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High leisure-time physical activity is associated with reduced risk of sudden cardiac death among men with low cardiorespiratory fitness

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**High leisure-time physical activity is associated with reduced risk of sudden cardiac death among men with low cardiorespiratory fitness**

**Short title: Physical activity, fitness and sudden cardiac death**

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**Brief Summary:**

In this study of 2656 randomly selected middle-aged men we found that participants with low cardiorespiratory fitness (CRF) and low leisure-time physical activity (LTPA) had a 2.2-times higher risk of sudden cardiac death (SCD) than men with high CRF and high LTPA. It seems that low LTPA increases the risk of SCD particularly among men with low CRF however, the level of LTPA does not modify the incidence of SCD among men with high CRF.

## ABSTRACT

**Background:** We studied the independent and joint associations of leisure-time physical activity (LTPA) and cardiorespiratory fitness (CRF) with the risk of sudden cardiac death (SCD) among middle-aged men.

**Methods:** The participants were 2656 randomly selected men aged 42-60 years at baseline who were followed for 19 years. LTPA was assessed using a questionnaire modified from the Minnesota LTPA Questionnaire and CRF using respiratory gas exchange analyzer during maximal exercise test. The participants were divided into four groups according to the level of LTPA and CRF dichotomized at the lowest tertiles.

**Results:** Men with low CRF had a 1.6 (95% CI 1.1-2.3,  $p=0.011$ ) times higher risk of SCD than men with high CRF after adjustment for conventional risk factors. Men with low LTPA had a 1.4 (95% CI 1.0-2.0,  $p=0.032$ ) times higher SCD risk than men with high LTPA after these adjustments. Men with low CRF and low LTPA had a 2.2 (95% CI 1.4 – 3.3) times higher SCD risk than men with high CRF and high LTPA adjusting for conventional risk factors ( $p=0.044$  for interaction).

**Conclusion:** It seems that low LTPA increases the risk of SCD particularly among men with low CRF but the level of LTPA does not modify the incidence of SCD among men with high CRF.

**Keywords:** Cardiorespiratory fitness, leisure-time physical activity, sudden cardiac death, exercise-stress test

## INTRODUCTION

Low cardiorespiratory fitness (CRF) and low leisure-time physical activity (LTPA) have been associated with increased risk of sudden cardiac death (SCD).<sup>1,2</sup> CRF measured by maximal oxygen uptake is considered the gold standard for assessing CRF<sup>3</sup>, and low CRF has been postulated to be the strongest risk factor for death from CHD and SCD.<sup>4-6</sup> Regular physical activity is known to result in important health benefits, including protection against adverse cardiovascular outcomes.<sup>1,7,8</sup> However, there are no studies on the joint association of LTPA and CRF regarding the risk of SCD in large population-based follow-up studies. We therefore investigated the independent and joint associations of LTPA assessed by a detailed questionnaire and CRF measured by maximal oxygen uptake during a maximal exercise test with the risk of SCD among randomly selected middle-aged men followed for a total of 25 years. We hypothesized that a high LTPA is especially beneficial for decreasing the risk of SCD among men with a low CRF.

## MATERIAL AND METHODS

The present report is based on data from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), an ongoing epidemiological follow-up study designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in men.<sup>9-11</sup> A total of 3433 men aged 42 to 60 years from eastern Finland who were randomly selected from the population registry were invited to participate, and 3235 (94%) men were eligible for the study. Altogether 2682 (83%) men participated in the baseline examinations. A total of 2656 men with complete data on LTPA, CRF and other exercise test variables (82% of those eligible) were included in the present analyses.

Baseline examinations were conducted between March 1984 and December 1989.<sup>10</sup> The study was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland. Each participant provided written informed consent.

Maximal symptom-limited exercise stress tests were performed between 8 a.m. and 10 a.m. using an electrically braked cycle ergometer.<sup>10</sup> The standardized exercise testing protocol involved an increase in the workload of 20 watts per minute. CRF was expressed in metabolic equivalents (METs). One MET corresponds to an oxygen uptake of 3.5 mL/kg per minute.<sup>12</sup> Maximal oxygen uptake was measured directly from the respiratory gases. For safety reasons, all exercise 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.<sup>13</sup> The ECG was recorded continuously with a Kone 620 electrocardiograph (Kone, Turku, Finland). The ECG was printed at 30-second intervals during exercise and after at least 5 minutes of recovery while the participant was sitting on the bicycle. ST segment depression was defined as exercise-induced horizontal or down-sloping at least 1.0mm ST segment depression at 80ms after the J point or any ST depression of more than 1.0mm at 80ms after the J point in the ECG.<sup>14</sup>

LTPA was assessed using the KIHD LTPA Questionnaire that was modified from the Minnesota LTPA Questionnaire.<sup>10,15,16</sup> The KIHD LTPA Questionnaire has been validated in the present study population and the Minnesota LTPA Questionnaire in other cohorts.<sup>16,17</sup> The questionnaire includes the most common physical activities of Finnish middle-aged men. The participants were asked to report the frequency (sessions per month), duration (hours and minutes per session) and

intensity (translated into METs) of each physical activity. A trained study nurse helped the participants to fill out the questionnaire, and a physician completed the questionnaire, if needed. Energy consumption (kcal/day) during LTPA was computed using data obtained from the questionnaire.

Resting blood pressure was measured by a study nurse one week prior to the exercise test.<sup>13</sup> Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Lifelong exposure to smoking (cigarette pack-years) was estimated with a questionnaire and computed as the product of the number of years spent smoking and the number of tobacco products smoked daily at the time of examination.<sup>13</sup> The consumption of alcohol in the previous 12 months was assessed with the Nordic Alcohol Consumption Inventory.<sup>18</sup> The collection of blood specimens and the measurement of fasting serum lipids and lipoproteins were done according to standard protocols.<sup>19</sup> Serum high-sensitivity C-reactive protein (hs-CRP) was measured with an immunometric assay (Immulite High Sensitivity C-reactive protein Assay, DPC, Los Angeles, CA, USA). Type 2 diabetes was defined as fasting blood glucose of at least 6.7 mmol/l or a clinical diagnosis of type 2 diabetes with dietary, oral or insulin treatment. A prevalent CHD was defined as a previous myocardial infarction, angina pectoris, the use of nitroglycerin for chest pain once a week or more frequently or chest pain as the reason for premature termination of the exercise test at baseline. Coronary interventions were defined as percutaneous coronary intervention or coronary artery bypass surgery having been performed due to clinical reasons during follow-up. The information was collected from the coronary intervention registry and combined with the study data. The age-predicted maximal heart rate during exercise test was computed as  $220 - \text{age}$ . The age-predicted MET during exercise test was computed as  $14.7 - 0.11 \times \text{age}$ .<sup>20</sup> The QT interval was measured

from resting ECG using a standard protocol. The amplitude of the R and S waves were also measured from resting ECG using a standard protocol to estimate left ventricular hypertrophy.

All deaths that occurred by the end of 2008 were included. There were no losses during the follow-up. All deaths were checked from hospital documents, wards of health centers and death certificates. The sources of information consisted of interviews, hospital documents, death certificates, autopsy reports and medico-legal reports together with the clinical and ECG findings of the paramedical staff. The diagnostic classification of events was based on symptoms, ECG findings, cardiac enzyme elevations, autopsy findings (80%) and the history of CHD. The deaths were coded using the International Classification of Diseases Ninth Revision or Tenth Revision. The deaths were determined as SCDs when they occurred within 24 hours after the onset of an abrupt change in symptoms when autopsy data did not reveal a non-cardiac cause of sudden death or due to unsuccessful resuscitation from ventricular tachycardia or ventricular fibrillation. The deaths due to aortic aneurysm rupture, cardiac rupture, cardiac tamponade or pulmonary embolism were not determined as SCDs. All documents related to the death were cross-checked in detail by two physicians. All deaths were ascertained from the Finnish national death registry.

For the statistical analyses, we created four groups according to the level of CRF and LTPA as dichotomized variables by using a cut-point of 7.9 METs for CRF and 191 kcal/day for LTPA representing the lowest tertiles. A MET value of 7.9 corresponds to the intensity of heavy shoveling or moderate biking (e.g. 22 km/h).<sup>12</sup> An energy consumption of 191 kcal corresponds to approximately 30 minutes of brisk walking or gardening for a 75kg male.<sup>12</sup> Group 1, which was used as a reference,



consisted of men with high CRF and high LTPA. Group 2 consisted of men with high CRF and low LTPA. Group 3 consisted of men with low CRF and high LTPA. Group 4 consisted of men with low CRF and low LTPA. The independent association between CRF and LTPA as continuous variables on the risk of SCD was analyzed using Cox regression models. The proportional hazard assumption was verified for each risk factor by plotting Schoenfeld residuals against survival time transformed into natural logarithms. All covariates fulfilled the proportionality assumption. Hazard ratios (HR) with 95% confidence intervals (CI) were adjusted for age, prevalent type 2 diabetes and CHD, smoking, alcohol consumption, BMI, systolic blood pressure, serum low density lipoprotein (LDL) cholesterol, exercise-induced ST segment depression and serum hs-CRP, later referred to as conventional risk factors. These covariates were selected on the basis of their previously established role as predictive factors for CHD death.<sup>21-23</sup> Missing values (maximum of 3% in each group) were replaced by the mean of these variables from the study population. The cumulative incidence of SCD in each group was calculated using the Kaplan-Meier method. Associations with a p-value of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics 20.0 for Mac (SPSS Inc, Chicago, Illinois).

## RESULTS

The mean (SD) of CRF was 8.6 (2.1) METs and the mean (SD) of LTPA was 373 (335) kcal/day. The baseline characteristics of the men stratified by CRF and LTPA are shown in Table 1. Men with low CRF had higher burden of conventional CHD risk factors. Proportions of performed coronary intervention in the risk groups are shown in table 1, the proportions were similar among those with SCD (data not shown). The mean energy expenditure of LTPA was higher among men with high CRF than among men with low CRF (384 vs. 350 kcal/day,  $p=0.020$ ). The mean of maximal heart rate during exercise test was 155 beats/min, and 1992 (75%) men reached over 85% of the age-adjusted maximal heart rate. A total of 1968 (73%) men reached over 85% of the age-predicted CRF level in METs.

Men with low CRF had a 1.6 (95% CI 1.1-2.3,  $p=0.011$ ) times higher risk of SCD than men with high CRF after adjustment for conventional risk factors (age, prevalent type 2 diabetes and CHD, smoking, alcohol consumption, BMI, systolic blood pressure, serum LDL cholesterol, exercise-induced ST segment depression and serum hs-CRP). CRF as a continuous variable was also inversely associated with the risk of SCD (hazard ratio 0.82, 95% CI 0.74-0.90,  $p<0.001$ ) after adjustment for conventional risk factors. Men with low LTPA had a 1.4 (95% CI 1.0-2.0,  $p=0.032$ ) times higher risk of SCD than men with high LTPA after adjustment for conventional risk factors. The energy expenditure, frequency, duration or intensity of LTPA as continuous variables was not associated with the risk of SCD. There was no difference in SCD risk between men with low CRF and high LTPA and men with high CRF and high LTPA.

The cumulative incidence of SCD was highest among men with low CRF and low LTPA (Group 4) and second highest among men with low CRF and high LTPA (Group 3), whereas there was no difference in survival between two other groups (Figure 1). Men with low CRF and low LTPA (Group 4) had a 2.2 times higher risk of SCD than men with high CRF and high LTPA (Group 1) after adjustment for conventional risk factors (Table 2). The risk of SCD was not statistically significantly increased among men with high CRF and low LTPA (Group 2) or men with low CRF and high LTPA (Group 3) when compared to men with high CRF and high LTPA (Group 1) after adjustment for conventional risk factors (Table 2). The interaction between CRF and LTPA on the risk of SCD was statistically significant ( $p=0.044$ ). The risk of CHD and all-cause death was also highest among men with low CRF and low LTPA (Group 4) after adjustment for conventional risk factors (Table 2). Further adjustment for coronary interventions during follow-up or the use of beta-blockers, QT interval or left ventricular hypertrophy at baseline had no marked effect on these associations (data not shown).

The incidence of all-cause mortality and death from CHD was increased among men with low CRF regardless of the amount of LTPA (Table 2).

## **DISCUSSION**

This prospective study shows that low CRF is a more important predictor for future risk of SCD than low LTPA in middle-aged men. The most important finding of our study is that low LTPA was associated with increased risk of SCD among men with

low CRF but not among men with high CRF. However, the amount of LTPA did not modify the association between CRF and the incidence of SCD.

Previous studies have shown the importance of high LTPA and CRF as independent and risk factors for myocardial infarction, CHD and all-cause mortality.<sup>1,2,4,5,24</sup> It has been argued that vigorous exercise might trigger SCD, especially among unfit men.<sup>25,26</sup> However, the consensus seems to be that physical activity is beneficial for preventing long-term risk of SCD.<sup>1,27,28</sup> Some of the studies regarding LTPA and the risk of SCD have been performed by asking about the level of LTPA from the spouse of the decedent after the death that may have resulted in biased results.<sup>1,29</sup> As a randomized controlled trial would be difficult to be performed because of the relatively low occurrence of SCD, problems related to adherence to long-term exercise programs and the large number of participants required, a cohort study seems most suitable to study the association between LTPA and the risk of SCD. However, there are no previous long-term cohort studies aimed at investigating the independent and joint associations of CRF and LTPA with the risk of SCD in middle-aged men.

Although the present study was not designed to investigate the mechanisms behind the observed associations, some explanation can be postulated. The level of CRF is determined by physical exercise in addition to underlying genetic and lifestyle factors.<sup>7,30,31</sup> The development of coronary collaterals have been shown to reduce the risk of death during myocardial infarction.<sup>32</sup> Exercise of at least moderate intensity has been shown to induce the growth of coronary collaterals.<sup>33</sup> Thus, one possible explanation for our finding is that men with low LTPA have not developed as good coronary collateral circulation than men with good high LTPA particularly if they have low CRF and have therefore increased risk of SCD. Another possible

mechanism for the observed association might be ischemic precondition that occurs when the myocardium is subject to repeated short-term ischemia without infarction. Ischemic preconditioning leads to a protective reaction of the myocardium, the mechanisms of which are not entirely clear yet.<sup>34</sup> Physical activity may cause ischemic preconditioning in the myocardium particularly among men with low CRF who have increased likelihood of having undiagnosed and asymptomatic CHD. Physical activity may improve vagal control of heart rate and regulation of cardiac autonomic function and increase in cardiac output, left ventricular function with oxygen utilization. Although the causal nature of these associations remains to be investigated, it is likely that higher levels of CRF and physical activity improve atherosclerotic risk profile, reduces inflammation and improves endothelial function, thereby decreasing the risk of future cardiac events. Physical inactivity leads to elevated levels of blood pressure and serum lipids, insulin resistance, and obesity, all of which predispose to the development of fatal CHD events.<sup>35</sup> Low CRF is also associated to an increased risk of nonfatal myocardial infarctions, which also increases the risk of SCD.<sup>36</sup> The level of CRF is not only determined by the amount of physical exercise but also by several life-style factors, body composition and genetic factors, therefore high LTPA level is not always correlated with high CRF.<sup>30,31,35</sup> Despite the improvements in levels of risk factors, physical activity may not always improve objectively assessed CRF. Genomic factors of the response of CRF to regular exercise are divergent, and it is important to keep in mind that the heterogeneity in results among the various studies of familial resemblance for physical activity or inactivity level may reflect population differences, sample sizes, or dissimilar ascertainment of physical activity or sedentarism.<sup>37</sup>

A limitation of this study is that the participants were middle-aged men, and therefore the findings can not be generalized to elderly and female populations. On the other hand, middle-aged men are a particular risk group for SCD that emphasizes the clinical importance of our current findings. It would be important to study whether increased LTPA resulted in increased CRF and thereby decreased the risk of SCD among men with low CRF at baseline. We assessed CRF only at baseline in this long-term follow-up study, so we cannot draw conclusions about these issues based on the present data. However, we have previously shown that long-term changes in CRF are associated with all-cause mortality.<sup>38</sup> It has also been argued that LTPA might be reduced prior to death because of diseases and other factors which lead to a decreased level of LTPA and an increased risk of SCD.<sup>29</sup> However, we had a very long follow-up time and reliable data on confounding factors, which diminishes the likelihood of this confounding factor. Among other strengths in this study was that the participation rate was high, there were no losses during the follow-up, CRF was analyzed directly from respiratory gases and LTPA was assessed with a validated questionnaire developed specifically for the KIHD study.<sup>16</sup>

The present findings suggest that low LTPA is associated with an increased risk of SCD among men with low CRF. Therefore, the assessment of physical activity using a questionnaire and CRF using maximal exercise testing could be used to improve the identification of men at increased risk of SCD. Men with low CRF and low LTPA should be urged to increase the amount of physical activity and treat other CHD risk factors.

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**Competing interest** None declared

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**Ethics approval** This study was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland.

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**Table 1.** The means and proportions of baseline characteristics in the four groups according to the level of cardiorespiratory fitness and leisure-time physical activity

	High CRF with high LTPA (Group 1)	High CRF with low LTPA (Group 2)	Low CRF with high LTPA (Group 3)	Low CRF with low LTPA (Group 4)	Total
Participants (n)	1228	546	546	336	2656
Age (years)	52	52	55	54	53
Type 2 diabetes (%)	4.3	3.8	9.3	6.3	5.5
History of coronary heart disease (%)	17.5	16.8	41.9	39.9	25.2
History of smoking (Pack Years)	6	9	10	12	9
Alcohol consumption (g/week)	75	72	81	76	76
Body mass index (kg/m <sup>2</sup> )	26.4	25.8	28.1	28.3	26.9
Systolic blood pressure (mmHg)	133	133	137	136	134
Serum LDL cholesterol (mmol/l)	4.0	4.1	4.1	4.1	4.0
Exercise-induced ST depression (%)	8.6	5.8	11.5	7.3	8.6
hs C-Reactive protein (CRP) (mg/l)	2.1	2.1	3.1	3.16	2.4
Cardiorespiratory fitness (MET)	9.9	9.5	6.4	6.4	8.6
Cardiorespiratory fitness VO <sub>2</sub> (ml/kg/min)	34.7	33.3	22.4	22.4	30.1
LTPA energy consumption (kcal/day)	507	107	503	101	373
LTPA duration (hours/week)	2.9	0.8	3.1	0.7	2.2
LTPA intensity (METs)	4.8	4.3	4.4	4.1	4.5
LTPA frequency (sessions/week)	3.1	1.2	3.3	1.2	2.5
Performed coronary intervention n (%)	150 (12%)	104 (19%)	64 (12%)	61 (18%)	379 (14%)

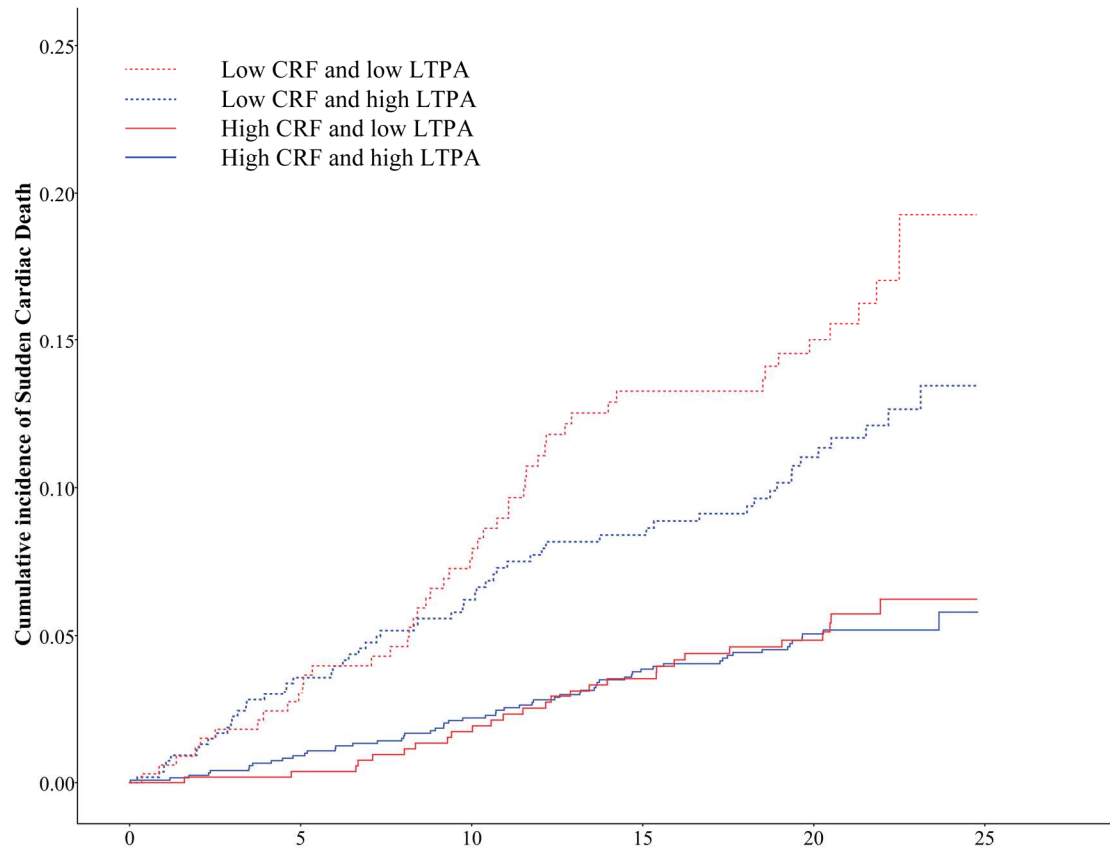
Cardiorespiratory fitness (CRF) with a cut-point at the lowest tertile (7.9 metabolic equivalents). Leisure-time physical activity (LTPA) was assessed with the KIHD LTPA Questionnaire that was modified from the Minnesota LTPA Questionnaire. Measured in energy consumption per day with a cut-off point at the lowest tertile (191 kcal/day). Coronary interventions were defined as percutaneous coronary intervention or coronary artery bypass surgery having been performed due to clinical reasons during follow-up.

**Table 2.** The risk of sudden cardiac death and death from coronary heart disease and all causes according to the level of cardiorespiratory fitness and leisure-time physical activity

	High CRF with high LTPA (Group 1)	High CRF with low LTPA (Group 2)	Low CRF with high LTPA (Group 3)	Low CRF with low LTPA (Group 4)	Total
Risk for sudden cardiac death					
Hazard Ratio <sup>1</sup>	1	1.0	1.3	2.2	
95% Confidence interval		0.6-1.7	0.8-1.9	1.4-3.3	
p		1.000	0.250	0.001	
n (%)	59 (4.8%)	28 (5.1%)	57 (10.4%)	49 (14.6%)	193 (7.3%)
Risk for death from coronary heart disease					
Hazard Ratio <sup>1</sup>	1	0.96	1.5	2.3	
95% Confidence interval		0.6-1.5	1.1-2.2	1.6-3.4	
p		0.848	0.023	<0.001	
n (%)	91 (7.4%)	43 (7.9%)	89 (16.3%)	71 (21.1%)	294 (11.1%)
Risk for death from all causes					
Hazard Ratio <sup>1</sup>	1	1.1	1.6	1.8	
95% Confidence interval		0.8-1.3	1.3-1.9	1.4-2.2	
p		0.651	<0.001	<0.001	
n (%)	314 (25.6%)	151 (27.7%)	260 (47.6%)	161 (47.9%)	886 (33.4%)

Cardiorespiratory fitness (CRF) Leisure-time physical activity (LTPA) <sup>1</sup>Analyzed with cox-regression test with adjustment for age, prevalent type 2 diabetes and CHD, smoking, alcohol consumption, BMI, systolic blood pressure, serum LDL cholesterol, exercise-induced ST segment depressions and serum hs-CRP.

**Figure 1.** Kaplan-Meier plot. The cumulative incidence of sudden cardiac death in the four groups according to the level of cardiorespiratory fitness and leisure-time physical activity. Group 1: Men with high CRF and high LTPA. Group 2: Men with high CRF and low LTPA. Group 3: Men with low CRF and high LTPA. Group 4: Men with low CRF and low LTPA.



Number at risk:	Years from baseline to Sudden Cardiac Death					
	0	5	10	15	20	25
Group 1	1228	1166	1105	918	382	
Group 2	546	518	484	403	174	
Group 3	546	475	420	341	144	
Group 4	336	299	258	202	88	
Total	2656	2458	2267	1864	788	