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## Cardiorespiratory Fitness Attenuates the Increased Risk of Sudden Cardiac Death Associated With Low Socioeconomic Status

Emerging evidence suggests an inverse association between socioeconomic status (SES) and adverse cardiovascular disease (CVD) outcomes that is attributed primarily to poor lifestyle behaviors.[1] More recently, lower SES has been associated with an increased incidence of sudden cardiac death (SCD), an enormous public health concern that accounts for approximately 50% of all coronary heart disease-related death.[2] Cardiorespiratory fitness (CRF), which represents an integrity of cardiopulmonary and muscular system to perform and sustain physical activity, is independently associated with CVD risk factors and outcomes.[3] Importantly, higher CRF has been demonstrated to exert a favorable effect on the incidence of SCD, independently of potential CVD-related confounders,[4] but whether CRF also attenuates the incidence of SCD among underserved populations remains unclear. Thus, this prospective study tested the hypothesis that SES and CRF are independently associated with the incidence of SCD and that CRF attenuates the association between SES and the incidence of SCD.

This prospective study was based on a population-based sample of 2,368 men, aged 42 to 61 years, who were followed in the Kuopio Ischemic Heart Disease cohort. The Kuopio Ischemic Heart Disease study protocol was approved by the Research Ethics Committee of the University of Eastern Finland. SES was characterized using self-reported questionnaires via combined measures of income, education, occupation, occupational prestige, material standard of living, and housing conditions, and was categorized into tertiles as well as low SES and high SES based on median values. CRF was directly measured by peak oxygen uptake ($VO_{2peak}$) during progressive exercise testing to volitional fatigue. CRF was classified by tertiles of $VO_{2peak}$ value based on age-specified CRF categories: low ($22.2 \pm 4.7$ ml/kg per min), moderate ($29.9 \pm 3.2$ ml/kg per min) and high ($38.1 \pm 5.5$ ml/kg per min) as well as into unfit ($24.3 \pm 5.1$ ml/kg per min) and fit ($36.0 \pm 5.8$ ml/kg per min) categories based on median values of age-specific $VO_{2peak}$ percentiles. The joint associations of SES and CRF with SCD were based on the following four possible combinations (High SES-Fit, Low SES-Fit, High SES-Unfit, and Low SES-Unfit).

SCD was defined as a fatal event that occurred within 1 hour after the onset of symptoms or within 24 hours when autopsy data did not reveal a noncardiac cause of SCD or after a fatal cardiac arrest following successful resuscitation from ventricular tachycardia and/or ventricular fibrillation. Data on SCDs were derived from interviews with family members, hospital records, death certificates, autopsy reports, and medico-legal documents. We used Cox proportional hazard models adjusted for potential confounders to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of SCD according to each exposure.

During a 27.6-year median follow-up, 268 SCD occurred. After adjusting for confounding factors (model 1), men with low SES were at increased risk for SCD (HR 1.38, 95% CI: 1.02 to1.87), but this association was attenuated (HR 1.33, 0.98 to 1.80) when additionally adjusted for CRF (model 2). Higher levels of CRF were associated with lower risk of SCD (HR 0.66, 0.46 to 0.95) after adjusting for potential confounders including SES. In joint associations of SES and CRF with SCD, low SES-Unfit had significantly higher risk of SCD (HR 2.04, 1.37 to 3.02), but low SES-Fit was not significantly associated with an increased risk of SCD (1.41, 0.92 to 2.16), compared with their high SES-Fit counterparts (Table 1).

The major findings of this prospective study were that both low SES and high CRF were significantly and independently associated with a higher and lower incidence of SCD, respectively, and that the association between SES and SCD was dependent on CRF. Most importantly, the novel findings of this prospective study were that the incidence of SCD associated with low SES was the highest in unfit men, while the incidence of SCD was significantly attenuated in fit men with low SES. Taken together, these findings from this prospective study extend the favorable impact of CRF on survival outcomes in socioeconomically disadvantaged populations, consistent with findings from a previous study, which found that moderate-to-high levels of CRF attenuate the incidence of CVD mortality in men with low SES.[5]

Lifestyle risk factors and disadvantaged neighborhood infrastructure may be implicated in the incidence of SCD in underserved populations,[1,2] thereby underscoring the need for policies and programs focused on modifying lifestyle risk factors that are associated with low SES in order to lower the incidence of SCD[1]. Furthermore, the levels of leisure-time physical activity appear to be relatively low in individuals with low SES,[6] suggesting that SES-related inequalities in physical activity levels may stem, in part, from differences in lifestyle behavior. Thus, our findings

Table 1
Patient and joint associations of socioeconomic status and cardiorespiratory fitness with risk of sudden cardiac death

| Socioeconomic status (SES) | Events/Total (268/2368) | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|---|---|---|---|
| High SES | 81/961 | 1 (reference) | 1 (reference) |
| Moderate SES | 75/569 | 1.34 (0.97-1.85) | 1.32 (0.95-1.82) |
| Low SES | 112/838 | 1.38 (1.02-1.87) | 1.33 (0.98-1.80) |
| Cardiorespiratory fitness (CRF) | | | |
| Low | 132/782 | 1 (reference) | 1 (reference) |
| Moderate | 78/774 | 0.70 (0.52-0.95) | 0.72 (0.53-0.98) |
| High | 58/812 | 0.64 (0.45-0.93) | 0.66 (0.46-0.95) |
| Combined SES and CRF | | *Adjusted HR (95% CI) | |
| High SES / Fit | 42/710 | 1 (reference) | |
| Low SES / Fit | 46/484 | 1.41 (0.92-2.16) | |
| High SES / Unfit | 85/624 | 1.57 (1.06-2.34) | |
| Low SES / Unfit | 95/550 | 2.04 (1.37-3.02) | |

CI= confidence interval; CRF= cardiorespiratory fitness; HR= hazard ratio; SES= socioeconomic status
Model 1: Adjusted for age, smoking, alcohol consumption, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, anti-hypertensive medication, family history of coronary heart disease, history of cardiovascular disease, and physical activity. Model 2: adjusted for model 1 plus CRF when SES is exposure or SES when CRF is exposure.

that CRF attenuated the incidence of SCD in men with low SES highlight that importance of enhancing physical activity levels due to its widespread benefits and inherently inexpensive nature as a strategy for lowering the incidence of SCD, thereby improving survival outcomes in underserved populations.[1]

There is a methodologic limitation to be acknowledged in this prospective study. First, this prospective study included only middle-aged Caucasian men, thus limiting the generalizability of our findings to women, other race and/or ethnicity, and age groups. Nevertheless, the strength of this prospective study was the use of directly measured peak oxygen consumption using metabolic gas analysis, which provides an objective and quantitative measure of CRF.

In conclusion, SES and CRF are independently associated with the incidence of SCD and that high levels of CRF modifies the association between SES and the incidence of SCD in the general population.

## Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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## Meta-Analysis of Efficacy of Sacubitril/Valsartan in Heart Failure With Preserved Ejection Fraction

Randomized controlled trials (RCTs) of sacubitril/valsartan have suggested possible clinical benefit among patients with heart failure with preserved ejection fraction (HFpEF). The phase II PARAMOUNT (Prospective comparison of ARNI with ARB [angiotensin-receptor blockers] on Management Of HFpEF) trial found sacubitril/valsartan to significantly reduce natriuretic peptide concentrations and left atrial size, compared with valsartan.[1] In the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in HFpEF) trial, although sacubitril/valsartan did not meet the primary endpoint of a statistically significant reduction in total HF hospitalizations or cardiovascular death, the p-value was marginal and results trended towards benefit.[2] Most recently, in the PARALLAX-HF (A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients; NCT03066804) trial,[3] compared with