Cardiorespiratory fitness and nonfatal cardiovascular events: A population-based follow-up study

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Background To examine the prognostic value of cardiorespiratory fitness (CRF) with risk of first major nonfatal myocardial infarction (MI), stroke, and heart failure (HF) events.

Methods Cardiorespiratory fitness, as measured by maximal oxygen uptake, was assessed at baseline in a prospective cohort of 2,089 men aged 42 to 61 years.

Results During a mean (SD) follow-up of 19.1 (8.4) years, 522 nonfatal acute MI events, 198 acute all-cause nonfatal stroke events, and 221 nonfatal HF events were recorded. The hazard ratio per 1-metabolic-equivalent increase in CRF was 0.93 (95% CI 0.88-0.97) for nonfatal MI, 0.94 (95% CI 0.87-1.01) for nonfatal stroke, and 0.84 (95% CI 0.78-0.91) for nonfatal HF events after adjustment for cardiovascular risk factors (age, systolic blood pressure, body mass index, history of cardiovascular disease, diabetes, smoking, alcohol use, serum creatinine, low-density lipoprotein levels, physical activity, and socioeconomic status). Further adjustment for left ventricular hypertrophy and resting heart rate did not attenuate these associations. Addition of CRF to conventional cardiovascular disease risk factors significantly improved both discrimination (C index) and category free net reclassification index (cf-NRI) for nonfatal MI (change in C index, 0.015 [95% CI 0.010-0.020] and change in cf-NRI 0.27, \(P < .01\)) and HF (change in C index 0.040 [95% CI 0.010-0.060] and change in cf-NRI 0.88, \(P < .01\)).

Conclusion In this Finnish population, there is a strong, inverse, and independent association between CRF and acute nonfatal MI and HF risk. (Am Heart J 2016;184:55-61.)

Cardiovascular fitness is an important and modifiable risk factor associated with mortality. Multiple studies have demonstrated a consistent, inverse association between cardiorespiratory fitness (CRF) and mortality even after adjustment for traditional risk factors.\(^{1,2}\) However, whether these associations persist in relation to nonfatal cardiovascular events has not been evaluated before. Given the significance of physical activity and good CRF toward primary prevention of cardiovascular disease (CVD), the need to ascertain the relationship between fitness level and nonfatal cardiovascular events remains important. Cardiorespiratory fitness is a measure of assessing cardiac and respiratory functioning. Directly measured VO\(_2\)max, an objective and quantitative measure of CRF, is the criterion standard for measuring the amount of oxygen consumption during exercise.\(^{3,4}\) The individual CRF levels have been shown to be a stronger predictor of mortality compared with traditional risk factors, including smoking, hypertension, high cholesterol, and type 2 diabetes mellitus\(^{5,6}\) as well as other exercise test variables, such as ST-segment depression, and hemodynamic responses.\(^{5}\) The association between CRF and mortality has been proposed to persist across the life-span,\(^7\) with a single measurement of CRF in midlife being strongly associated with lifetime risk decades later. On the other hand, very few studies have assessed the relationship between CRF and risk of nonfatal first time cardiovascular events.\(^{8,10}\) In
addition, usefulness of CRF towards cardiovascular risk assessment beyond conventional CVD risk factors remains unknown. To help clarify evidence, we assessed whether CRF, as assessed by the criterion standard method of oxygen consumption during exercise testing, would predict nonfatal cardiovascular events including acute myocardial infarction (MI), stroke, or heart failure (HF) in the general population.

Methods

Study population

The study population is a representative sample of men living in the city of Kuopio and its surrounding rural communities in Eastern Finland. Subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study, a longitudinal population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes. The men were 42 to 61 years of age during baseline examinations performed between March 20, 1984, and December 5, 1989. Of 3,235 potentially randomly selected eligible men, 2,682 (83%) volunteered to participate in this study, 186 did not respond to the invitation, and 367 declined to give informed consent. The present analysis is based on 2,089 men with no missing data on exercise test variables, covariates, and nonfatal cardiovascular events (nonfatal coronary events, stroke, and HF). The study was approved by the Research Ethics Committee of the University of Eastern Finland, and each participant gave written informed consent.

Assessment of CRF

Maximal oxygen uptake, which was used as a measure of CRF, was assessed by using respiratory gas exchange analyzer during cycle ergometer exercise test. A maximal symptom-limited exercise tolerance test was performed between 8:00 and 10:00 AM using an electrically braked cycle ergometer. The standardized testing protocol comprised a 3-minute warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min with the direct analyses of respiratory gases (Medical Graphics, St Paul, MN). A detailed description of the measurement of VO₂max has been described elsewhere. The VO₂max was defined as the highest value for or the plateau of oxygen uptake. The VO₂max was also expressed in metabolic equivalents (METs) of oxygen consumption. One MET corresponds to an oxygen uptake of 3.5 mL/kg per minute and it is a standard scale for expressing exercise capacity. Maximal exercise workload (in watts) was defined as the highest workload achieved during the exercise test. Exercise workload was also divided by body weight in kilograms. For safety reasons, all tests were supervised by an experienced physician with the assistance of an experienced nurse. The electrocardiogram (ECG), blood pressure, and heart rate were registered during the exercise test. Exercise ECG was recorded continuously with the Kone 620 electrocardiograph device (Kone, Turku, Finland). Standard resting 12-lead ECG was also recorded and heart rate was defined from resting ECG. The ECG criterion for left ventricular hypertrophy was based on either the Sokolow-Lyon or Romhilt-Estes point score.

Assessment of risk factors

The lifelong exposure to smoking (cigarette pack-years) was estimated as the product of the number of years smoked and the number of tobacco products smoked daily. Smoking was also categorized as never, former, and current smokers. Resting blood pressure was measured between 8 and 10 AM with a random-zero sphygmomanometer. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. Body mass index was computed as the ratio of weight in kilograms to the square of height in meters. Diabetes was defined as a fasting blood glucose level greater than 121 mg/dL (>6.7 mmol/L) or clinical diagnosis of diabetes with dietary, oral, or insulin treatment. The collection of blood specimens and the measurement of serum lipids, lipoproteins, creatinine, and glucose have been described elsewhere. Assessment of physical activity was based on validated self-reported questionnaires.

Ascertainment of incident nonfatal cardiovascular events

All incident CVD cases that occurred from study enrollment (March 1984 and December 1989) through 2011 were included. There were no losses to follow-up. All study participants are under continuous surveillance for the development of new CVD events. The sources of information on MI, all stroke, and HF were based on hospital records and medicolegal reports. The diagnostic classification of HF cases was coded according to the International Classification of Disease, Tenth Revision codes (I50.0-I50.9, I11, I42.0-I42.9). The diagnosis of HF was based on a history of heart disease, physical examination by a doctor, laboratory investigations including the determination of N-terminal pro-ß-type natriuretic peptide, as well as echocardiography and ECG findings. The diagnosis of nonfatal stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting more than 24 hours with no apparent cause other than a vascular origin. Each suspected stroke (International Classification of Disease, Tenth Revision codes I60-I69 and G45-G46) was classified into (1) a definite stroke, (2) no stroke, or (3) unclassifiable events. Data on nonfatal acute coronary events were obtained by computer linkage to the national hospital discharge. Diagnostic information was collected from hospitals and classified using identical diagnostic criteria, based on cardiac symptoms, ECG findings, and biomarker elevation. If a participant had multiple nonfatal coronary events during
the follow-up, the first event was considered the end point. A cardiologist collected and classified the coronary events.

**Statistical analyses**

Values of skewed variables were log transformed to achieve approximately symmetrical distributions. Descriptive analyses summarized baseline characteristics by participants. Cross-sectional associations of measures of CRF with several predictors of incident CVD were assessed using linear regression models adjusted for age. The primary outcome was incident nonfatal MI, stroke, and HF. Incident nonfatal MI, stroke, and HF rates per 1,000 person-years of follow-up were calculated across quartiles of CRF. Cumulative hazard curves were constructed for the risk of incident CVD across quartiles of CRF. The shape of the association of nonfatal acute MI events, 198 acute all-cause nonfatal stroke events, and 221 nonfatal incident HF events were recorded. Cardiorespiratory fitness was modestly, though significantly associated with age (r = 0.35), BMI (r = 0.36), resting heart rate (r = −0.20), and fasting blood glucose levels (r = 0.17). Somewhat weaker but significant correlations were observed with systolic blood pressure (r = 0.13), total cholesterol (r = 0.06), and the amount of alcohol consumed (r = 0.09). Cardiorespiratory fitness levels were significantly lower in men with prevalent CHD at baseline, current smokers, subjects with prevalent

### Table I. Baseline participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 2089)</th>
<th>CVD (n = 747)</th>
<th>Without CVD (n = 1342)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.1 (4.9)</td>
<td>54.0 (4.1)</td>
<td>52.6 (5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 (13.5)</td>
<td>27.4 (3.5)</td>
<td>26.6 (3.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cigarettes (packs/day x years of smoking)</td>
<td>8.1 (16.0)</td>
<td>8.9 (16.2)</td>
<td>7.7 (15.9)</td>
<td>.840</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134.2 (16.9)</td>
<td>136.8 (17.8)</td>
<td>132.7 (16.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>89.5 (22.9)</td>
<td>89.6 (23.5)</td>
<td>88.6 (14.5)</td>
<td>.366</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (%)</td>
<td>132 (6.6%)</td>
<td>34 (4.4%)</td>
<td>98 (7.7%)</td>
<td>.014</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>106 (5.5%)</td>
<td>57 (7.7%)</td>
<td>49 (3.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>785 (37.4%)</td>
<td>349 (46.2%)</td>
<td>436 (33%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximal oxygen uptake (mL kg⁻¹ min⁻¹)</td>
<td>30.2 (8.0)</td>
<td>28.3 (8.1)</td>
<td>31.2 (7.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximal oxygen uptake (mL/min)</td>
<td>2398.0 (625.7)</td>
<td>2279.8 (633.0)</td>
<td>2463.8 (612.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>METs</td>
<td>8.6 (2.3)</td>
<td>8.1 (2.3)</td>
<td>8.9 (2.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Values are mean (SD) or %.

* One metabolic equivalent corresponds to an oxygen uptake of 3.5 mL kg⁻¹ min⁻¹ during maximal exercise test.

Results

Baseline characteristics

The mean age of participants at baseline was 53.1 (4.9) years. Mean VO₂max was 30.2 (8.0) mL kg⁻¹ min⁻¹, which corresponds 8.6 (2.3) METs. Baseline descriptive characteristics of the 2,089 participants are shown in Table I. During an average (SD) follow-up of 19.1 (8.4) years, 522 nonfatal acute MI events, 198 acute all-cause nonfatal stroke events, and 221 nonfatal incident HF events were recorded. Cardiorespiratory fitness was modestly, though significantly associated with age (r = 0.35), BMI (r = 0.36), resting heart rate (r = −0.20), and fasting blood glucose levels (r = 0.17). Somewhat weaker but significant correlations were observed with systolic blood pressure (r = 0.13), total cholesterol (r = 0.06), and the amount of alcohol consumed (r = 0.09). Cardiorespiratory fitness levels were significantly lower in men with prevalent CHD at baseline, current smokers, subjects with prevalent
diabetes, and those with a history of hypertension at baseline (Supplementary Table I). Nonexercise test–based CRF was significantly correlated with measured CRF ($r = 0.52$).

Cardiorespiratory fitness and nonfatal acute MI, stroke, and HF

Incident rates per 1000 person-years of follow-up for nonfatal MI and HF are observed to decrease across quartiles of CRF (Supplementary Figure 1). There was an inverse association between CRF and incident nonfatal MI and HF rates. Cumulative hazard curves demonstrated a greater risk of new-onset nonfatal MI and HF events among men in the bottom quartile of CRF levels compared with those in the top quartile ($P$ value for log-rank test $< .001$) (Figure 1). Figure 2 and Supplementary Figure 2 show that the HRs for incident nonfatal MI and HF decreased with increasing levels of CRF in analyses adjusted for established risk factors for CVD. Table II shows the associations of CRF with incident MI, stroke, and HF events. The HR per 1-MET increase in CRF was 0.93 (95% CI 0.88-0.97) for nonfatal MI, 0.94 (95% CI 0.87-1.01) for nonfatal stroke, and 0.84 (95% CI 0.78-0.91) for nonfatal HF events after adjustment for established cardiovascular risk factors (age, systolic blood pressure, BMI, history of CVD, diabetes, smoking, alcohol use, serum creatinine, low-density lipoprotein levels, physical activity, and socioeconomic status). Further adjustment for additional risk factors did not substantially attenuate these associations (Table II). In a comparison of extreme quartiles of CRF levels, the corresponding adjusted HRs were 0.74 (95% CI 0.55-0.99) for nonfatal MI, 0.91 (95% CI 0.58-1.44) for nonfatal stroke, and 0.49 (95% CI 0.30-0.80) for nonfatal HF, respectively. Hazard ratios did not vary markedly by levels of prespecified established risk factors (Supplementary Figure 3). Addition of CRF to a conventional CVD risk score significantly improved discrimination for both nonfatal MI (change in $C$ index 0.015; 95% CI 0.010-0.020) and HF (change in $C$ index 0.040, 95% CI 0.010-0.060), and reclassification with change in category free net reclassification index for nonfatal MI of 0.27 (0.13-0.42) and for nonfatal HF of 0.88 (0.53-1.24) (see Figure 3).

Discussion

In the present study, we found a strong, inverse, and independent association between directly measured CRF and nonfatal MI and HF events. Greater levels of CRF were associated with a lower risk of nonfatal cardiovascular events besides stroke in a graded fashion, which were independent of known risk factors in this population-based sample of men. Previous studies have consistently demonstrated an increased risk of incident CVD and mortality from CVD-related causes with lower levels of CRF,9,10,20-22 with evidence suggesting that an incremental improvement in CRF can result in reduced incidence of cardiovascular events. A meta-analysis reported that a 1-MET higher level of maximal aerobic capacity (equivalent to 1km/h higher running or jogging speed) was associated with a 15% reduction in risk of CVD.5 In our study, a 1-unit increase in long-term CRF (as measured by maximal oxygen uptake) was associated with a 7% reduced risk of incident nonfatal MI and 16% decrease in risk of incident nonfatal HF events, per 1-MET increment in CRF.

Although the causal nature of these associations remains to be investigated, it is likely that higher levels of CRF improve cardiovascular risk profile, thereby decreasing the risk of future CVD events. Several physiological and metabolic mechanisms underpin the association of low CRF with increased risk of CVD. Lower levels of physical activity are associated with endothelial dysfunction which contributes to preclinical atherosclerosis.10 Physical inactivity with poor CRF leads to
elevated levels of blood pressure and serum lipids, insulin resistance, and obesity, all of which predispose to the development of CVD. On the other hand, regular physical activity may increase the capacity of endothelial cells to evoke vasodilatation in the early stages of atherosclerosis thus retarding its progression.23,24 Physical activity also protects against the development of CVD by having a favorable effect on CVD risk factors,25-29 and may help improve CRF increasing cardiac output, left ventricular function and oxygen utilization, and the formation of collateral vessels.6,30 There are also suggestions that physical activity regulates cardiac autonomic function and vagal control of heart rate, therefore reducing risk of ventricular arrhythmias and subsequent risk of HF.8,31

It has been reported that physical activity may provide anti-inflammatory effects and increasing levels of CRF are
associated with a reduction in levels of inflammatory markers like C-reactive protein.\textsuperscript{32-34} Because elevated levels of C-reactive protein have been implicated with an increased risk of HF, there is a possibility that the association between improved CRF and reduced risk of HF might be mediated through the anti-inflammatory effects of physical activity. In addition to modifying serum cholesterol levels, exercise training may also affect the risk of nonfatal cardiovascular events through other pathways. It is shown that people in exercise groups also had significantly lower levels of interleukins (interleukin18) and several biomarkers of insulin resistance and hemostatic factors, indicating that exercise may exert its effects via pathways of inflammation-characterized atherothrombosis and insulin resistance.\textsuperscript{34} In addition, exercise training may regulate white adipose tissue mass and the expression of adipokines reducing chronic inflammation. Recent evidence suggests that levels of markers of subclinical heart disease including natriuretic peptides and cardiac troponin T are modulated by regular moderate-intensity physical activity. However, additional research including exercise intervention trials would help discover the mechanistic pathways through which physical training and exercise could prevent CVD.\textsuperscript{35}

Cardiorespiratory fitness is also influenced by a genetic component, besides a modifiable component which includes the duration, intensity, frequency, and type of physical activity.\textsuperscript{21,36} Therefore, interventions that improve CRF may have an interaction with health status, physical fitness, and other individual characteristics in modulating the overall risk of CVD. However, we did not observe any significant difference in the impact of CRF on nonfatal CVD events according to different age groups, and in those with diabetes, hypertension, or prior coronary heart disease suggesting a consistent association of CRF in modulating the risk of incident nonfatal CVD in individuals with different levels of risk factors. Using a conventional risk factor model, we found that the addition of CRF significantly improved risk discrimination and reclassification for nonfatal MI and HF events. There are no comparable population studies showing the value of objectively assessed CRF in risk discrimination and reclassification with regard to first nonfatal cardiovascular events. However, on the basis of our study CRF is an important risk predictor, which can help screen individuals at high risk of CVD who may benefit most from exercise training.

The main strengths of our study include prospective design, complete follow-up, and detailed information on potential confounders. The use of an objective measure of CRF prevented any misclassification of exposure, which was a limitation in previous studies. This study was focused on nonfatal MI, stroke, and HF events showing the importance of CRF in the prevention of first acute MI and HF events, which is not well studied previously. An accurate assessment of CRF directly from respiratory gases can be easily converted to METs (as an indirect measure) which are usually defined from all exercise testing methods increasing generalizability of our results. A null association was observed with a composite acute nonfatal stroke outcome, which could not be further subclassified by stroke subtypes using the available data. The current study only included men from an ethnically and genetically homogenous population, which limits the generalization of our data to women and other diverse populations.

In summary, a higher level of CRF is independently associated with a decrease in incidence of acute nonfatal MI and HF events in a representative population of middle-aged men. Our data warrant larger future studies to evaluate this relationship further.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C index (95% CI)</th>
<th>change in C index (95% CI)</th>
<th>change in cf NRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Conventional risk factors(^*) 0.63(0.61-0.65)</td>
<td>0.01 (0.00, 0.02)</td>
<td>0.27 (0.13, 0.42); (P &lt; .01)</td>
</tr>
<tr>
<td></td>
<td>plus CRF 0.65(0.62-0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>Conventional risk factors(^*) 0.71(0.68-0.75)</td>
<td>0.04 (0.01, 0.06)</td>
<td>0.88 (0.53, 1.24); (P &lt; .01)</td>
</tr>
<tr>
<td></td>
<td>plus CRF 0.75(0.72-0.78)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) age, systolic blood pressure, diabetes, smoking status, total cholesterol, HDL-c

Change in nonfatal CVD risk discrimination and reclassification after the addition of information on CRF to conventional risk factors.
Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.10.019.

References