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Percentage of age-predicted cardiorespiratory fitness and risk of sudden cardiac death: a prospective cohort study

Brief running title: Fitness and sudden cardiac death

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Abstract

Background The inverse associations between cardiorespiratory fitness (CRF) and vascular outcomes are previously established. However, there has been no previous prospective evaluation of the relationship between percentage of age-predicted CRF (%age-predicted CRF) and risk of sudden cardiac death (SCD).

Objective We aimed to assess the association of %age-predicted CRF with SCD risk in a long-term prospective cohort study.

Methods Cardiorespiratory fitness was assessed using the gold standard respiratory gas exchange analyser in 2,276 men who underwent cardiopulmonary exercise testing**.** The age-predicted CRF estimated from a regression equation for age was converted to %age-predicted CRF using (achieved CRF/age-predicted CRF)*100. Hazard ratios (HRs) (95% confidence intervals, CIs) were calculated for SCD.

Results During a median follow-up of 28.2 years, 260 SCDs occurred. There was a dose-response relationship between age-predicted CRF and SCD. A 1 standard deviation increase in %age-predicted CRF was associated with a decreased risk of SCD in analysis adjusted for established risk factors (HR 0.60; 95% CI 0.53–0.70), which remained consistent on further adjustment for several potential confounders including alcohol consumption, physical activity, socioeconomic status and systemic inflammation (HR 0.73; 95% CI 0.62–0.85). The corresponding adjusted HRs (95% CIs) were 0.34 (0.23-0.50) and 0.52 (0.34-0.79) respectively, when comparing extreme quartiles of %age-predicted CRF levels. The HRs for the associations of absolute CRF levels with SCD risk in the same participants were similar.

Conclusions Percentage of age-predicted CRF is continuously, strongly and independently associated with risk of SCD and it is comparable to absolute CRF as a risk indicator for SCD.

Keywords: percentage of age-predicted cardiorespiratory fitness; cardiopulmonary exercise testing; cardiorespiratory fitness; sudden cardiac death; cohort study; risk factor

Introduction

Clinical exercise testing with the assessment of cardiorespiratory fitness (CRF) is a functional risk assessment tool.[1] During recent years, the assessment of CRF has achieved further merit and is considered to be a vital part of cardiovascular risk assessment.[2] Peak oxygen uptake (VO_{2peak}) is commonly used as a measure of CRF and its gold standard measure is maximal-effort cardiopulmonary exercise testing (CPET) with ventilatory expired gas analysis.[3] A wealth of data based on large-scale epidemiological studies provide consistent evidence on strong inverse and independent associations between CRF and vascular outcomes as well as all-cause mortality.[2, 4, 5]

VO_{2peak} is strongly influenced by age, a key determinant of CRF levels.[6] There are some earlier evidence which suggest that CRF expressed as a percentage of the value predicted on the basis of age (percentage of age-predicted CRF, %age-predicted CRF) is inversely associated with cardiovascular disease (CVD) and coronary heart disease (CHD).[2, 7] Percentage of age-predicted CRF may be a better risk indicator for fatal cardiac outcomes compared to absolute CRF. No study has previously assessed the association between %age-predicted CRF and SCD. In this context, we aimed to study the prospective association of %age-predicted CRF with the risk of SCD in a population-based cohort of men. To put the strength of the association of %age-predicted CRF with the risk of SCD into context, a comparison was made with the association between absolute CRF and SCD risk in the same sample.

Methods

Study design and participants

For the current study, we employed the Kuopio Ischaemic Heart Disease (KIHD) study, a population-based prospective cohort study designed to investigate investigate potential risk factors for atherosclerotic CVD and other related chronic disease outcomes. In total, 3433 randomly selected men were potentially

eligible for the study and of these, 3235 were actually eligible for inclusion. Of the 3235 men, 2682 volunteered to participate and 553 declined to give informed consent or did not respond to the invitation. Baseline examinations were performed between March 1984 and December 1989. A random subset of participants at baseline underwent re-examinations at 4, 11 and 20 years after baseline. Given that data on CRF repeat measurements were only available in 584 participants, we employed only baseline data for the current analysis. The current analysis is based on 2,276 men who had complete data on %age-predicted CRF, absolute CRF, potential confounders and SCD outcomes. The study was approved by the Research Ethics Committee of the University of Eastern Kuopio. The research reported in this paper adhered to the Declaration of Helsinki guidelines. Each participant included in the study provided written informed consent. This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary Table 1**).

Assessment of %age-predicted CRF

Peak oxygen uptake, used as a measure of CRF, was assessed using a respiratory gas analyzer (Medical Graphics, MCG, St. Paul, Minnesota) during a submaximal symptom-limited cycle ergometer exercise tolerance test.[8]All exercise tests were conducted under the supervision of an experienced physician and assisted by an experienced nurse to ensure safety, and electrocardiogram, blood pressure, and heart rate were registered during the exercise test. The VO_{2peak} was defined as the highest value for or the plateau of oxygen uptake. The VO_{2peak} was expressed in metabolic equivalents (METs), which was the unit used in the regression equation used to estimate age-predicted CRF.[9] One MET corresponds to an oxygen uptake of 3.5 ml/kg/min.[10] Age-predicted CRF was estimated using the regression equation 18.4-(0.13 x age) and the %age-predicted CRF was defined as: (achieved CRF/age-predicted CRF)*100.[9, 11]

Assessment of risk markers

Details on the collection of blood specimens and the measurement of blood biomarkers including serum lipids, lipoproteins and glucose have been described in previous reports.[12] High-sensitivity C-reactive protein (hsCRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). Self-administered questionnaires were used to assess sociodemographic characteristics, lifestyle characteristics such as smoking and alcohol consumption, baseline diseases and use of medication. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in metres. Adulthood socioeconomic status (SES) was assessed as reported previously.[13]

Ascertainment of outcomes

We included all SCDs that occurred from study enrollment through to 2017. The sources of information on SCDs were based on a comprehensive review of available hospital records, questionnaires administered to health workers, interviews with informants, registers of deaths as well as death certificates and medico-legal reports. A death was determined to be an SCD when it occurred within 1 hour of the onset of an abrupt change in symptoms or within 24 hours after the onset of symptoms, including non-witnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death.[10] The witnessed subject was to have been alive and symptom free within 1 hour before the event.

Statistical analysis

Baseline data were summarised using descriptive statistics presented as means (standard deviation, SD),

median (interquartile range, IQR) and (N) percentages. We calculated partial correlation coefficients to assess the cross-sectional associations of %age-predicted CRF with several risk factors and markers. Hazard ratios (HRs) with 95% confidence intervals (CIs) for SCD were calculated using Cox proportional hazard models, after confirming no major departure from the assumptions of the proportionality of hazards using Schoenfeld residuals. We explored the shape of the relationship between %age-predicted CRF and SCD by calculating HRs within quartiles of baseline %age-predicted CRF and plotted against mean values of %age-predicted CRF within each quartile. Floating variances were used to calculate 95% CIs for the log hazard ratio in each group (including the reference group), to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile).[14] The dose-response nature of the association was characterised using a restricted cubic spline with knots at the 5th, 35th, 65th and 95th percentiles of the distribution of %age-predicted CRF in a multivariable adjusted model. Percentage of age-predicted CRF was modelled as both continuous [per SD increase] and categorical (quartiles) variables. Hazard ratios were progressively adjusted for in three models: (Model 1) smoking status, history of diabetes, systolic blood pressure (SBP), total cholesterol and high-density lipoprotein cholesterol (HDL-C); (Model 2) model 1 plus BMI, FPG, alcohol consumption, prevalent CHD, use of cholesterol medication, prevalent atrial fibrillation (AF), physical activity and SES and (Model 3) model 2 plus hsCRP. To assess statistical evidence of any differences in associations across levels/categories of pre-specified individual level characteristics, we performed subgroup analyses using tests of interaction. To account for any biases due to reverse causation, sensitivity analysis involved excluding the first five years of follow-up. Direct comparisons were made to the association of absolute CRF with SCD risk in the same set of participants. All statistical analyses were conducted using Stata MP version 16 (Stata Corp, College Station, Texas).

Results

Baseline characteristics and correlates of %age-predicted CRF

The mean (SD) age and %age-predicted CRF at baseline was 53 (5) years and 86.3 (21.5)% respectively (**Table 1**). Weak to moderately strong inverse correlations were observed between %age-predicted CRF and the following: age, alcohol consumption, BMI, blood pressure, lipids (total cholesterol and triglycerides) and hsCRP. Weak positive correlations were observed for physical activity and HDL-C. Percentage of age-predicted CRF was strongly and positively correlated with absolute CRF (r=0.76). Values of %age-predicted CRF were significantly lower in men with diabetes compared with men without diabetes, smokers compared to non-smokers, men with prevalent CHD compared to men without prevalent CHD and men using lipid-lowering medication compared to men not using lipid-lowering medication.

%age-predicted CRF and risk of SCD

During a median (IQR) follow-up of 28.2 (19.1-30.6) years (54,836 person-years at risk), a total of 260 SCDs were recorded. In analyses adjusted for several cardiovascular risk factors (smoking status, history of diabetes, SBP, total cholesterol and HDL-C), %age-predicted CRF was approximately linearly and inversely associated with SCD (**Figure 1A**). A restricted cubic spline curve showed the risk of SCD decreased steeply and continuously with increasing %age-predicted CRF from to 52 to 102%, beyond which there was no further decrease in the risk of SCD (*p*-value for non-linearity=.006) (**Figure 1B**). **Table 2** shows the association of %age-predicted CRF with SCD. In analysis adjusted for smoking status, history of diabetes, SBP, total cholesterol and HDL-C, the HR (95% CI) per 1 SD increase in %age-predicted CRF for SCD was 0.60 (0.53-0.70), which was minimally attenuated to 0.72 (0.62-0.84) after further adjustment for BMI, FPG, alcohol consumption, prevalent CHD, use of cholesterol medication,

prevalent AF, physical activity and SES. The HR (95% CI) remained consistent on additional adjustment for hsCRP 0.73 (0.62-0.85). Alternatively, comparing the top versus bottom quartile of %age-predicted CRF, the corresponding adjusted HRs (95% CIs) for SCD were 0.34 (0.23-0.50), 0.51 (0.33-0.77) and 0.52 (0.34-0.79) respectively. The associations demonstrated did not vary significantly by levels or categories of several clinically relevant characteristics, except for evidence of effect modification by total cholesterol (*p* for interaction=.01). (**Figures 2**). A stronger inverse association between % age-predicted CRF and SCD was observed in men with lower total cholesterol levels (<5.84 mmol/l) compared to men with higher levels (≥5.84 mmol/l). The association between %age-predicted CRF and SCD persisted in analyses that excluded the first five years of follow-up in the whole population (**Supplementary Table 2**).

In analyses that assessed the association of absolute CRF with SCD risk in the same set of study participants with consistent adjustment for confounders, the HRs were similar to those of the main analyses (**Table 3**).

Discussion

Key findings

In this population-based prospective cohort study of men, we found strong independent associations of %age-predicted CRF with SCD, which was consistent with a continuous dose-response relationship. The restricted cubic spline curve showed the risk of SCD decreased steeply and continuously with increasing % age-predicted CRF levels. The associations of %age-predicted CRF with SCD risk remained generally consistent across several clinically relevant subgroups, except for evidence of effect modification by total cholesterol.

Comparison with other studies

Few studies have assessed the relevance of CRF as an independent predictor of SCD at the population level. The risk of SCD in asymptomatic US men and women was significantly lower in those with moderate to high levels of CRF.[15] We have also shown that that directly measured VO_{2peak} is related to SCD in a population of middle-aged men.[16] In the current study, %age-predicted CRF was correlated with CRF, as measured by VO_{2peak}..[3, 17] In recent evaluations, we showed that VO_2 at AT and VO_2 at VT were each strongly, inversely, linearly and independently associated with the risk of fatal cardiovascular and all-cause mortality events.[18, 19] There is however limited data on the potential clinical application of %age-predicted CRF as a useful CPET variable. However, Myers and colleagues has earlier compared exercise capacity with other clinical and exercise test variables including the percentage of the age-predicted exercise capacity.[11] They demonstrated that absolute peak CRF was a slightly stronger predictor of the risk of overall death than the percentage of the age-predicted exercise capacity.[11] Our current results on % age-predicted CRF and SCD outcomes cannot be directly compared to these earlier findings with different CRF definitions and main outcomes.

Mechanisms involved

Percentage of age-predicted CRF is an index of aerobic exercise capacity and determined by habitual aerobic activity. It has been shown that moderate intensity regular exercise for at least 6 months can improve aerobic exercise capacity by 1 MET.[20] These pathways involve both physiological and metabolic processes which include: (i) improvement in levels of vascular risk factors such as lipids, glucose, blood pressure, biomarkers of insulin resistance and cardiac function;[21, 22] (ii) reduction in inflammatory markers;[23] (iii) improvement in endothelial function;[24] (iv) regulation of white adipose tissue;[25] and (v) increase in cardiac output, left ventricular function, oxygen utilization, and the formation of collateral vessels;[11, 24]. Some evidence suggests that high CRF is related to attenuated coronary calcification and increased plaque stabilization.[2] Another mechanism by which good % age-predicted CRF may be

protective of SCD is the effect of regular physical activity on cardiac autonomic regulation. Increasing evidence supports the role of impairment in cardiac autonomic function among subjects who are vulnerable to fatal arrhythmias.[2627] Though habitual aerobic physical activity ultimately improves CRF, several other factors are involved which include baseline health and fitness status, type, duration, and intensity of physical activity, as well as genetic factors. Genetic factors account for 25-40% of the variation in CRF level.[28]

Implications of Findings

Large epidemiological studies have not been able to identify specific risk markers for SCD in the general population even though risk markers for atherosclerosis may help to identify those at risk of SCD. The best-known predictor of death is depressed left ventricular ejection fraction (LVEF), which has been consistently associated with an increased risk of SCD in patient populations. Nonetheless, LVEF is limited by low sensitivity, as the majority of people who suffer from SCD have a preserved LVEF. Over the last decade, the volume of literature in support of CPET use in risk assessment has increased tremendously, triggering the release of recommendations by guideline bodies and associations.[3] The strong and graded nature of the relationship between %age-predicted CRF and SCD risk suggests that %age-predicted CRF may be potentially suitable for population-level risk assessment. Given the underutilization of CPET parameters, there have been calls for continued research into their clinical utility across all patient populations.[29]

Strengths and limitations

We have conducted the first prospective evaluation of the association between %age-predicted CRF and SCD risk. SCD is a relatively rare event in the general population, however, we employed a large cohort that was prospectively followed over two decades with no losses to follow-up recorded. Our sample comprised an ethnically and genetically homogeneous cohort representative of middle-aged men who

may have CVD risk factors. We performed comprehensive and robust statistical analyses which included adjustment for several available confounders, assessment of dose-response associations, subgroup analyses in clinically relevant groups and sensitivity analyses. There were some limitations, including inability to generalise the findings to women, younger and older age groups and other ethnicities. It would have been interesting to have a similar cohort with women which could be compared to the cohort of men. In the KIHD study, CRF was assessed using a cycling exercise test protocol and studies on treadmill exercise testing will be needed. The actual peak oxygen uptake may be lower during a cycling exercise protocol due to localized muscular fatigue compared to using a treadmill protocol. Due to lifestyle changes, chronic disease and aging, measurement errors and recall bias in exposure estimation in prospective cohort studies, analysis using only baseline measurements of an exposure could underestimate the true strength of any association between exposure and outcome (i.e. "regression dilution bias"[30]). Though the associations were strong, these observed associations could still be underestimates because of the inability to correct for regression dilution bias, as the findings were based on single baseline values of %age-predicted CRF. Our reproducibility substudies of CRF measurements within the KIHD study showed a high within-person variability in CRF levels measured many years apart (regression dilution ratio=0.58).[31] As commonly recognized with observational study designs, residual confounding due to unknown or unmeasured confounding remained a potential alternative explanation for a causal relationship of our findings; however, causality is not a limiting issue of the observed results as we aimed to primarily evaluate a new clinically measurable and useful functional risk marker for assessing SCD for other potential risk assessment tests.

Conclusions

Percentage of age-predicted CRF is continuously, strongly and independently associated with risk of SCD and it is comparable to absolute CRF as a risk indicator for SCD in a general population of men. These findings suggest that good VO_{2peak} is inversely related to SCD risk in a general population.

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Competing interest All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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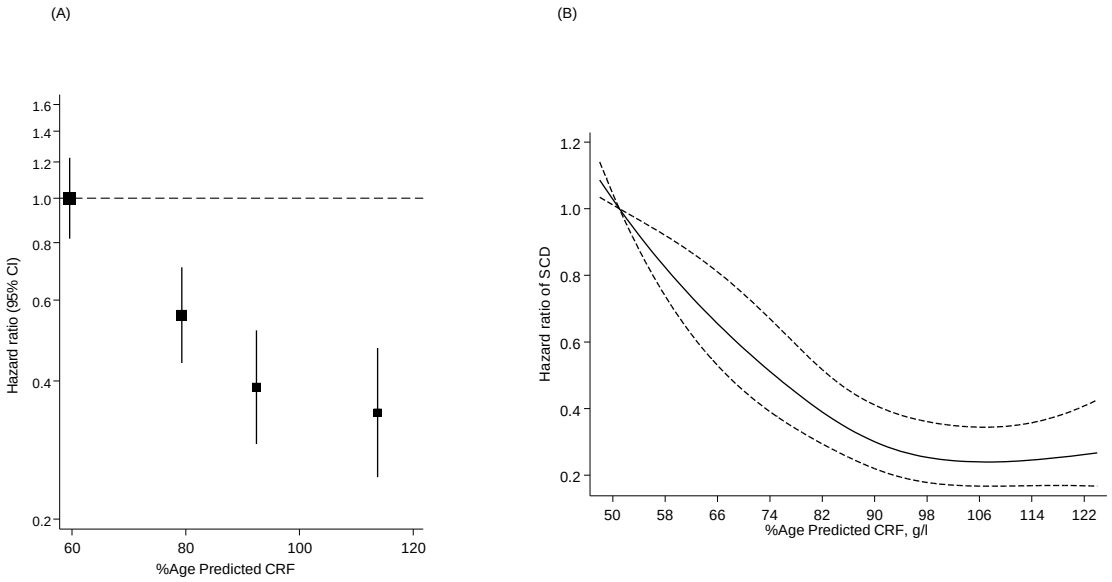
Figure Legends

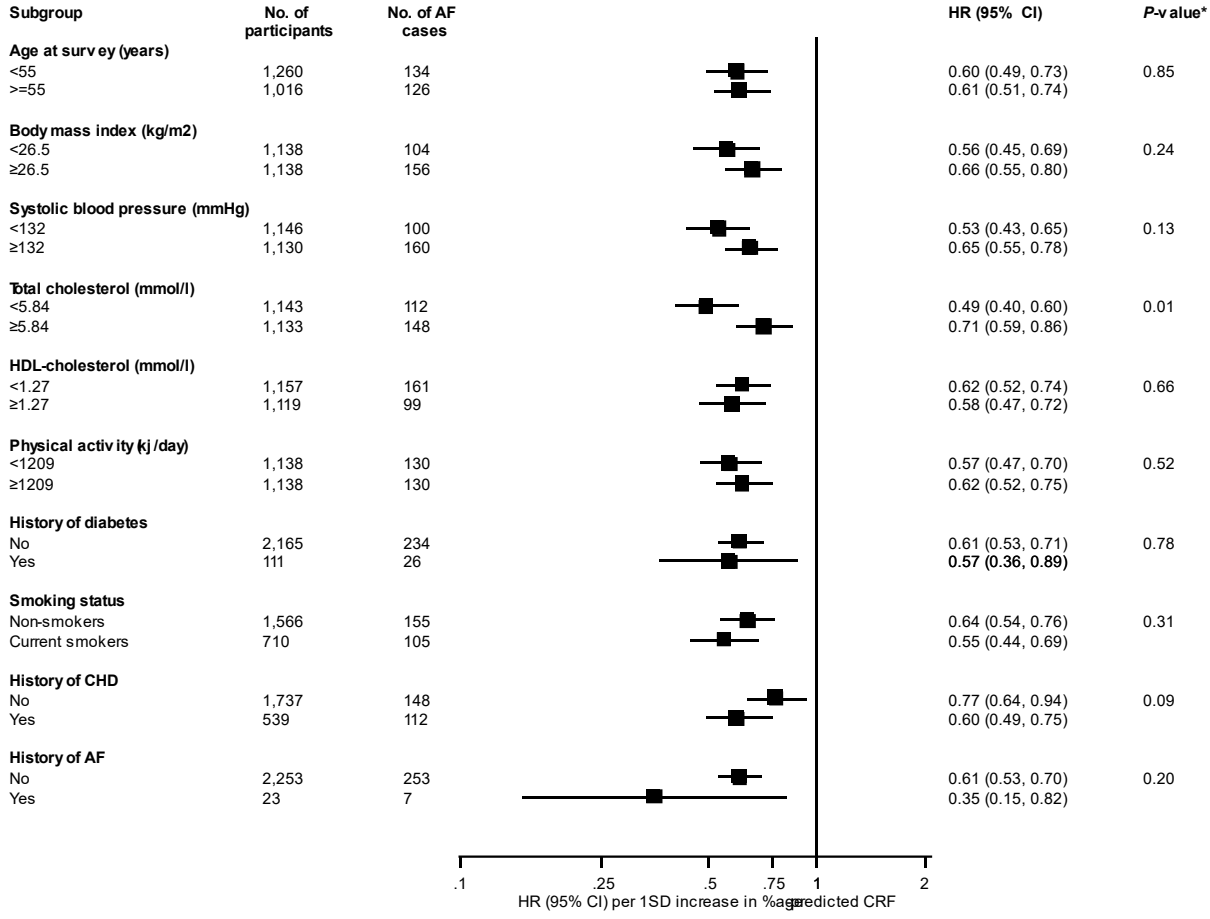
Figure 1. Shape of association between %age-predicted CRF and sudden cardiac death



%age-predicted, percentage of age-predicted; CRF, cardiorespiratory fitness

(A) Hazard ratios for sudden cardiac death by quartiles of %age-predicted CRF using floating absolute risks; (B) Restricted cubic spline of the hazard ratios of sudden cardiac death with %age-predicted CRF Models were adjusted for smoking status, history of diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol

Figure 2. Association of %age-predicted CRF with sudden cardiac death in clinically relevant subgroups



Hazard ratios were adjusted for smoking status, history of diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol; %age-predicted, percentage of age-predicted; AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol; and physical activity are median values.

Table 1. Baseline participant characteristics and correlates of percentage of age-predicted CRF

	Mean (SD), median (IQR), or %	Pearson correlation r (95% CI)[a]	Percentage difference (95% CI) in values of percentage of age-predicted exercise capacity per 1 SD higher or compared to reference category of correlate[b]
Percentage of age-predicted exercise capacity	86.3 (21.5)	-	-
Questionnaire/Prevalent conditions			
Age at survey (years)	52.9 (5.1)	-0.10 (-0.14, -0.06)***	-2.09% (-2.97, -1.21)***
Alcohol consumption (g/week)	32. (6.4-91.9)	-0.09 (-0.13, -0.05)***	-1.91% (-2.86, -0.97)***
History of diabetes			
No	2,165 (95.1)	-	ref
Yes	111 (4.9)	-	-14.93% (-18.98, -10.88)***
Smoking status			
Other	1,566 (68.8)	-	ref
Current	710 (31.2)	-	-7.33% (-9.21, -5.44)***
History of CHD			
No	1,737 (76.3)	-	ref
Yes	539 (23.7)	-	-16.64% (-18.61, -14.68)***
History of AF			
No	2,253 (99.0)		ref
Yes	23 (1.0)		-0.91% (-9.74, 7.92)
Medication for dyslipidemia			
No	2,263 (99.4)	-	ref
Yes	013 (0.6)	-	-24.47% (-36.15, -12.80)***
Physical measurements			
BMI (kg/m^2)	26.9 (3.5)	-0.37 (-0.40, -0.33)***	-7.91% (-8.73, -7.09)***
SBP (mmHg)	134 (17)	-0.14 (-0.18, -0.10)***	-2.96% (-3.84, -2.09)*
DBP (mmHg)	89 (10)	-0.12 (-0.17, -0.08)***	-2.68% (-3.56, -1.81)***
Physical activity (kj/day)	1208 (628-1988)	0.13 (0.09, 0.17)***	2.73% (1.85, 3.60)***
CRF (ml/min)	2407 (633)	0.76 (0.74, 0.78)***	16.29% (15.72, 16.87)***
Blood-based markers			
Total cholesterol (mmol/l)	5.91 (1.07)	-0.08 (-0.12, -0.04)*	-1.73% (-2.61, -0.85)**
HDL-C (mmol/l)	1.29 (0.30)	0.26 (0.22, 0.29)***	5.50% (4.65, 6.35)***
Triglycerides (mmol/l)	1.09 (0.79-1.54)	-0.31 (-0.35, -0.28)***	-6.77% (-7.61, -5.92)***
Fasting plasma glucose (mmol/l)	5.33 (1.19)	-0.20 (-0.23, -0.16)***	-4.21% (-5.07, -3.34)***
High-sensitivity CRP (mg/l)	1.24 (0.69-2.37)	-0.35 (-0.38, 0.31)***	-7.45% (-8.28, -6.62)***

AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; [a], Pearson correlation coefficients between percentage of age-predicted exercise capacity and the row variables;. [b], Percentage change in values of percentage of age-predicted exercise capacity per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean values of percentage of age-predicted exercise capacity for the category versus the reference); asterisks indicate the level of statistical significance: *, p<0.05; **, p<0.01; ***, p<0.001

Table 2. Association between percentage of age-predicted CRF and risk of sudden cardiac death

Percentage of age-predicted exercise capacity	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	260 / 2,276	0.60 (0.53 to 0.70)	<.001	0.72 (0.62 to 0.84)	<.001	0.73 (0.62 to 0.85)	<.001
Quartile 1	108 / 569	ref		ref		ref	
Quartile 2	66 / 569	0.56 (0.41 to 0.76)	<.001	0.70 (0.51 to 0.97)	.032	0.71 (0.52 to 0.98)	.039
Quartile 3	47 / 569	0.39 (0.27 to 0.55)	<.001	0.54 (0.37 to 0.79)	.001	0.56 (0.38 to 0.81)	.002
Quartile 4	39 / 569	0.34 (0.23 to 0.50)	<.001	0.51 (0.33 to 0.77)	.001	0.52 (0.34 to 0.79)	.002

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation

Model 1: Adjusted for smoking status, history of diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein-cholesterol

Model 2: Model 1 plus body mass index, fasting plasma glucose, alcohol consumption, prevalent coronary heart disease, use of cholesterol medication, prevalent atrial fibrillation, total physical activity and socioeconomic status

Model 3: Model 2 plus high-sensitivity C-reactive protein

Table 3. Association between CRF and risk of sudden cardiac death

CRF (ml/min)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	260 / 2,276	0.70 (0.60 to 0.81)	<.001	0.74 (0.63 to 0.87)	<.001	0.75 (0.64 to 0.88)	<.001
Quartile 1	112 / 573	ref		ref		ref	
Quartile 2	68 / 565	0.56 (0.41 to 0.76)	<.001	0.61 (0.44 to 0.83)	.002	0.61 (0.45 to 0.84)	.002
Quartile 3	34 / 569	0.30 (0.20 to 0.45)	<.001	0.33 (0.22 to 0.51)	<.001	0.34 (0.22 to 0.51)	<.001
Quartile 4	46 / 569	0.46 (0.32 to 0.68)	<.001	0.51 (0.34 to 0.76)	.001	0.52 (0.35 to 0.77)	.001

See abbreviations and explanations from the Table 2.

SUPPLEMENTARY MATERIAL

Supplementary Table 1	STROBE Statement
Supplementary Table 1	Association between percentage of age-predicted CRF and risk of sudden cardiac death, on excluding the first 5 years of follow-up

Supplementary Table 1. STROBE Statement

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 3-4
Methods			
Study design	4	Present key elements of study design early in the paper	Study design and participants
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Study design and participants
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Study design and participants
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Statistical analyses
Study size	10	Explain how the study size was arrived at	Statistical analyses
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analyses
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analyses
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical analyses
		(*c*) Explain how missing data were addressed	Not applicable

		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Statistical analyses
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Study design and participants
		(b) Give reasons for non-participation at each stage	Study design and participants
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Tables 2-3; Figures 1-2
		(*b*) Report category boundaries when continuous variables were categorized	Results; Tables 2-3; Figures 1-2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results; Figure 2; Supplementary Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion - Summary of main findings
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

Supplementary Table 1. Association between percentage of age-predicted CRF and risk of sudden cardiac death, on excluding the first 5 years of follow-up

Percentage of age-predicted exercise capacity	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	223 / 2,171	0.65 (0.56 to 0.76)	<.001	0.77 (0.65 to 0.91)	.002	0.78 (0.66 to 0.92)	.004
Quartile 1	88 / 543	ref		ref		ref	
Quartile 2	59 / 543	0.62 (0.44 to 0.87)	.005	0.76 (0.54 to 1.08)	.12	0.77 (0.54 to 1.09)	.14
Quartile 3	40 / 543	0.42 (0.28 to 0.61)	<.001	0.56 (0.37 to 0.84)	.005	0.58 (0.38 to 0.87)	.009
Quartile 4	36 / 542	0.38 (0.25 to 0.57)	<.001	0.54 (0.35 to 0.84)	.006	0.56 (0.36 to 0.87)	.009

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation

Model 1: Adjusted for smoking status, history of diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein-cholesterol

Model 2: Model 1 plus body mass index, fasting plasma glucose, alcohol consumption, prevalent coronary heart disease, use of cholesterol medication, prevalent atrial fibrillation, total physical activity and socioeconomic status

Model 3: Model 2 plus high-sensitivity C-reactive protein