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

Sae Young Jae,^{1,8} Sudhir Kurl,² Kanokwan Bunsawat,³ Barry A. Franklin,⁴ Jina Choo,⁵
Setor K. Kunutsor,^{6,7} Jussi Kauhanen,² Jari A Laukkanen^{2,8}

¹Department of Sport Science, University of Seoul, Seoul, Republic of Korea. ²Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland. ³Department of Internal Medicine, Division of Geriatrics, University of Utah, Salt Lake City, Utah, USA. ⁴Preventive Cardiology and Cardiac Rehabilitation, William Beaumont Hospital, Royal Oak, MI, USA. ⁵College of Nursing, Korea University, Seoul, Republic of Korea. ⁶National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK. ⁷Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK. ⁸Division of Urban Social Health, Graduate School of Urban Public Health, University of Seoul, Seoul, Republic of Korea.

Running head: Socioeconomic status, fitness, and risk of mortality

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Corresponding Author: Sae Young Jae, PhD.

Health and Integrative Physiology Laboratory, Department of Sport Science, University of Seoul, 90 Jeonnon-dong, Dongdaemun-gu, Seoul 130-743, South Korea.

E-mail: syjae@uos.ac.kr, Phone : 82-2-6490-2953 Fax: 82-2-6490-5204

1 **ABSTRACT (249 words)**

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

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

11 **Results:** During a 25-year median follow-up, 1116 ACM and 512 CVD mortality events
12 occurred. After adjusting for potential confounders, men with low SES were at increased risks
13 for ACM (hazard ratio [HR] 1.49, 95% Confidence Interval [CI]: 1.30-1.71) and CVD
14 mortality (HR 1.38, 1.13-1.69). Higher levels of CRF were associated with lower risks of ACM
15 (HR 0.54, 0.45-0.64) and CVD mortality (HR 0.53, 0.40-0.69). In joint associations of SES
16 and CRF with mortality, low SES-unfit had significantly higher risks of ACM (HR 2.15, 1.78-
17 2.59) and CVD mortality (HR 1.95, 1.48-2.57), but low SES-fit was not associated with a
18 heightened risk of CVD mortality (1.09, 0.80-1.48) as compared with their high SES-fit
19 counterparts.

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

23
24 **Key words:** socioeconomic status, cardiorespiratory fitness, mortality

Commented [SK1]: I don't agree with this conclusion based on the results. Should rather be "moderate-to-high levels of CRF were not associated with an excess risk of CVD mortality in men with low SES."

1 INTRODUCTION

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

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

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

21 METHOD

22 Participants

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

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

8 **Socioeconomic status**

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

Commented [SK2]: Should it no be ≥ 10 and < 10 ?

1 **Cardiorespiratory fitness**

2 Peak oxygen uptake ($\text{VO}_{2\text{peak}}$), an objective marker of CRF, was directly assessed using
3 a computerized metabolic measurement system (Medical Graphics, St. Paul, MN, USA) during
4 progressive exercise testing to volitional fatigue on an electrically braked cycle ergometer. The
5 methodology for the direct measurement of $\text{VO}_{2\text{peak}}$ has been previously described.¹² Briefly,
6 the standardized testing protocol included a 3-min warm-up at 50 watts (W; 1 W = 6.12
7 kgm/min), followed by 20 W/min increases in workload with direct analyses of expired
8 respiratory gases. $\text{VO}_{2\text{peak}}$ was defined as the highest attained value for oxygen consumption
9 and/or a plateau in oxygen uptake at maximal exercise.

10 Categories of CRF were standardized based on methods as previously suggested.^{13, 14}
11 Briefly, participants were stratified into four age groups: 42 to 47 years, 48-53 years, 54 to 59
12 years, and >60 years, and then we defined CRF categories by tertiles of $\text{VO}_{2\text{peak}}$ value within
13 each age group. We combined the individual CRF categories from each age group to form the
14 following age-specified CRF categories: lower (mean 22.2 ± 4.7 ml/kg/min), moderate
15 (29.9 ± 3.2 ml/kg/min), and higher (38.1 ± 5.5 ml/kg/min). CRF was also classified into unfit
16 (24.3 ± 5.1 ml/kg/min) and fit (36.0 ± 5.8 ml/kg/min) based on median values of age-specific
17 $\text{VO}_{2\text{peak}}$ percentiles.

18 **Other measurements**

19 Resting blood pressure was measured twice using a random-zero sphygmomanometer in
20 the seated position following 5 and 10 minutes of quiet rest. The mean of these 2 values was
21 used as resting blood pressure. Body mass index was computed as the ratio of weight in
22 kilograms (kg) to the square of height in meters (m). Smoking habits, presence of chronic
23 diseases, medications, and related demographic/lifestyle information were evaluated via a
24 standardized self-administered questionnaire. Self-reported activity levels were assessed using

1 a 12-month physical activity history modified from the Minnesota Leisure-Time Physical
2 Activity Questionnaire with the estimated energy expenditure expressed as kcal/day. Alcohol
3 ingestion was assessed using the Nordic Alcohol consumption inventory. The collection of
4 blood samples, measurement of serum lipids, lipoproteins, and glucose, definitions of type 2
5 diabetes have been previously described.¹²

6 **Ascertainment of outcomes**

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

13 **Statistical Analysis**

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

1 SES and CRF on the risk of death were examined using 4 combined groups based on the median
2 values of SES and CRF (high SES-Fit, low SES-Fit, high SES-Unfit, and low SES-Unfit). Our
3 reference group was the high SES-Fit cohort. The survival probability for ACM and CVD
4 mortality in each group was presented using Kaplan-Meier survival curves. Statistical
5 significance was set at $p < 0.05$. All tests for statistical significance were two-sided. Analyses
6 were conducted using the SPSS version 22.0 (SPSS, Armonk, NY).

7 RESULTS

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

13 During a 25-year median follow-up (interquartile ranges: 18-27 years), 1,116 ACM and
14 512 CVD mortality events occurred. **The associations of potential confounders with mortality**
15 **risk are provided as a supplementary material.** Table 2 summarizes the HR and 95% CIs for
16 mortality by SES score and CRF level. After adjusting for potential confounders, the lowest
17 levels of SES were at significantly increased risk for ACM (hazard ratio [HR] 1.49, 95%
18 Confidence Interval [CI]: 1.30-1.71) and CVD mortality (HR 1.38, 1.13-1.69), as compared
19 with their high-level SES counterparts (reference). Each 1 score increase in SES was associated
20 with a 4-5% higher the risk of mortality after adjusting for covariates (table 2).

21 In contrast, higher levels of CRF were associated with lower risks of ACM (HR **0.54,**
22 **0.45-0.64**) and CVD mortality (HR **0.53, 0.40-0.69**) after adjusting for potential confounders.
23 Each 1 ml/kg/min increment in CRF was associated with a 4-5% lower the risk of mortality
24 after adjusting for covariates.

1 Compared with high SES-fit as a reference, low SES-unfit had significantly higher risks
2 of ACM (HR 2.15, 1.78-2.59) and CVD mortality (HR 1.95, 1.48-2.57), but low SES-fit was
3 not associated with a heightened risk of CVD mortality (HR 1.09, 0.80-1.48). However, ACM
4 remained significantly higher in low SES-fit versus high SES-fit counterparts (HR 1.49, 1.23-
5 1.81). The Kaplan-Meier survival analysis showed that the survival rates of CVD mortality in
6 low SES-Fit were similar to that of high SES-Fit cohort (Figure 1).

7 DISCUSSION

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

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

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

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

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

1 Because the association between low SES and a heightened risk of subclinical and future
2 atherosclerosis²⁷ has been recently reported,²⁸ these data suggest that CRF-related decreased
3 surrogate markers of subclinical atherosclerosis may serve as a potential underlying mechanism
4 explaining the reduced mortality in fit, low SES individuals. Clearly, additional studies are
5 needed to further clarify the mechanisms underlying the protective effect of CRF on CVD
6 mortality in individuals with low SES.

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

16 **CONCLUSIONS**

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

22 **ACKNOWLEDGES**

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24 Research Institute of Public Health, and University of Eastern Finland, Kuopio, Finland, for

1 data collection in the study.

2 **AUTHOR CONTRIBUTION**

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

10 **DECLARATION OF CONFLICTING INTERESTS**

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

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6

FIGURE LEGEND

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

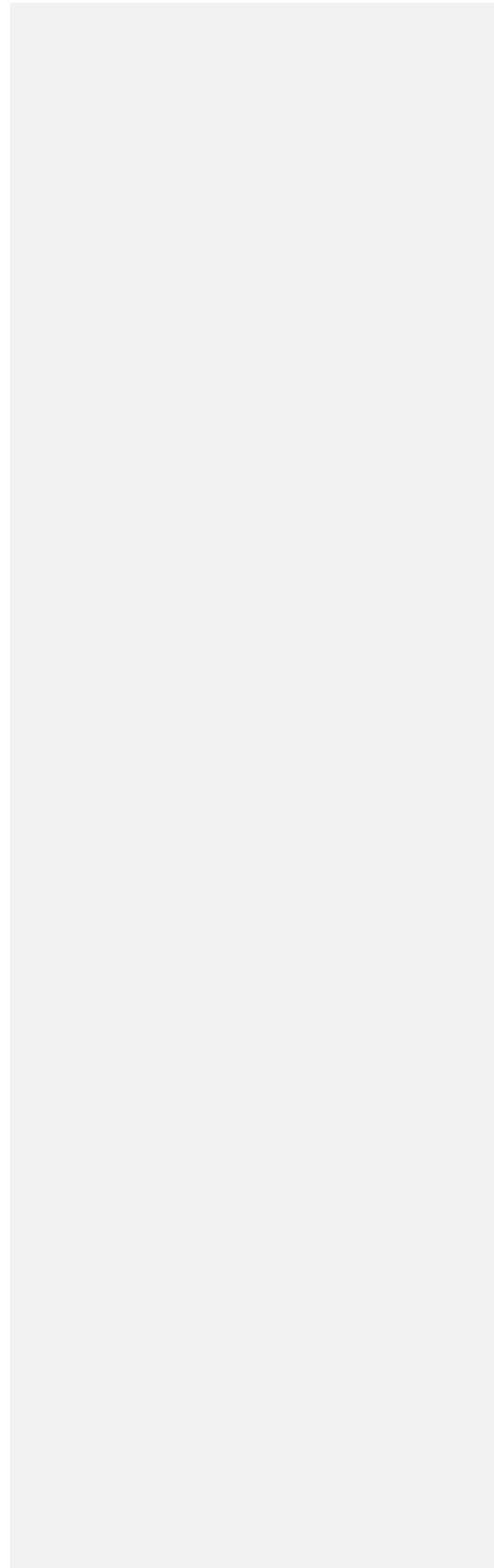


Table 1. Baseline characteristics of the participants by tertiles of socioeconomic status score (n=2,368).

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	
	Deaths/Total	Adjusted model HR (95% CI)	Events/Total	Adjusted model HR (95% CI)
Socioeconomic status (SES)				
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)
<i>P-value</i>		<i><0.001</i>		<i>0.005</i>
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)
<i>P-value</i>		<i>< 0.001</i>		<i><0.001</i>

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.

