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Prediction of Cardiovascular Mortality by Estimated Cardiorespiratory Fitness Independent of Traditional Risk Factors: The HUNT Study

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Abstract

Objective: To assess the predictive value of estimated cardiorespiratory fitness (eCRF) and evaluate the additional contribution of traditional risk factors in cardiovascular disease (CVD) mortality prediction.

Participants and Methods: The study included healthy men (n=18,721) and women (n=19,759) aged 30 to 74 years. A nonexercise algorithm estimated cardiorespiratory fitness. Cox proportional hazards models evaluated the primary (CVD mortality) and secondary (all-cause, ischemic heart disease, and stroke mortality) end points. The added predictive value of traditional CVD risk factors was evaluated using the Harrell C statistic and net reclassification improvement.

Results: After a median follow-up of 16.3 years (range, 0.04-17.4 years), there were 3863 deaths, including 1133 deaths from CVD (734 men and 399 women). Low eCRF was a strong predictor of CVD and all-cause mortality after adjusting for established risk factors. The C statistics for eCRF and CVD mortality were 0.848 (95% CI, 0.836-0.861) and 0.878 (95% CI, 0.862-0.894) for men and women, respectively, increasing to 0.851 (95% CI, 0.839-0.863) and 0.881 (95% CI, 0.865-0.897), respectively, when adding clinical variables. By adding clinical variables to eCRF, the net reclassification improvement of CVD mortality was 0.014 (95% CI, −0.023 to 0.051) and 0.052 (95% CI, −0.023 to 0.127) in men and women, respectively.

Conclusion: Low eCRF is independently associated with CVD and all-cause mortality. The inclusion of traditional clinical CVD risk factors added little to risk discrimination and did not improve the classification of risk beyond this simple eCRF measurement, which may be proposed as a practical and cost-effective first-line approach in primary prevention settings.

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Cardiorespiratory fitness (CRF) is a strong predictor of future cardiovascular (CV) health and reduced mortality,[1-4] but it is not routinely measured in clinical practice.[5] Several studies have found that low CRF is a stronger determinant of adverse CV disease (CVD) outcomes than traditional clinical risk factors.[4,6,7] Although documented to improve classification and discrimination of risk for CVD events beyond conventional risk factors,[6,8] it is not included in common risk algorithms, presumably because of the costly and time-consuming procedure of exercise testing that requires trained personnel and expensive equipment.

A simple estimation of CRF (eCRF) level, through nonexercise algorithms based on easily available clinical and self-reported variables, has been proposed as a promising alternative that overcomes the practical issues of directly measured CRF in health care settings.[6,9-11] An intriguing idea of eCRF algorithms is their utility in risk prevention settings, potentially serving as a practical and cost-effective tool to stratify risk of future CVD and identifying individuals in need of structured physical activity (PA) and medical and lifestyle interventions. Recent studies have documented significant associations between eCRF algorithms and a variety of outcomes, such as fatal and nonfatal CVD events

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and all-cause mortality,[6,12-14] reporting relative risks comparable to those obtained with directly measured CRF. Before broad implementation in clinical practice, however, these algorithms should be compared to the predictive value of traditional risk factors usually measured in primary care settings.

A recent study[15] concluded that lifestyle factors such as smoking, PA, diet, and alcohol consumption added little to risk models using clinical variables such as blood pressure (BP), cholesterol level, and family history of CVD in terms of predictive value. However, others have reported that CRF may improve risk stratification in persons assessed as being at high and low risk for CVD based on clinical risk algorithms.[16-18] Given the simplicity and cost-effectiveness, and the potential for preventing manifestation of traditional clinical risk factors, an evaluation of modifiable lifestyle factors, such as eCRF, may be a preferable first-line approach in risk stratification. To the best of our knowledge, no study has assessed the incremental predictive value of sets of traditional CVD risk factors above and beyond a simple eCRF. Hence, the aim of the present study was to investigate the independent predictive value of eCRF in CVD and all-cause mortality and further evaluate the added predictive value of traditional clinical and lifestyle risk factors in a large population of healthy men and women.

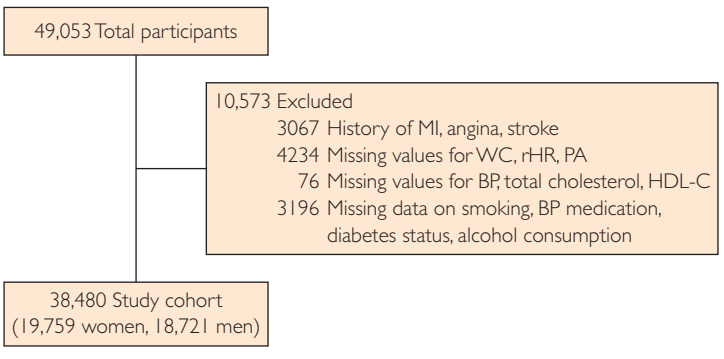

FIGURE. Participant flowchart. Participants in the Nord-Trøndelag Health Study who were 30 to 74 years old (n=49,053) were considered for this analysis; 10,573 were excluded for various reasons, leaving a study cohort of 38,480 participants. BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; PA = physical activity; rHR = resting heart rate; WC = waist circumference.

PARTICIPANTS AND METHODS

Study Population

Between August 1995 and June 1997, the entire adult population (≥20 years of age) in Nord-Trøndelag County in Norway was invited to participate in a large health survey (Nord-Trøndelag Health Study [HUNT] 2). Details about the HUNT study have been described elsewhere.[19]

Inclusion criteria for the present analysis were age 30 to 74 years (N=49,053) and no history of CVD (myocardial infarction, angina pectoris, or stroke) at baseline. A total of 3067 participants with these conditions were excluded. After further exclusions for missing data (N=7506), a total of 38,480 participants (19,759 women and 18,721 men) were included in the analyses (Figure).

Clinical Measures and Questionnaire-Based Information

The clinical examination included height, weight, BP, waist circumference (WC), and resting heart rate (rHR)[19]; BP and rHR were measured using a Dinamap 845XT (Critikon Inc). A self-administered questionnaire provided information about leisure time PA, smoking habits, diabetes status, alcohol consumption, and family history of CVD. Participants reported the intensity and duration of PA performed weekly. Based on responses to the PA questions, we divided the participants into 2 categories according to current recommendations: (1) vigorous-intensity exercise training for 20 or more minutes per day on 3 or more days per week for a total of 75 or more minutes per week and/or moderate-intensity exercise training for 30 or more minutes per day on 5 or more days per week (≥150 min/wk) or (2) not meeting the recommendations.[20]

The participants were asked about their usual intake of alcoholic beverages, indicated by their usual number of drinks over a typical 2-week period. We categorized participants into 4 groups (abstainer, 0 drinks, 1-4 drinks, or ≥5 drinks in 2 weeks). Family history of CVD was defined as MI or stroke in a first-degree relative (father, mother, siblings, or children) before the age of 60 years.

Estimated CRF

A nonexercise prediction model was used to estimate CRF (peak oxygen consumption).[11]

In the current model, PA at 2 levels (meeting or not meeting the current recommendations on average over the past year) was used. The sex-specific models consisted of age, WC, PA, and rHR. The following algorithms were used to predict each individual's eCRF.

$$\text{Women } (R^2, 0.52; \text{standard error of estimate, } 5.37):$$
$$78.00 - (0.297 \cdot \text{Age}) - (0.270 \cdot \text{WC}) - (0.110 \cdot rHR) + (2.674 \cdot \text{PA})$$

$$\text{Men } (R^2, 0.58; \text{standard error of estimate, } 5.88):$$
$$105.91 - (0.334 \cdot \text{Age}) - (0.402 \cdot \text{WC}) - (0.144 \cdot rHR) + (3.102 \cdot \text{PA})$$

where PA = 1 if following the current recommendations for PA or 0 if not. The participants were further classified into low, medium, and high groups of eCRF on the basis of age (10-year categories) and sex-specific tertiles of eCRF.[6] These eCRF algorithms were highly comparable to previously published nonexercise prediction algorithms, and the accuracy of our model is similar to that of other studies.[9-11,21]

Follow-up and Ascertainment of Outcomes

Our study had a virtually complete follow-up because of the unique 11-digit Norwegian person identification number that allows accurate matching to the National Cause of Death Register. The primary end point was CVD mortality (*International Classification of Diseases, Ninth Revision* and *Tenth Revision*); in addition, we assessed mortality from all causes, ischemic heart disease (IHD), and stroke.

The study was approved by the regional committee for medical research ethics, the Norwegian Data Inspectorate, and the National Directorate of Health. The study is in conformity with Norwegian laws and the Declaration of Helsinki.

Statistical Analyses

Baseline characteristics of participants were compared using analysis of variance and χ^2 tests. Cox proportional hazards regression analyses were used to assess the association between eCRF levels and CVD mortality, all-cause mortality, IHD mortality, and stroke mortality. The proportional hazards assumption was satisfied with the use of Schoenfeld residuals. The basic models were age adjusted by entering attained age as the time scale (model 1), while model 2 was adjusted for age and clinical variables: hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg), elevated total serum cholesterol (>6.9 mmol/L in participants 30-49 years and >7.8 mmol/L in participants ≥50 years),[22] and high-density lipoprotein cholesterol (HDL-C) (<1.0 mmol/L in men and <1.3 mmol/L in women). Model 3 was adjusted for age and disease status (use of BP medication, family history of CVD, diabetes status). Model 4 was adjusted for age and lifestyle risk factors (smoking status and alcohol consumption). Model 5 was adjusted for all of the previously listed covariates. In a sensitivity analysis, we excluded the first 3 years of follow-up to account for the possibility of unknown subclinical diseases that could influence the association between eCRF and mortality.

Harrell C statistics[23] assessed model discrimination (the ability of a marker to differentiate between individuals who did or did not die of CVD). We also calculated change in C statistics, integrated discrimination improvement (IDI), and relative IDI[24-27] after inclusion of various confounding factors together with eCRF. For example, we compared the C statistics of the eCRF model alone with a model that included both eCRF and clinical variables (hypertension, total cholesterol, and HDL-C). A reclassification table was generated to assess improvement in prediction performance when adding traditional risk factors to eCRF alone.[28,29] We chose risk categories with cut points at less than 5%, 5% to less than 10%, 10% to less than 20%, and 20% or greater for CVD death[30] for models with and without clinical variables, lifestyle factors, and disease status. We calculated net correct reclassification separately for those who died of CVD causes (events) and those who survived until the end of follow-up (nonevents), and the total net reclassification improvement (NRI) was calculated as

$$\widehat{\text{NRI}} = (\hat{\text{P}}\text{up, events} - \hat{\text{P}}\text{down, events}) + (\hat{\text{P}}\text{down, nonevents} - \hat{\text{P}}\text{up, nonevents})$$

where $\hat{\text{P}}$ is the proportion of participants moving up or down in terms of predicted risk category.[26] For testing the null hypothesis that NRI = 0 and IDI = 0, we used an asymptotic test as suggested by Pencina et al.[26] We constructed 95% CIs for NRI and IDI based

on 1000 bootstrap samples and performed a likelihood ratio test.[25,28]

Finally, we repeated the analyses using all-cause, IHD, and stroke mortality. The statistical analyses were conducted using Stata statistical software, version 13.1 (StataCorp) and RStudio, version 3.3.1 (R Foundation for Statistical Computing). All statistical tests were 2-sided, and $P<.05$ was considered significant.

RESULTS

Baseline characteristics of the study participants, stratified by sex and eCRF, are presented in Table 1. Participants with a lower level of age-relative eCRF had higher levels of most traditional CV risk factors at baseline.

Of a total of 3863 deaths, 1133 from CVD (734 men and 399 women) were registered during a median follow-up of 16.3 years (range, 0.04-17.4 years). Hazard ratios for CVD and all-cause mortality by tertiles of age-relative eCRF and per metabolic equivalent (MET) increase in eCRF are presented in Table 2; eCRF was inversely associated with the risk of CVD and all-cause mortality in both men and women. The age-adjusted risk reductions per MET increase were approximately 15% for all-cause (0.85; 95% CI, 0.83-0.87 and 0.87; 95% CI, 0.84-0.91 for men and women, respectively) and 20% for CVD mortality (0.78; 95% CI, 0.75-0.82 and 0.77; 95% CI, 0.71-0.83 for men and women, respectively). These estimates were only slightly attenuated after adjustment for traditional clinical risk factors, lifestyle factors, and disease status (0.82; 95% CI, 0.78-0.87 in men, and 0.85; 95% CI, 0.78-0.92 in women, respectively, for CVD mortality). The association between eCRF and CVD and all-cause mortality was dose dependent across tertiles of eCRF for both sexes and had similar patterns for the secondary outcomes of IHD

TABLE 1. Baseline Characteristics of the 38,480 Study Participants, Stratified by Sex and Estimated CRF Level[a,b]

Characteristic	Men (N=18,721)			Women (N=19,759)		
	Low CRF level (n=6163)	Medium CRF level (n=6267)	High CRF level (n=6291)	Low CRF level (n=6470)	Medium CRF level (n=6579)	High CRF level (n=6710)
Age (y)	49.2 (11.5)	48.5 (11.4)	47.6 (11.2)[c]	49.1 (11.5)	48.3 (11.4)	47.2 (11.0)[c]
Body mass index (kg/m^2)	29.1 (3.5)	26.3 (2.5)	24.4 (2.3)[c]	29.6 (4.8)	25.4 (3.1)	23.4 (2.6)[c]
Waist circumference (cm)	99.9 (8.0)	91.3 (5.1)	84.9 (5.4)[c]	91.1 (10.6)	79.3 (6.8)	72.6 (5.7)[c]
Resting heart rate (bpm)	78.4 (12.4)	70.6 (10.2)	63.9 (9.5)[c]	80.6 (12.9)	74.7 (10.7)	69.2 (9.6)[c]
Blood pressure (mm Hg)						
Systolic	142.5 (18.1)	138.3 (16.9)	134.5 (16.2)[c]	138.2 (21.5)	131.5 (19.9)	126.6 (18.3)[c]
Diastolic	86.4 (11.1)	82.9 (10.6)	79.4 (10.2)[c]	82.3 (11.8)	78.4 (10.7)	75.2 (10.2)[c]
Hypertension	3521 (57.1)	2816 (44.9)	2124 (33.8)[c]	2885 (44.6)	2004 (30.5)	1442 (21.5)[c]
Total cholesterol (mmol/L)	6.1 (1.1)	5.9 (1.1)	5.7 (1.0)[c]	6.1 (1.2)	5.9 (1.2)	5.7 (1.2)[c]
High total cholesterol	798 (12.9)	657 (10.5)	403 (6.4)[c]	900 (13.9)	650 (9.9)	468 (7.0)[c]
HDL-C (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.4 (0.3)[c]	1.4 (0.4)	1.5 (0.4)	1.6 (0.4)[c]
Low HDL-C	1561 (25.3)	1017 (16.2)	608 (9.7)[c]	2432 (37.6)	1550 (23.6)	965 (14.4)[c]
CRF (peak oxygen consumption, mL/kg/min)	39.1 (5.5)	44.7 (4.5)	49.3 (4.7)[c]	30.7 (5.0)	35.3 (4.3)	38.9 (4.2)[c]
CRF (METs)	11.2 (1.6)	12.8 (1.3)	14.1 (1.3)[c]	8.8 (1.4)	10.1 (1.2)	11.1 (1.2)[c]
Recommended PA	2111 (34.3)	3777 (60.3)	5385 (85.6)[c]	1672 (25.8)	3241 (49.3)	5468 (81.5)[c]
Current smoker	1922 (31.2)	1985 (31.7)	1728 (27.5)[c]	2242 (34.7)	2215 (33.7)	2128 (31.7)[d]
Diabetes mellitus	180 (2.9)	127 (2.0)	68 (1.1)[c]	186 (2.9)	80 (1.2)	43 (0.6)[c]
Blood pressure medication	801 (13.0)	503 (8.0)	319 (5.1)[c]	1002 (15.5)	557 (8.5)	385 (5.7)[c]
Family history of CVD	1797 (29.2)	1800 (28.7)	1811 (28.8)	2181 (33.7)	2245 (34.1)	2040 (30.4)[c]
Alcohol consumption[e]	317 (5.1)	401 (6.4)	421 (6.7)	85 (1.3)	131 (2.0)	202 (3.0)[c]

[a]bpm = beats per minute; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; HLD-C = high-density lipoprotein cholesterol; MET = metabolic equivalent; PA = physical activity.

[b]Values are presented as mean (SD) or No. (percentage) of participants. Analysis of variance or χ^2 tests were used to test the difference between groups in each sex.

[c]$P<.001$.

[d]$P<.05$.

[e]Consumption of 5 or more alcoholic drinks over a typical 2-week period.

TABLE 2. Hazard Ratios (95% CIs) for All-Cause and Cardiovascular Disease Mortality[a]

Estimated CRF[b]	Deaths (No.)	Model 1[c]	Model 2[d]	Model 3[e]	Model 4[f]	Model 5[g]
All-cause mortality						
Men						
High	559	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Medium	767	1.26 (1.13-1.41)	1.23 (1.10-1.37)	1.25 (1.12-1.39)	1.25 (1.12-1.39)	1.20 (1.07-1.34)
Low	976	1.58 (1.43-1.76)	1.50 (1.35-1.67)	1.53 (1.37-1.70)	1.60 (1.45-1.78)	1.47 (1.32-1.64)
P for trend		<.001	<.001	<.001	<.001	<.001
Per 1 MET		0.85 (0.83-0.87)	0.86 (0.84-0.88)	0.86 (0.83-0.88)	0.85 (0.82-0.87)	0.87 (0.84-0.90)
Women						
High	390	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Medium	486	1.07 (0.94-1.22)	1.06 (0.93-1.21)	1.05 (0.92-1.20)	1.08 (0.94-1.23)	1.06 (0.92-1.21)
Low	685	1.44 (1.27-1.64)	1.41 (1.23-1.60)	1.36 (1.20-1.55)	1.47 (1.30-1.67)	1.37 (1.20-1.57)
P for trend		<.001	<.001	<.001	<.001	<.001
Per 1 MET		0.87 (0.84-0.91)	0.88 (0.84-0.92)	0.90 (0.86-0.94)	0.86 (0.83-0.90)	0.89 (0.86-0.93)
Cardiovascular disease mortality						
Men						
High	155	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Medium	236	1.30 (1.13-1.70)	1.30 (1.06-1.59)	1.34 (1.09-1.64)	1.36 (1.11-1.67)	1.25 (1.02-1.54)
Low	343	1.97 (1.63-2.38)	1.76 (1.45-2.14)	1.80 (1.48-2.19)	2.01 (1.66-2.43)	1.67 (1.37-2.03)
P for trend		<.001	<.001	<.001	<.001	<.001
Per 1 MET		0.78 (0.75-0.82)	0.80 (0.77-0.84)	0.80 (0.77-0.84)	0.78 (0.75-0.82)	0.82 (0.78-0.87)
Women						
High	79	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Medium	114	1.15 (0.86-1.53)	1.07 (0.80-1.43)	1.08 (0.81-1.44)	1.16 (0.87-1.55)	1.05 (0.78-1.40)
Low	206	1.94 (1.49-2.52)	1.65 (1.26-2.17)	1.65 (1.27-2.16)	1.99 (1.53-2.60)	1.55 (1.18-2.03)
P for trend		<.001	<.001	<.001	<.001	<.001
Per 1 MET		0.77 (0.71-0.83)	0.81 (0.75-0.89)	0.83 (0.76-0.90)	0.76 (0.70-0.83)	0.85 (0.78-0.92)

[a]CRF = cardiorespiratory fitness; MET = metabolic equivalent.
[b]Low, medium, and high estimated CRF were defined as tertiles of age-specific categories.
[c]Model 1: Adjusted for age by including the attained age as the time scale.
[d]Model 2: Adjusted for age and clinical variables (hypertension, total cholesterol, high-density lipoprotein cholesterol).
[e]Model 3: Adjusted for age and disease status (use of blood pressure medication, family history of cardiovascular disease, diabetes status).
[f]Model 4: Adjusted for age and lifestyle factors (smoking status, alcohol consumption).
[g]Model 5: Adjusted for age and all other risk factors.

and stroke mortality (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). The results were not substantially altered when we excluded the first 3 years of follow-up (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

The Harrell C statistics for eCRF and CVD mortality were 0.848 (95% CI, 0.836-0.861) and 0.878 (95% CI, 0.862-0.894) for men and women, respectively (Table 3). Lifestyle factors (smoking status and alcohol consumption) were associated with a difference in C statistic of 1% to 2% (0.862; 95% CI, 0.850-0.874 and 0.887; 95% CI, 0.872-0.902 for men and women, respectively), while addition of clinical variables to eCRF was associated with a difference in C statistic of 0.3% (0.851, 95% CI: 0.839-0.863) and 0.3% (0.881; 95% CI, 0.865-0.897) for men and women, respectively, and the addition of disease status to eCRF was associated with a difference in C statistic of 0.3% (0.851; 95% CI, 0.839-0.864) and 0.5% (0.883; 95% CI, 0.868-0.899) for men and women, respectively.

The changes in C statistic for secondary outcomes of IHD and stroke mortality are presented in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org). The addition of lifestyle factors (ie, smoking status and alcohol consumption) to eCRF was associated with a difference in C statistics of 2.3% ($P<.001$) and 1.3% ($P=.02$) when predicting IHD in men and women, respectively, and a difference of 0.5% ($P=.01$) with the addition of clinical variables and 0.7% ($P=.001$) with the addition of disease status when predicting IHD in men.

TABLE 3. C Statistics (95% CIs) for the Estimated CRF Algorithm With Addition of Traditional Risk Factors[a]

Variable	Men				Women			
	All-cause mortality[b]	Change in C statistic	CVD mortality[b]	Change in C statistic	All-cause mortality[b]	Change in C statistic	CVD mortality[b]	Change in C statistic
eCRF	0.812 (0.804-0.821)	NA	0.848 (0.836-0.861)	NA	0.798 (0.787-0.809)	NA	0.878 (0.862-0.894)	NA
eCRF + clinical variables[c]	0.813 (0.805-0.821)	0.001 (0.000-0.001)	0.851 (0.839-0.863)	0.003 (0.001-0.005)	0.798 (0.787-0.809)	0.0001 (−0.000 to 0.000)	0.881 (0.865-0.897)	0.003 (−0.000 to 0.006)
eCRF + lifestyle factors[d]	0.824 (0.816-0.832)	0.012 (0.009-0.014)	0.862 (0.850-0.874)	0.014 (0.010-0.018)	0.810 (0.799-0.820)	0.012 (0.008-0.015)	0.887 (0.872-0.902)	0.009 (0.005-0.014)
eCRF + disease status[e]	0.814 (0.805-0.822)	0.001 (0.000-0.002)	0.851 (0.839-0.864)	0.003 (0.001-0.005)	0.800 (0.789-0.810)	0.002 (0.000-0.003)	0.883 (0.868-0.899)	0.005 (0.002-0.010)
eCRF + all risk factors[f]	0.826 (0.818-0.834)	0.013 (0.011-0.016)	0.867 (0.855-0.879)	0.019 (0.014-0.024)	0.812 (0.802-0.822)	0.014 (0.010-0.018)	0.895 (0.881-0.910)	0.017 (0.011-0.023)

[a]CRF = cardiorespiratory fitness; CVD = cardiovascular disease; eCRF = estimated CRF; NA = not applicable.
[b]Adjusted for age.
[c]Hypertension, total cholesterol, high-density lipoprotein cholesterol.
[d]Smoking status, alcohol consumption.
[e]Disease status (use of blood pressure medication, family history of cardiovascular disease, diabetes status).
[f]Clinical variables, lifestyle factors, and disease status.

Classification of CVD mortality with the use of eCRF alone and with the addition of traditional clinical risk factors are presented in Table 4. Only 2.6% and 6.8% of men and women with CVD mortality, respectively, were correctly reclassified to a higher risk category, and among those who survived, the enhanced model with clinical risk factors incorrectly classified more people to a higher risk category than to a lower risk category, giving a net correct classification of nonevents of −1.2% and −1.6% in men and women, respectively, and a total NRI of 0.014 (95% CI, −0.023 to 0.051) and 0.052 (−0.023 to 0.127). The IDI was 0.002 (95% CI, 0.001-0.004) and 0.004 (95% CI, 0.001-0.008) for men and women, respectively, and the relative IDI was estimated at 0.028 (95% CI, −0.003 to 0.059) and 0.073 (95% CI, 0.006-0.140). We observed net correct reclassifications of 7.9% among men with CVD death and 0.1% among those without CVD death after adding lifestyle factors (smoking status and alcohol intake) to eCRF, and NRI was estimated at 0.080 (95% CI, 0.031-0.129). The relative IDI was estimated at 0.152 (95% CI, 0.074-0.230). Among women, the addition of lifestyle factors had a negligible effect on reclassification of those with and without CVD death, resulting in an overall nonsignificant NRI of 0.029 (95% CI, −0.020 to 0.078; P=.202) and a relative IDI of 0.060 (−0.007 to 0.127) (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org). The addition of disease status to eCRF correctly reclassified 8.8% of women with CVD death with almost no net reclassification among survivors (0.04%) (total NRI, 0.088; 95% CI, 0.031-0.145), whereas in men, there was almost no net reclassification among either those with CVD death (1.5%) or survivors (0.5%) (total NRI, 0.020; 95% CI, −0.015 to 0.055). The relative IDIs were estimated at 0.085 (95% CI, 0.018-0.152) for men and 0.224 (95% CI, 0.087-0.361) for women (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this prospective study of apparently healthy men and women, we found that eCRF was a strong independent predictor of future CVD mortality independent of traditional CVD risk factors. Furthermore, traditional risk

TABLE 4. Reclassification of Risk of Cardiovascular Disease Mortality After Addition of Clinical Variables to Estimated Cardiorespiratory Fitness[a,b]

	Estimated fitness + clinical variables[c]							
Estimated CRF	<5%	5%-<10%	10%-<20%	≥20%	Total	Classified as higher risk	Classified as lower risk	Net correctly reclassified
Men								
CVD death						81 (11.0)	62 (8.4)	2.6%
<5%	219	41	0	0	260 (35.4)			
5%-<10%	38	175	27		240 (32.7)			
10%-<20%	0	14	109	13	136 (18.5)			
≥20%	0	0	10	88	98 (13.4)			
Total	257 (35.0)	230 (31.3)	146 (19.9)	101 (13.8)	734 (100.0)			
Without CVD death						917 (5.1)	699 (3.9)	−1.2%
<5%	13,612	591	0	0	14,203 (79.0)			
5%-<10%	501	1733	283	0	2517 (14.0)			
10%-<20%	0	163	775	43	981 (5.5)			
≥20%	0	0	35	251	286 (1.6)			
Total	14,113 (78.5)	2487 (13.8)	1093 (6.1)	294 (1.6)	17,987 (100.0)			
						NRI	0.014 (−0.023 to 0.051)[d]	
						IDI	0.002 (0.001 to 0.004)[d]	
						Relative IDI	0.028 (−0.003 to 0.059)[d]	
						P for LR test	<.001	
Women								
CVD death						55 (13.8)	28 (7.0)	6.8%
<5%	177	34	0	0	211 (52.9)			
5%-<10%	16	68	16	0	100 (25.1)			
10%-<20%	0	10	56	5	71 (17.8)			
≥20%	0	0	2	15	17 (4.3)			
Total	193 (48.4)	112 (28.1)	74 (18.5)	20 (5.0)	399 (100.1)			
Without CVD death						711 (3.7)	398 (2.1)	−1.6%
<5%	17,137	545	0	0	17,682 (91.3)			
5%-<10%	293	715	152	0	1160 (6.0)			
10%-20%	0	87	298	14	399 (2.1)			
≥20%	0	0	18	101	119 (0.6)			
Total	17,430 (90.0)	1347 (7.0)	468 (2.4)	115 (0.6)	19,360 (100.0)			
						NRI	0.052 (−0.023 to 0.127)[d]	
						IDI	0.004 (0.001 to 0.008)[d]	
						Relative IDI	0.073 (0.006 to 0.140)[d]	
						P for LR test	<.001	

[a]CRF = cardiorespiratory fitness; CVD = cardiovascular disease; IDI = integrated discrimination improvement; LR = likelihood ratio; NRI = net reclassification improvement.

[b]Data are presented as No. (percentage) of participants unless indicated otherwise. Percentages may not total 100 because of rounding.

[c]Total cholesterol, high-density lipoprotein cholesterol, hypertension.

[d]Bootstrapped 95% CI.

factors for CVD did not considerably improve the clinically relevant measures of discrimination and reclassification of CVD death when added to the eCRF.

This is the first major study to fully assess the contribution of various risk factors to eCRF in CVD risk classification. Previous studies have reported that the addition of eCRF[6,14] or CRF measured from exercise testing[6,8,31] to the established risk factors significantly improved the discrimination and reclassification of risk of CVD death and all-cause mortality. Our study found small improvements in disease risk discrimination and reclassification when traditional CVD risk factors were added to eCRF, thus extending prior observations that CRF may be the most powerful predictor of CV health and mortality.[4,7,18]

Traditional clinical variables (BP, total cholesterol, and HDL-C) have long been established as independent CVD risk factors and provide excellent discrimination of CVD death.[8,32-34] In clinical practice, these risk factors are among the key variables included in CVD risk prediction algorithms and are widely used to guide decision making in pharmacological treatment.[30,35,36] In our study, the addition of these clinical variables to eCRF correctly reclassified 13.8% of cases among women into a higher risk category but incorrectly reclassified 7.0% of cases into a lower risk category, with a net correct classification of 6.8% among women with CVD death. Among men, 11% of the cases were correctly reclassified to a higher risk category but 8.4% were incorrectly reclassified to a lower risk category, with a net gain in reclassification proportion of 2.6%. The addition of clinical variables reclassified only 0.4% more cases into the 20% or higher risk category. Furthermore, adding clinical variables to eCRF did not improve net classification of nonevents for either sex; actually, a larger proportion of survivors were incorrectly reclassified to a higher risk category. Therefore, the total NRIs suggest that the addition of clinical variables did not improve the risk reclassification in both men and women. Importantly, the clinical risk factors included may also be on the causal pathway from CRF to CVD, further highlighting the importance of intervening on the CRF level in both primordial and primary prevention of CVD.

Family history of CVD, history of diabetes mellitus, and taking BP medications are integral components of various risk prediction algorithms and are included in the guidelines of the American College of Cardiology/American Heart Association on the assessment of CVD risk.[30] Our findings suggest that the addition of these variables provided a minimal improvement in discrimination of risk and did not improve risk classification of CVD death in men. Nonetheless, the addition of diabetes status, family history of CVD, and taking BP medication improved the discrimination and reclassification of CVD events among women, emphasizing the importance of these variables together with eCRF in risk prevention settings.

Lifestyle risk factors have important effects on CVD risk and are also part of the American Heart Association's 2020 goals for CVD reduction.[34] Our findings among women are consistent with those from previous reports[15] documenting the negligible effects of smoking status and alcohol intake on the reclassification of CVD risk. However, the addition of alcohol consumption and smoking status to eCRF improved the risk discrimination and reclassification among men in our study, suggesting the importance of including smoking status and alcohol use in the risk prediction algorithm.

We observed 18% and 15% lower risk of CVD death in men and women, respectively, associated with each 1-MET (approximately 3.5 mL/kg per min) higher eCRF. Our findings of strong and independent increases in risk of death from all causes and CVD associated with low eCRF are in line with the results of previous studies making use of eCRF algorithms to predict cause-specific outcomes.[6,13]

The main strengths of the present study are the relatively large sample of men and women, detailed information on a broad range of traditional CVD risk factors, and ascertainment of different major outcomes in a prospective design. The use of discrimination statistics and reclassification across relevant risk thresholds adds clinical relevance to previous association studies of eCRF and premature death. A recent study comparing the prediction performance for CVD events with measured CRF by exercise testing and an eCRF algorithm reported only slight increases in discrimination and reclassification statistics

when adding exercise-tested CRF to the more simple eCRF, providing further evidence for these algorithms as valid surrogate measures of CRF.[6] The proposed method of eCRF is also convenient, practical, cost-effective, and easy to implement in large-scale primary prevention programs.

The use of self-reported PA may be considered a limitation of our study because of the potential for misclassification. However, in prospective studies, the nature of the misclassification is most likely nondifferential in relationship to future disease and therefore likely to yield underestimates of the true effects. Further, available objective measurement methods for PA (ie, accelerometers) would be less practical in health care settings. The HUNT study population is ethnically homogeneous and predominantly white, and thus the generalizability of our data in an ethnically diverse population is limited. Therefore, the validation and refinement of the eCRF algorithm in other cohorts are needed to consolidate external generalizability. Furthermore, we recognize that eCRF and other CVD risk factors may have changed during our follow-up period. Nonetheless, this may be a potential strength of our study, emphasizing that a single measure of eCRF at baseline maintains its effect on the reclassification of CVD death at long-term follow-up.[8]

CONCLUSION

Our findings suggest that assessments of nonexercise eCRF together with easily assessed measures such as smoking status, alcohol consumption, and disease status may have a major impact in the identification of individuals at risk of future CVD. Although we recognize that clinical variables such as BP and lipids are key causal factors for CVD mortality, our study found trivial improvements in CVD risk discrimination and reclassification. Therefore, particularly in an era of widespread application of electronic health records and emphasis on primary prevention of IHD/CVD, determining CRF by eCRF may be a simple, practical, and cost-effective method[6,9] that also aids in predicting long-term CVD risk in populations and individual patients. These results might also be useful for effective risk communication between clinicians and patients to highlight the general and specific health benefits of CRF.

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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: **BP** = blood pressure; **CRF** = cardiorespiratory fitness; **CV** = cardiovascular; **CVD** = CV disease; **eCRF** = estimated CRF; **HDL-C** = high-density lipoprotein cholesterol; **HUNT** = Nord-Trøndelag Health Study; **IDI** = integrated discrimination improvement; **IHD** = ischemic heart disease; **MET** = metabolic equivalent; **NRI** = net reclassification improvement; **PA** = physical activity; **rHR** = resting heart rate; **WC** = waist circumference

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