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Effect of Cardiorespiratory Fitness on Risk of Sudden Cardiac Death in Overweight/Obese
Men Aged 42 to 60 Years

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Running title: Fitness, fatness, and sudden cardiac death

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ABSTRACT

The purpose of this study was to examine the individual and combined associations of cardiorespiratory fitness (fitness) and body mass index (BMI) with the risk of sudden cardiac death (SCD) in middle-aged men. This prospective study was based on a population sample of 2,357 men aged 42-60 years, who were followed up in the Kuopio Ischemic Heart Disease cohort study. Fitness was directly measured by peak oxygen uptake (VO_{2peak}) during progressive exercise testing to volitional fatigue. Participants were divided into 4 groups (fit-normal weight, unfit-normal weight, fit-overweight/obese, and unfit-overweight/obese) based on the median values of fitness and BMI. A total of 253 (10.7%) SCDs occurred during an average follow-up of 22 years. After adjusting for potential confounders, the hazard ratio (HR) and 95% confidence interval (CI) for SCD was 1.80 (95% CI, 1.21-2.68) for BMI ≥ 30.0 kg/m² vs. the normal weight cohort, that is, BMI corresponding to 18.5–24.9 kg/m². However, these associations were no longer statistically significant after adjusting for VO_{2peak} (1.49, 95% CI, 0.98-2.24). Compared with the lower levels of fitness, upper levels of fitness had a 39% lower risk of SCD (HR 0.61, 95% CI, 0.40-0.92) after adjusting for potential confounders, including BMI. In the combined associations of fitness and BMI with the risk of SCD, unfit-overweight/obese men had 1.80 times (95% CI, 1.06-3.06) higher risk of SCD, but fit-overweight/obese men were not at increased risk of SCD (HR 1.22, 95% CI, 0.66-2.25) as compared with their fit-normal weight counterparts. In conclusion, both overweight/obesity and fitness were independently associated with the risk of SCD; however, fitness appears to attenuate the risk of SCD in overweight/obese men, suggesting that improving fitness may reduce the risk of SCD in this population.

Key words: Sudden cardiac death, obesity, cardiorespiratory fitness

The relative contributions of body habitus and cardiorespiratory fitness (fitness) on the risk of sudden cardiac death (SCD) remain unclear, and no previous study has examined the impact of fitness in attenuating the adverse effects of overweight/obesity on the risk of SCD. Because higher fitness is generally associated with a lower risk of SCD, independent of potential confounding factors, including body habitus,^{1,2} the potential impact of both fitness and body mass index (BMI) on the risk of SCD requires clarification.³ This study examines the individual and combined associations of body habitus and fitness on the long-term risk of SCD in middle-aged men. We hypothesized that overweight/obesity and fitness would predict the risk of SCD, but that fitness would attenuate the risk of SCD in overweight/obese men.

METHODS

Subjects initially included 3,235 eligible participants from an ongoing prospective population-based cohort study in eastern Finland (the Kuopio Ischemic Heart Disease Study: KIID), 2,357 (aged 42-60 years) of whom had baseline examinations performed between 1984 and 1989 to investigate risk factors for cardiovascular disease and related health outcomes. The study was approved by the Research Ethics Committee of the University of Eastern Finland (Kuopio, Finland) and all participants provided written informed consent.

Resting blood pressure was measured twice using a random-zero sphygmomanometer in the seated position following 5 and 10 minutes of quiet rest. The mean of these 2 values was used as resting blood pressure. BMI was computed as the ratio of weight in kilograms (kg) to the square of height in meters (m), and participants were categorized into 3 groups: normal weight (18.5–24.9 kg/m²); overweight (25.0–29.9 kg/m²); and, obese (≥ 30.0 kg/m²), using conventional body habitus criteria.

Smoking habits, presence of chronic diseases, medications, and related demographic/lifestyle information were evaluated via a standardized self-administered

questionnaire. Self-reported activity levels were assessed using a 12-month physical activity history modified from the Minnesota Leisure-Time Physical Activity Questionnaire and expressed as kcal/day. The collection of blood samples, measurement of serum lipids, lipoproteins, and glucose, and definitions of hypertension and type 2 diabetes have been previously described.² Peak oxygen uptake (VO_{2peak}), a marker of cardiorespiratory fitness, was directly measured using a calibrated, computerized metabolic measurement system (Medical Graphics, St. Paul, MN, USA) during progressive exercise testing to volitional fatigue on an electrically braked cycle ergometer. The standardized testing protocol included a 3-min warm-up at 50 watts (W; 1 W ~6 kpm/min), followed by 20 W/min increases in workload with direct analyses of expired respiratory gases. VO_{2peak} was defined as the highest attained value for oxygen consumption and/or a plateau in oxygen uptake at maximal exercise, and expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O₂/kg/min)⁴ to divide fitness levels into tertiles; low (<7.6 METs), middle (7.6–9.4 METs), and upper (>9.4 METs), based on VO_{2peak} percentiles. To determine the association of combined fitness and BMI on the risk of SCD, participants were divided into 4 groups (fit-normal weight (≥ 8.6 METs, <26.5 kg/m²), unfit-normal weight (<8.6 METs, <26.5 kg/m²), fit-overweight/obese (≥ 8.6 METs, ≥ 26.5 kg/m²), and unfit-overweight/obese (<8.6 METs, ≥ 26.5 kg/m²) based on median values of fitness and BMI for the entire cohort.

We included all SCDs that occurred from study enrollment through 2014. There were no losses to follow-up in the KIID study, since participants (using Finnish personal identification codes) were under continued annual surveillance for the occurrence of non-fatal or fatal CVD events, including incident cases and deaths. Sources of information on SCD and other cardiovascular outcomes were based on a comprehensive review of all available hospital records, health center wards, informant interviews, health practitioner questionnaires,

study electrocardiograms, death certificate registers, medico-legal reports, or combinations thereof. The diagnostic classification of SCDs was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of coronary heart disease along with corresponding documentation from hospital and paramedic staff. A SCD was defined when it occurred within 1 h of the onset of an abrupt increase in symptomatology or within 24 h after the onset of symptoms, including non-witnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death or after successful resuscitation from ventricular tachycardia and/or ventricular fibrillation. The witnessed subject was to have been seen, symptom-free, within 1 h before the event. Apparent SCDs that occurred in out-of-hospital environments were also counted if the triggering events/circumstances were accurately documented in physician-reviewed hospital reports. Symptomatic cardiac arrhythmias or events that did not lead to death during the following 24 h were not considered as SCDs. An Independent Events Committee, masked to clinical data, classified the outcomes.

Data are expressed as mean \pm standard deviation for continuous variables and as proportions for categorical variables. Baseline characteristic comparisons of the participants with and without SCD were performed using independent Student's *t* test for continuous variables and chi-square tests for categorical variables. We calculated the hazard ratio (HR) and 95% confidence intervals (CI) via a multivariable Cox proportional hazard model with adjustment for confounding factors to determine the relations of fitness and BMI, using categorical variables, to the risk of SCD. The combined associations of fitness and BMI on the risk of SCD were examined using combined groups (fit-normal BMI, unfit-normal BMI, fit-high BMI and unfit- high BMI). Our reference group was the fit-normal BMI cohort. The survival probability for SCD in each group was presented using Kaplan-Meier survival

curves. Statistical significance was set at $p < 0.05$. All tests for statistical significance were two-sided. Analyses were conducted using the SPSS version 21.0 (SPSS, Armonk, NY).

RESULTS

A total of 253 (10.7%) SCDs occurred during an average of 22 years follow-up. Men experiencing SCD had greater age, BMI, systolic and diastolic blood pressures, low-density lipoprotein cholesterol, triglycerides, glucose, smoking, previous myocardial infarction, diabetes, and hypertension, but lower high-density lipoprotein cholesterol and VO_{2peak} (all $p < 0.05$) at baseline as compared with men who did not experience SCD (Table 1). Table 2 summarizes the HR and 95% CI of incident SCD with specific reference to BMI and fitness. After adjusting for age, smoking, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertension, family history of coronary heart disease, previous myocardial infarction, and physical activity (Model 1), the HR and 95% CI for incident SCD was 1.10 (95% CI, 0.79–1.55) for BMI 25.0–29.9 and 1.80 (95% CI, 1.21–2.68) for BMI ≥ 30.0 vs. normal weight (BMI 18.5–24.9). However, these associations were no longer statistically significant after adjusting for VO_{2peak} (1.49, 95% CI, 0.98–2.24 for BMI ≥ 30.0 vs. normal weight) (Model 2). Table 2 also summarizes the HR and 95% CIs for incident SCD in the upper versus lower fitness which was 0.55 (95% CI, 0.37–0.81) after adjusting for conventional risk factors (Model 1), and this lower risk persisted even after adjusting for BMI (HR 0.61, 95% CI, 0.40–0.92). Figure 1 shows the combined associations of fitness and BMI on the risk of SCD. Compared with fit-normal weight men as a reference, unfit-overweight/obese men had 1.80 times (95% CI, 1.06–3.06) higher risk of SCD after adjusting for age, smoking, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertension, family history of coronary heart disease, previous myocardial infarction, and physical activity. In

contrast, fit-overweight/obese men were not at increased risk of SCD (RR 1.22, 95% CI, 0.66–2.25) as compared with their fit-normal weight counterparts. The Kaplan-Meier survival analysis showed that the survival rate of SCD in fit-overweight/obese men was similar to that of fit-normal weight cohort (Figure 2).

DISCUSSION

Our findings indicate that both fitness and overweight/obesity were associated with lower and higher risks of SCD, respectively. Interestingly, the association between overweight/obesity and SCD was dependent on fitness levels, whereas higher levels of fitness were independently associated with a lower risk of SCD, regardless of BMI. Furthermore, a novel finding from our study was that overweight/obese, unfit men had a greater risk of SCD as compared with normal weight, fit men; however, overweight/obese, fit men had a similar risk of SCD as compared with their normal weight, fit counterparts. These findings suggest that fitness may favorably modify the relationship between overweight/obesity and the risk of SCD. This is the first long-term prospective study demonstrating that fitness may reduce or eliminate the increased risk of SCD in overweight/obese individuals. These findings are compatible with previous reports that obese, fit individuals have similar mortality risks as normal weight, fit individuals^{5, 6, 7} and extend the prophylactic role of fitness to incident SCD in overweight/obese individuals. In particular, our results further substantiate existing evidence regarding the “fat but fit” protective paradox,⁸ demonstrating that increased fitness appears to attenuate the risk of SCD in overweight/obese Finnish men, using conventional BMI criteria to define body habitus. Thus, improving fitness should be encouraged to reduce the risk of SCD in overweight/obese individuals.

It is generally agreed that obesity contributes to cardiovascular diseases through multiple structural derangements and functional abnormalities⁹ that, over time, may lead to an

increased risk of atrial and ventricular arrhythmias.^{10, 11} Furthermore, several studies suggested that obesity per se was associated with an increased risk of SCD.^{12, 13} In the Atherosclerosis Risk in Communities study,¹² obesity was related to the incidence of SCD over a 12.6 year follow-up. However, the impact of obesity on the risk of SCD has remained controversial.^{14, 15} We believe that these conflicting data may be attributed, at least in part, to the inability to account for fitness as a potential confounding variable.¹⁶ Previous studies have reported that estimated or directly measured fitness were strongly associated with a lower risk of SCD, independent of potential confounders, including body habitus.^{1, 2} In the present study, although higher BMI was associated with a greater risk of SCD, this risk appreciably diminished when we adjusted for fitness. Accordingly, our results provide new perspectives on the important role of fitness in the prevention of SCD in both normal weight and overweight/obese phenotypes.

Several potential mechanisms may contribute to the role of fitness in attenuating the risk of SCD among overweight/obese men. The association between impaired autonomic nervous system function and a heightened risk of SCD has been previously reported.¹⁷ High fitness, which is positively related to increased vagal tone,¹⁸ is also independently associated with reduced risks of developing atrial fibrillation¹⁹ and threatening ventricular arrhythmias.²⁰ This suggests that fitness-related increased vagal outflow may serve as a potential underlying mechanism explaining the lower risk of SCD in fit,²¹ overweight/obese individuals. It is interesting to note that individuals who approach or exceed their age and gender predicted VO_{2peak} tend to have coronary lesions that are characterized by a lower lipid volume, higher fibrous volume, and a greater fibrous cap thickness than do individuals with a lower percentage of predicted VO_{2peak} .²² Clearly, additional studies are needed to further clarify the

precise mechanisms underlying the protective effects of fitness on SCD in overweight/obese individuals.

We acknowledge several methodologic limitations. Our study population included only men, limiting the generalizability of our findings to women. Although we adjusted for potential confounders to predict the independent associations between body habitus and fitness on the risk of SCD, it is possible that residual variables that were not measured may have influenced the observed difference in relative risks. Moreover, we used a single measurement of fitness at baseline to predict the risk of SCD and did not correct for serial changes in aerobic capacity over time or, for that matter, potential regression dilution bias. Despite these limitations, the strengths of this study included the long-term follow-up and directly measured VO_{2peak} , which was not considered in previous studies.

In conclusion, our results demonstrate that both overweight/obesity and fitness were independently associated with the long-term risk of SCD in middle-aged men. However, higher levels of fitness appeared to attenuate the risk of SCD in overweight/obese men, suggesting that increasing fitness should be strongly encouraged to improve survival in this patient population.

Disclosures

The authors have no conflicts of interest to declare.

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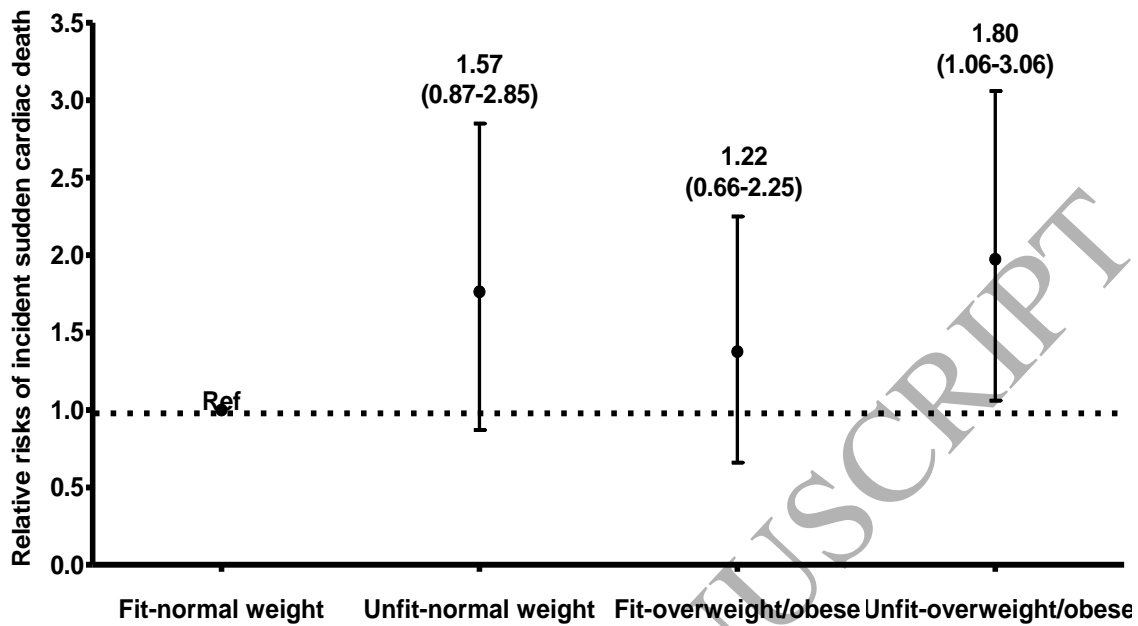
Figure Legends.

Figure 1. Combined associations of body mass index and cardiorespiratory fitness on the risk of sudden cardiac death. The results were adjusted for age, smoking, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertension, family history of coronary heart disease, previous myocardial infarction, and physical activity.

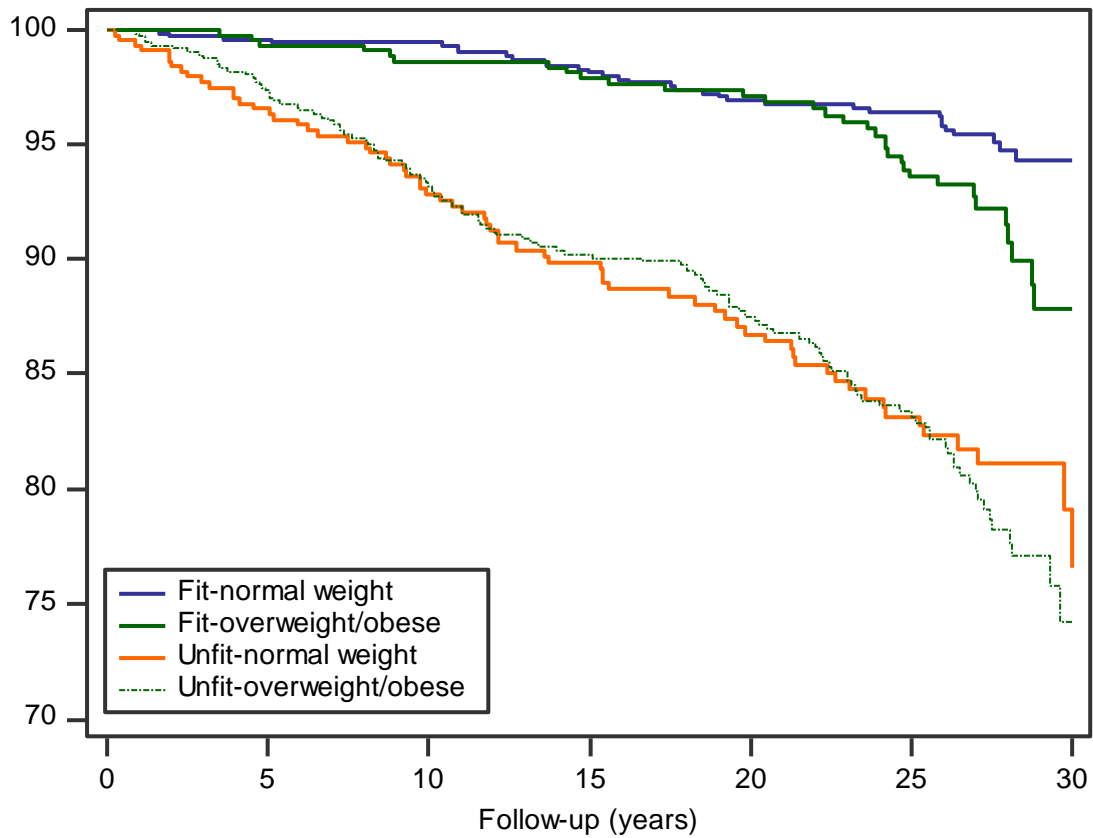


Figure 2. Kaplan-Meier survival curves for sudden cardiac death by combined body habitus and cardiorespiratory fitness.

Table 1. Baseline characteristics of the participants with and without sudden cardiac death during follow-up.

Variable	Sudden Cardiac Death		<i>p</i> value
	NO (n=2104)	YES (n=253)	
Age (years)	52.7±5	54.2±4.3	<0.001
Body mass index (kg/m ²)	26.7±3.4	27.8±3.7	<0.001
Smoker	30.6%	43.1%	<0.001
Family history of coronary heart disease	48.9%	54.2%	0.066
Prior myocardial infarction	5.6%	22.5%	<0.001
Diabetes mellitus	4.9%	11.1%	<0.001
Hypertension	28.5%	41.5%	<0.001
Systolic blood pressure (mmHg)	133.5±16.7	139.2±17.4	<0.001
Diastolic blood pressure (mmHg)	88.6±10.5	90.8±9.8	0.002
High-density lipoprotein cholesterol (mmol/L)	1.30±0.3	1.24±0.3	0.003
(mg/dL)	50.3±12	49.0±12	
Low-density lipoprotein cholesterol (mmol/L)	4.02±1.0	4.26±1.0	<0.001
(mg/dL)	155.5±39	164.7±39	
Triglycerides (mmol/L)	1.27±0.8	1.47±1.0	<0.001
(mg/dL)	112.5±70.9	130.2±88	
Glucose (mmol/L)	4.74±1.1	5.03±1.5	<0.001
(mg/dL)	85.4±19.8	90.6±27.0	
Leisure time physical activity (kcal/day)	367.9±335	370.8±336	0.900
Peak oxygen uptake (mL/kg/min)	30.7±7.9	26.3±7.6	<0.001

Values are presented as mean ± SD or as a percentage

Table 2. Hazard ratio (HR) and 95% confidence interval (CI) for incident sudden cardiac death by body habitus and cardiorespiratory fitness

Variable	N	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Body Mass Index (kg/m²)				
18.5–24.9	737	1 (ref)	1 (ref)	1 (ref)
25.0–29.9	1216	1.38 (1.01-1.89)	1.10 (0.79-1.55)	1.01 (0.72-1.42)
≥30.0	404	2.51 (1.77-3.57)	1.80 (1.21-2.68)	1.49 (0.98-2.24)
Fitness (mL/kg/min)				
<26.7	765	1 (ref)	1 (ref)	1 (ref)
26.7-33.0	784	0.47 (0.36-0.63)	0.75 (0.55-1.02)	0.80 (0.58-1.10)
>33.0	808	0.24 (0.17-0.34)	0.55 (0.37-0.81)	0.61 (0.40-0.92)

Model 1: Adjusted for age, smoking, systolic blood pressure, high-density lipoprotein

cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertension, family history of coronary heart disease, previous myocardial infarction, and physical activity.

Model 2: Model 1 plus fitness when corrected for body mass index; and, body mass index when corrected for fitness