Prediction of 30-Year Risk for Cardiovascular Mortality by Fitness and Risk Factor Levels
The Cooper Center Longitudinal Study

Chanaka D. Wickramasinghe, MD; Colby R. Ayers, MS; Sandeep Das, MD, MPH; James A. de Lemos, MD; Benjamin L. Willis, MD, MPH; Jarett D. Berry, MD, MS

Background—Fitness and traditional risk factors have well-known associations with cardiovascular disease (CVD) death in both short-term (10 years) and across the remaining lifespan. However, currently available short-term and long-term risk prediction tools do not incorporate measured fitness.

Methods and Results—We included 16,533 participants from the Cooper Center Longitudinal Study (CCLS) without prior CVD. Fitness was measured using the Balke protocol. Sex-specific fitness levels were derived from the Balke treadmill times and categorized into low, intermediate, and high fit according to age- and sex-specific treadmill times. Sex-specific 30-year risk estimates for CVD death adjusted for competing risk of non-CVD death were estimated using the cause-specific hazards model and included age, body mass index, systolic blood pressure, fitness, diabetes mellitus, total cholesterol, and smoking. During a median follow-up period of 28 years, there were 1123 CVD deaths. The 30-year risk estimates for CVD mortality derived from the cause-specific hazards model demonstrated overall good calibration (Nam-D’Agostino χ² [men, P=0.286; women, P=0.664] and discrimination (c statistic; men, 0.81 [0.80–0.82] and women, 0.86 [0.82–0.91]). Across all risk factor strata, the presence of low fitness was associated with a greater 30-year risk for CVD death.

Conclusions—Fitness represents an important additional covariate in 30-year risk prediction functions that may serve as a useful tool in clinical practice. (Circ Cardiovasc Qual Outcomes. 2014;7:597-602.)

Key Words: cardiovascular diseases • mortality • risk factors

It is now well established that short-term (10-year) risk prediction of cardiovascular disease (CVD) mortality is not representative of an individual’s lifetime risk for CVD.1-4 This observation has prompted recommendations from clinical prevention guidelines to consider long-term risk prediction equations as an adjunct to currently available short-term risk equations.5-7 However, to our knowledge, long-term risk prediction tools that incorporate traditional risk factors are not widely available for clinical use. Furthermore, there are no long-term risk prediction tools available that incorporate measured cardiorespiratory fitness, a powerful but under-recognized risk marker for CVD.

Fitness measured by graded exercise testing provides an objective assessment of prior physical activity and is robustly associated with long-term cardiovascular risk.8,9 Recently, we observed that a single measure of low fitness is associated with a consistent increase in CVD death risk across short-, intermediate-, and long-term follow-up.9 In addition, we also observed that a single measure of fitness was associated with marked differences in the lifetime risk for CVD death in men across multiple risk factor categories.8 Therefore, the purpose of our study was to construct a clinically useful 30-year risk prediction tool that included fitness and traditional risk factors to estimate long-term risk for CVD death in both men and women using a well-characterized cohort from the Cooper Center Longitudinal Study (CCLS).

Methods

Cohort

We enrolled participants from the CCLS, which is an ongoing prospective study at the Cooper Clinic in Dallas, TX.10,11 For this particular study, we included all participants between 20 and 90 years of age with a complete clinical examination at the Cooper Clinic enrolled before 1981 with ≥25 years of follow-up (n=17,272). These individuals were either self-referred or were referred by their employer or personal physician. We excluded participants with a prior history of myocardial infarction (n=739), resulting in a final cohort of 16,533 individuals. The majority of study participants were white, well educated, and from middle to upper socioeconomic strata. Informed consent for clinical examination and follow-up was obtained, and the study was reviewed and approved annually by the institutional review board of the Cooper Institute and the University of Texas Southwestern Medical Center.

Participants underwent a clinical examination at the Cooper Clinic that included a standardized physical examination by the physician,
WHAT IS KNOWN

• It is now well established that short-term (ie, 10-year) risk for cardiovascular disease (CVD) may not reflect the impact of risk factor burden on lifetime risk for CVD, especially in younger individuals with high risk factor burden.

• In addition, several previous studies have demonstrated a consistent, inverse association between cardiorespiratory fitness and CVD mortality in people with and without prevalent CVD at baseline.

• Despite the robust association between cardiorespiratory fitness and CVD mortality, there are no long-term risk prediction tools available that incorporate measured cardiorespiratory fitness, a powerful but under-recognized risk marker for CVD.

WHAT THE STUDY ADDS

• In our current study, we have constructed a clinically useful, sex-specific 30-year risk estimator that incorporates both traditional risk factors and fitness levels.

Fasting blood cholesterol, triglyceride, glucose levels, and a maximal treadmill exercise test. Personal history was self-reported, and smoking status was obtained from a standardized questionnaire. Details of the clinical examination and the study cohort have been previously described.10–12

Fitness Measurement

Fitness was measured by a maximal treadmill exercise test using the Balke protocol.10–12 In the Balke protocol, the treadmill speed is initially set at 88 m/min. In the first minute, grade is set at 0% followed by 2% in the second minute. Thereafter, the grade is increased by 1% every minute. The grade remains the same after 25 minutes, but the speed is increased 5.4 m/min for each additional minute until the test is terminated. Participants were encouraged to exert maximal effort and not to hold onto the railing. The test was terminated by participant-reported exhaustion or by the supervising physician for medical reasons. The test times using this protocol correlate highly with directly measured maximal oxygen uptake (r=0.92) and allow for estimation of fitness level in metabolic equivalents (METs).1,3

Each participant’s exercise time can be classified into age- and sex-specific fitness levels by comparing with age- and sex-specific normative data on treadmill performance within the CCLS. For the present study, all models were constructed using continuous measures of fitness in METs. For the purpose of presentation, we report selected, sex-specific fitness thresholds for 50-year-olds in the CCLS, corresponding to low, intermediate, and high fitness in men (8, 10, and 12 METs, respectively) and women (6, 8, and 10 METs, respectively). In the present study, no individual was excluded on the basis of performance on the exercise treadmill portion of the examination.

Mortality Surveillance

Participants were followed from the date of initial complete clinical examination until death or end of follow-up on December 31, 2006. Before the development of the National Death Index in 1979, follow-up was completed by direct mail, telephone, contact with employer, and matching of records with social security administration files. After 1979, all-cause mortality and deaths because of CVD (indicated by International Classification of Disease, Ninth Revision codes 390.0–458.9 or equivalent codes from International Classification of Disease, Eighth Revision or International Classification of Disease, Tenth Revision) were included in the primary analysis. Additional details on follow-up of the CCLS cohort have been described previously.10–12

Statistical Analysis

We assessed the association between both traditional risk factors (age [per 10 years], diabetes mellitus [yes/no], systolic blood pressure [per 20 mmHg], total cholesterol [per 40 mg/dL], body mass index [per 3 kg/m²], and smoking [yes/no]) and fitness (per standard deviation) on long-term (30-year) risk for CVD death in both men and women using the cause-specific hazards model.14 Details of this method have been described previously.14 Additional sensitivity analysis was performed after including high-density lipoprotein and adjusting for fitness (n=6420).

Briefly, we used standard Cox regression to estimate the association between measured baseline covariates and CVD death separately for men and women. Similarly, a separate Cox regression model was used to estimate the association between measured baseline covariates and non-CVD death (ie, the competing cause of death). Estimated survival functions were obtained separately from the standard Cox model for both CVD and non-CVD mortality and were used to estimate overall survival as follows: $S(t_{i−1})=S_{CVD}(t_{i−1})\times S_{non-CVD}(t_{i−1})$, where $S(t_{i−1})$ is the overall survival probability at event time $t_{i−1}$, $S_{CVD}(t_{i−1})$ is the survival probability for CVD death at event time $t_{i−1}$, and $S_{non-CVD}(t_{i−1})$ is the survival probability for non-CVD death at event time $t_{i−1}$. The 30-year cumulative incidence of CVD death adjusted for competing risk was then estimated as $I_{CVD}(30)=\sum S_{CVD}(t_{i−1})\times S(t_{i−1})$, where $I_{CVD}(30)$ is the cumulative incidence function at 30 years for CVD death, $S_{CVD}(t_{i−1})$ is the hazard function of CVD death at event time $t_{i−1}$, and $S(t_{i−1})$ is the overall survival probability at event time $t_{i−1}$. The assumptions of the Cox proportional hazard model were verified by ensuring that the Schoenfeld residuals for each of the covariates included in the model had no significant association with study time.

To assess model performance, we constructed time-dependent receiver operating characteristic curves to calculate the Harrell C statistic.15–17 Calibration of our model was assessed with the Hosmer–Lemeshow (Nam-D’Agostino $\chi^2$) test by comparing the risk estimates from our model (cause-specific model) with risk estimates created from a modified Kaplan–Meier method as proposed by Gaynor et al.18 In addition, we performed 10-fold cross-validation in sex-specific cohorts to account for the fact that we assessed model performance on the same data on which it was developed, demonstrating overall good calibration (Nam-D’Agostino $\chi^2$ [men, $P=0.140$; women, $P=0.100$]).

Finally, a risk score calculator was constructed in Microsoft Excel to create a clinically useful, sex-specific 30-year risk estimator that incorporates both traditional risk factors and fitness levels. This risk calculator is now available for clinical use at www.lifetimerisk.org. All statistical analyses were performed using SAS, version 9.3 for Windows.

Results

The CCLS represents a low-risk cohort with higher levels of traditional risk factors in men compared with women (Table 1). After >400,000 person-years of follow-up (median, 28 [26–31] years), there were 1123 CVD deaths and 1970 non-CVD deaths. The hazard ratios with 95% confidence intervals for traditional risk factors and fitness are shown in Table 2. As expected, higher levels of traditional risk factors were associated with an increased risk for CVD mortality in both men and women, with expected sex differences for both diabetes mellitus and smoking. In sensitivity analyses among participants with measured high-density lipoprotein (n=6420), we observed that the contribution of
Table 1. Characteristics of Cohort in the Cooper Center Longitudinal Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=13627)</th>
<th>Women (n=2906)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.7±9.5</td>
<td>41.5±10.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.3±14.2</td>
<td>113.7±14.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81±9.8</td>
<td>75.6±9.6</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>213±38.7</td>
<td>201±37.6</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>6.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>23</td>
<td>15.2</td>
</tr>
<tr>
<td>Fitness level (METs)</td>
<td>10.9±2.3</td>
<td>8.6±1.9</td>
</tr>
<tr>
<td>CVD deaths, n</td>
<td>1027</td>
<td>96</td>
</tr>
<tr>
<td>All-cause deaths, n</td>
<td>2745</td>
<td>348</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>27.6±5.5</td>
<td>28±4.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9±3.5</td>
<td>22.2±3.5</td>
</tr>
</tbody>
</table>

Data are represented as mean±SD for continuous variables and percentages for categorical variables. BMI indicates body mass index; CVD, cardiovascular disease; and METs, metabolic equivalents.

With the aid of a novel analytic approach, we have constructed a 30-year risk prediction function for CVD death in both men and women using a multivariable risk prediction model that includes measured physical fitness and other traditional risk factors and accounts for competing risk. This 30-year risk model is now available for clinical use at www.lifetimerisk.org. In addition, this model allows for the extension of our prior work to include both men and women across all age and risk factor categories.

We and others have shown that short-term (ie, 10-year) risk for CVD may not reflect the impact of risk factor burden on lifetime risk for CVD, especially in younger individuals with high risk factor burden.1-4,8,14,19,20 This discordance between short-term and lifetime risk reflects the dominant effect of age in 10-year risk equations.1-4,8,14,19,20 To address this limitation and promote more effective risk communication, current national guidelines for primary prevention suggest consideration of long-term risk for CVD as an adjunct to short-term risk prediction functions.5-7 Several previous studies have described the association between levels of fitness and the risk for CVD mortality, demonstrating a consistent, inverse association between fitness and mortality in people with and without prevalent CVD at baseline.3,4,21-23 In our prior work, we observed that low fitness in midlife in men was associated with a much greater difference in 30-year risk for CVD mortality compared with participants with high fitness levels (18.4% versus 10.1%), despite similar risks at 10 years (2.3% versus 1.2%; Figure 2A). Similar findings were observed in women across all risk factor subgroups. For example, among women with diabetes mellitus, low fitness was associated with a greater 30-year risk for CVD death compared with high fitness (11.4% versus 5.4%), despite similar risk at 10 years (0.8% versus 0.35%; Figure 2B).

Finally, in an effort to create a clinically useful risk prediction tool to estimate the association between fitness and long-term CVD risk, we created a risk estimator that can be used to calculate 30-year risks for CVD mortality using data easily obtained in the clinical setting (www.lifetimerisk.org). Using the risk calculator, we were able to estimate the association between fitness (in METs) and long-term CVD risk, demonstrating the importance of fitness across multiple risk factor categories. For example, a 55-year-old nonsmoking woman with a fitness level of 6 METs, diabetes mellitus, total cholesterol of 240 mg/dL, body mass index of 25 kg/m², and a systolic blood pressure of 160 mm Hg has a 30-year risk for CVD death of 25.6%, which is reduced to 13% in the presence of higher fitness (METs 10). Similar findings were observed in men across all levels of risk factor strata (Figure 3).

Discussion

Table 2. Hazard Ratios With 95% Confidence Intervals for 30-Year Risk for Cardiovascular Disease Death in Men and Women

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 y)</td>
<td>2.22 (2.06–2.38)</td>
<td>3.10 (2.44–3.94)</td>
</tr>
<tr>
<td>SBP (per 20 mmHg)</td>
<td>1.40 (1.30–1.51)</td>
<td>1.17 (0.94–1.46)</td>
</tr>
<tr>
<td>BMI (per 3 kg/m²)</td>
<td>1.10 (1.04–1.16)</td>
<td>1.18 (1.01–1.37)</td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>1.37 (1.15–1.63)</td>
<td>2.02 (0.97–4.18)</td>
</tr>
<tr>
<td>T. Cholesterol (per 40 mg/dL)</td>
<td>1.21 (1.14–1.29)</td>
<td>1.08 (0.87–1.34)</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>1.38 (1.20–1.60)</td>
<td>1.96 (1.16–3.30)</td>
</tr>
<tr>
<td>METs (per SD)</td>
<td>0.84 (0.82–0.88)</td>
<td>0.82 (0.70–0.95)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index, METs, metabolic equivalents; SBP, systolic blood pressure; SD, standard deviation; and T. Cholesterol, total cholesterol.
Offspring Cohort; however, their work did not include fitness. Because this model allows for the incorporation of continuous covariates, we were able to apply this method and create reliable long-term risk estimates across all risk factor and fitness subgroups for both men and women. For example, with the knowledge of an individual’s risk factor profile such as age, systolic blood pressure, total cholesterol, body mass index, and fitness level, a clinician is able to calculate a 30-year risk estimate for CVD death in the office setting, making the present approach particularly relevant for the practicing clinician.

**Absolute Versus Relative Risk Difference**
Previous studies on the associations between fitness and CVD outcomes report relative risk differences as opposed to absolute risk differences, and hence the magnitude of the difference in long-term CVD risk between low and high physical fitness levels may be less apparent. These studies have consistently shown that low fitness is associated with a 60% to 70% higher relative risk for CVD death in the short-term. Similar to these previous studies, we also observed a higher relative risk in both the short-term and long-term. However, by extending the time horizon across the lifespan, we extend this prior work to provide additional insight into the effects of low fitness on lifetime and absolute risks for CVD mortality. For example, a 55-year-old low-fit woman (ie, METs 6) with diabetes mellitus and stage II hypertension has a 10-year risk for CVD death of 1.9% compared with 0.8% in the presence of high fitness (METs 10). At 30 years, the risk for CVD death is estimated to be 23.9% (low fit) and 12.1% (high fit). Thus, although the relative difference in risk for CVD death is similar at both 10 and 30 years, the absolute risk difference for CVD death at 10 and 30 years is more apparent (1.1% versus 11.8%), highlighting the cumulative effects of fitness on long-term CVD risk. Hence, our risk calculator clarifies the long-term risk associated with differences in fitness levels. These data may be useful to the practicing clinician by providing more effective risk communication to promote adherence to healthy lifestyle patterns.

**Lifetime Risk for CVD in Women**
Current CVD risk prediction algorithms assess only short-term CVD risk and classify >98% of women <60 years of age as low

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**Figure 1.** Calibration by deciles of predicted 30-year risk of cardiovascular disease for men and women.

**Figure 2.** Risk for cardiovascular disease (CVD) mortality (%) according to selected risk factors and fitness strata in 50-year-old men (A) and women (B) for 30 years. A reflects estimated 30-year risk for CVD mortality adjusted for competing risk in 50-year-old man with systolic blood pressure of 160 mm Hg according to low, intermediate, and high fitness levels (in metabolic equivalents [METs]); B reflects estimated 30-year risk for CVD mortality adjusted for competing risk in 50-year-old woman with diabetes mellitus according to low, intermediate, and high fitness levels (in METs).
short-term risk for CVD. However, >1 in 3 of these women with low short-term risk will develop CVD in their lifetime.

Therefore, clinical practice guidelines recommend the use of long-term or lifetime risk for CVD especially in women. However, to our knowledge, limited tools are available that incorporate additional lifestyle variables into long-term risk prediction in women. Based on our prior work, we believe fitness may represent an important determinant of long-term risk in women. Recently, we showed that addition of fitness to traditional risk factors improved risk classification in women even after 25 years of follow-up (Net Reclassification Index=0.131, P<0.05). In the present paper, we extend this prior work to provide a clinically useful, sex-specific 30-year risk estimator that incorporates both traditional risk factors and objectively measured fitness levels. The ability to estimate an individual long-term risk for CVD death is of particular importance in women, given their prominent low short-term risk. This in turn may help motivate select patient groups such as those with established CVD risk factors to begin and adhere to structured exercise programs.

Limitations

The present study has several limitations. First, the CCLS represents a unique cohort of well-educated white participants with high socioeconomic status and low risk factor burden compared with the general population. However, in prior work we have shown that despite the low prevalence of risk factors within the CCLS, the effect of risk factors on long-term CVD mortality was similar to that observed in the general population. Furthermore, we were not able to validate our findings in an external cohort, because to our knowledge there are no available cohorts of asymptomatic adults with exercise testing of this size and with this degree of long-term follow-up. Therefore, we think that our findings provide the best, currently available Web site (lifetimerisk.org) we have constructed a clinically useful, sex-specific 30-year risk estimator that incorporates both traditional risk factors and fitness levels.

Second, we used a single measurement of fitness to calculate 30-year risk for CVD death. We appreciate that fitness levels may have changed during the follow-up period, and undoubtedly updated measures of fitness over time would have resulted in more robust results. However, we feel that this actually represents a significant strength of our findings, providing clinicians with an estimate of long-term CVD risk on the basis of a single, current measure of traditional risk factors and fitness level.

Finally, the cause of death in the present study was determined from the National Death Index. Although this may have resulted in potential misclassification of CVD and non-CVD death, prior literature suggests that death certificate data represent a reliable strategy for identification of cause of death, particularly at <85 years of age.

In summary, in a large well-characterized cohort with no prior CVD, the presence of low fitness was associated with an increased long-term (30 year) risk for CVD death across all ages, sex, and risk factor strata. With the use of our currently available Web site (lifetimerisk.org) we have constructed a clinically useful, sex-specific 30-year risk estimator that incorporates both traditional risk factors and fitness levels.

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Disclosures

None.

References

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