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Impact of Cardiorespiratory Fitness on Survival in Men with Low Socioeconomic Status

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ABSTRACT (249 words)

Aims: Although both low socioeconomic status (SES) and poor cardiorespiratory fitness (CRF) are associated with increased chronic disease and heightened mortality, it remains unclear whether moderate-to-high levels of CRF are associated with survival benefits in low SES populations. This study evaluated the hypothesis that SES and CRF predict all-cause mortality (ACM) and cardiovascular disease (CVD) mortality and that moderate-to-high levels of CRF may attenuate the association between low SES and increased mortality.

Methods: This study included 2,368 men, who were followed in the Kuopio Ischemic Heart Disease Study cohort. CRF was directly measured by peak oxygen uptake during progressive exercise testing. SES was characterized using self-reported questionnaires.

Results: During a 25-year median follow-up, 1116 ACM and 512 CVD mortality events occurred. After adjusting for potential confounders, men with low SES were at increased risks for ACM (hazard ratio [HR] 1.49, 95% Confidence Interval [CI]: 1.30-1.71) and CVD mortality (HR 1.38, 1.13-1.69). Higher levels of CRF were associated with lower risks of ACM (HR 0.54, 0.45-0.64) and CVD mortality (HR 0.53, 0.40-0.69). In joint associations of SES and CRF with mortality, low SES-unfit had significantly higher risks of ACM (HR 2.15, 1.78-2.59) and CVD mortality (HR 1.95, 1.48-2.57), but low SES-fit was not associated with a heightened risk of CVD mortality (1.09, 0.80-1.48) as compared with their high SES-fit counterparts.

Conclusion: Both SES and CRF were independently associated with subsequent mortality; however, moderate-to-high levels of CRF were associated independently with a lower risk of CVD mortality in men with low SES.

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Key words*: socioeconomic status, cardiorespiratory fitness, mortality*

INTRODUCTION

Socioeconomic status (SES), typically evaluated using education, annual income, place of residence, occupation, or combinations thereof, has been shown to be an important determinant of several health outcomes.[1] Low SES is strongly associated with increased all-cause mortality (ACM) and cardiovascular disease (CVD) events and mortality, which have been linked to established CVD risk factors and unhealthy lifestyle habits.[1, 2]

Individuals with low SES are reported to have lower levels of leisure-time physical activity when compared to their higher SES counterparts.[2] The lower levels of physical activity in individuals with low SES may be due, at least in part, to reduced cardiorespiratory fitness (CRF), which is an important determinant of cardiovascular outcomes and mortality in the general population and predictive of prognosis and survival in diseased populations.[3-6]

Accumulating studies suggest that CRF has a protective effect in attenuating ACM and CVD mortality in 'at risk' populations.[7, 8] A meta-analysis demonstrated that individuals with low SES appear to have relatively low CRF levels compared to individuals with high SES.[9] Therefore, CRF may, at least in part, contribute to the above-referenced socioeconomic differences in survival. However, it remains unclear whether the potential impact of CRF confers survival benefits among underserved populations within the general population. The present study evaluated the hypothesis that SES and CRF would predict ACM and CVD mortality and that moderate-to-high levels of CRF would attenuate the association between low SES and heightened mortality.

METHOD

Participants

This investigation included participants from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), which is an ongoing prospective population-based long-term study to

evaluate risk factors for CVD and related health outcomes in a randomly selected sample of men in Kuopio and the surrounding communities in eastern Finland. The participants initially included 3,235 eligible men who resided in the town of Kuopio or its surrounding rural communities. At baseline, examinations were conducted on 2,682 men between March 1984 and December 1989 and 2,368 men aged 42 to 61 years with complete data were included in the present study. The study was approved by the Research Ethics Committee of the University of Eastern Finland (Kuopio, Finland), and all participants provided written informed consent.

Socioeconomic status

SES was characterized using self-reported questionnaires via a summary index that combined measures of income, education, occupational prestige, material standard of living, and housing conditions. Income was divided into quintiles over the past 12 months. Education was classified into four categories: less than an elementary education; completion of elementary education; completion of middle school or a part of middle school; and completion of high school or above. The occupational status (occupational prestige) of participants on the basis of self-reported primary lifetime occupation was classified into three categories as white collar (professional and managerial staff, low-paid clerical workers); blue collar (manual laborers in construction, mining, manufacturing, or forestry); and farmer, including those who spent most of their employed activities in the agricultural sector. Standard of living was evaluated using a material possession index based on self-reports of ownership of 12 items (color TV, video tape recorder, freezer, dish washer, car, motor cycle, telephone, summer cottage, house trailer, motor boat, sailing boat, and ski mobile). The combined SES index ranged from 0 to 25, with higher values indicating lower SES.[10, 11] SES index was classified by tertiles: low SES (>11), middle SES (10-8), and high SES (<7), and classified into low SES (>10) and high SES (<9) based on median values.

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Cardiorespiratory fitness

Peak oxygen uptake (VO_{2peak}), an objective marker of CRF, was directly assessed using a computerized metabolic measurement system (Medical Graphics, St. Paul, MN, USA) during progressive exercise testing to volitional fatigue on an electrically braked cycle ergometer. The methodology for the direct measurement of VO_{2peak} has been previously described.[12] Briefly, the standardized testing protocol included a 3-min warm-up at 50 watts (W; 1 W = 6.12 kgm/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.

Categories of CRF were standardized based on methods as previously suggested.[13, 14] Briefly, participants were stratified into four age groups: 42 to 47 years, 48-53 years, 54 to 59 years, and >60 years, and then we defined CRF categories by tertiles of VO_{2peak} value within each age group. We combined the individual CRF categories from each age group to form the following age-specified CRF categories: lower (mean 22.2±4.7 ml/kg/min), moderate (29.9±3.2 ml/kg/min), and higher (38.1±5.5 ml/kg/min). CRF was also classified into unfit (24.3±5.1 ml/kg/min) and fit (36.0±5.8 ml/kg/min) based on median values of age-specific VO_{2peak} percentiles.

Other measurements

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. Body mass index was computed as the ratio of weight in kilograms (kg) to the square of height in meters (m). 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 with the estimated energy expenditure expressed as kcal/day. Alcohol ingestion was assessed using the Nordic Alcohol consumption inventory. The collection of blood samples, measurement of serum lipids, lipoproteins, and glucose, definitions of type 2 diabetes have been previously described.[12]

Ascertainment of outcomes

All deaths that occurred from study enrollment through to the end of 2014 were included in the analysis. No losses to follow-up were recorded in the KIHD study as participants are under continuous annual surveillance for the development of incident disease and deaths. Data on deaths were ascertained from hospital documents, health center wards, death certificates and medico-legal reports. Outcomes were coded using the International Classification of Disease codes.

Statistical Analysis

Data are expressed as mean ± standard deviation for continuous variables and as proportions for categorical variables. Baseline characteristic comparisons of the participants with low, middle, and high SES were performed using a one-way analysis of variance for continuous variables with normal distribution or the Kruskal-Wallis test for continuous ones with non- normal distribution and the chi-square (χ^2) test for categorical ones. We calculated the hazard ratio (HR) and 95% confidence intervals (CI) via a multivariable Cox proportional hazard model, adjusting for potential confounding variables (age, smoking, alcohol, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertensive medication, family history of coronary heart disease, history of CVD, and physical activity) to determine the associations of SES and CRF, using categorical (tertiles) and continuous variables, to the risk of death. The joint effects of

SES and CRF on the risk of death were examined using 4 combined groups based on the median values of SES and CRF (high SES-Fit, low SES-Fit, high SES-Unfit, and low SES-Unfit). Our reference group was the high SES-Fit cohort. The survival probability for ACM and CVD mortality 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 22.0 (SPSS, Armonk, NY).

RESULTS

Baseline characteristics of the study participants grouped by tertiles of SES score are shown in Table 1. Men with low SES had higher age, history of CVD, incident hypertension and resting systolic blood pressure, and low-density lipoprotein cholesterol, but lower alcohol consumption, leisure time physical activity and peak oxygen uptake (all $p<0.05$) at baseline as compared to men with high SES (Table 1).

During a 25-year median follow-up (interquartile ranges: 18-27 years), 1,116 ACM and 512 CVD mortality events occurred. The associations of potential confounders with mortality risk are provided as a supplementary material. Table 2 summarizes the HR and 95% CIs for mortality by SES score and CRF level. After adjusting for potential confounders, the lowest levels of SES were at significantly increased risk for ACM (hazard ratio [HR] 1.49, 95% Confidence Interval [CI]: 1.30-1.71) and CVD mortality (HR 1.38, 1.13-1.69), as compared with their high-level SES counterparts (reference). Each 1 score increase in SES was associated with a 4-5% higher the risk of mortality after adjusting for covariates (table 2).

In contrast, higher levels of CRF were associated with lower risks of ACM (HR 0.54, 0.45-0.64) and CVD mortality (HR 0.53, 0.40-0.69) after adjusting for potential confounders. Each 1 ml/kg/min increment in CRF was associated with a 4-5% lower the risk of mortality after adjusting for covariates.

Compared with high SES-fit as a reference, low SES-unfit had significantly higher risks of ACM (HR 2.15, 1.78-2.59) and CVD mortality (HR 1.95, 1.48-2.57), but low SES-fit was not associated with a heightened risk of CVD mortality (HR 1.09, 0.80-1.48). However, ACM remained significantly higher in low SES-fit versus high SES-fit counterparts (HR 1.49, 1.23-1.81). The Kaplan-Meier survival analysis showed that the survival rates of CVD mortality in low SES-Fit were similar to that of high SES-Fit cohort (Figure 1).

DISCUSSION

In the present study, both low SES and high CRF were significantly associated with higher and lower risks of ACM and CVD mortality, independent of potential confounding variables. However, the novel findings from our study were that the risk of ACM and CVD mortality associated with low SES were the highest in unfit men, whereas the risk of CVD mortality was significantly attenuated in fit men with low SES. These findings suggest that CRF may favorably modify the relationship between SES and the risk of mortality, highlighting the prophylactic role of CRF to enhance survival in underserved populations. Thus, improving CRF should be encouraged to reduce the risk of CVD mortality in individuals with low SES.

To our knowledge, only two previous studies have reported that CRF contributed to the socioeconomic differential in ACM and survival after acute myocardial infarction.[15, 16] The former study suggested that differences in impaired estimated functional capacity explained as much as 47% of the SES-mortality associations among patients with suspected coronary artery disease.[16] The latter study reported that functional status using self-reported questionnaires explained ~30% of the association between SES and long-term mortality after acute myocardial infarction.[15] However, these studies did not directly measure CRF using gas analysis. Our results suggest that directly measured moderate-to-high levels of CRF attenuate the risk of mortality associated with low SES.

Our results are consistent with previous studies demonstrating that patients with lower SES have reduced functional capacity as determined by treadmill exercise testing.[17-19] Furthermore, a meta-analysis found that individuals with low SES appear to have relatively low CRF levels as compared with individuals of high SES, independent of physical activity.[9] In the present study, men with low SES had lower levels of directly measured peak oxygen uptake (by 3.8 ml/kg/min at baseline) as compared to men with high SES. Considering that each 1 metabolic equivalent (MET = 3.5 ml/kg/min) increase in functional capacity is associated with a 13% and 15% lower risk of ACM and CVD events,[20] our findings suggest that reduced CRF may contribute to social inequalities in health, and should be a target for improving survival in socioeconomically disadvantaged populations.

Several potential mechanisms may serve to explain the role of CRF-mediated alterations on the association between SES and mortality. Although CRF is partially explained by genetic variation, CRF is highly reflective of the magnitude and intensity of leisure-time physical activity, which is dose-dependent and is associated with a substantially reduced risk of mortality.[21] Individuals with lower SES may have limitations to regular physical activity participation, including relatively unsafe outdoor exercise environments, fewer accessible recreation facilities, and reduced opportunities to engage in leisure time physical activity,[22] which may contribute to their reduced CRF.

In addition, the association between SES and increased mortality is largely mediated by cardiovascular risk factors.[2] High CRF also attenuates the risk of mortality in overweight/obese individuals, those with diabetes mellitus or metabolic syndrome and at any given atherosclerotic CVD risk factor profile.[7, 8, 23, 24] Moreover, higher levels of CRF are associated with a decreased prevalence of coronary artery calcium, carotid artery intima media thickness, and pulse wave velocity, even in individuals with cardiometabolic risk factors.[25, 26]

Because the association between low SES and a heightened risk of subclinical and future atherosclerosis[27] has been recently reported,[28] these data suggest that CRF-related decreased surrogate markers of subclinical atherosclerosis may serve as a potential underlying mechanism explaining the reduced mortality in fit, low SES individuals. Clearly, additional studies are needed to further clarify the mechanisms underlying the protective effect of CRF on CVD mortality in individuals with low SES.

We acknowledge several methodological limitations to our study. Our study population included only Caucasian men, limiting the generalizability of our findings to women and other races/ethnicities. SES was assessed using self-reported questionnaires, rather than review of individual records. Moreover, we used a single measurement of SES and CRF at baseline to predict the risk of death and did not correct for serial changes in SES (upward or downward shift) and CRF over time or, for that matter, potential regression dilution bias.[29] Despite these limitations, the strengths of this study included that we directly measured peak oxygen consumption using metabolic gas analysis, which provides an objective and quantitative measure of aerobic capacity that is widely accepted as the gold standard measure of CRF.[30]

CONCLUSIONS

In this population-based study of middle-aged men, our findings indicate that both SES and CRF were independently associated with ACM and CVD mortality. However, moderate-to-high levels of CRF appeared to attenuate the risk of CVD mortality in this cohort. These unique data have important implications for public health interventions designed to enhance survival in underserved populations.

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data collection in the study.

AUTHOR CONTRIBUTION

All authors contributed to the conception and design of the study. JAL, JK and SK contributed to the data acquisition. SYJ, SK, SKK and JAL contributed to the analysis, or interpretation of data for the study. SYJ, JAL, SKK, SK, and JC designed the methodoligical approach, collaborated on the statistical analyses. SYJ, JAL, and SKK drafted the manuscript. SKK, KB, JC and BAF critically revised the manuscript. All authors provided critical scientific and editorial contributions to the manuscript draft. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

DECLARATION OF CONFLICTING INTERESTS

The authors have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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FIGURE LEGEND

Figure 1. The Kaplan-Meier survival curves for all-cause and CVD mortality by combined of socioeconomic status and cardiorespiratory fitness

Table 1. Baseline characteristics of the participants by tertiles of socioeconomic status score (n=2,368).

Variables	High SES (n=961)	Middle SES (n=569)	Low SES (n=838)	p value
Socioeconomic status score	4.2±2.0	9.0±0.8	13.0±1.8	<0.001
Age (years)	51.6±5.5	52.9±5.0	54.3±4.2	<0.001
Body mass index (kg/m^2)	26.8±3.4	26.9±3.6	27.0±3.8	0.314
Smokers (%)	25.5	34.8	38.1	<0.001
Alcohol consumption (g/week)	39 (10-91)	23 (5-88)	26 (4-98)	<0.001
Family history of coronary heart disease (%)	49.7	49.9	47.3	0.296
History of cardiovascular disease (%)	28.2	38.4	48.1	<0.001
Diabetes (%)	4.8	4.9	6.7	0.063
Hypertensive medication (%)	18.7	22.3	26.4	<0.001
Systolic blood pressure (mmHg)	133.1±16.2	134.3±17.3	135.3±17.9	0.014
Diastolic blood pressure (mmHg)	88.7±10.3	88.8±10.9	88.8±10.6	0.963

High-density lipoprotein cholesterol (mmol/L)	1.28±0.29	1.29±0.31	1.31±0.32	0.069
Low-density lipoprotein cholesterol (mmol/L)	3.90±0.98	4.09±0.98	4.15±1.05	<0.001
Triglycerides (mmol/L)	1.33±0.85	1.27±0.69	1.32±0.86	0.299
Glucose (mmol/L)	4.77±1.12	4.77±1.10	4.84±1.39	0.392
Leisure time physical activity (kcal/day)	320 (177-506)	254 (136-441)	266 (133-460)	<0.001
Peak oxygen uptake (mL/kg/min)	32.0±7.7	30.1±8.3	28.2±7.6	<0.001

Mean±SD or percentage.

Table 2. Hazard ratio (HR) and 95% confidence interval (CI) for all-cause and cardiovascular mortality by socioeconomic status and cardiorespiratory fitness.

Variables	All-cause mortality		Cardiovascular mortality	
Socioeconomic status (SES)	Deaths/Total	Adjusted model HR (95% CI)	Events/Total	Adjusted model HR (95% CI)
Each 1 score increase	1116/2368	1.05 (1.03-1.06)	512/2368	1.04 (1.02-1.06)
High SES	344/961	1 (reference)	151/961	1 (reference)
Moderate SES	275/569	1.22 (1.05-1.43)	139/569	1.32 (1.06-1.65)
Low SES	497/838	1.49 (1.30-1.71)	222/838	1.38 (1.13-1.69)
P-value		*<0.001*		*0.005*
Cardiorespiratory fitness (CRF)				
Each 1 ml/kg/min increase	1116/2368	0.96 (0.95-0.97)	512/2368	0.95 (0.93-0.96)
Low	483/782	1 (reference)	249/782	1 (reference)
Moderate	349/774	0.69 (0.59-0.80)	153/774	0.67 (0.54-0.84)
High	284/812	0.54 (0.45-0.64)	110/812	0.53 (0.40-0.69)
P-value		*< 0.001*		*<0.001*

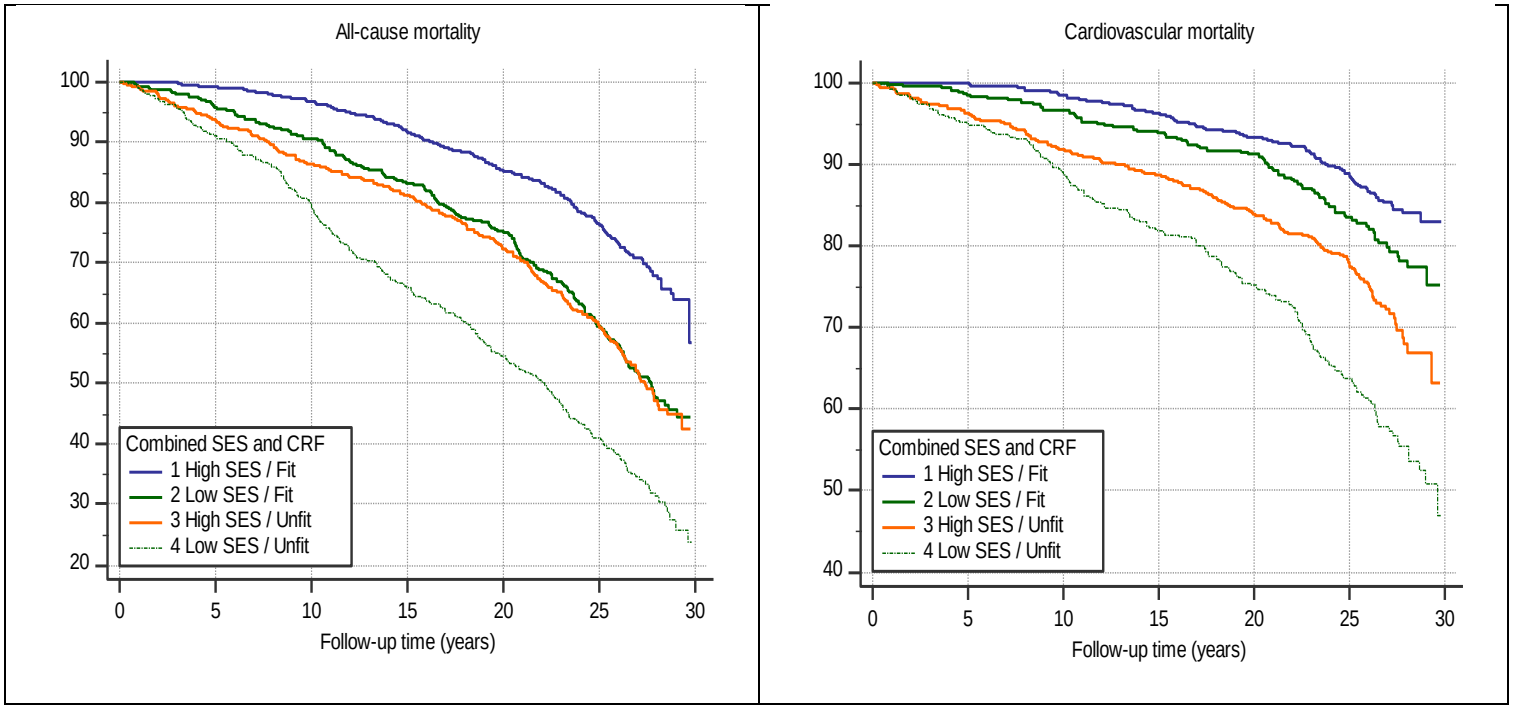
Adjusted for age, smoking, alcohol consumption, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertensive medication, family history of coronary heart disease, history of cardiovascular disease, and physical activity.

Table 3. Joint association of socioeconomic status and cardiorespiratory fitness on the risk of all-cause and cardiovascular mortality.

Variables	**All-cause mortality**		**Cardiovascular mortality**	
	Deaths/Total (1116/2368)	Adjusted Model HR (95% CI)	Deaths/Total (512/2368)	Adjusted Model HR (95% CI)
High SES / Fit	210/710	1 (reference)	93/710	1 (reference)
Low SES / Fit	239/484	1.49 (1.23-1.81)	82/484	1.03 (0.73-1.46)
High SES / Unfit	298/624	1.51 (1.24-1.83)	151/624	1.59 (1.18-2.14)
Low SES / Unfit	369/550	2.15 (1.78-2.59)	186/550	2.20 (1.64-2.94)

Adjusted for age, smoking, alcohol consumption, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, hypertensive medication, family history of coronary heart disease, history of cardiovascular disease, and physical activity. SES and CRF were divided into 4 combined groups (high SES-Fit, low SES-Fit, high SES-Unfit, and low SES-Unfit) based on the median values of SES and CRF.

Figure 1.


All-cause mortality
100
90
80
70
60
50
40
30
20
0
5
10
15
20
25
30
Follow-up time (years)
Combined SES and CRF
1 High SES / Fit
2 Low SES / Fit
3 High SES / Unfit
4 Low SES / Unfit
Cardiovascular mortality
100
90
80
70
60
50
40
0
5
10
15
20
25
30
Follow-up time (years)
Combined SES and CRF
1 High SES / Fit
2 Low SES / Fit
3 High SES / Unfit
4 Low SES / Unfit