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Cardiorespiratory Fitness and the Risk of Serious Ventricular Arrhythmias: A Prospective Cohort Study

Brief title: Fitness and serious ventricular arrhythmias

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ABSTRACT

Cardiorespiratory fitness (CRF) is an established risk factor for cardiovascular disease (CVD) outcomes. However, the relationship of CRF with risk of ventricular arrhythmias (VAs) is unknown. We aimed to assess the prospective association of CRF with the risk of serious VAs. CRF, as measured by maximal oxygen uptake, was assessed using a respiratory gas exchange analyser in 2,299 middle-aged men in the Kuopio Ischemic Heart Disease prospective cohort. We corrected for within-person variability in CRF levels using data from repeat measurements taken 11 years apart. During a median follow-up of 25.3 (interquartile range, 18.7-27.2) years, 73 serious VAs were recorded. The age-adjusted regression dilution ratio of CRF was 0.58 (95% confidence interval [CI]: 0.53-0.64). In analysis adjusted for age, the hazard ratio (HR) (95% CI) for serious VAs per 1 standard deviation increase in CRF was 0.64 (0.49-0.84). The association persisted on additional adjustment for body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease (CHD), smoking, history of diabetes, cholesterol, alcohol consumption, and physical activity 0.64 (0.47 to 0.86). The corresponding adjusted HRs (95% CIs) were 0.29 (0.14-0.59) and 0.29 (0.13-0.62), respectively, when comparing the top versus bottom tertiles. The associations were stronger on correction for regression dilution bias, remained consistent on exclusion of men with a history of CHD, and did not vary importantly in several relevant clinical subgroups. CRF is inversely associated with future risk of serious VAs, independently of several CVD risk factors. Further research is needed to assess the causal relevance of these findings.

Keywords: cardiorespiratory fitness; maximal oxygen uptake; ventricular arrhythmias; regression dilution; risk factor

Abbreviations

BMI = body mass index

BP = blood pressure

CI = confidence interval

CRF = cardiorespiratory fitness

CHD = coronary heart disease

CVD = cardiovascular disease

HR = hazard ratio

PA = physical activity

RDR = regression dilution ratio

SD = standard deviation

SCD = sudden cardiac death

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Introduction

Physical activity (PA) is well established to have important health benefits and these include the prevention of several adverse vascular and non-vascular outcomes.[1-3] Cardiorespiratory fitness (CRF), as measured by maximal oxygen uptake (VO_{2max}) and considered the gold standard for assessing aerobic exercise capacity, is an indicator of cardiopulmonary function, and largely reflects level of PA, as well as genetic components.[4-7] CRF is an established and independent risk marker for coronary heart disease (CHD), composite cardiovascular disease (CVD) outcomes, as well as all-cause mortality.[8] Emerging evidence also suggests that higher levels of CRF are protective of atrial fibrillation (AF), which is the most common arrhythmia worldwide with clinical significance.[9, 10] Serious ventricular arrhythmias (VAs), including ventricular tachycardia (VT) and ventricular fibrillation (VF), are life threatening arrhythmias and their common manifestation is sudden cardiac death (SCD), typically occurring in the setting of structural heart disease;[11] CHD is the single most common etiologic factor predisposing patients to VF.

Major CVD risk factors for SCD, such as hypertension, smoking, obesity, and diabetes are also arrhythmogenic substrates.[12] Given that CHD, SCD and VAs have shared risk factors and with the established relationship between CRF and these outcomes (CHD and SCD),[13, 14] we hypothesized that CRF would be linked to the risk of VAs. Despite acute coronary artery occlusion being the main trigger for VAs,[12] the pathogenesis of VAs is still poorly understood. It appears that other additional factors may be involved. Potentially, CRF may be an emerging risk factor for VAs; however, to date, there has been no previous prospective evaluation of the association of CRF with risk of serious VAs. In this context, we aimed to assess the nature and magnitude of the prospective association of CRF with risk of serious VAs (VT and/or VF), using a population-based cohort of 1,974 apparently healthy men from eastern Finland. We have previously shown that CRF exhibits high within-person variability,[15] which could be the result of measurement errors in its estimation, lifestyle changes, aging, and chronic disease. Therefore, analysis using only baseline measurements of CRF could underestimate the true strength of any association between CRF and outcome (i.e. "regression dilution bias"[16]). To clarify this issue, using repeat measurements of CRF performed several years apart in a random sample of participants, we estimated and corrected for the effect of this regression dilution bias.

Methods

Study population

Our study population is based on the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a general population-based prospective cohort study comprising of a representative sample of men aged 42-61 years recruited from the city of Kuopio and its surrounding rural communities in eastern Finland. A complete description of the study design, objectives, and sampling strategy has been previously described.[17] The actual baseline cohort consisted of 2,682 participants who had baseline measurements performed between 03/01/1984 and 12/31/1989. In the current analysis, complete information on CRF, relevant covariates, and outcomes was available for 2,299 men. The research protocol was approved by the institutional review board of the University of Eastern Finland. All study procedures were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Assessment of CRF and covariates

Details of the measurements of CRF and risk markers have been described in previous reports.[18-22] Briefly, maximal oxygen uptake (VO_{2max}) was used as a measure of CRF, which was assessed using a respiratory gas exchange analyser during cycle ergometer exercise testing. Repeat measurements of CRF were performed 11 years after baseline in a random subset of the study participants.[23, 24] The cholesterol content of lipoprotein fractions were measured from fresh samples after combined ultracentrifugation and precipitation and were assessed enzymatically (Boehringer Mannheim, Mannheim, Germany).[23] Self-administered questionnaires were used to assess smoking, alcohol consumption, blood pressure (BP), use of medication, and baseline diseases.[23] History of CHD was based on a previous myocardial infarction, angina pectoris, the use of nitroglycerin for chest pain once a week or more frequently for chest pain. Physical activity (PA) was assessed from a 12-month physical activity history modified from the Minnesota Leisure-Time Physical Activity Questionnaire.[25]

Ascertainment of outcomes

All serious VAs that occurred from study enrollment to 12/31/2013 were included. Outcomes were collected by linkage to the National Hospital Discharge Register. The diagnostic classification of VAs was coded according to ICD-9 codes (427.41) or ICD-10 codes (I47.2, I49.0) codes. The definition of non-sustained or sustained VT and/or VF was based on electrocardiography, leading to hospital records documentation.[26] Documents were cross-checked in detail by two physicians. The Independent Events Committee, masked to clinical data, performed classification of outcomes.

Statistical Analyses

Variables with skewed distributions were natural log transformed to achieve approximately symmetrical distributions. Descriptive data were presented as means (standard deviation, SD) or medians (interquartile range, IQR) reported for continuous variables and n (percentages) for categorical variables. The partial correlation coefficients were calculated using linear regression models adjusted for age, to assess the cross-sectional associations of CRF with various risk markers. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models, after confirming no major departure from the assumptions of proportionality of hazards using Schoenfeld residuals.[27] CRF was modelled as both continuous [per SD increase] and categorical (tertiles) variables. Hazard ratios were calculated with adjustment for confounders in three models: (model 1) age; (model 2) model 1 plus systolic blood pressure (systolic BP), prevalent CHD, smoking status and history of diabetes mellitus; (model 3) model 1 plus history of hypertension, total cholesterol, alcohol consumption, and physical activity. To quantify and correct for within-person variability (regression dilution bias) in CRF levels, which is, the extent to which an individual's CRF measurements vary around the long-term average exposure levels ("usual levels"),[28] adjusted regression dilution ratios (RDRs) were calculated by regressing available repeat measurements of CRF on baseline values.[29] This involved dividing the estimated disease association (log hazard ratio and its 95% confidence intervals) by the RDR. Finally, we used formal tests of interaction tests to assess statistical evidence of effect modification by individual characteristics, such as age, BMI, and other clinically relevant characteristics. All statistical analyses were conducted using Stata version 15 (Stata Corp, College Station, Texas).

Results

The overall mean [standard deviation (SD)] age and CRF of study participants at baseline were 53 (5) years and 30.3 (8.0) ml/kg/min, respectively (**Table 1**). The age-adjusted mean CFRF was 30.2 ml/kg/min. CRF was weakly to moderately correlated with several risk markers. There were inverse correlations of CRF with age, alcohol consumption, BMI, BP, total cholesterol, and fasting plasma glucose; whereas, positive correlations were observed with PA and HDL-C. Repeat measurements of CRF taken at 11 years after baseline were available in a random sample of 576 men. The overall age-adjusted RDR of CRF was 0.58 (95% CI: 0.53 to 0.64), suggesting that the association of CRF with risk of serious VAs using baseline measurements of CRF only, could under-estimate the risk by [(1/0.58)-1]*100 = 72%.

During a median (interquartile range) follow-up of 25.3 (18.7-27.2) years, 73 incident serious VAs (annual rate 1.44/1,000 person-years at risk; 95% CI: 1.15 to 1.82) were recorded. Cumulative hazard curves demonstrated a lower risk of VAs among males in the top tertile of CRF levels compared to those in the bottom tertile (P<.001 for log-rank test; **Figure 1**). The age-adjusted HR per 1 SD increase in CRF was 0.64 (95% CI: 0.49 to 0.84), which persisted on additional adjustment for systolic BP, prevalent CHD, smoking status and history of diabetes was 0.68 (95% CI: 0.51 to 0.91). Comparing the extreme tertiles of CRF levels, the corresponding adjusted HRs were 0.29 (95% CI: 0.14 to 0.59) and 0.33 (95% CI: 0.16 to 0.69), respectively. Correction for regression dilution bias strengthened the respective associations (**Table 2**). The overall results remained consistent in a third model that adjusted for age, history of hypertension, total cholesterol, alcohol consumption, and physical activity. Given that CHD is a major risk factor for cardiac arrhythmias, we repeated the analysis after excluding participants with a history of CHD. The associations remained qualitatively similar, 0.59 (95% CI: 0.42 to 0.82) and 0.69 (95% CI: 0.49 to 0.98), respectively per 1 SD increase in CRF, on adjustment for age and further for systolic BP, prevalent CHD, smoking status and history of diabetes. The association between CRF and risk of VAs was not significantly modified by any clinically relevant characteristic (**Figure 2**).

Discussion

We have conducted the first prospective evaluation of the association between CRF and risk of serious VAs in a cohort of middle-aged Finnish men aged 42-61 years. Our descriptive analyses showed mean CRF levels of this population were consistent with reference ranges of CRF provided by a representative population of Finnish men and women aged 57-78

years.[30] Evaluation of the associations showed that CRF, an index of cardiorespiratory functioning and exercise capacity, was inversely associated with future risk of serious VAs and independent of several established and emerging CVD risk factors. In an analysis that corrected for within-person variability in CRF values, we also observed that using baseline measurements of CRF only to assess the association between CRF and serious VAs could underestimate the strength of the association under-estimate by about 72%. There was no evidence of effect modification on the association by several clinically relevant characteristics.

We are unable to compare the current findings in the context of previous work, as to our knowledge this is the first study to evaluate the prospective association between CRF and serious VAs. However, several epidemiological studies have consistently and robustly shown that CRF is inversely and independently associated with CVD, as well as all-cause mortality.[5, 6, 8, 20, 31] This association has been demonstrated for CVD specific endpoints, such as acute myocardial infarction,[22] CHD,[20] stroke,[32] SCD,[13, 31] heart failure,[33] as well as AF.[10, 33] Our current findings are, therefore, not surprising, given that VAs and these CVD outcomes share many common risk factors. Nevertheless, given that this is the first prospective study to evaluate this association, other large-scale prospective studies are still needed to confirm the current findings.

Several mechanisms have been postulated to underpin the protective effects of CRF on CVD and all-cause mortality outcomes, and these include both physiological and metabolic processes, such as (i) beneficial modulation of CVD risk factors[34, 35]; (ii) regulation of cardiac autonomic function and vagal control of heart rate;[36] (iii) reduction in inflammation;[37, 38] and (iv) improvement in endothelial function, BP and lipid levels.[39, 40] It is possible that the association demonstrated between CRF and serious VAs may also be exerted via some of these pathways. However, further research is needed to elucidate the mechanistic pathways involved in the relationship between CRF, serious VAs and SCD.

The overall evidence suggests that enhanced CRF through physical activity (particularly aerobic activity) yields significant cardiovascular benefits even in individuals at an advanced age. There is established evidence that a physically active lifestyle which promotes good CRF levels, has significant health benefits and is associated with reduced risk of mortality.[8] Both the 2008 and 2018 Physical Activity Guidelines[41, 42] recommend 150 to 300 minutes per week of moderate-intensity physical activity or 500 to 1,000 MET-minutes of moderate-to-vigorous physical activity, with emphasis on low-to-moderate intensity physical activity due to better adherence and safety issues at the population level.

However, majority of the general population do not comply with these recommendations. The 2018 Physical Activity Guidelines[42] further provide methods of promoting physical activity levels and these include: (i) individual level interventions which are based on behavioral change theories; (ii) school-based and community-wide physical activity programs; (iii) environmental and policy changes that improve access to physical activity; and (iv) information and communication technology. Clinicians should also be encouraged to promote regular physical activity in their patients. The established body of epidemiological and clinical evidence demonstrates that CRF is a potentially stronger predictor of CVD and mortality than established risk factors such as smoking, hypertension, high cholesterol, and type 2 diabetes mellitus. In addition, CRF is a simple, widely available measure that can be measured easily in clinical practice and adds additional prognostic value beyond conventional risk factors in predicting CVD and mortality risk.[8, 43, 44] CRF should be considered a vital sign and measured in clinical practice, as it can provide health professionals with further information to improve the management of patients and encourage life-style strategies that can reduce CVD risk.[45] Further research is needed to evaluate if measurement of CRF can be used to help assess the risk of VAs in both general and specific populations, including patients with previous CVD and those with common cardiovascular risk factors or symptoms.

Several strengths of this study deserve mention, and these include the large-scale population-based prospective cohort design comprising of apparently healthy middle-aged men at study entry; long and complete follow-up for all participants; access to a comprehensive panel of lifestyle and biological markers, which allowed adequate adjustment for potential confounders; and the presence of repeat measurements of CRF, which allowed correction for within-person variability in CRF levels. There were a number of limitations, which also deserve consideration. First, the inability to extrapolate the findings to women and other ethnicities. Second, the low event rate for serious VAs (N= 73), which precluded assessment of effect modification by relevant clinical characteristics on the association. Third, the possibility of residual confounding given the observational design. Fourth, the RDR was estimated from only a subset of participants who were randomly sampled at 11 years' follow-up for repeat assessments of CRF, which may constitute a potential bias. Further studies are needed with repeat measurements in larger numbers of participants over different intervals in order to assess CRF variability in greater detail (e.g., assessment of any changes in mean levels and variability over time). This information will enable time-dependent correction for regression dilution. Finally, we included only those serious VT/VF cases which

led to hospital register documentation. This meant that very short (non-sustained) VT/VF episodes might have been missed out; but this could only happen if these patients did not present at the hospital.

CONCLUSION

CRF is inversely associated with future risk of serious VAs, independently of several established and emerging cardiovascular risk factors. Further research is needed to replicate these findings, assess the causal relevance of the association and evaluate whether information on CRF levels can be used to identify individuals at high risk of serious VAs in clinical practise.

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Table 1. Baseline participant characteristics

	Overall (N=2,299) Mean (SD) or median (IQR) or n (%)	**Pearson correlation r (95% CI)[a]**
CRF (ml/kg/min)	30.26 (8.00)	-
Questionnaire/Prevalent conditions		
Age at survey (years)	53 (5)	-0.36 (-0.40, -0.32)***
Alcohol consumption (g/week)	31.9 (6.4-92.5)	-0.09 (-0.14, -0.05)***
History of diabetes	81 (3.5)	-
Current smokers	720 (31.3)	-
History of hypertension	686 (29.8)	-
History of CHD	544 (23.7)	-
Physical measurements		
BMI (kg/m^2)	26.9 (3.5)	-0.37 (-0.40, -0.33)***
SBP (mmHg)	134 (17)	-0.13 (-0.17, -0.09)***
DBP (mmHg)	89 (10)	-0.14 (-0.18, -0.10)***
Physical activity (kj/day)	1210 (631-1988)	0.13 (0.09, 0.17)***
Lipid markers		
Total cholesterol (mmol/l)	5.91 (1.07)	-0.07 (-0.11, -0.03)***
HDL-C (mmol/l)	1.29 (0.30)	0.27 (0.23, 0.31)***
Metabolic and renal markers		
Fasting plasma glucose (mmol/l)	5.33 (1.19)	-0.20 (-0.24, -0.16)***
Serum creatinine (µmol/1)	89.6 (21.5)	-0.02 (-0.07, 0.02)
Estimated GFR (ml/min/1.73 m^2)	87.2 (17.2)	-0.04 (-0.09, -0.00)

BMI = body mass index; CHD = coronary heart disease; CRF = cardiorespiratory fitness; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; SD = standard deviation; SBP = systolic blood pressure; asterisks indicate the level of statistical significance: *, p<0.05; **, p<0.01; ***, p<0.001; [a], Pearson correlation coefficients between CRF and the row variables

Table 2. Association of cardiorespiratory fitness and ventricular arrhythmias

CRF (ml/kg/min)	**Events/ Total**	**Model 1**		**Model 2**		**Model 3**	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P-value*
		Baseline CRF					
Per 1 SD increase in CRF	73 / 2,299	0.64 (0.49 to 0.84)	<.001	0.68 (0.51 to 0.91)	.009	0.67 (0.51 to 0.88)	.004
T1 (16.06-26.87)	31 / 767	ref		ref		ref	
T2 (26.88-33.26)	31 / 766	0.86 (0.52 to 1.43)	.56	0.89 (0.53 to 1.49)	.66	0.88 (0.53 to 1.45)	.61
T3 (33.27-65.40)	11 / 766	0.29 (0.14 to 0.59)	<.001	0.33 (0.16 to 0.69)	.003	0.32 (0.15 to 0.65)	.002
		Usual CRF[a]					
Per 1 SD increase in CRF	73 / 2,299	0.47 (0.30 to 0.73)	<.001	0.52 (0.32 to 0.85)	.009	0.50 (0.31 to 0.80)	.004
T1 (16.06-26.87)	31 / 767	ref		ref		ref	
T2 (26.88-33.26)	31 / 766	0.77 (0.32 to 1.85)	.56	0.82 (0.34 to 1.99)	.66	0.80 (0.33 to 1.91)	.61
T3 (33.27-65.40)	11 / 766	0.12 (0.03 to 0.40)	<.001	0.15 (0.04 to 0.53)	.009	0.14 (0.04 to 0.48)	.002

CI = confidence interval; CRF = cardiorespiratory fitness; HR = hazard ratio; ref = reference; T = tertile; SD = standard deviation;

[a], indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

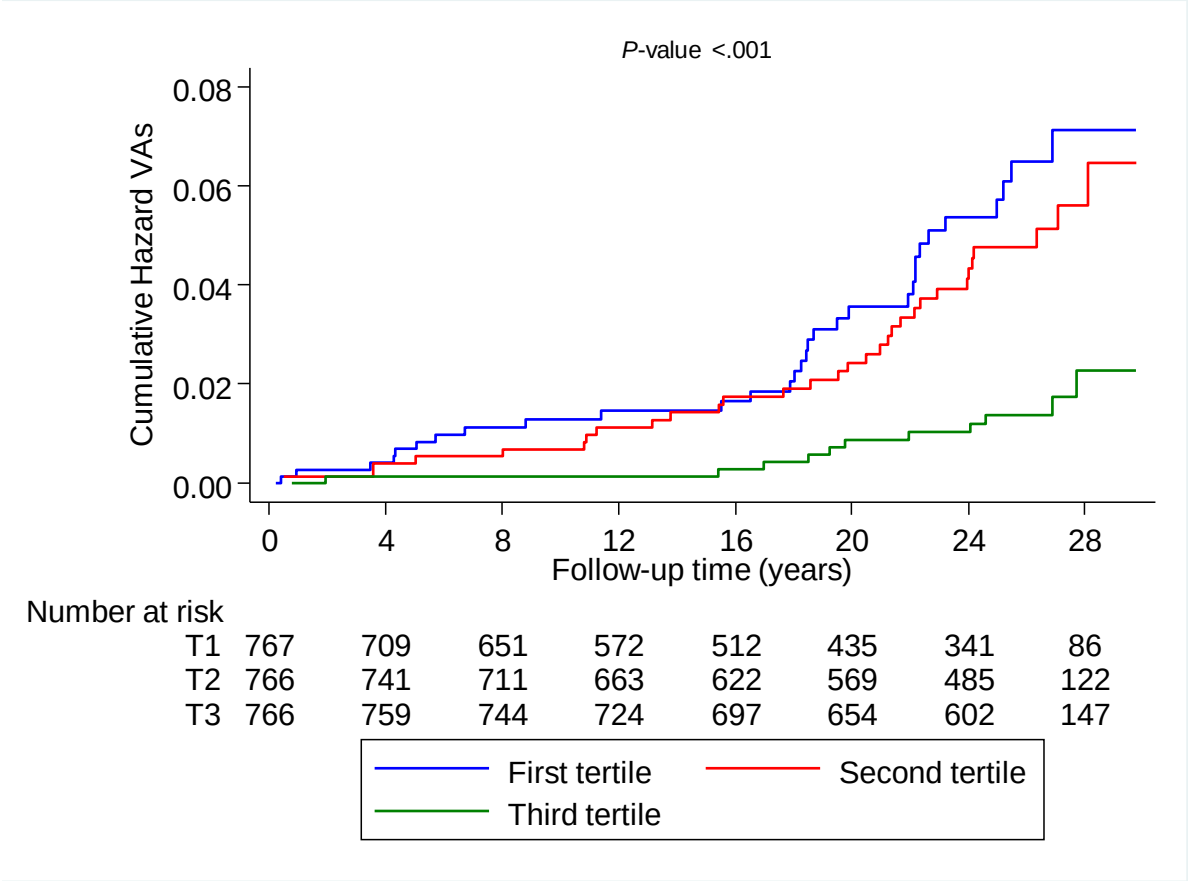
Model 1: Adjusted for age

Model 2: Model 1 plus systolic blood pressure, prevalent coronary heart disease, smoking status, and history of diabetes

Model 3: Model 1 plus history of hypertension, total cholesterol, alcohol consumption, and physical activity

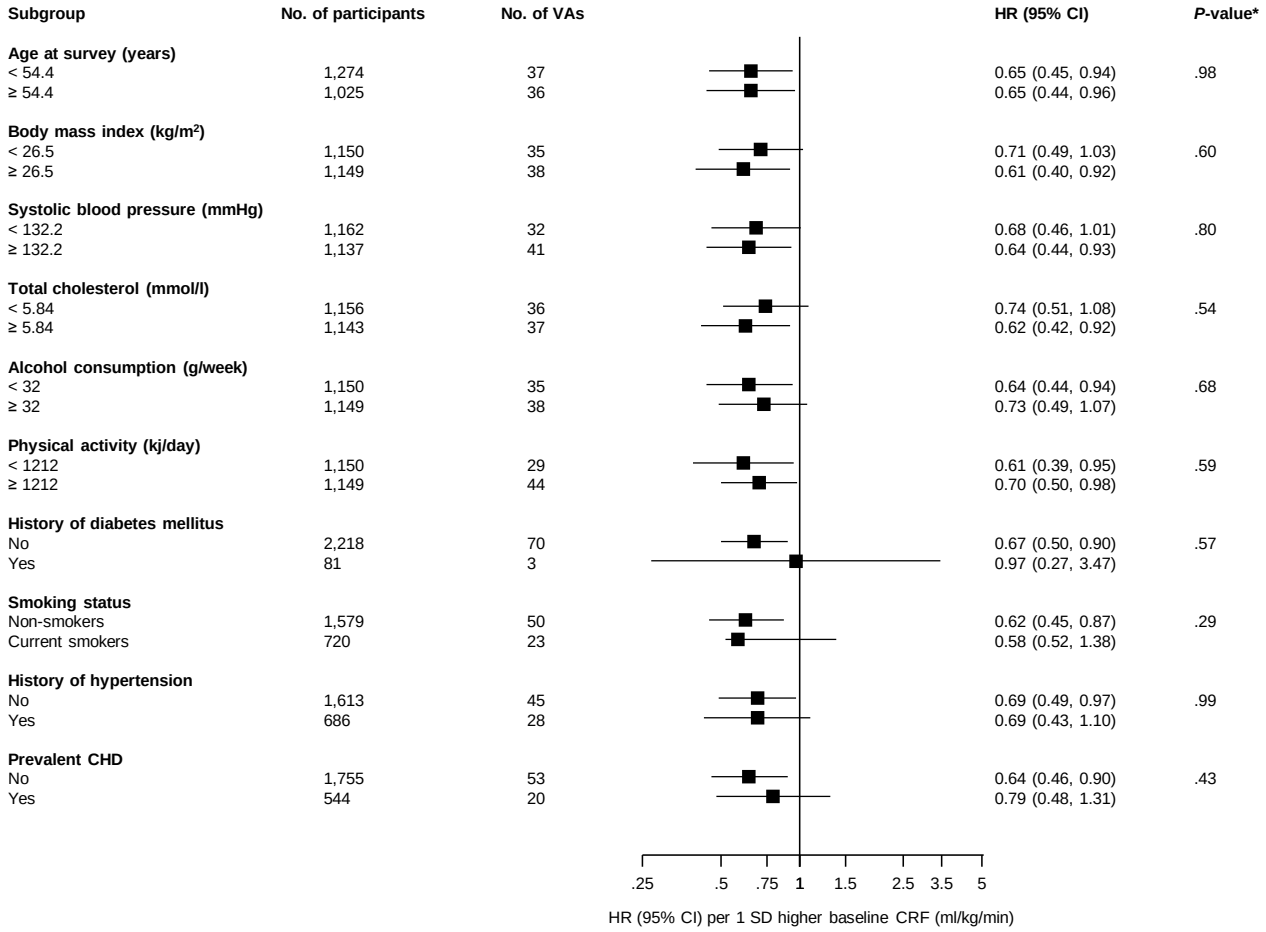
Figure legend

Figure 1: Cumulative hazard curves for serious ventricular arrhythmias according to the tertiles of cardiorespiratory fitness



T = tertile; Vas = ventricular arrhythmias

Figure 2. Association of cardiorespiratory fitness with ventricular arrhythmias in clinically relevant subgroups



CI = confidence interval; CHD = coronary heart disease; CRF = cardiorespiratory fitness; HR = hazard ratio; SD = standard deviation; Vas = ventricular arrhythmias; HRs are adjusted for age, systolic blood pressure, prevalent coronary heart disease, smoking status, and history of diabetes; hazard ratios are reported per 1 SD increase in CRF; *, *p*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, total cholesterol, alcohol consumption, and physical activity are based on median values.