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Cardiorespiratory Fitness Is Related to the Risk of Sudden Cardiac Death

A Population-Based Follow-Up Study

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Objectives Our aim was to examine the relation of cardiorespiratory fitness with sudden cardiac death (SCD) in a population-based sample of men.

Background Very limited information is available about the role of cardiorespiratory fitness in the prediction of SCD.

Methods This population study was based on 2,368 men 42 to 60 years of age. Cardiorespiratory fitness was defined by using respiratory gas exchange analyzer and maximal workload during cycle ergometer exercise test.

Results During the 17-year follow-up, there were 146 SCDs. As a continuous variable, 1 metabolic equivalent (MET) increment in cardiorespiratory fitness was related to a decrease of 22% in the risk of SCD (relative risk: 0.78, 95% confidence interval: 0.71 to 0.84, $p < 0.001$). In addition to cardiorespiratory fitness, ischemic ST-segment depression during exercise testing, smoking, systolic blood pressure, prevalent coronary heart disease, family history of coronary heart disease, and type 2 diabetes mellitus were related to the risk of SCD. The Harrell C-index for the total model discrimination was 0.767, while cardiorespiratory fitness provides modest improvement (from 0.760 to 0.767) in the risk prediction when added with all other risk factors. The integrated discrimination improvement was 0.0087 ($p = 0.018$, relative integrated discrimination improvement 0.11) when cardiorespiratory fitness was added in the model. However, the net reclassification index (−0.018) was not statistically significantly improved ($p = 0.703$).

Conclusions Cardiorespiratory fitness is a predictor of SCD in addition to that predicted by conventional risk factors. There was a slight improvement in the level of discrimination, although the net reclassification index did not change while using cardiorespiratory fitness with conventional risk factors. (J Am Coll Cardiol 2010;56:1476–83)

Despite the recognition that sudden cardiac arrest accounts for one-half of all coronary heart disease (CHD)-related deaths and presents as the first manifest of the disease in approximately 20% to 30% of the deaths, there is no information on the relationship between cardiorespiratory fitness and the risk of sudden cardiac death (SCD) among the general population (1). Because a large majority of SCDs occur among more general segments of the population, the problem will require screening methods applicable to the general population. However, the majority of the studies on risk markers of arrhythmic events have focused on the patients with a specific heart disease, often advanced. Large epidemiological surveys have not been able to identify specific risk markers for SCD in the general population even though general risk markers for atherosclerosis do identify risk of SCD nonspecifically (2,3).

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It is suggested that the most important marker of risk yielded by the exercise test is the measure of exercise capacity (4–7). Exercise capacity can be measured by either direct measurement of oxygen consumption or indirectly as functional capacity. Previous population-based studies have

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looked at the ability of indirectly defined functional capacity to predict total mortality and other cardiovascular events (8–11). However, there are no data available to show if low cardiorespiratory fitness is associated with an increased risk of SCD. This study was conducted to investigate the predictive value of cardiorespiratory fitness with respect to the risk of SCD in a population-based random sample of men. We explored the possibility that low cardiorespiratory fitness may allow early identification of persons at increased risk for SCD.

Methods

Study population. This study was designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men. Subjects were a randomly selected sample of 3,433 men age 42 to 60 years who resided in the town of Kuopio or its surrounding rural communities. Of those invited, 2,682 (83%) participated in the study, and subjects with complete data on exercise testing with maximal oxygen consumption volume (VO_{2max}, 2,368 men) were included in the analyses. Men who could not participate ($n = 314$) were older (age 54.5 years vs. 52.9 years, $p = 0.001$) and had more often prevalent CHD (35.9% vs. 23.8%, $p = 0.001$), and their high-sensitivity C-reactive protein level was higher (3.63 mmol/l vs. 2.28 mmol/l, $p < 0.001$) as compared with men who were included in the final analysis. All other main variables including alcohol consumption, cigarette smoking, serum low- and high-density lipoprotein cholesterol, type 2 diabetes mellitus, waist-to-hip ratio, systolic blood pressure, and family history of CHD, maximal heart rate, and ischemic ST-segment depression during exercise did not differ statistically significantly. Baseline examinations were conducted between March 1984 and December 1989 (12). The study was approved by the research ethics committee of the University of Eastern Finland, Kuopio, Finland. Each participant gave written informed consent.

Assessment of cardiorespiratory fitness and exercise electrocardiography. A maximal symptom-limited exercise tolerance test was performed between 8:00 AM and 10:00 AM using an electrically braked cycle ergometer (12). The standardized testing protocol comprised of an increase in the workload of 20 W/min with the direct analyses of respiratory gases (Medical Graphics, St. Paul, Minnesota). The VO_{2max} was defined as the highest value for or the plateau of oxygen uptake. The VO_{2max} was also expressed in metabolic equivalents (METs). One MET corresponds to an oxygen uptake of 3.5 ml/kg/min. Maximal exercise workload 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 (10). Electrocardiography was recorded continuously with the Kone 620 electrocardiograph (Kone, Turku, Finland). Electrocardiography was printed at 30-s intervals during exercise and at least 5 min of recovery while the subject was sitting on the bicycle. The criteria for ischemia in electrocardiography during exercise and recovery were horizontal or downsloping ST-segment depression 1.0 mm at 80 ms after J point or any ST-segment depression of >1.0 mm at 80 ms after J point (13).

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 at the time of examination (12). Resting blood pressure was measured between 8:00 AM and 10:00 AM with a random-zero sphygmomanometer (14). The use of medications and the diagnosis of diseases were collected at baseline examination by an internist.

Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. Leisure-time physical activity was assessed from a 12-month Leisure-Time Physical Activity Questionnaire (12). The collection of blood specimens and the measurement of serum lipids and lipoproteins, insulin, and glucose have been described elsewhere (14). Serum C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-reactive protein Assay, DPC, Los Angeles, California). Body mass index was computed as the ratio of weight in kilograms to the square of height in meters.

Classification of SCD. All deaths that occurred by the end of 2005 were checked from the hospital documents, wards of health centers, and death certificates. The sources of information were interviews, hospital documents, death certificates, autopsy reports, and medicolegal reports (15). There were no losses to follow-up. The diagnostic classification of events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80%), and history of CHD. Deaths were coded using to the International Classification of Diseases-9th Revision, codes 410 to 414 for non-SCD and 798.1 for SCD; or the International Classification of Diseases-10th Revision, codes I20 to I25 for non-SCD and I46 for SCD.

A death was determined SCD when it occurred either within 1 h after the onset of an abrupt change in symptoms or within 24 h after onset of symptoms when autopsy data did not reveal a noncardiac cause of sudden death. The deaths due to aortic aneurysm rupture, cardiac rupture or

Abbreviations and Acronyms

CHD = coronary heart disease
CI = confidence interval
HDL = high-density lipoprotein
IDI = integrated discrimination index
LDL = low-density lipoprotein
MET = metabolic equivalent
NRI = net reclassification index
RR = relative risk
SCD = sudden cardiac death
VO_{2max} = maximal oxygen consumption volume

tamponade, and pulmonary embolism were not included as SCD. The independent events committee blinded to clinical data performed classification of deaths.

Statistical analysis. Differences in baseline characteristics were examined using the analysis of variance and the chi-square test. Descriptive data are presented as means and percentages. Risk factors for main outcomes were analyzed using the multivariate Cox model. Cardiorespiratory fitness was entered into forced SPSS Cox proportional hazards' models. Cox models were adjusted for age and other risk factors, which were selected on the basis of their previously established role as a well-defined predictive factor on the basis of overall evidence and available data. Thus, risk covariates were chosen based on their clinical relevance. The analyses were also performed among men with high (unhealthy) and low (healthy) pre-test probability for cardiovascular events. The unhealthy subgroup included men with a history of CHD or typical angina pectoris, cardiac insufficiency, claudication, stroke, cardiomyopathy, arrhythmias, chronic obstructive pulmonary disease, pulmonary tuberculosis, bronchial asthma, or cancer.

Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. The fit of the proportional-hazards' model was examined by plotting the hazard functions in different categories of risk factors over time. The proportional hazards assumption was verified for all variables by inspection of the plots of Schoenfeld residual for covariates. The linearity assumption was satisfied for all continuous variables, and it was assessed with Martingale residuals for each continuous variable against survival time. The cumulative survival from SCD according to cardiorespiratory fitness (METs) was calculated using the Kaplan-Meier method adjusting for age. A p value <0.05 was considered statistically significant. These statistical analyses were performed using SPSS version 14.0 for Windows (SPSS, Inc., Chicago, Illinois).

The C-statistics index was calculated to assess the model discrimination, the ability of the model to correctly identify subjects with respect to SCD (16). The Harrell C-index was primary measure of discrimination (17). On the basis of C-statistics, the incremental value of cardiorespiratory fitness in addition to previously documented cardiovascular risk factors was evaluated. The C-index of the total multivariable model minus the C-index for model without the risk factor of interest represents the incremental value of the certain factor. Additionally, we calculated the integrated discrimination improvement (IDI), relative IDI, discrimination slope, and binary R^2 for the model with and without cardiorespiratory fitness.

We assessed risk reclassification (18) by sorting the predicted risk for model into 3 categories (<6%, 6% to 20%, and >20%) according to recent statements (19). We also computed the net reclassification index (NRI) (20), which compares the shifts in reclassified categories by observed outcome. This measure determines net percentages of men who do and do not have a SCD over the follow-up period who were correctly reclassified using the new function. We defined the Hosmer-Lemeshow statistics for the reclassification of quintiles.

Results

Baseline characteristics. The mean of VO_{2max} was 30.2 ml/kg/min (8.6 METs, range 10.2 to 65.4 ml/kg/min), and the mean maximal workload was 181 W (range 40 to 420 W). The distributions of common baseline characteristics are shown in Table 1, and exercise test findings are presented in Table 2. The most common reasons for stopping the exercise test were leg fatigue (n = 1,118), exhaustion (n = 366), breathlessness (n = 322), and pain in

Table 1 Baseline Characteristics

Age, yrs	52.9 (5.1)
Body mass index, kg/m^2	26.9 (3.5)
Waist-to-hip ratio	0.95 (0.06)
Smokers, %	31.9
Cigarette smoking, pack-yrs*	8.4 (16.5)
Alcohol consumption, g/week	74.2 (121.4)
Serum total cholesterol, mmol/l	5.91 (1.07)
Serum LDL cholesterol, mmol/l	4.04 (1.01)
Serum HDL cholesterol, mmol/l	1.29 (0.30)
Serum triglycerides, mmol/l	1.28 (0.82)
Systolic blood pressure, mm Hg	134.0 (16.8)
Diastolic blood pressure, mm Hg	88.9 (10.5)
Blood glucose, mmol/l	4.77 (1.18)
Serum insulin, mU/l	11.6 (7.0)
High sensitivity C-reactive protein, mmol/l	2.28 (3.35)
Physical activity, kcal/week†	978.8 (1,220.9)
Mean intensity of physical activity, MET†	5.78 (1.79)
Diagnosed diseases and family histories, %	
Coronary heart disease	23.8
History of myocardial infarction	7.4
Family history of coronary heart disease	49.3
Coronary bypass surgery	0.6
History of hypertension	30.1
Family history of hypertension	47.4
Cardiac insufficiency	6.6
Cardiomyopathy	2.1
Cerebrovascular disease	2.4
Claudication	3.8
Arrhythmias‡	15.8
Pulmonary disease§	12.5
Cancer	1.6
Type 2 diabetes mellitus	5.1
Regular use of medications, %	
Antihypertensive medication	21.1
Medication for dyslipidemia	8.6
Beta-blocker	17.3
Acetylsalicylic acid	6.9

Values are mean (SD) or %. *Pack-years denotes the lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination. †Conditioning physical activity was assessed using the 12-month Leisure Time Physical Activity Questionnaire. ‡Arrhythmias included extrasystolic, regular, or paroxysmal atrial fibrillation, and supraventricular tachycardia. §Pulmonary diseases included bronchial asthma, chronic obstructive pulmonary disease, and pulmonary tuberculosis.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metabolic equivalent.

Table 2 Baseline Resting and Exercise Characteristics

Maximal oxygen uptake, ml/kg/min	30.2 (2.28)
Maximal oxygen uptake, l/min	2.40 (0.64)
Metabolic equivalents*	8.6. (2.3)
Exercise workload, W†	181.4 (51.9)
Exercise workload, W/kg†	2.29 (0.68)
Maximal oxygen pulse, ml/beat	16.1 (10.9)
Maximal heart rate, beats/min	155 (25)
85% of age-predicted heart rate during exercise, %	75.5
Resting heart rate, beats/min	62 (11)
Maximal systolic blood pressure, mm Hg	202.7 (28.2)
Abnormal resting ECG findings, %‡	9.8
Exercise-induced myocardial ischemia, %§	8.3
Peak respiratory gas exchange ratio, VCO_2/VO_2	1.09 (0.14)

Values are mean (SD) or %. *One metabolic equivalent corresponds to an oxygen uptake of 3.5 ml/kg/min during maximal exercise test. †Maximal exercise workload was defined as highest workload achieved during the exercise test. ‡Includes abnormal T wave, ST-segment changes, or Q waves on resting electrocardiogram (ECG). §Criteria for myocardial ischemia on ECG were horizontal or downsloping ST-segment depression 1.0 mm at 80 ms after J point or any ST-segment depression of >1.0 mm at 80 ms after J point.

Table 3 Strongest Risk Factors for Sudden Cardiac Death Among Men

	Relative Risk*	95% CI	p Value
Cardiorespiratory fitness, per 1 MET†	0.78	0.71–0.84	<0.001
Ischemic ST-segment depression during exercise testing (yes vs. no)	2.33	1.50–3.62	<0.001
Cigarette smoking, per 10 pack-yrs‡	1.27	1.19–1.36	<0.001
Systolic blood pressure, per 10 mm Hg	1.13	1.03–1.23	0.009
Prevalent coronary heart disease, yes vs. no	1.68	1.17–2.41	0.005
Family history of coronary heart disease, yes vs. no	1.62	1.16–2.27	0.005
Type 2 diabetes mellitus, yes vs. no	1.75	1.04–2.95	0.038

*Relative risks are adjusted for age, alcohol consumption, high-sensitivity C-reactive protein, serum low-density lipoprotein and high-density lipoprotein cholesterol, waist-to-hip ratio, and maximal heart rate during exercise in a Cox forced multivariable model. Sudden cardiac death was defined when the arrest occurred within 24 h after onset of any symptoms. †Exercise capacity was measured directly during exercise testing using a respiratory gas analyzer, VO_{2max} 3.5 ml/kg/min = 1 MET. ‡Pack-years denotes the lifelong exposure to smoking that was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.
CI = confidence interval.

the leg muscles, joints, or back (n = 121). The test was discontinued because of abnormal cardiorespiratory findings in 262 men. These included chest pain (n = 85), arrhythmias (n = 74), a marked change in systolic or diastolic blood pressure (n = 53), ischemic electrocardiographic changes (>3 mm ST-segment depression [n = 36]), or dizziness (n = 14).

Numbers of outcome events during follow-up. The average follow-up time to death or the end of follow-up was 17.6 years (range 0.3 to 22.3 years). There were 146 SCDs. A total of 123 SCDs (84.2%) occurred in out-of-hospital conditions, and 105 (71.9%) of all SCDs deaths were due to documented ventricular tachycardia, ventricular fibrillation, or death with autopsy revealing no other reason for death. The numbers of all-cause death and non–sudden death from CHD were 625 and 207, respectively.

Strongest risk factors for SCD. The strongest significant risk factors for SCD are shown in Table 3. When adjusted also for the use medications for hypertension and dyslipidemia and the use of aspirin, the results remained the same. Exclusion of SCDs occurring in the first 5 years of follow-up did not change the main results, and the cumulative survival curves according to METs continued to diverge during the follow-up period (Fig. 1). Among men with very good cardiorespiratory fitness (≥12 METS), no SCDs were observed. Analogously with direct oxygen consumption, low peak exercise workload as an indirect measure was related to the risk of SCD. The risk of SCD was 0.85 (95% confidence interval [CI]: 0.79 to 0.92, $p < 0.001$) per 20-W increment in maximal workload.

Smoking, cardiorespiratory fitness, prevalent CHD, systolic blood pressure, ischemic ST-segment depression during exercise testing, family history of CHD, and type 2 diabetes were most important discriminating risk factor for SCD on the basis of Harrell C-index. The Harrell C-index for the model discrimination was 0.767, and the discrimination values for most import factors were 0.746 without smoking, 0.760 without cardiorespiratory fitness, 0.761 without prevalent CHD, 0.761 without systolic blood pressure, 0.766 without ischemic ST-segment depression during exercise testing, 0.767 without family history of CHD, and 0.767 without type 2 diabetes. Cardiorespiratory fitness for the model increased the Harrell C-index from 0.760 to 0.767, showing the incremental value of cardiorespiratory

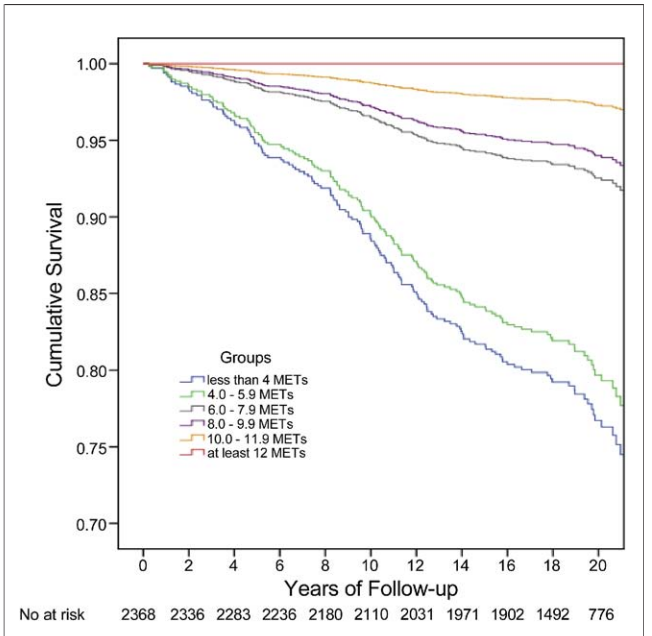

Figure 1 Proportions of SCD According to Achieved METs During Maximal Exercise Testing

The proportions of sudden cardiac death (SCD) are shown by Kaplan-Meier curves according to achieved metabolic equivalents (METs) during maximal exercise testing. The cut-offs were <4 METs (n = 37 **[blue line]**), 4.0 to 5.9 METs (n = 271 **[green line]**), 6.0 to 7.9 METs (n = 611 **[gray line]**), 8.0 to 9.9 METs (n = 840 **[purple line]**), 10.0 to 11.9 METs (n = 437 **[orange line]**), and ≥12 METs (n = 172 **[red line]**).

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Table 4 Comparison of Sudden Cardiac Death Prediction Models Without (Model 1) and With (Model 2) Cardiorespiratory Fitness

Predictor	Model 1*	Model 2*
Age	0.038 ± 0.002 (0.084)	0.023 ± 0.002 (0.286)
Alcohol consumption	0.001 ± 0.001 (0.111)	0.001 ± 0.001 (0.113)
Cigarette smoking	0.228 ± 0.036 (<0.001)	0.221 ± 0.037 (0.001)
Serum LDL cholesterol	0.112 ± 0.080 (0.162)	0.106 ± 0.080 (0.183)
Serum HDL cholesterol	−0.437 ± 0.331 (0.187)	−0.270 ± 0.332 (0.415)
High-sensitivity C-reactive protein	0.024 ± 0.018 (0.180)	0.015 ± 0.019 (0.407)
Type 2 diabetes mellitus	0.616 ± 0.267 (0.021)	0.542 ± 0.269 (0.038)
Waist-to-hip ratio	0.910 ± 0.442 (0.528)	0.176 ± 0.622 (0.914)
Systolic blood pressure	0.138 ± 0.045 (0.002)	0.119 ± 0.046 (0.009)
Prevalent coronary heart disease	0.580 ± 0.185 (0.002)	0.462 ± 0.189 (0.005)
Family history of coronary heart disease	0.488 ± 0.173 (0.004)	0.493 ± 0.172 (0.005)
Maximal heart rate	−0.099 ± 0.031 (0.002)	−0.035 ± 0.039 (0.374)
Ischemic ST-segment changes during exercise	0.855 ± 0.227 (<0.001)	0.803 ± 0.228 (<0.001)
Cardiorespiratory fitness	—	−0.190 ± 0.058 (<0.001)
Harrell C-index (95% CI)†	0.761 (0.723–0.800)	0.767 (0.731–0.804)
Hosmer-Lemeshow chi-square‡	14.47 (0.070)	10.99 (0.202)

Dash indicates variable not included in the model. *Beta-coefficients from Cox proportional hazards model for variables shown. Values are β-coefficient ± SE (p value) unless otherwise indicated. †The Harrell C-index measures discrimination with 95% confidence intervals. ‡The Hosmer-Lemeshow chi-square measures the calibration of model; chi-square >20 suggests lack of calibration.
CI = confidence interval.

fitness in predicting SCD. When maximal workload was used as a value of cardiorespiratory fitness instead of VO_{2max}, model discrimination was 0.766, representing that workload and VO_{2max} are comparable additive risk factors for SCD.

The comparison of SCD prediction models without and with cardiorespiratory fitness is shown in Table 4. The IDI was 0.0087 ($p = 0.018$), showing the significant level of discrimination improvement when cardiorespiratory fitness was added in the model. Relative IDI value for the model was 0.11. Discrimination slope was 0.901 for the model that included the previously established risk markers (model 1) shown in Table 4. After adding cardiorespiratory fitness in the model, the discrimination slope increased to 0.907. Consistently, binary R^2 increased from 0.101 to 0.109 after adding cardiorespiratory fitness into the multivariable model 1.

The role of reclassification as a measure of cardiorespiratory fitness is shown in Table 5. The numbers of men reclassified because of assessment of cardiorespiratory fitness is an important additional measure. According to this analysis, an almost equal number of case subjects had reclassification upward rather than downward by the addition of cardiorespiratory fitness to the risk model (11 vs. 12), although more control subjects had their risk reclassified upward than downward (103 vs. 73) (Table 5).

Cardiorespiratory fitness, CHD, and all-cause death. Cardiorespiratory fitness was also related to an increased risk of CHD death and all-cause mortality. One MET increment in cardiorespiratory fitness (VO_{2max}, 3.5 ml/kg/min) was related a decreased risk of CHD death (relative risk [RR]: 0.69, 95% CI: 0.64 to 0.73, $p < 0.001$) and all-cause death (RR: 0.77, 95% CI: 0.74 to 0.80, $p < 0.001$), after adjustment for age. After adjustment for other risk factor including maximal heart rate and ischemic ST-segment depression during exercise, the respective risks were 0.78 (95% CI: 0.71 to 0.86, $p < 0.001$) for CHD death and 0.83 (95% CI: 0.72 to 0.87, $p < 0.001$) for all-cause death. The respective risks were 0.85 (95% CI: 0.79 to 0.91, $p < 0.001$) for CHD

Table 5 Effect of Adding Cardiorespiratory Fitness to Traditional Risk Factors: Reclassification of Men Between Predicted Cardiovascular Risk Categories and Comparison of Observed and Predicted Risk of Sudden Cardiac Death

Model Without Cardiorespiratory Fitness Risk (%)	Model With Cardiorespiratory Fitness Risk (%)		
	0% to <6%	6% to <20%	>20%
Cases (n = 146)			
0% to <6%, n	38	8	
% reclassified	—	22.1%	
6% to 20%, n	8	52	3
% reclassified	12.7%	—	4.8%
>20%, n		4	33
% reclassified		12.1%	—
Controls (n = 2,222)			
0% to <6%, n	1,531	81	
% reclassified	—	5.3%	
6% to 20%, n	66	430	22
% reclassified	12.7%	—	4.2%
>20%, n		12	80
% reclassified		15.0%	—
Cases/Total			
0% to <6%	2.4%	9.0%	—
6% to 20%	10.8%	10.7%	12.0%
>20%	—	25.0%	29.2%

Dashes indicate variables not included in the model. A total of 204 subjects were reclassified as to risk level: 11 cases upward and 12 cases downward; 103 controls upward and 78 controls downward; net reclassification index = −0.018 (p = 0.703).

death and 0.88 (95% CI: 0.85 to 0.92, $p < 0.001$) for all-cause death for 20-W increment in maximal workload.

Cardiorespiratory fitness (VO_{2max}) for the model increased the Harrell C-index from 0.760 to 0.772 when predicting all-cause mortality. When maximal workload was used as a measure for cardiorespiratory fitness instead of VO_{2max}, full model discrimination for all-cause mortality was 0.770. The IDI was 0.0154 ($p = 0.0001$, relative IDI 0.11) for VO_{2max} and 0.0129 ($p = 0.0001$, relative IDI 0.09) for maximal workload, respectively. While assessing reclassification capacity, NRI value was 0.042 ($p = 0.018$) for VO_{2max} and 0.033 ($p = 0.030$) for maximal workload when all-cause mortality was used as an outcome event.

Cardiorespiratory fitness and the risk of SCD according to health status. Mean VO_{2max} values and for the numbers of SCD were 32.5 ml/kg/min (SD: 7.5 ml/kg/min) and 44 events for healthy men, and 27.3 ml/kg/min (SD: 7.6 ml/kg/min) and 102 events for unhealthy men, respectively. Multivariable adjusted risks were similar in magnitude for SCD showing a linear relationship between cardiorespiratory fitness and SCD, and no statistically significant interaction was found for this relation according to health status. Increase in VO_{2max} of 1 MET was related to a 20% (RR: 0.80, 95% CI: 0.67 to 0.95, $p = 0.011$) risk reduction for healthy men and a 25% (RR: 0.75, 95% CI: 0.68 to 0.83, $p < 0.001$) risk reduction for men with previously known disease, respectively.

Discussion

The main finding of this observational study is that low cardiorespiratory fitness is a predictor of SCD in a large general population of middle-aged men. This study demonstrates that a given 1-MET increment in cardiorespiratory fitness reduces the risk of SCD by a constant proportion, corresponding to a 22% adjusted risk reduction.

Cardiorespiratory fitness yields a modest improvement in SCD prediction. Maximal workload and VO_{2max} are both additional predictors of SCD. There was a slight improvement in the level of discrimination, although the NRI did not improve significantly while using cardiorespiratory fitness. The direct assessment of cardiorespiratory fitness with respiratory gas exchange yields no marked improvement in the C-index. Our study shows that maximal workload, which is an easily available method for defining cardiorespiratory fitness, is sufficient for the prediction of SCD.

Prognostic power of cardiorespiratory fitness. The important novel finding is that cardiorespiratory fitness provides independent prognostic information particularly for SCD after adjusting for other conventional risk variables such as smoking, hypertension, history of CHD, and type 2 diabetes. Therefore, the awareness of individual cardiorespiratory fitness may give additional valuable information of further risk for SCD. Consistent with our current findings, the risk reduction per 1-MET change in physical fitness has been 10% to 24% in overall mortality (10,11,21). Population-based studies have also found an association of physical activity and cardiorespiratory fitness with the incidence of CHD (12,22). Other previous studies have reported that physical activity (23,24) and good cardiorespiratory fitness (11,25,26) reduce the risk of premature death among persons with unfavorable risk profile.

Possible mechanisms of low cardiorespiratory fitness as a risk factor for SCD. The epidemiological background of low cardiorespiratory fitness associated with increased risk of SCD is not clear. Physically fit patients with multivessel coronary artery disease who achieved 10 METs during exercise testing had a very good survival rate, whereas a low physical fitness of <6 METs indicates a higher mortality, regardless of the extent of coronary atherosclerosis or left ventricular function (27). Even patients with angiographically defined 3-vessel disease who achieved a minimum exercise capacity of 7 to 10 METs had an excellent survival (28). In a subgroup who was treated by primary angioplasty (29), exercise capacity seems to add prognostic information, although exercise-induced ST-segment depression did not have a prognostic value, highlighting the independent prognostic power of low cardiorespiratory fitness compared to progression of coronary artery disease. However, some evidence for the possible antiatherogenic effect of good cardiorespiratory fitness is derived from clinical trials, which have shown that physical activity alone (29,30) or combined with low-fat diet or comprehensive lifestyle modification (31) with concomitant improvement in cardiorespiratory fitness, retards the progression of atherosclerosis. Our study showed the increased SCD risk among healthy subjects with low cardiorespiratory fitness as well as among subjects with cardiovascular-related diseases and low cardiorespiratory fitness. These findings generalize the application of cardiorespiratory fitness as a risk stratifier of SCD beyond the patient groups considered at increased risk of SCD compared to the general population.

One potential explanation of association of low cardiorespiratory fitness to SCD is the effect of physical activity to cardiac autonomic regulation. Increasing evidence supports the role of impairment in cardiac autonomic function among subjects with SCD (32–34). Cardiorespiratory fitness is related to vagal modulation of heart rate, providing additional evidence that good cardiorespiratory fitness has beneficial effects on cardiovascular autonomic function and may reduce fatal ventricular arrhythmias (32–34). Consistent with these findings, a population-based study of French civil servants demonstrated that heart rate recovery, a measure of parasympathetic nervous system tone, was predictive of SCD (35).

Although physical activity may be an appropriate therapy for the unfit subjects, inactivity may not be the only cause of being unfit. Subclinical disease or genetics may also be involved (36). As VO_{2max} is used as a measure of cardiorespiratory fitness, it is important to understand the relative

contributions of genetic endowment and environmental influences in its determination. The genetic contribution of cardiorespiratory fitness is estimated to vary from 20% to 40% (37,38). Cardiorespiratory fitness has 2 main components: a heritable component and a component acquired from aerobic exercise training.

Future directions. It is probable that the incidence of SCD can be reduced by a combination of several approaches aimed at preventing its occurrence. Integrative research may open new strategies both for risk stratification of larger patient groups and for new therapeutic options (1). Low cardiorespiratory fitness may perform as a substantial risk marker for SCD in the general population and among patients with low to intermediate risk for SCD, but because of observational nature of this study, it does not allow any estimation of possible impact of physical training on the incidence of SCD.

We tested the additional value by using accuracy and discrimination analysis. In our current study, we have followed the current recommendations for reporting novel risk markers such as cardiorespiratory fitness (19,20). First, we have shown that cardiorespiratory fitness, as defined directly or indirectly, adds to the prognostic information of the established risk factors, which have been included in the multivariable model with supplemental hard outcomes. Second, we have reported the discrimination capacity of cardiorespiratory fitness and the effect of cardiorespiratory fitness and its predictive discrimination. Third, our additional statistical tests show the level of discrimination between men classified with and without the use of cardiorespiratory fitness in addition to other risk factors. Fourth, the accuracy of the discrimination of the assessment of cardiorespiratory fitness has been reported by using reclassification. We reclassified men to see the changes in risk levels by the use of cardiorespiratory fitness as an additional risk marker for SCD, but the result was not significant. Finally, taking together all reported steps of the study, the risk-decreasing role of good cardiorespiratory fitness can be used as a valuable marker in the prediction of SCD in general population.

Study limitations. This follow-up study may have been biased by the participants receiving advice on how to change their lifestyle when appropriate, and study findings also being reported to their physicians. However, such advice probably led to an underestimation, rather than overestimation, of the prognostic significance of cardiorespiratory fitness (38,39). Our representative sample of men makes it possible to generalize the observed results in male populations, although the results on exercise testing and the risk of SCD should be confirmed in female populations. The obvious limitation is the lack of data on ejection fraction and left ventricular mass in the whole population sample, although low ejection fraction is known to be a marker for the risk of SCD. Nevertheless, we have previously shown that left ventricular systolic function and mass are normal in this population (40); thus, it is very unlikely that these factors could have strong effects on the currently reported findings. The subjects were randomly selected in the cohort.

Conclusions

Our results suggest that unfit middle-aged men who have low exercise capacity have an increased risk of SCD, whereas among subjects with very good exercise tolerance, SCD is a highly uncommon event. Low levels of cardiorespiratory fitness may provide valuable information when the future risk of SCD is estimated, but may not provide incremental utility over prediction based on traditional risk factors.

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