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Cardiorespiratory Fitness, Inflammation, and Risk of Sudden Cardiac Death in Middle-Aged Men

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Inflammation and cardiorespiratory fitness (CRF) are each independently related to the risk of sudden cardiac death (SCD). The interplay between CRF, inflammation and SCD is not well understood. We aimed to study the separate and joint associations of inflammation (high-sensitivity C-reactive protein [hsCRP]) and CRF with SCD risk in a cohort of Caucasian men. In 1,749 men aged 42 to 61 years without a history of coronary heart disease at baseline, serum hsCRP was measured using an immunometric assay, and CRF was assessed using a respiratory gas exchange analyzer during exercise testing. hsCRP was categorized as normal and high (≤3 and >3 mg/L, respectively) and CRF as low and high (median cutoff). A total of 148 SCD events occurred during a median follow-up of 28.9 years. Comparing high versus normal hsCRP, the multivariable-adjusted hazard ratio (95% confidence interval) for SCD was 1.65 (1.11 to 2.45), which remained similar on further adjustment for CRF 1.62 (1.09 to 2.40). Comparing high versus low CRF, the multivariable-adjusted hazard ratio for SCD was 0.61 (0.42 to 0.89), which remained persistent after adjustment for hsCRP 0.64 (0.44 to 0.93). Compared with normal hsCRP-low CRF, normal hsCRP-high CRF was associated with a decreased SCD risk of 0.65 (0.43 to 0.99), high hsCRP-low CRF was associated with an increased SCD risk of 1.72 (1.10 to 2.69), with no evidence of a relationship between high hsCRP-high CRF and SCD risk 0.86 (0.39 to 1.88). Positive additive and multiplicative interactions were found between hsCRP and CRF. In a middle-aged Finnish male population, both hsCRP and CRF are independently associated with SCD risk. However, high CRF levels appear to offset the increased SCD risk related to high hsCRP levels. **(Am J Cardiol 2022;174:166−171)**

Introduction

Although conventional coronary heart disease (CHD) risk factors explain a proportion of sudden cardiac death (SCD) events,[1] they are not usually observed in all SCD victims.[2] Furthermore, single risk factors are limited in their ability to identify patients at high risk of SCD. There is a need to identify additional risk markers or their combinations that could predict SCD risk and also counteract the adverse effects of common SCD risk factors. Elevated levels of circulating inflammatory markers such as C-reactive protein (CRP) have been shown to be associated with an increased risk of SCD.[3,4] Cardiorespiratory fitness (CRF) is an indicator of cardiopulmonary function and can be increased through increased physical activity (PA) and exercise training.[5] Cardiorespiratory fitness is an established and independent risk marker for several cardiovascular outcomes, including SCD.[6-9] We and others have previously shown that high CRF levels can offset or attenuate the increased risk of adverse outcomes because of other risk factors.[7,10-13] Whether high CRF levels could also attenuate or offset the increased risk of SCD due to inflammation has not yet been explored. In this context, using a population-based prospective cohort of 1,749 middle-aged Finnish men without a history of CHD at study entry, we aimed to (1) study the joint effects of inflammation (as measured by high-sensitivity CRP [hsCRP]) and CRF on the risk of SCD and (2) confirm the existing associations of CRP and CRF with the risk of SCD.

Methods

We used the Kuopio Ischemic Heart Disease population-based prospective cohort study comprising a representative sample of middle-aged and older men aged 42 to 61 years recruited from Kuopio and its surrounding rural communities in eastern Finland. A representative sample of 3,433 potentially eligible men was invited for screening

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See page 170 for disclosure information.

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examinations between March 1984 and December 1989. Of the total number of men, 3,235 were found to be eligible, 367 declined to participate, and 186 did not respond to the invitation, leaving 2,682 (83%) men who agreed to participate in the study.[9] For this analysis, men with a prevalent history of CHD (defined as previous myocardial infarction, angina pectoris, the use of nitroglycerin for chest pain once a week or more frequently, or chest pain) were excluded (n = 542). This left 1,749 men with no missing data on the exposures, covariates, and SCD outcomes for the current analysis (Supplementary Material 1). The Research Ethics Committee of the University of Eastern Finland approved the study protocol, and written informed consent was obtained from all participants.

Assessment of risk markers, clinical characteristics, and physical examinations have been described previously.[9] Briefly, serum hsCRP was measured using an immunometric assay (Immulite High-Sensitivity CRP assay, Diagnostic Product Corporation, Los Angeles, California).[14] Cardiorespiratory fitness, measured by peak oxygen uptake (VO_{2peak}), was assessed using respiratory gas exchange analyzers (Medical Graphics, MCG, St. Paul, Minnesota) during progressive cycle ergometer exercise testing to volitional fatigue.[7,10] A self-reported questionnaire was used to assess socioeconomic status (SES), which involved a summary index that combined factors such as income, education, occupational prestige, material standard of living, and housing conditions. The composite SES index ranged from 0 to 25, with higher values indicating lower SES.[12]

We included all SCD cases that occurred from study entry through 2017. All Kuopio Ischemic Heart Disease study participants are under continuous annual monitoring (using personal identification codes) for incident outcomes, including SCDs. Information on SCDs was based on a comprehensive review of available hospital records, questionnaires administered to health workers, interviews with informants, registers of deaths and death certificates, and medico-legal reports. A death was determined to be an SCD when it occurred within 1 hour of the onset of an abrupt change in symptoms or within 24 hours after the onset of symptoms, including nonwitnessed cases when clinical and autopsy findings did not reveal a noncardiac cause of sudden death.[9] The witnessed subject was to have been alive and symptom-free within 1 hour before the event.[9]

Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for SCD. To maintain consistency with previous reports,[11,15,16] hsCRP was categorized as normal and high (≤3 and >3 mg/L, respectively) and CRF as low and high based on median cutoffs. To evaluate the joint associations, study participants were divided into 4 groups according to categories of hsCRP and CRF: normal hsCRP-low CRF; normal hsCRP-high CRF; high hsCRP-low CRF; and high hsCRP-high CRF. Interactions between hsCRP and CRF were examined on both the additive and multiplicative scales in relation to SCD risk. Interaction on an additive scale means that the combined effect of 2 exposures is larger (or smaller) than the sum of the individual effects of the 2 exposures, whereas interaction on a multiplicative scale means that the combined effect is larger (or smaller) than the product of the individual effects.[17] Additive interactions were assessed using the "relative excess risk because of interaction" (RERI), computed for binary variables as $RERI_{HR}=HR_{11}-HR_{10}-HR_{01}+1$,[18] where HR_{11} is the HR of the outcome (i.e., SCD) if both risk factors are present, HR_{10} is the HR of the outcome if 1 risk factor is present and the other is absent, with HR_{01} being vice versa. Multiplicative interactions were assessed using the ratio of $HRs=HR_{11}/(HR_{10}xHR_{01})$.[18] A positive additive interaction is indicated if RERI>0, and a positive multiplicative interaction is indicated if the ratio of HRs>1. Formal tests of interaction were also used to assess if age modified the association of hsCRP or CRF with SCD. All statistical analyses were conducted using STATA/MP Statistical Software: Release 16 (StataCorp LLC., College Station, Texas).

Results

The overall mean (SD) age of men at baseline was 52 (5) years. Values of CRF were approximately normally distributed in the study population (Supplementary Material 2). The mean (SD) CRF at baseline was 31.9 (7.5) ml/kg/min. The median (interquartile [IQR]) CRF was 31.4 (26.9 to 36.3) ml/kg/min, corresponding to 9.0 (7.7 to 10.4) metabolic equivalents (METs) (1 MET corresponds to an oxygen uptake of 3.5 ml/kg/min). Age-standardized values of CRF based on methods previously suggested[19] are provided in Supplementary Material 3. The median (IQR) of hsCRP was 1.15 (0.65 to 2.13) mg/L (Table 1). At baseline, men with high hsCRP-Low CRF were more likely to consume alcohol, had lower SES, more likely to be current smokers and have type 2 diabetes mellitus (T2DM), have higher levels of body mass index, blood pressure, and fasting plasma glucose, and lower levels of high-density lipoprotein cholesterol (HDL-C). During a median (IQR) follow-up of 28.9 (21.2 to 30.8) years, 148 SCD events were recorded. Compared with men who had normal hsCRP levels, men with high hsCRP had an increased risk of SCD after adjustment for age (Figure 1, Model 1), which was attenuated to 1.65 (95% CI: 1.11 to 2.45) on further adjustment for body mass index, systolic blood pressure, smoking, T2DM, alcohol consumption, total cholesterol, HDL-C, and SES (Model 2) (Figure 1, Model 2). The association was minimally attenuated after further adjustment for CRF (Figure 1, Model 3). On adjustment for the covariates in Model 2, high CRF was associated with a decreased risk of SCD compared with low CRF (Figure 1), which was slightly attenuated on additional adjustment for hsCRP 0.64 (95% CI: 0.44 to 0.93) (Figure 1, Model 3).

Kaplan-Meier curves showed the risk for SCD was highest for the high hsCRP-low CRF group compared with other groups (p value for log-rank test<0.001; Supplementary Material 4). Compared with normal hsCRP-low CRF, multivariable analysis (Model 2) showed that normal hsCRP-high CRF was associated with a decreased SCD risk of 0.65 (95% CI: 0.43 to 0.99), high hsCRP-low CRF was associated with an increased SCD risk 1.72 (95% CI: 1.10 to 2.69), with no evidence of an association for high hsCRP-high CRF and SCD risk 0.86 (95% CI: 0.39 to 1.88) (Figure 1). Results of interaction analysis showed the RERI was 0.8 and the ratio of HRs was 1.3, indicating the

Table 1
Baseline characteristics of study participants overall and according to categories for the combination of high-sensitivity C-reactive protein and cardiorespiratory fitness

Characteristics	Overall (n=1749) Mean ± SD or median (IQR)	Normal hsCRP-Low CRF (n=686) Mean ± SD or median (IQR)	Normal hsCRP-High CRF (n=790) Mean ± SD or median (IQR)	High hsCRP-Low CRF (n=189) Mean ± SD or median (IQR)	High hsCRP-High CRF (n=84) Mean ± SD or median (IQR)	*p*-Value
High sensitivity C-reactive protein (mg/l)	1.15 (0.65-2.13)	1.19 (0.73-1.77)	0.80 (0.51-1.33)	5.28 (90-8.81)	4.65 (3.77-7.87)	
Cardiorespiratory fitness (ml/kg/min)	31.9 ± 7.5	26.4 ± 3.8	37.8 ± 5.3	24.6 ± 4.7	36.6 ± 3.9	
Age (years)	52 ± 5	54 ± 5	51 ± 5	53 ± 5	50 ± 6	<.001
Alcohol consumption (g/week) / (units/week)*	32.3 (6.7-89.7) / 4.03 (0.84-11.21)	32.6 (6.1-95.8) / 4.07 (0.76-11.98)	28.0 (6.7-77.4) / 3.50 (0.84-9.68)	54.0 (10.9-140.0) / 6.75 (1.37-17.50)	30.5 (7.5-109.2) / 3.81 (0.94-13.65)	<.001
Socioeconomic status†	7.92 ± 4.22	8.43 ± 4.10	7.28 ± 4.24	8.65 ± 4.07	8.05 ± 4.55	<.001
Type 2 diabetes mellitus	47 (2.7%)	27 (3.9%)	9 (1.1%)	9 (4.8%)	2 (2.4%)	.002
Current smokers	516 (29.5%)	203 (29.6%)	183 (23.2%)	94 (49.7%)	36 (42.9%)	<.001
Body mass index (kg/m^2)	26.7 ± 3.4	27.5 ± 3.4	25.6 ± 2.7	28.9± 4.4	26.6± 2.9	<0.001
Systolic blood pressure (mmHg)	134 ± 16	137 ± 17	131 ± 15	139 ± 18	132 ± 13	<.001
Diastolic blood pressure (mmHg)	89 ± 10	91 ± 11	87 ± 10	92 ± 12	89 ± 10	<.001
Total cholesterol (mmol/l) / (mg/dl)	5.86 ± 1.03 / 226.8 ± 39.9	5.92 ± 1.02 / 228.9 ± 39.4	5.81 ± 1.04 / 224.5 ± 40.2	5.92 ± 1.04 / 229.1 ± 40.2	5.83 ± 1.04 / 225.4 ± 40.4	.15
High density lipoprotein cholesterol (mmol/l) / (mg/dl)	1.30 ± 0.29 / 50.4 ± 11.3	1.27 ± 0.28 / 49.2 ± 10.8	1.36 ± 0.30 / 52.7 ± 11.8	1.17 ± 0.24 / 45.2 ± 9.3	1.30 ± 0.26 / 50.3 ± 10.1	<.001
Fasting plasma glucose (mmol/l) / (mg/dl)	5.27 ± 1.02 / 95.0 ± 19.1	5.39 ± 1.09 / 97.1 ± 19.6	5.13 ± 0.87 / 92.4 ± 15.6	5.49 ± 1.24 / 98.9 ± 22.3	5.20 ± 1.06 / 93.6 ± 19.1	<.001
Sudden cardiac deaths	148 (8.5%)	69 (10.1%)	42 (5.3%)	30 (15.9%)	7 (8.3%)	<.001

CRF = cardiorespiratory fitness; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; SD = standard deviation.

* One unit of alcohol equals 10 ml or 8 g of pure alcohol.

† Assessment of socioeconomic status (SES) is based on a self-reported questionnaire that involved a summary index that combined factors such as income, education, occupational prestige, material standard of living, and housing conditions. The composite SES index ranged from 0 to 25, with higher values indicating lower SES.

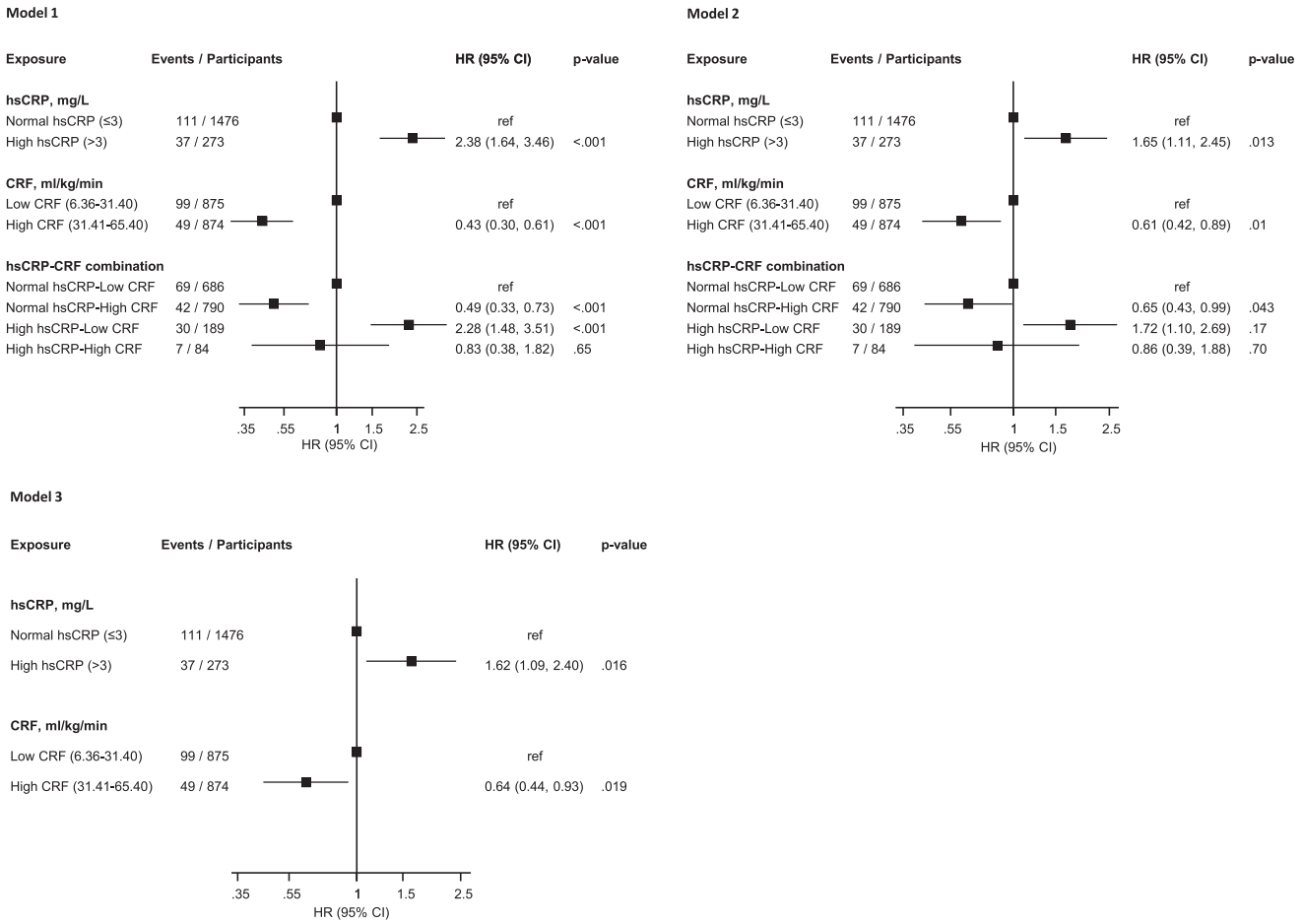

Figure 1. Separate and joint associations of high-sensitivity C-reactive protein and cardiorespiratory fitness with risk of sudden cardiac death. CI = confidence interval; CRF = cardiorespiratory fitness; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; ref = reference; Model 1: Adjusted for age; Model 2: Model 1 plus body mass index, systolic blood pressure, smoking status, history of type 2 diabetes, alcohol consumption, total cholesterol, high-density lipoprotein cholesterol, and socioeconomic status; Model 3: Model 2 plus CRF for hsCRP or hsCRP for CRF.

presence of both additive and multiplicative interactions. The association of hsCRP with SCD risk was not modified by age (p value for interaction = 0.93), and neither was the association between CRF and SCD risk modified by age (p value for interaction = 0.97).

Discussion

Consistent with previous reports,[3,4,6,7] we confirmed that high levels of hsCRP were associated with increased SCD risk, and high levels of objectively measured CRF were associated with decreased risk of SCD. The associations were independent of several established risk factors and mutual adjustment for each exposure. New findings based on the joint associations of hsCRP and CRF showed that the risk of SCD was decreased in men with normal hsCRP and high CRF and increased in men with elevated hsCRP and low CRF. However, the increased risk of SCD due to elevated levels of hsCRP was attenuated to null by high CRF levels. In interaction analysis, the association between both combined exposures (i.e., a combination of high hsCRP and low CRF) and SCD risk exceeded the sum or product of their associations considered separately.

Inflammation is known to play an important role in coronary atherosclerosis initiation and progression leading to clinical CHD events,[20] which is the common pathological substrate in victims of SCD.[21] Inflammation also has a pathophysiological role in the conversion of stable to unstable atherosclerotic plaques, which also underlie most cases of SCD in adults.[22] Other pathophysiological explanations for the association between inflammation and SCD include a high burden of continuing systemic inflammation and subclinical atherosclerosis and direct involvement in ventricular arrhythmogenesis or its arrhythmic substrates, which lead to SCD.[4] The mechanistic pathways underlying the association between high levels of CRF and reduced risk of SCD may be through the effects of increased and regular habitual PA and exercise training, which confers good CRF. PA may exert protective effects on SCD through antiatherogenic effects,[23,24] anti-inflammatory actions,[25,26] beneficial modulation of cardiovascular markers such as lipids, glucose, body weight, blood pressure, natriuretic peptides, and cardiac troponin T,[27,28] favorable modulation of cardiac autonomic function, which may reduce the risk of fatal arrhythmias,[29] and improvement in endothelial function.[30] Results of the interaction analysis suggest the

underlying mechanisms for SCD may include important interactions between chronic inflammation and fitness levels.

These findings add to the increasing literature on the ability of high CRF levels to reduce the risk of chronic diseases, promote longevity, and attenuate or neutralize the adverse effects of other cardiovascular risk factors.[7,10] Although CRF levels are determined by a combination of PA, genetics, and lifestyle factors, increasing levels of PA and exercise training generally promote good CRF.[31] It is known that most populations do not achieve general PA recommendations despite the implementation of population-wide approaches to promote PA. At-risk populations for SCD especially need more education on the substantial health benefits of PA and its potential to offset the risk of disease or death attributable to other factors. Furthermore, there should be widened access to various PA and exercise training resources that are both feasible and attractive for these populations.

In addition to being the first evaluation of the interplay between inflammation, fitness and risk of SCD, other strengths include the population-based prospective cohort design, use of a relatively large sample without a history of CHD at study entry, the long-term follow-up of the cohort, and the use of an objective gold standard measure of CRF. The limitations included (1) the inability to generalize the results to women or other populations; (2) the relatively low event rate for SCDs given the general population profile with no history of CHD; it was particularly low in men with both high CRF and high hsCRP, which could have reduced the power to demonstrate an association; (3) the potential for biases such as residual confounding; (4) unavailability of data on all potential inflammatory diseases such as rheumatic or inflammatory bowel diseases which may have impacted on hsCRP levels; and (5) the potential for regression dilution bias given the use of single baseline levels of the exposures and the long-term follow-up of the cohort; hsCRP exhibits high within-person variability over long-term follow-up (regression dilution ratio = 0.57[14]). Hence, our observed associations could have been underestimated. The findings, therefore, need to be interpreted with caution, given the limitations. Nevertheless, given that high levels of CRF have consistently been shown to attenuate or offset the increased risk of adverse outcomes because of other risk factors, our findings may represent true associations.

In conclusion, in a Finnish male population aged 42 to 61 years, both hsCRP and CRF are each independently associated with an increased risk of SCD. There is also an interplay between hsCRP, CRF, and SCD risk. High fitness levels appear to offset the increased SCD risk related to high levels of hsCRP.

Disclosures

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.03.032.

1. Grundy SM, D'Agostino Sr RB, Mosca L, Burke GL, Wilson PW, Rader DJ, Cleeman JI, Roccella EJ, Cutler JA, Friedman LM. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood Institute workshop. *Circulation* 2001;104:491–496.
2. Spooner PM, Zipes DP. Sudden death predictors: an inflammatory association. *Circulation* 2002;105:2574–2576.
3. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595–2599.
4. Hussein AA, Gottdiener JS, Bartz TM, Sotoodehnia N, DeFilippi C, See V, Deo R, Siscovick D, Stein PK, Lloyd-Jones D. Inflammation and sudden cardiac death in a community-based population of older adults: the Cardiovascular Health Study. *Heart Rhythm* 2013;10:1425–1432.
5. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisløff U. American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016;134:e653–e699.
6. Laukkanen JA, Laukkanen T, Khan H, Babar M, Kunutsor SK. Combined effect of sauna bathing and cardiorespiratory fitness on the risk of sudden cardiac deaths in Caucasian men: a long-term prospective cohort study. *Prog Cardiovasc Dis* 2018;60:635–641.
7. Jae SY, Bunsawat K, Kurl S, Kunutsor SK, Fernhall B, Franklin BA, Laukkanen JA. Cardiorespiratory fitness attenuates the increased risk of sudden cardiac death associated With low socioeconomic status. *Am J Cardiol* 2021;145:164–165.
8. Laukkanen JA, Kunutsor SK, Yates T, Willeit P, Kujala UM, Khan H, Zaccardi F. Prognostic relevance of cardiorespiratory fitness as assessed by submaximal exercise testing for all-cause mortality: a UK Biobank prospective study. *Mayo Clin Proc* 2020;95:867–878.
9. Laukkanen JA, Mäkikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study. *J Am Coll Cardiol* 2010;56:1476–1483.
10. Jae SY, Kurl S, Bunsawat K, Franklin BA, Choo J, Kunutsor SK, Kauhanen J, Laukkanen JA. Impact of cardiorespiratory fitness on survival in men with low socioeconomic status. *Eur J Prev Cardiol* 2021;28:450–455.
11. Kunutsor SK, Jae SY, Mäkikallio TH, Kurl S, Laukkanen JA. High fitness levels offset the increased risk of chronic obstructive pulmonary disease due to low socioeconomic status: a cohort study. *Respir Med* 2021;189. 106647.
12. Kunutsor SK, Jae SY, Mäkikallio TH, Laukkanen JA. High fitness levels attenuate the increased risk of heart failure due to low socioeconomic status: a cohort study. *Eur J Clin Invest* 2022:.e13744.
13. Kunutsor SK, Jae SY, Mäkikallio TH, Laukkanen JA. Cardiorespiratory fitness, inflammation, and risk of chronic obstructive pulmonary disease in middle-aged men: a COHORT STUDY. *J Cardiopulm Rehabil Prev* 2022.
14. Kunutsor SK, Seidu S, Blom AW, Khunti K, Laukkanen JA. Serum C-reactive protein increases the risk of venous thromboembolism: a prospective study and meta-analysis of published prospective evidence. *Eur J Epidemiol* 2017;32:657–667.
15. Jae SY, Heffernan KS, Kurl S, Kunutsor SK, Kim CH, Johnson BD, Franklin BA, Laukkanen JA. Cardiorespiratory fitness, inflammation,

and the incident risk of pneumonia. *J Cardiopulm Rehabil Prev* 2021;41:199–201.
16. Kunutsor SK, Khan H, Laukkanen T, Laukkanen JA. Joint associations of sauna bathing and cardiorespiratory fitness on cardiovascular and all-cause mortality risk: a long-term prospective cohort study. *Ann Med* 2018;50:139–146.
17. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol* 2011;26:433–438.
18. Li R, Chambless L. Test for additive interaction in proportional hazards models. *Ann Epidemiol* 2007;17:227–236.
19. Kokkinos P, Faselis C, Franklin B, Lavie CJ, Sidossis L, Moore H, Karasik P, Myers J. Cardiorespiratory fitness, body mass index and heart failure incidence. *Eur J Heart Fail* 2019;21:436–444.
20. Koenig W, Khuseyinova N, Baumert J, Thorand B, Loewel H, Chambless L, Meisinger C, Schneider A, Martin S, Kolb H, Herder C. Increased concentrations of C-reactive protein and IL-6 but not IL-18 are independently associated with incident coronary events in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984−2002. *Arterioscler Thromb Vasc Biol* 2006;26:2745–2751.
21. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation* 2012;125:620–637.
22. Sudha ML, Sundaram S, Purushothaman KR, Kumar PS, Prathiba D. Coronary atherosclerosis in sudden cardiac death: an autopsy study. *Indian J Pathol Microbiol* 2009;52:486–489.
23. Hambrecht R, Niebauer J, Marburger C, Grunze M, Kälberer B, Hauer K, Schlierf G, Kübler W, Schuler G. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol* 1993;22:468–477.
24. Rauramaa R, Halonen P, Väisänen SB, Lakka TA, Schmidt-Trucksäss A, Berg A, Penttilä IM, Rankinen T, Bouchard C. Effects of aerobic physical exercise on inflammation and atherosclerosis in men: the DNASCO Study: a six-year randomized, controlled trial. *Ann Intern Med* 2004;140:1007–1014.
25. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 2002;13:561–568.
26. Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler Thromb Vasc Biol* 2002;22:1869–1876.
27. deFilippi CR, de Lemos JA, Tkaczuk AT, Christenson RH, Carnethon MR, Siscovick DS, Gottdiener JS, Seliger SL. Physical activity, change in biomarkers of myocardial stress and injury, and subsequent heart failure risk in older adults. *J Am Coll Cardiol* 2012;60:2539–2547.
28. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, Liu S, Song Y. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2015;4:e002014.
29. Tulppo MP, Mäkikallio TH, Seppänen T, Laukkanen RT, Huikuri HV. Vagal modulation of heart rate during exercise: effects of age and physical fitness. *Am J Physiol* 1998;274:H424–H429.
30. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, Schoene N, Schuler G. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000;342:454–460.
31. Lavie CJ, Kokkinos P, Ortega FB. Survival of the fittest-promoting fitness throughout the life span. *Mayo Clin Proc* 2017;92:1743–1745.