myocardial infarction [MI] or stroke) or cancer at baseline; achieving 85% or more of the individual's age-predicted maximal heart rate (220 – age) during the treadmill exercise testing; BMI ≥18.5 kg/m^2; ≥1 year of follow-up; complete data on CRF, mortality outcomes, covariables and all parameters included in the CRF algorithms (17). These criteria resulted in 43,356 individuals (21% women) aged 20 to 84 years who underwent 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 CDC Lipid Standardization Program (20).

Physical activity

A formerly validated questionnaire was used to assess self-reported leisure-time physical activity (21). A five-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 10-20 miles (level 3); and walking or jogging > 20 miles (level 4). Walking and jogging were used as the basis for physical activity because they were the most common activities in this population. A second physical activity index was defined as inactive (levels 0-2) and active (levels 3, 4) to match as closely as possible the consensus recommendation of 150 minutes 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 based on age- (20-39, 40-49, 50-59, ≥ 60 yr) and sex-specific thirds of METs distribution.

Estimated CRF

Four different sex-specific algorithms were created to estimate CRF, based on age, BMI (or percent body fat), WC, RHR, physical activity index (in two or five levels) and smoking status, as previously described and validated (17). For a higher applicability, the present analyses focus on those algorithms that include BMI (rather than body fat) and physical activity in two levels (rather than five):

Women

Estimated CRF $_{(METs)}$ = 14.7873 + (age × 0.1159) – (age^2 × 0.0017) – (BMI × 0.1534) – (WC × 0.0085) – (RHR × 0.0364) + (active × 0.5987) – (smoker × 0.2994)

Men

Estimated CRF $_{(METs)}$ = 21.2870 + (age × 0.1654) – (age^2 × 0.0023) – (BMI × 0.2318) – (WC × 0.0337) – (RHR × 0.0390) + (active × 0.6351) – (smoker × 0.4263)

where active = 1 if the participant was classified as physically active, 0 if inactive; and smoker = 1 if current smoker, 0 if not. Once the algorithms were implemented, participants were classified into lower, middle and upper groups based on age- (20-39, 40-49, 50-59, ≥ 60 yr) and sex-specific thirds of METs distribution.

Assessment of outcomes

Participants were followed from baseline examination until the date of death or 31 December 2003. Mortality surveillance was based on the national death index (NDI). The underlying cause of death was determined from the NDI report or by a nosologist's review of official death certificates. CVD 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 non-fatal CVD events was ascertained in a subsample of 18,095 individuals (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 is 65% to 75% (26). Baseline health histories and clinical measures were similar between responders and non-responders and between early and late responders (27).

Non-fatal CVD endpoints were defined as diagnosis by a physician of MI, stroke, or 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 percentage of agreement between reported events and participants' medical records was 88, 100, and 89% for MI, revascularization, and stroke, respectively (26).

Statistical Analysis

Participants' baseline characteristics were summarized based on sex and estimated CRF level, using analysis of the variance (ANOVA) 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). Multivariable analyses included these covariables: age (years), examination year, alcohol intake [heavy drinker or not: >14 and >7 drinks / wk for males and females, respectively (29)], presence or absence of hypercholesterolemia (total cholesterol ≥240 mg/dL or previous physician diagnosis), hypertension (resting blood pressure ≥ 140/90 mm Hg or previous physician diagnosis), diabetes mellitus (fasting blood glucose ≥126 mg/dL, previous physician diagnosis or use of insulin), abnormal resting or exercise ECG, and

parental history of CVD. Sensitivity analyses compared the performance of the algorithms with five and two levels of physical activity, and also excluded intermediate covariables 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 CRF and estimated CRF, we constructed ROC curves with corresponding areas under the curve (AUC). 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 non-cases (30). 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 four 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 is defined as a dichotomous variable (current smoker or not).

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

$$NRI = [P(\text{up}|\text{case}) - P(\text{down}|\text{case}) + P(\text{down}|\text{non-case}) - P(\text{up}|\text{non-case})] \times 100$$

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 Inc.) and all p values are 2-sided with an alpha level of 0.05.

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, heavy drinkers (except in women), to have hypercholesterolemia, diabetes mellitus, hypertension or abnormal ECG.

The median (25–75th percentiles) follow-up period for mortality was 14.5 (5.7–20.1) years. A total of 1,934 participants died, 627 from CVD. For non-fatal CVD incidence, follow-up period was 7.7 (2.9–16.5) years and 1,049 cases were registered. **Tables 2** and **3** show HRs and 95% CIs by CRF levels. In men, both measured CRF and estimated CRF were inversely associated with risk of all-cause mortality (HR per 1-MET increase, measured CRF: 0.87, 0.85-0.89; estimated CRF: 0.85, 0.82-0.88), CVD mortality (measured CRF: 0.83, 0.79-0.86; estimated CRF: 0.81, 0.77-0.86), and non-fatal CVD incidence (measured CRF: 0.90, 0.87-0.93; estimated CRF: 0.89, 0.85-0.93), after adjustments for potential confounders (table 2). In women, both measured CRF and estimated CRF were inversely associated with risk of all-cause mortality (measured CRF: 0.91, 0.85-0.99; estimated CRF: 0.87, 0.75-0.99) and non-fatal CVD incidence (measured CRF: 0.77, 0.67-0.90; estimated CRF: 0.76, 0.58-0.99) (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. C-statistic values (AUC) were slightly higher for measured CRF than estimated CRF. In both cases, the discriminative ability was always higher for CVD mortality than for any other outcome. In general, c-statistic values were higher in women than men. The lowest c-statistic value was 0.61 (estimated CRF discriminating non-fatal CVD incidence in men) and the highest was 0.74 (measured CRF discriminating CVD mortality in women). As it can be observed in **Table 5**, the discriminative ability of estimated CRF was higher to that from any of its modifiable components, separately or together, in men and women, and for all outcomes.

Finally, **Table 6** shows 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 was 12.3% for men ($p<0.05$) and 19.8% for women ($p<0.001$).

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

DISCUSSION

The purpose of the present study was to investigate the association of estimated CRF, based on longitudinal algorithms, with disease-specific mortality and non-fatal CVD events in middle-aged men and women. Previous studies had shown that these (17) and other non-exercise 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 of non-fatal CVD as well as all-cause and CVD 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 those with limited exercise capacity. Data from the ACLS and other epidemiologic studies indicate that individuals 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 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 on patients in clinical practice or health maintenance plans.

The risk reduction per 1-MET increase observed in our study is consistent with previous findings using measured CRF (9), and also with the only study so far investigating estimated CRF and mortality (18). Similar to our results, these studies have suggested a 10-20% risk reduction per 1-MET increase, with the effect being slightly higher for CVD events than for all-cause mortality (9,18). Between genders, our findings indicate a similar protective trend in men and women, although in females there was no association with CVD 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 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 women (41). The discriminative capacity (c-statistic) of our models for CVD mortality (from 0.68 to 0.74) was close to that observed for the Framingham risk score and other similar prediction models (0.75-0.80), based on the combination of multiple independent risk markers (30). The c-statistic values reported by Stamatakis et al. (18) for CVD deaths were also comparable (0.73-75).

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 lifestyle 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, systolic and diastolic blood pressures, and were more likely to be physically active and less likely to be smokers, to have hypercholesterolemia, diabetes mellitus or hypertension.

Notable features make this a robust set of findings: the possibility to compare risk predictive capacity between measured CRF and estimated CRF; a large set of major outcomes studied (all-cause mortality, CVD mortality and non-fatal CVD incidence); the large sample size and long follow-up; and the broad range of potential confounders taken into account. Some limitations must also be mentioned and addressed in future research. Measured CRF was not directly assessed by gas analysis, but indirectly calculated from treadmill speed and grade. Although CPX is considered the gold standard, both assessed and calculated METs from exercise tests have 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 non-Hispanic whites, well-educated and with professional positions, so 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.

In conclusion, 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 risk of non-fatal CVD and all-cause and disease-specific mortality. In addition to identifying people at risk, this method can be potentially utilized to provide more appropriate exercise recommendations that reflect initial CRF levels.

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Table 1 Baseline Characteristics of Study Participants by Sex and Estimated CRF Level, Aerobics Center Longitudinal Study 1974-2002

Characteristic	**Men** (n = 34,211)			**Women** (n = 9,145)		
	Estimated CRF			**Estimated CRF**		
	Lower (n = 11,402)	**Middle** (n = 11,405)	**Upper** (n = 11,404)	**Lower** (n = 3,048)	**Middle** (n = 3,049)	**Upper** (n = 3,048)
Age (years)	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) †
Measured CRF (METs)	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 CRF (METs)	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)
Blood pressure (mmHg)						
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) †
Physically Active	645 (5.7)	1,505 (13.2)	5,157 (45.2) †	143 (4.7)	314 (10.3)	1,224 (40.2) †
Current smokers	2,766 (24.3)	1,983 (17.4)	915 (8.0) †	338 (11.1)	301 (9.9)	148 (4.9) †
Heavy drinkers	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 means (SD). CRF, cardiorespiratory fitness; MET, metabolic equivalent. Analysis of the variance (ANOVA) was used to test differences between groups in each sex: * $p<0.01$; † $p<0.001$.

Table 2 Hazard Ratios for Disease-specific Mortality and Non-fatal CVD According to CRF Levels in Men

	Measured CRF			**Estimated CRF**		
	cases / n	Hazard Ratios (95% CI)		cases / n	Hazard Ratios (95% CI)	
		Model 1 *	Model 2 †		Model 1 *	Model 2 †
All-cause mortality						
Lower	793/11329	1 (ref)	1 (ref)	642/11402	1 (ref)	1 (ref)
Middle	524/12164	0.64 (0.57-0.71)	0.68 (0.61-0.76)	557/11405	0.74 (0.66-0.82)	0.79 (0.70-0.88)
Upper	401/10718	0.49 (0.44-0.55)	0.56 (0.49-0.63)	519/11404	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		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 mortality						
Lower	304/11329	1 (ref)	1 (ref)	249/11402	1 (ref)	1 (ref)
Middle	164/12164	0.52 (0.43-0.63)	0.60 (0.49-0.72)	170/11405	0.59 (0.48-0.71)	0.66 (0.54-0.80)
Upper	109/10718	0.34 (0.27-0.43)	0.45 (0.36-0.57)	158/11404	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		0.78 (0.75-0.81)	0.83 (0.79-0.86)		0.76 (0.72-0.80)	0.81 (0.77-0.86)
Non-fatal CVD						
Lower	353/4335	1 (ref)	1 (ref)	309/4048	1 (ref)	1 (ref)
Middle	346/5140	0.72 (0.62-0.83)	0.80 (0.69-0.93)	327/4902	0.76 (0.65-0.89)	0.84 (0.71-0.98)
Upper	278/4985	0.47 (0.40-0.55)	0.57 (0.48-0.67)	341/5510	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		0.87 (0.84-0.89)	0.90 (0.87-0.93)		0.84 (0.80-0.88)	0.89 (0.85-0.93)

CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; MET, metabolic equivalent. * 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).

Table 3 Hazard Ratios for Disease-specific Mortality and Non-fatal CVD According to CRF Levels in Women

	Measured CRF			**Estimated CRF**		
	cases / n	Hazard Ratios (95% CI)		cases / n	Hazard Ratios (95% CI)	
		Model 1 *	Model 2 †		Model 1 *	Model 2 †
All-cause mortality						
Lower	109/3143	1 (ref)	1 (ref)	74/3048	1 (ref)	1 (ref)
Middle	66/3076	0.92 (0.68-1.25)	0.91 (0.67-1.24)	77/3049	0.83 (0.60-1.14)	0.82 (0.59-1.13)
Upper	41/2926	0.75 (0.52-1.07)	0.74 (0.52-1.07)	65/3048	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		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 mortality						
Lower	25/3143	1 (ref)	1 (ref)	21/3048	1 (ref)	1 (ref)
Middle	16/3076	1.05 (0.56-1.97)	1.08 (0.57-2.04)	15/3049	0.63 (0.32-1.22)	0.70 (0.35-1.37)
Upper	9/2926	0.80 (0.37-1.72)	0.89 (0.41-1.94)	14/3048	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		0.92 (0.78-1.09)	0.95 (0.81-1.13)		0.83 (0.63-1.08)	0.84 (0.64-1.12)
Non-fatal CVD						
Lower	42/1206	1 (ref)	1 (ref)	27/1024	1 (ref)	1 (ref)
Middle	15/1175	0.35 (0.19-0.63)	0.36 (0.20-0.66)	27/1239	0.64 (0.38-1.11)	0.73 (0.42-1.26)
Upper	15/1254	0.35 (0.19-0.63)	0.38 (0.21-0.69)	18/1372	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		0.75 (0.65-0.87)	0.77 (0.67-0.90)		0.69 (0.54-0.89)	0.76 (0.58-0.99)

CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; MET, metabolic equivalent. * 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).

Table 4 Discrimination Statistics of Measured CRF and Estimated CRF for Disease-specific Mortality and Non-fatal CVD

	Measured CRF			**Estimated CRF**		
	All-cause mortality	**CVD mortality**	**Non-fatal CVD**	**All-cause mortality**	**CVD mortality**	**Non-fatal CVD**
Men (n = 34,211)						
Cases	1,718	577	977 *	1,718	577	977 *
Area under the curve	0.67	0.72	0.62	0.63	0.68	0.61
(95% CI) †	(0.66-0.69)	(0.70-0.74)	(0.60-0.64)	(0.61-0.64)	(0.66-0.70)	(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 *
Area under the curve	0.70	0.74	0.71	0.64	0.73	0.68
(95% CI) †	(0.66-0.73)	(0.68-0.80)	(0.64-0.77)	(0.60-0.68)	(0.66-0.81)	(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 non-cases captured by combined middle and upper CRF groups.

Table 5 Area under the curve (AUC) for the modifiable constituent components of the non-exercise CRF algorithms (separately and clustered) and for estimated CRF

	AUC (95% CI)					
	Men (n = 34,211)			**Women** (n = 9,145)		
	All-cause mortality	**CVD mortality**	**Non-fatal CVD** *	**All-cause mortality**	**CVD mortality**	**Non-fatal 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).

Table 6 Reclassification of the Predicted Risk of All-cause Mortality in Men and Women on the basis of Estimated CRF vs. 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)						
Lower (highest risk)	487	132	23	468	250	12.7
Middle	232	230	95			
Upper	74	162	283			
Non-cases (n=32,493)						
Lower (highest risk)	6,758	3,406	596	6,886	6,760	-0.4
Middle	2,964	5,126	2,758			
Upper	814	3,108	6,963			
Net Reclassification improvement (NRI)			12.3 % (p<0.05)			
Women						
Cases (n=216)						
Lower (highest risk)	54	16	4	81	36	20.8
Middle	37	24	16			
Upper	18	26	21			
Non-cases (n=8,929)						
Lower (highest risk)	1,794	874	306	2,099	2,007	-1.0
Middle	868	1277	827			
Upper	372	859	1,752			
Net Reclassification improvement (NRI)			19.8 % (p<0.001)			

CRF, cardiorespiratory fitness.