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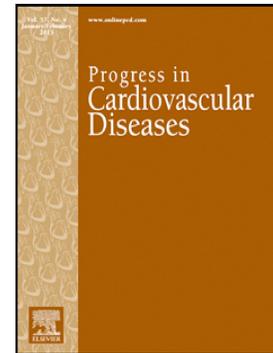
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**Combined Effect of Sauna Bathing and Cardiorespiratory Fitness on the Risk of Sudden Cardiac Deaths in Caucasian Men: a Long-Term Prospective Cohort Study**

**Short title:** Sauna, cardiorespiratory fitness, and SCD

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**Conflicts of interest:** None

**Abstract**

Both cardiorespiratory fitness (CRF) and frequency of sauna bathing (FSB) are each strongly and independently associated with sudden cardiac death (SCD) risk. However, the combined effect of CRF and FSB on SCD risk has not been previously investigated. We evaluated the joint impact of CRF and FSB on the risk of SCD in the Kuopio Ischemic Heart Disease prospective cohort study of 2,291 men aged 42-61 years at recruitment. Objectively measured CRF and self-reported sauna bathing habits were assessed at baseline. CRF was categorized as low and high (median cutoffs) and FSB as low and high (defined as  $\leq 2$  and 3-7 sessions/week respectively). Multivariable adjusted hazard ratios (HRs) with confidence intervals (CIs) were calculated for SCD. During a median follow-up of 26.1 years, 226 SCDs occurred. Comparing high vs low CRF, the HR (95% CIs) for SCD in analysis adjusted for several established risk factors was 0.48 (0.34-0.67). Comparing high vs low FSB, the corresponding HR was 0.67 (0.46-0.98). Compared to men with low CRF & low FSB, the multivariate-adjusted HRs of SCD for the following groups: high CRF & high FSB; high CRF & low FSB; and low CRF & high FSB were 0.31 (0.16-0.63), 0.49 (0.34-0.70), and 0.71 (0.45-1.10) respectively. In a general male Caucasian population, the combined effect of high aerobic fitness (as measured by CRF) and frequent sauna baths is associated with a substantially lowered risk of future SCD compared with high CRF or frequent sauna bathing alone.

**Key Words:** Cardiorespiratory fitness; sauna; sudden cardiac death

**Abbreviations**

BMI - body mass index

CHD - coronary heart disease

CRF - cardiorespiratory fitness

CRP - C-reactive protein

CV- Cardiovascular

CVD - cardiovascular disease

ECG - electrocardiogram

FSB - frequency of sauna bathing

KIHD - Kuopio Ischaemic Heart Disease

PA –Physical activity

SCD - sudden cardiac death

SES - socio-economic status

VO<sub>2max</sub> - maximal oxygen uptake

ACCEPTED MANUSCRIPT

Sudden cardiac death (SCD) is a global public health problem which accounts for 15-20% of all deaths,<sup>1</sup> and coronary heart disease (CHD) is known to be the most common pathology underlying SCD.<sup>2</sup> Though SCD and CHD share common atherosclerotic risk factors<sup>3</sup> and these factors explain a large proportion of the risk of SCD;<sup>4</sup> its pathogenesis is still not fully established as many cases are idiopathic<sup>5</sup> and it also appears other additional factors may be involved. These atherosclerotic risk factors are often absent in a large proportion of SCD victims,<sup>6</sup> which makes the identification of individuals at increased SCD risk and its prevention a difficult undertaking.

Cardiorespiratory fitness (CRF), as measured by maximal oxygen uptake ( $VO_{2max}$ ), is an indicator of cardiovascular (CV) and pulmonary function, an index of the level of physical activity (PA), and is considered to be the gold standard for assessing aerobic capacity.<sup>7</sup> CRF has been shown to be consistently and independently associated with a reduced risk of major adverse cardiovascular outcomes including SCD, among general population settings.<sup>8-11</sup> Evidence also suggests that CRF might improve SCD risk prediction beyond that of traditional risk factors.<sup>9</sup> Sauna bathing, a traditional Finnish activity which is commonly used for the purposes of pleasure, relaxation, and wellness, and becoming a popular activity in many other countries,<sup>12, 13</sup> has been observed to be linked to several health benefits. These include improvement in the pain and symptoms associated with musculoskeletal diseases;<sup>14</sup> treatment of chronic headache;<sup>15</sup> improvement in CV function<sup>16, 17</sup> and reduced risk of respiratory diseases,<sup>18, 19</sup> hypertension,<sup>20</sup> and neurocognitive disease.<sup>21</sup> Recent long-term observational epidemiological evidence has shown that having frequent sauna baths is independently associated with a reduced risk of SCD.<sup>22</sup>

Although CRF and sauna bathing are each associated with a reduced risk of SCD in the general population, the combined effect of these risk markers on the risk of SCD is not known. We hypothesized that a combination of high CRF and frequent sauna bathing may

further reduce the risk of SCD in the general population. In this context, using a population-based prospective cohort of 2,291 Caucasian men, we evaluated the combined association of CRF and frequency of sauna bathing (FSB) with the risk of SCD. To enable direct comparisons, we initially assessed the separate associations of CRF and FSB with the risk of SCD.

## **METHODS**

### **Study Design and Population**

Participants in this study were part of the Kuopio Ischemic Heart Disease (KIHD) risk factor study, which is an ongoing population-based prospective cohort study comprising a representative sample of middle-aged men aged 42-61 years recruited from the town of Kuopio or its surrounding rural communities in eastern Finland. A detailed report of recruitment methods for the KIHD study has been described in previous papers.<sup>21, 23</sup> A representative sample of 3,433 randomly selected potentially eligible men were invited for screening examinations carried out between March 1984 and December 1989. Of this number, 3,235 were found to be eligible and 2,682 (78%) provided consent to participate in the study. In the current analyses, 2,291 men had complete information on CRF and FSB, relevant covariates and SCD outcomes. The study protocol was approved by the Research Ethics Committee of the University of Eastern Finland and written informed consent was obtained from all participants. The investigation was concordant with the principles outlined in the Declaration of Helsinki and its future amendments.

### **Measurement of Risk Markers**

Participants were instructed to fast overnight, abstain from alcohol consumption for at least 3 days, and to keep away from smoking for at least 12 hours prior to blood specimen

collections. The cholesterol contents of serum lipoprotein fractions and triglycerides were measured enzymatically (Boehringer Mannheim, Germany). Serum C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). The assessment of age, smoking, alcohol consumption, level of physical activity, socio-economic status (SES), prevalent diseases, medication history, and family history of diseases employed the use of self-administered health and lifestyle questionnaires.<sup>24</sup> History of type 2 diabetes was defined as having a clinical diagnosis of diabetes and regular treatment with diet or medications, fasting plasma glucose  $\geq 7.0$  mmol/l, or according to self-reports. 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 or chest pain. The validated KIHD 12-month leisure-time physical activity history questionnaire was used to assess the energy expenditure of PA.<sup>25, 26</sup> Adulthood socioeconomic status was assessed as a combined index of income, education, occupation, occupational prestige, material standard of living, and housing conditions, all of which were assessed with self-reported questionnaires.<sup>27, 28</sup> Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. Resting blood pressure was measured between 08:00 and 10:00 hours with a random-zero sphygmomanometer using a standardized protocol.

### **Assessment of CRF and FSB**

CRF, as measured by  $VO_{2max}$ , was assessed using respiratory gas exchange analyzers (Medical Graphics, MCG, St. Paul, Minnesota) during cycle ergometer exercise testing as described in detail elsewhere.<sup>21</sup> Briefly, a maximal symptom-limited exercise tolerance test was performed between 08:00 and 10:00 hours using an electrically braked cycle ergometer. The standardized testing protocol comprised of a 3-minute warm-up at 50W followed by a

step-by-step increase in workload by 20W/min with direct analyses of respiratory gases. An experienced physician assisted by a nurse supervised the exercise tests and ensured safety. Assessment of FSB was based on a traditional Finnish sauna which has air with a relative humidity of 10 to 20%. The recommended temperature for a sauna bath is from 80°C to 100°C at the level of the bather's head, but it is lower at the floor-level which ensures efficient ventilation and makes sure the conditions are comfortable for sauna bathers.<sup>29</sup> The weekly frequency and duration of sauna sessions and temperature in the sauna room were assessed by a self-administered questionnaire.<sup>20, 21</sup> An experienced nurse checked the questionnaires at the time of baseline examination.

### **Ascertainment of Outcomes**

All SCDs that occurred from study enrollment through to 2014 were included in the current analyses. No losses to follow-up were recorded in the KIHHD study as participants are under continuous annual surveillance for the development of incident disease and deaths.<sup>30</sup> The sources of information on SCD were based on a comprehensive review of all available records of hospitals and health centres, health practitioner questionnaires, informant interviews, study electrocardiograms (ECGs), death certificate registers, and medico-legal reports. The diagnostic classification of SCDs was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of CHD as well as with the clinical history and findings from hospital and paramedic staff. A SCD was diagnosed when the death 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 SCD or after successful resuscitation from ventricular tachycardia and/or ventricular fibrillation.<sup>9</sup>

Classification of outcomes was performed by the Independent Events Committee members

who were masked to clinical data.

### Statistical Analyses

We presented descriptive data as means (standard deviation, SD) or medians (interquartile range, IQR) for continuous variables and percentages for categorical variables. Hazard ratios (HRs) with 95% confidence intervals (CIs) for outcomes were calculated using Cox proportional hazard models, after confirming no major departure from the proportionality of hazards assumptions.<sup>31</sup> CRF was categorized into low and high CRF based on median cut-offs of CRF, while FSB was categorized into low and high FSB (defined as  $\leq 2$  and 3-7 sauna sessions per week respectively), to maintain consistency with a previous report.<sup>32</sup> As with the previous report,<sup>32</sup> we created these categories based on the distribution of the data and findings from our previous studies conducted on the topic.<sup>21, 22</sup> For the association of one exposure (e.g. CRF) with SCD risk, formal tests of interaction were used to assess if the association was modified by the other exposure (e.g. FSB) and vice versa. The combined association of CRF and FSB with SCD risk was based on the following four possible combinations: high CRF & high FSB; low CRF & high FSB; high CRF & low FSB; and low CRF & low FSB. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

## RESULTS

### Baseline Characteristics

Baseline characteristics of study participants are summarized in **Table 1**. The mean (SD) age and body mass index (BMI ;SD) of study participants at baseline was 53 (5) years and 26.9 (3.5) kg/m<sup>2</sup> respectively. About 4% and 24% of study participants had a history of type 2 diabetes and CHD respectively on study entry. The mean (SD) of CRF and median

(interquartile range, IQR) FSB was 30.3 (8.0) ml/kg/min and 2 (1-2) sessions per week respectively. The average temperature of the sauna room was 79 °C.

### **Associations of CRF and FSB with SCD**

During a median (IQR) follow-up of 26.1 (19.1-28.1) years, a total of 226 SCDs occurred. Compared to men with low CRF, the age-adjusted HR of SCD for men with high CRF was 0.30 (95% CI: 0.22 to 0.41). The HR was attenuated to 0.46 (95% CI: 0.33 to 0.65) on further adjustment for several established CV disease (CVD) risk factors (BMI, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, history of type 2 diabetes, prevalent CHD, alcohol consumption) and it remained consistent on additional adjustment for socio-economic status and C-reactive protein 0.48 (95% CI: 0.34 to 0.67) (**Table 2**). The HR for SCD persisted on additional adjustment for FSB 0.48 (95% CI: 0.34 to 0.67).

In age-adjusted analysis, the HR for SCD comparing men with high versus low FSB was 0.59 (95% CI: 0.40 to 0.85). The HR was minimally attenuated to 0.67 (95% CI: 0.46 to 0.98) on further adjustment for several established CVD risk factors and other potential confounders (**Table 2**). The HR for SCD was less robust on further adjustment for CRF; 0.69 (95% CI: 0.47 to 1.00). There was no statistically significant evidence of effect modification by CRF or FSB on the associations ( $p$ -values for interactions  $> 0.10$ ) (**Figure 1**).

### **Joint Associations of CRF and FSB with SCD Risk**

Cumulative hazard curves showed reduced risk of SCD among participants with high CRF & high FSB compared with other groups ( $p$ -value for log-rank test  $< 0.0001$  for all; **Figure 2**).

The combined associations of CRF and FSB with the risk of SCD are reported in **Table 3**.

Compared to men with low CRF & low FSB, the age-adjusted HRs of SCD for the following

groups: high CRF & high FSB; high CRF & low FSB; and low CRF & high FSB were 0.18 (95% CI: 0.09 to 0.36), 0.30 (95% CI: 0.22 to 0.43), and 0.62 (95% CI: 0.40 to 0.96), respectively. The HRs were 0.31 (95% CI: 0.16 to 0.63), 0.49 (95% CI: 0.34 to 0.70), and 0.71 (95% CI: 0.45 to 1.10), respectively, after further adjustment for several established and other potential CVD risk factors.

## DISCUSSION

### Summary of Main Findings

In this population-based prospective study of Finnish men, we have shown that CRF and FSB are each independently associated with a reduced risk of SCD. These findings are consistent with previous published studies on the topic.<sup>8,9,22</sup> The association of each exposure with SCD was independent of the other exposure and there was no evidence of effect modification by either exposure. On evaluation of the combined association of CRF and FSB with the risk of SCD, the association was strongest for men with high CRF & high FSB followed by men with high CRF & low FSB. The combined exposure of high CRF and high FSB was more strongly associated with the risk of SCD when compared with the SCD risk associated with each exposure. Though overall, the findings suggest that compared to FSB, CRF is a stronger risk indicator for SCD; it must be acknowledged that CRF was objectively assessed, while FSB were based on self-reported questionnaires. However, the estimation of CRF by self-reported variables has been suggested to be a good surrogate to objectively measured CRF.<sup>33</sup> Though to our knowledge, this is the first prospective study to demonstrate the combined effect of CRF and FSB on the risk of SCD, we have recently reported on the joint association of CRF and FSB on the risk of CVD and all-cause mortality.<sup>32</sup> A number of studies have also suggested substantial beneficial changes in CV function when PA is combined with sauna exposure.<sup>34-36</sup>

### Possible Explanations for Findings

Increasing levels of PA and exercise training, particularly aerobic activity generally confers good CRF,<sup>37</sup> which has consistently shown to be strongly protective of vascular and non-vascular disease as well as mortality via physiological and metabolic processes.<sup>38</sup> However, the level of CRF is not solely determined by physical exercise or PA, but a combination of PA, genetics, and other lifestyle factors. As discussed in previous reports, the pathophysiological mechanisms of action underlying the findings of a protective effect of CRF on SCD risk include an antiatherogenic effect of aerobic activity;<sup>39, 40</sup> anti-inflammatory effects of physical activity;<sup>41, 42</sup> beneficial modulation of circulating CV markers such as lipids, glucose, natriuretic peptides and cardiac troponin T;<sup>43, 44</sup> beneficial effects of PA on cardiac autonomic function, which may reduce the risk of fatal arrhythmias;<sup>45</sup> and improvement in endothelial function as well as reductions in risk factors such as body weight and blood pressure.<sup>46, 47</sup> Several pathways have been postulated for the impact of passive heat exposure, such as sauna bathing, on CVD and mortality risk. These include reduction in systemic blood pressure;<sup>20</sup> improvement in endothelial function;<sup>48, 49</sup> reduction in oxidative stress;<sup>50, 51</sup> beneficial modulation of the autonomic nervous system;<sup>52</sup> positive alteration in levels of circulating CVD risk factors such as natriuretic peptides;<sup>53</sup> improved arterial stiffness, arterial compliance, and intima media thickness;<sup>16, 50, 53, 54</sup> and substantial improvement of the musculoskeletal and cardiorespiratory system<sup>55</sup> as well as CV function.<sup>29, 56, 57</sup> Given common antecedent pathways implicated in the risk of vascular disease and SCD, the evidence suggests that sauna exposure may confer protective effects on SCD risk via these processes. There is also evidence to suggest that the adaptations produced by an ordinary sauna bath corresponds to that produced by moderate or high intensity PA such as walking.<sup>58</sup> As the mechanistic pathways underlying the relationships of CRF and sauna

exposure with SCD risk are similar, the substantially stronger protective effect of the combination of both exposures (high CRF & high FSB) on SCD risk might suggest a multiplicative effect of both exposures; however, given the absence of a significant evidence of interaction and the small numbers in the subgroups, further investigation in large samples are needed.

### **Implications of Findings**

We have shown a substantially reduced risk of future SCD in middle-aged men who frequently have sauna baths and have high aerobic fitness levels at baseline. The findings also show that objectively assessed high CRF levels confer more protection compared with frequent sauna bathing alone and that the risk reduction associated with sauna bathing is more evident in people with high CRF. Also the association of FSB with risk of SCD was slightly attenuated on further adjustment for CRF. It is therefore suggestive that the beneficial effects of sauna bathing may be dependent on baseline CRF, but this is not clear and further investigation may be required. The health benefits of regular PA and its ability to promote longevity needs no further description, as these are well known and consistently reported in the medical literature. Sauna bathing is now emerging as an activity which may have therapeutic potential for adverse health outcomes. Sauna bathing has been used for the treatment and improvement of symptoms associated with several acute and chronic conditions such as rheumatic disease,<sup>59</sup> headache,<sup>15</sup> and skin diseases.<sup>60</sup> Sauna bathing has also been recently reported to have protective effects on the long-term risk of CVD and non-CVD.<sup>18, 20-22</sup> Further research is warranted into the mechanistic pathways involved in beneficial effects of sauna exposure on adverse health outcomes and its potential to reduce the risk of SCD in general population settings. Sauna bathing has a good safety profile and is well tolerated in both the healthy young and old; indeed, it has even been observed to be safe

among those with stable cardiac conditions.<sup>29, 56</sup> Given that sauna bathing is commonly used in Nordic countries, it appears potential health implications may not be applicable in other populations. However, sauna bathing is emerging as a common activity in many other countries<sup>12, 13</sup> and there is increasing research on its potential health benefits on a global scale.

### **Strengths and Limitations**

To our knowledge, this is the first prospective evaluation of the combined effect of CRF and FSB on the incidence of SCD. Other strengths include the well characterized sample of men who were representative of the general Finnish male population; the complete and long-term follow-up of the cohort; adjustment for a comprehensive panel of confounders; and the objective assessment of CRF using respiratory gas analyses. There were some limitations of the current study and these include the assessment of FSB using self-reported questionnaires, which is prone to misclassification bias. Other limitations include the inability to generalize the findings to women and the possibility of residual confounding due to unmeasured confounders such as trajectories of blood pressure measurements over the course of follow-up, physiological and psychosocial factors, and nutritional status. Reverse causation may also be implicated for study findings, whereby healthier individuals were more likely to tolerate and enjoy sauna baths as opposed to individuals who were ill.

### **Conclusions**

In a general male Finnish population, the combined effect of high CRF and FSB is associated with a substantially lowered risk of future SCD compared with high CRF or FSB alone.

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**Table 1.** Baseline Characteristics of Study Participants

	Mean (SD) or median (IQR) or n (%)
Cardiorespiratory fitness (ml/kg/min)	30.3 (8.0)
Frequency of sauna bathing (times/week)	2 (1-2)
<b>Questionnaire/Prevalent conditions</b>	
Baseline age (years)	53 (5)
Alcohol consumption (g/week)	74.0 (121.6)
History of type 2 diabetes	79 (3.5)
Current smoking	717 (31.3)
History of CHD	542 (23.7)
<b>Physical measurements</b>	
BMI (kg/m <sup>2</sup> )	26.9 (3.5)
SBP (mmHg)	134 (17)
DBP (mmHg)	89 (10)
Physical activity (KJ/day)	1,537 (1,400)
Socio-economic status	8.42 (4.23)
<b>Lipid markers</b>	
Total cholesterol (mmol/l)	5.91 (1.07)
HDL-C (mmol/l)	1.29 (0.30)
Triglycerides (mmol/l)	1.09 (0.79-1.54)
<b>Metabolic, inflammatory, and renal markers</b>	
Fasting plasma glucose (mmol/l)	5.33 (1.19)
C-reactive protein (mg/l)	1.24 (0.69-2.37)
Serum creatinine (μmol/l)	89.6 (21.5)
Estimated GFR (ml/min/1.73 m <sup>2</sup> )	87.2 (17.2)

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure

**Table 2.** Associations of Cardiorespiratory Fitness and Frequency of Sauna Bathing with Risk of Sudden Cardiac Death

Exposure categories	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
<b>Cardiorespiratory fitness (ml/kg/min)</b>							
Low CRF (6.36-30.02)	170 / 1,146	ref		ref		ref	
High CRF (30.03-65.40)	56 / 1,145	0.30 (0.22 to 0.41)	< 0.001	0.46 (0.33 to 0.65)	< 0.001	0.48 (0.34 to 0.67)	< 0.001
<b>Frequency of sauna bathing (sessions/week)</b>							
Low FSB ( $\leq 2$ )	194 / 1,799	ref		ref		ref	
High FSB (3-7)	32 / 492	0.59 (0.40 to 0.85)	0.005	0.66 (0.45 to 0.96)	0.030	0.67 (0.46 to 0.98)	0.039

CI, confidence interval; CRF, cardiorespiratory fitness; FSB, frequency of sauna bathing; HR, hazard ratio; ref, reference; cut-off for CRF was based on the median

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, history of type 2 diabetes, prevalent coronary heart disease, alcohol consumption

Model 3: Model 2 plus socioeconomic status and C-reactive protein

**Table 3.** Joint Associations of Cardiorespiratory Fitness and Frequency of Sauna Bathing With Risk of Sudden Cardiac Death

CRF (ml/kg/min) and frequency of sauna bathing (times/week)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Low CRF & Low FSB	147 / 937	ref		ref		ref	
High CRF & Low FSB	47 / 862	0.30 (0.22 to 0.43)	< 0.001	0.48 (0.33 to 0.68)	< 0.001	0.49 (0.34 to 0.70)	< 0.001
Low CRF & High FSB	23 / 209	0.62 (0.40 to 0.96)	0.034	0.69 (0.45 to 1.08)	0.11	0.71 (0.45 to 1.10)	0.13
High CRF & High FSB	9 / 283	0.18 (0.09 to 0.36)	< 0.001	0.30 (0.15 to 0.60)	0.001	0.31 (0.16 to 0.63)	0.001

CI, confidence interval; CRF, cardiorespiratory fitness; FSB, frequency of sauna bathing; HR, hazard ratio; ref, reference; cut-off for CRF was based on the median

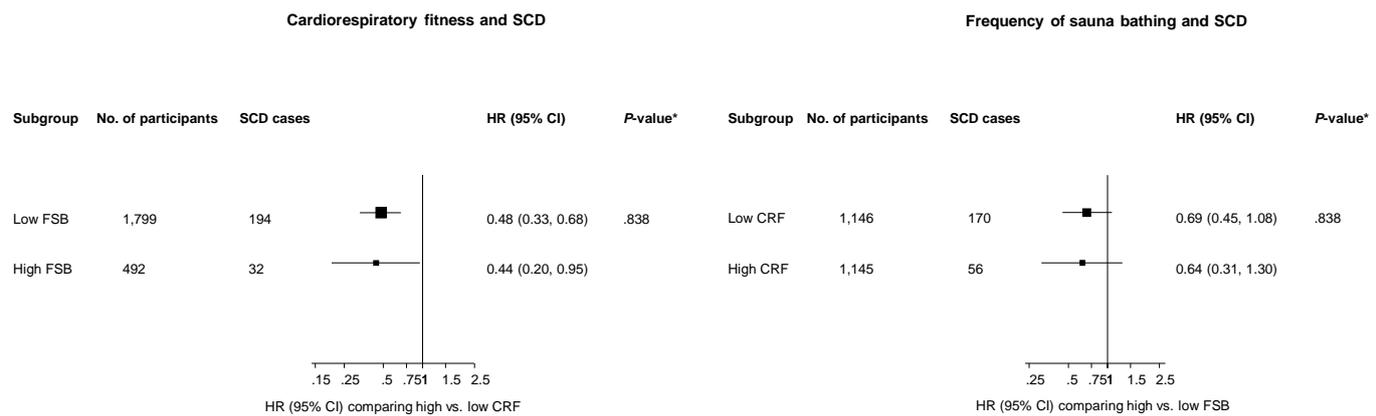
Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, history of type 2 diabetes, prevalent coronary heart disease, alcohol consumption

Model 3: Model 2 plus socioeconomic status and C-reactive protein

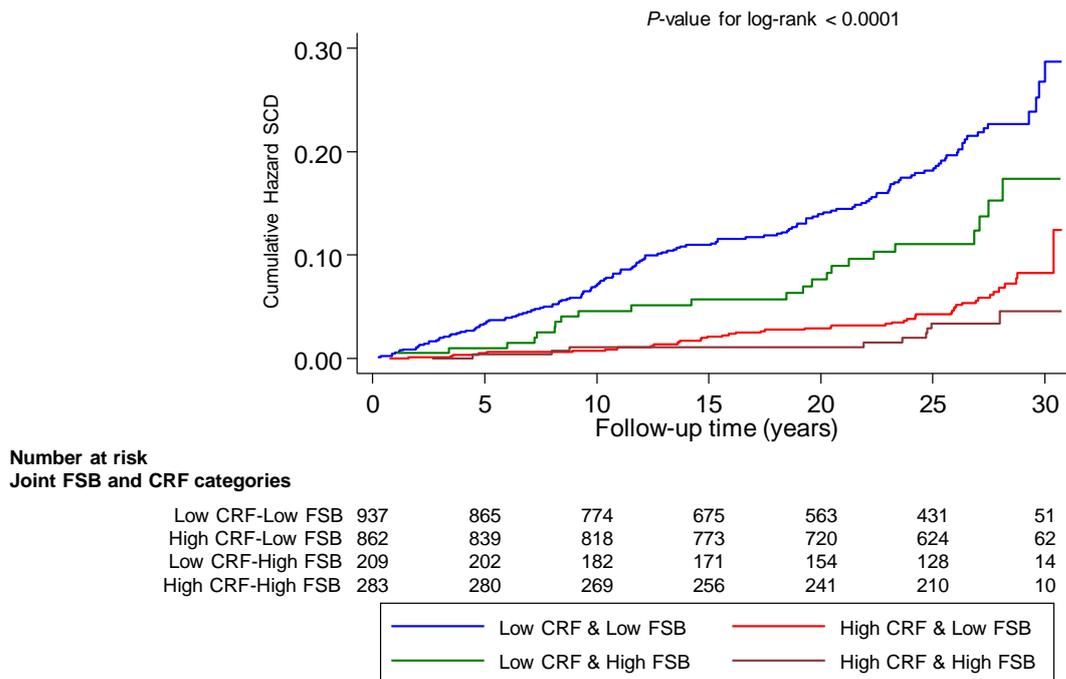
## Figure Legends

**Fig. 1.** Interactions of the Associations of CRF and Frequency of Sauna Bathing With Sudden Cardiac Death



CI, confidence interval; CRF, cardiorespiratory fitness; FSB, frequency of sauna bathing; HR, hazard ratio; HRs are adjusted for age, body mass index, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, history of type 2 diabetes, prevalent coronary heart disease, and alcohol consumption; \*, *p*-values for interaction

**Fig 2.** Cumulative Kaplan-Meier Curves for Sudden Cardiac Death During Follow-up According to CRF and Sauna Bathing Frequency Groups



CRF, cardiorespiratory fitness; FSB, frequency of sauna bathing