Accepted: 25 July 2017
DOI: 10.1002/ajim.22756

RESEARCH ARTICLE

WILEY AMERICAN JOURNAL OF INDUSTRIAL MEDICINE

Physical activity and 22-year all-cause and coronary heart disease mortality

Niklas Krause MD, MPH, PhD[1,2] | Onyebuchi A. Arah MD, MSc, DSc, MPH, PhD[2] | Jussi Kauhanen MD, PhD[3]

[1] Department of Environmental Health Sciences, Fielding School of Public Health, University of California, Los Angeles (UCLA), California

[2] Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles (UCLA), California

[3] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

Correspondence
Niklas Krause, University of California Los Angeles, 650 Charles E. Young Dr. South, 56-071 CHS, Box 961772, Los Angeles, CA 90095-1772.
Email: niklaskrause@ucla.edu

Background: This study explores the effects of occupational (OPA) and leisure time physical activity (LTPA) on mortality relative to cardiorespiratory fitness and pre-existing coronary heart disease (CHD).

Methods: Associations between OPA, measured as energy expenditure (kcal/day) and relative aerobic workload (%VO_2max), LTPA, and 22-year mortality among 1891 Finnish men were assessed by Cox regression models stratified by CHD and adjusted for 19 confounders.

Results: In fully adjusted models, each 10% of relative aerobic workload increased all-cause mortality by 13% and CHD mortality 28% ($P < 0.01$). Compared to healthy subjects, men with CHD experienced lower mortality risks due to OPA and higher risks due to LTPA. While LTPA had no effect among healthy men, in men with CHD each weekly hour of conditioning LTPA increased all-cause mortality risks by 10% and CHD mortality by14%.

Conclusion: OPA was positively associated with both all-cause and CHD mortality. LTPA was not protective. Among men with CHD, LTPA increased mortality risks.

KEYWORDS
cardiorespiratory fitness, energy expenditure, physical workload, prospective study, relative aerobic workload

1 | INTRODUCTION

The beneficial effects of leisure time physical activity (LTPA) on the circulatory system are well established,[1] but the literature on the health effects of occupational physical activity (OPA) remains inconsistent.[2] A meta-analysis of 21 prospective studies published between 1980 and 2010 concluded that both LTPA and moderate levels of OPA were beneficial for cardiovascular health.[1] In contrast, an updated meta-analysis of 23 prospective cohort studies published between 2011 and 2013 concluded that moderate and high levels of OPA are associated with an increased cardiovascular disease (CVD) risk.[3] Similarly, studies on CVD mortality and all-cause mortality have shown negative (eg, refs.[4–8]), no (eg, refs.[4,9–14]), and positive (eg, refs.[15,16–19]), associations with OPA. Several studies provide direct evidence for a paradoxical effect of physical activity where LTPA appears beneficial and OPA detrimental to cardiovascular health and longevity in the same study population.[15,20–22] Other studies indicated a u-shaped dose-response relationship between OPA and mortality with elevated risks associated with both sedentary and heavy work.[23–25] A recent study found OPA to be beneficial but heavy lifting work to be detrimental, especially if combined with low OPA and low LTPA pointing to interactions between different types of physical activity.[26]

Further, interactions of OPA with physical fitness reported for coronary heart disease (CHD) mortality[27] indicate that a discrepancy of physical job demands and individual aerobic work capacity (cardiorespiratory fitness) may determine the health effects of OPA. This has

Performance site: University of California, Los Angeles.

 © 2017 Wiley Periodicals, Inc.

been in fact demonstrated directly in the Kuopio Ischemic Heart Disease Risk Factor Study where individual measures of this discrepancy (relative aerobic workload or strain and percent oxygen reserve) but not absolute energy expenditure at work (kcal/day) predicted both 11-year progression of atherosclerosis and incidence of acute myocardial infarction (AMI).[28,29] However, there have been no studies of mortality using these relative measures of energy expenditure at work even though recommendations for safe levels of OPA are generally based on individual assessments of relative aerobic strain.[30]

This study, therefore, investigates if identical measures of OPA predict all-cause and CHD mortality in the same Finnish population-based sample where their effects on progression of atherosclerosis and incidence of AMI have already been investigated.[28,29] Differences in effect sizes between the non-symptomatic pre-clinical outcome (progression of atherosclerosis) and the symptomatic clinical outcomes (morbidity and mortality) can be utilized to assess the magnitude of the expected selection bias called "healthy worker effect" that may dilute, mask, or even reverse any true positive association between OPA and CVD. Workers with symptomatic CHD (activity-related chest pain) may leave physical demanding jobs (or not take them in the first place) leading to an accumulation of relatively more healthy workers with lower mortality risk in high OPA jobs and thus diluting any associated OPA risks while at the same time inflating the mortality risks in low OPA jobs. Such selection effects will not be triggered by asymptomatic atherosclerosis. Comparing the diluted effect of OPA on mortality in this study with the non-diluted effect on atherosclerosis in an earlier study of this cohort allows us to estimate the magnitude of this conservative selection bias.

This study will also address other methodological issues that may be responsible for the inconsistent literature on OPA and CVD, namely (i) reduce exposure misclassification bias by combining individual objective measures of cardiorespiratory fitness with detailed validated energy expenditure measures at work and their analysis as continuous rather than crude categorical variables; (ii) reduce confounding bias by adjustment for a comprehensive set of 19 demographic, biological, behavioral, and psychosocial CVD risk factors; and (iii) separately examine risks among workers without and with baseline CHD rather than excluding this vulnerable subgroup as has been common practice in most cohort studies. In aging worker populations, CHD is highly prevalent and these workers are generally less physically fit and therefore disproportionally at risk to experience excessive relative aerobic workloads at absolute levels of energy expenditure that may be safe for workers without CHD. In fact, in this study population, men with CHD were exposed to slightly higher absolute aerobic workloads than healthy men and over 50% of them were found to be exposed to relative aerobic strain in excess of the recommended maximum levels compared to about 28% of men without CHD.[28]

This study aimed to determine how OPA and LTPA were associated with mortality accounting for pre-existing CVD and known cardiovascular risk factors, statistical model specification, and healthy worker selection effects. Specifically, we investigated five hypotheses: (i) OPA is positively associated with mortality even after comprehensive adjustment for potential confounders; (ii) OPA interacts positively with baseline CVD at baseline, specifically, men with CVD have a higher mortality risk associated with OPA compared to healthy men; (iii) estimates of the effects of OPA depend on the choice of analytic model; (iv) mortality risks of OPA are underestimated due to the healthy worker effect; and (v) LTPA is negatively associated with mortality.

2 | STUDY POPULATION AND METHODS

2.1 | Study population

Subjects were participants in the prospective Kuopio Ischemic Heart Disease (KIHD) Risk Factor Study, an age-stratified population-based 30% random ethnically homogeneous[31] sample of Eastern Finnish men, residing in the city of Kuopio or its surrounding rural communities. Details of the study population have been published elsewhere.[32,33] Of 3433 eligible men aged 42, 48, 54, or 60 years, 198 could not be included because of death, serious disease, or migration away from the area. Two thousand six hundred eighty-two (82.9%) agreed to participate and underwent baseline examinations between March 1984 and December 1989. Repeat examinations were conducted after 4 and 11 years; however, in this study this information was only used in a few instances for substituting missing baseline values in the large baseline sample. Only baseline information was available for relative measures of energy expenditure (EE) at work used in this study. Participants who were not working at all at baseline or in the 12 months prior (n = 791) were excluded. The final study sample included 1891 participants with complete information on all key predictor and outcome variables and 19 covariates that were predetermined in earlier studies on OPA and progression of carotid atherosclerosis[28] and AMI incidence.[29]

2.2 | Assessment of cardiovascular health at baseline

At baseline, all participants filled out extensive questionnaire surveys, were interviewed about their work history, and underwent a comprehensive medical examination including several laboratory tests as described previously.[34] Participants were considered to have ischemic heart disease at baseline if they had a history of myocardial infarction or angina pectoris, currently used anti-angina medication, or had positive findings of angina from the London School of Hygiene cardiovascular questionnaire.[35] In this paper, we use the term "ischemic heart disease (IHD)" to define cardiovascular health at baseline only. Although the term IHD in general refers to the same subgroup of CVD as the term "coronary heart disease (CHD)," we use the latter term (CHD) only for CHD mortality during follow-up.

2.3 | Assessment of follow-up events

All-cause and CHD mortality were ascertained by record linkage to the National Death registry that is maintained for all Finnish citizens. Classification of death due to CHD was based on the underlying cause, reviewed at the National Center of Statistics of Finland, using the ninth revision of the International Classification of Diseases (ICD, codes 410-

414). Follow-up was censored at December 31, 2011, or date of death whichever occurred first. Follow-up time ranged from 0.36 to 27.76 years (mean 21.69 years).

2.4 | Assessment of occupational physical activity

Trained interviewers administered an OPA interview at baseline to men who had worked at least some time in the past 12 months. The interview addressed a typical workday. Subjects were asked, in increments of 15 min, how long they had performed the following activities at work: sitting, standing, walking on level ground, walking on uneven ground, climbing stairs, or any other activities. The 12 months test-retest correlation of 0.69 for the OPA interview indicated good reliability.[36] Lifetime job stability in the Kuopio region is relatively high[37] reducing the probability of misclassification of OPA during follow-up.

A self-administered baseline questionnaire provided information on work status (working full time, working part time, unemployed, retired, not working for other reason). Those not currently working were asked about the year when an unemployment or retirement period began, the number of days worked per week in the last job, and number of hours worked per day. For those working, workdays per week, the number of hours and minutes worked per day, and the number of days they missed work due to illness during the past 12 months were assessed. Occupation was also assessed and 3-digit coded according to the Finnish Classification of Occupations of Tilastokeskus (Center of Statistics of Finland).

2.5 | Absolute and relative measures of energy expenditure at work

Absolute EE at work (in kcal/day) was assessed from baseline interview data on time spent in various activities at their current job during a typical workday and reference data on the energy requirements (kcal/kg/hour) of these activities. Body weight was measured at the baseline medical examination. Cardiorespiratory fitness (VO_2max) was used to create two relative measures of EE that take workers' individual aerobic capacity into account and measure their relative aerobic workload: relative aerobic strain (RAS or %VO_2max) and percent oxygen uptake reserve (%VO_2Res). Other basic data gathered included the number of days and hours typically worked per week.

2.5.1 | Absolute energy expenditure per typical workday

EE per typical workday reflects the sum of the durations and intensities of each OPA. The duration (hours/typical day) of different physical activities at work was assessed by the occupational interview. The energy requirements of these activities were estimated as multiples of the baseline metabolic rate (MET) in kilocalories/kg/h of an average male with values of 1.6 for work while sitting, 2.4 for standing, 3.3 for walking on level ground, 4.9 for walking on uneven ground, 7.3 for climbing stairs and a mean value of 3.9 for other non-specified activities based on previously published data.[38,39] EE in kcal for each reported activity is calculated by multiplying the duration (hours per day) by the respective intensity (MET) and body weight (kg) of the individual. The sum of these estimates gives the EE measured in kcal per typical workday.

Although absolute EE was reassessed at 4-year and 11-year follow-up, this investigation used only baseline values because (i) incomplete follow-up data would otherwise reduce the sample size; (ii) previous analyses showed that the use of cumulative measures of EE resulted in only relatively small increases in predictive power compared to simple baseline measures of EE[28]; and (iii) cardiorespiratory fitness, an important co-determinant of the preferred relative exposure measure and of the health impact of OPA, was only available at baseline.

2.5.2 | Cardiorespiratory fitness

Cardiorespiratory fitness (also known as aerobic capacity or maximum oxygen uptake or VO_2max) was assessed by a maximal but symptom-limited exercise test on an electrically braked bicycle ergometer as explained in detail elsewhere.[33,40,41] Oxygen consumption was measured using respiratory gas exchange analysis. VO_2max was defined as the highest value or the plateau in oxygen uptake and was standardized by body weight and measured as mL O_2 per kg per minute.[40]

2.5.3 | Relative aerobic strain at baseline

RAS (%VO_2max) is a relative EE measure that expresses the physical demands of work in terms of energy needed to perform the job as a percentage of the individual worker's aerobic cardiorespiratory fitness or maximal work capacity.[42] RAS is the measure of relative aerobic workload that has traditionally been used to define recommended maximum levels of aerobic work demands.

2.5.4 | Percent oxygen uptake reserve at baseline

This is an alternative relative EE measure that expresses the physical demands of work in relation to the individual workers' aerobic cardiorespiratory fitness or maximal work capacity as the percentage of oxygen uptake reserve (%VO_2Res).[43] While RAS is based on the total EE at work including the energetic cost of metabolic rate for both rest and work activity, %VO_2Res is based on the EE associated with the work activity only and measured as %VO_2Res = (VO_2work−3.5)/(VO_2max−3.5] × 100% because the resting EE in general is defined as 1 MET = 3.5 mL O_2/kg per minute.[43,44] In our study, VO_2work was determined by calculating the weighted average of MET during work activities based on the occupational interview multiplied by 3.5 mL/kg per minute. Recently, %VO_2Res has been suggested as the preferred measure of relative EE for use in job analyses and epidemiological field studies because it allows for more adequate comparisons than %VO_2max when EE varies greatly in the study population. A further advantage of this measure is the fact that, in contrast to %VO_2max, %VO_2Res corresponds directly to percent heart rate reserve (%HRR) that can be measured more easily in the field than %VO_2Res itself.[43]

2.6 | Assessment of covariates

Covariates (listed in Table 1) were assessed at baseline, 4 years, and 11 years. For this analyses, repeat measures were only used in a few cases for substituting baseline values. Details of the measurement of these variables have been described previously.[34,45] In the following, we give a summary of the measurement of key covariates: Blood pressure was measured with a random-zero sphygmomanometer after a supine rest of 5 min. Three measurements were then taken while the subject was still supine, one while standing, and two while sitting, in that order. The average of these six measurements was used in our analyses. BMI was defined as weight in kilograms divided by height in meter squared. Use of cholesterol and blood pressure lowering medications was assessed by questionnaire. Alcohol consumption in grams per week during the past 12 months was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory.[46] Cigarette use was a four-level categorical variable: never smoked, former smoker, irregular smoker, and current regular smoker. LTPA, in hours per year, was measured using a modified version of the Minnesota LTPA questionnaire[47] that included the 16 most common LTPA of middle-aged Finnish men.[38] Respondents were asked to estimate the duration, frequency, and intensity of each of 16 activities performed for each of the 12 previous months. Our analyses use the average weekly minutes of conditioning vigorous (intensity of at least 6 MET) LTPA. Socioeconomic status (SES) was measured by personal income in Finnish Marks, social support at work from coworkers and supervisors was measured by several standard items, stress from work deadlines was measured by one item, and a 10-item mental strain index measured job stress as described previously.[34]

2.7 | Statistical analyses

The baseline characteristics of men with and without baseline IHD were compared using t-tests for continuous and chi square tests for categorical variables. Incidence rates were calculated using person-time data.

Associations between OPA and mortality outcomes were assessed with Cox proportional hazard models[48] adjusting incrementally for all covariates listed in Table 1 that were considered potential confounders, with the exception of cardiorespiratory fitness which is already an integral component of the two relative EE measures. The list of covariates is intentionally identical to the covariates used in two previous studies of OPA and 11-year progression of carotid atherosclerosis and incidence of AMI in order to facilitate direct comparisons.[28,29] All continuous variables were centered at the mean making the average rather than a zero value the reference for presented hazard ratios. For the few remaining categorical variables, the low risk category was chosen as reference. Each OPA measure was evaluated in separate models with incremental adjustment for potential confounders and inclusion of interaction terms. After examining categorized measures of OPA for non-linear trends, we explored both linear and quadratic OPA hazard models (the latter including both a linear and quadratic exposure term) using maximum likelihood ratio test statistics to assess fit. Models were incrementally adjusted for age, for all other covariates listed in Table 1, and for baseline IHD and OPA × IHD interaction terms. We also computed separate association measures for men with and without baseline IHD.

The product (interaction) term in our interaction model served to evaluate a "statistical" interaction in the sense of departure from *multiplicativity* in the joint effects of OPA but does not evaluate what has been termed "biological" or "causal" interaction in the sense of departure from *additivity* in the joint effects. Therefore, we also calculated the relative excess risk due to interaction (RERI) on an additive scale. A positive value for RERI>0 indicates that the combined effect of OPA and IHD is greater than the sum of their separate effects assuming monotonic effects of both exposures.[49,50] Finally, we performed analyses stratified by baseline IHD as a *preferred* alternative to these interaction models in order to allow for a more comprehensive account for covariate distributions that differed between IHD subgroups.

The estimated hazard ratio (HR) can be interpreted as the approximate instantaneous relative risk associated with a specified risk factor. The proportional hazards regression model is advantageous compared to logistic regression models or direct calculation of relative risks because it utilizes information about time to death event to provide an estimate of the average instantaneous relative risk (ie, the relative hazard or ratio of incidence rates) over short time intervals in which the outcome remains a rare event even for older groups. Separately for men without and with IHD, the proportional hazard (PH) assumption was tested using the goodness of fit testing approach based on Schoenfeld residuals and was not rejected by this global test when including all variables listed in Table 1 in the Cox model (stphtest command in Stata).[51] We also performed the PH test for each covariate separately (detailed option) and the null hypothesis of PH was rejected for the following covariates: plasma fibrinogen, systolic blood pressure, and cholesterol-lowering medication using 0.05 as the cut-off point. We used a stratified Cox (SC) model and obtained similar results to those from the regular Cox model. We present results from the regular Cox model. We calculated HR and associated 95% confidence interval (CI). We also calculated absolute risk differences in terms of extra incident cases per person-time for both IHD subgroups taking the higher a priori risk for CHD death among men with IHD into account. All analyses were performed using the statistical software Stata version 14.1 (StataCorp LP, College Station, TX).

This secondary data analyses was exempt from human subjects institutional review. The original study was approved by the University of Eastern Finland and by the University of California.

3 | RESULTS

3.1 | Characteristics of the study population

The average age in the study cohort was 51.8 years (SD 5.0), with 309, 321, 1149, 112 at age 42, 48, 54, and 60, respectively. Conditioning LTPA averaged 92 h (SD 106) per year, BMI 26.7 kg/m^2 (SD 3.5), alcohol consumption 74 g per week (SD 130), and 29% were current or former smokers. The distributions of independent variables by baseline IHD are listed in Table 1. Compared to men without IHD at baseline,

TABLE 1 Characteristics of the study population and distribution of independent variables by ischemic heart disease (IHD) status at baseline in the Kuopio Ischemic Heart Disease Risk Factor Study 1984-2005 (*N* = 1891)

	Men without IHD (*N* = 1565)		Men with IHD (*N* = 326)		Difference
Independent variables	*N* or Mean	(%) or (SD)	*N* or Mean	(%) or (SD)	*P*-value (*t*-test or chi-square test)
Occupational physical activitiy measures:					
Absolute energy expenditure per typical workday (kcal) at baseline	2078	(875)	2272	(970)	0.001
Relative aerobic strain (%VO_2max) at baseline	29.7	(12.1)	38.5	(16.5)	0.001
Reserve oxygen uptake (%VO_2Res) at baseline	22.6	(13.5)	31.5	(19.2)	0.001
Covariates:					
Age and technical factors					
Age (years)	51.5	(5.1)	53.5	(3.9)	0.001
Participant in placebo group of lipid lowering drug trial	135	(8.6%)	28	(8.6%)	0.983
Participant in treatment group of lipid lowering drug trial	136	(8.7%)	27	(8.3%)	0.811
Biological factors					
Blood glucose (mmol/L)	4.70	(0.91)	4.88	(1.39)	0.029
Plasma fibrinogen (g/L)	2.95	(0.52)	3.10 (0.58)		0.001
Body mass index	26.7	(3.4)	27.1	(3.8)	0.029
LDL-cholesterol (mmol/L)	3.99	(0.97)	4.17	(1.07)	0.003
HDL-cholesterol (mmol/L)	1.31	(0.29)	1.28	(0.32)	0.114
Systolic blood pressure	133.9	(16.0)	133.0	(18.3)	0.429
Lipid-lowering medication (yes)	4	(0.3%)	4	(1.2%)	0.014
Anti-hypertensive medication (yes)	179	(11.4%)	115	(35.3%)	0.001
Behavioral factors					
Alcohol consumption (g/week)	71.5	(111.9)	88.3	(196.4)	0.134
Cigarettes/day × years	142	(290)	210	(348)	0.001
Conditioning LTPA (min/week)	105	(117)	109	(145)	0.001
Cardiorespiratory fitness (VO_2max in mL O_2/kg/min)	32.8	(7.0)	27.5	(6.9)	0.001
Socio-economic status					
Personal income (1000 FIM/yr)	92.6	(56.7)	72.3	(37.4)	0.001
Psychosocial job factors					
Social support score at work (range 0-12)	6.5	(2.5)	6.5	(2.4)	0.882
Mental strain at work index (range 0-37)	11.5	(6.3)	13.4	(7.1)	0.001
Stress from work deadlines (yes)	357	(23%)	105	(32%)	0.001

men with IHD were 2 years older, earned 22% less, smoked more, had higher levels of biological risk factors, were less fit, experienced more mental strain and stress from deadlines at work, and worked about 1.6 h more per week. Men with IHD also expended more energy at work and experienced higher levels of relative aerobic workload.

3.2 | Mortality

During a total person-time at risk of 41 021 years, 661 deaths were registered (16.11% annual mortality rate); 508 deaths occurred among men without baseline IHD (14.78% annually) and 153 among men with IHD (23.04% annually). CHD was the underlying cause for 28% of deaths (4.49% annually mortality rate), 117 among men without IHD (3.40% annually), and 67 among men with IHD (10.09% annually).

3.3 | Comparison of model fit between linear and quadratic hazard functions

Hazard functions were modeled in linear (using the continuous variable of the OPA exposure measure) and in quadratic form (adding a

TABLE 2 Hazard ratios (HR) and 95% confidence intervals (CI) based on linear hazard modeling of the associations between occupational physical activity and 22-year all-cause mortality (661 deaths) for all men (n = 1891), men without (n = 1565), and men with (n = 326) ischemic heart disease (IHD)

		Absolute energy expenditure (Unit 500 kcal/day)			Relative aerobic strain (Unit 10%)			Percent oxygen uptake reserve (Unit 10%)		
Analysis Model	IHD status subgroup	HR	95%CI	*P*	HR	95%CI	*P*	HR	95% CI	*P*
Analyses of all men										
Model 1: Unadjusted	Combined	1.06	1.01-1.10	0.008[b]	1.24	1.18-1.30	0.000[b]	1.17	1.13-1.22	0.000[b]
Model 2: Age-adjusted	Combined	1.06	1.01-1.10	0.009[b]	1.21	1.15-1.27	0.000[b]	1.15	1.11-1.20	0.000[b]
Model 3: Fully adjusted[a]	Combined	1.00	0.95-1.04	0.874	1.13	1.07-1.20	0.000[b]	1.09	1.04-1.15	0.000[b]
Model 4: Model 3 plus adjustment for IHD	Combined	0.99	0.95-1.04	0.798	1.13	1.06-1.20	0.000[b]	1.09	1.04-1.15	0.001[b]
Interaction analyses										
Model 5: Model 4 plus OPA × IHD interaction term	No IHD	1.00	0.95-1.05	0.955	1.14	1.06-1.22	0.000[b]	1.10	1.03-1.16	0.003[b]
	With IHD	0.99	0.95-1.04	0.762	1.13	1.06-1.20	0.000[b]	1.10	1.04-1.15	0.001[b]
Departure from multiplicativity (OPA × IHD)	n/a	0.99	0.97-1.02	0.505	0.99	0.97-1.02	0.661	1.00	0.98-1.02	0.802
Departure from additivity (RERI)[c]	n/a	−0.01	−0.04 to 0.02	0.494	0.00	−0.03 to 0.03	0.989	0.00	−0.02 to 0.03	0.805
Stratified analyses										
Model 6: Unadjusted	No IHD	1.08	1.03-1.13	0.002[b]	1.25	1.18-1.32	0.000[b]	1.18	1.12-1.24	0.000[b]
	With IHD	0.96	0.88-1.05	0.362	1.15	1.05-1.25	0.002[b]	1.10	1.02-1.19	0.012[b]
Model 7: Age-adjusted	No IHD	1.08	1.03-1.13	0.002	1.22	1.14-1.29	0.000[b]	1.16	1.10-1.22	0.000[b]
	With IHD	0.96	0.88-1.05	0.413	1.14	1.05-1.25	0.003[b]	1.10	1.02-1.19	0.014[b]
Model 8: Fully adjusted[a]	No IHD	1.03	0.98-1.09	0.243	1.15	1.07-1.24	0.000[b]	1.11	1.05-1.19	0.001[b]
	With IHD	0.91	0.82-1.00	0.062	1.11	1.00-1.24	0.050	1.08	0.98-1.18	0.109

Kuopio IHD Risk Factor Study 1984-2011.

[a]HR adjusted for all covariates listed in Table 1 except cardio-respiratory fitness (VO_2max).

[b]$P < 0.05$.

[c]Relative excess risk due to interaction (RERI) on an additive scale using the nlcom post-estimation command in Stata: Values of 0 signal no additive interaction, >0 positive interaction, <0 negative interaction, assuming monotonicity of effects of both exposures. This row shows the beta-coefficients customarily used to determine RERI (and not the exponentiated values used in other rows to denote hazard ratios).

quadratic term of the continuous OPA variable). The quadratic function was explored because it may better reflect anticipated non-linear increases in CHD risk with increasing levels of OPA. Model fit was compared by maximum likelihood ratio tests that did not show any significant difference between fully adjusted linear and quadratic models of kilocalories (P values 0.98 for all-cause and 0.52 for CHD mortality), RAS (0.96 and 0.58), or %VO_2Res (0.70 and 0.73), respectively. Consequently, we only present results from the more parsimonious linear models in Tables 2–4.

3.4 | Interactions between baseline IHD and OPA

For absolute EE, no statistical interactions with baseline IHD were observed for all-cause mortality, but for CHD mortality interaction on the multiplicative scale cannot be ruled out (P = 0.15). Some statistical significant (P = 0.03) positive interactions were observed between IHD and RAS (RERI = 0.21, 95%CI = 0.02-0.39) and percent oxygen uptake reserve (RERI = 0.16, 95%CI = 0.16-0.31) in fully adjusted models indicating supra-additivity of OPA and IHD effects (see Table 3).

3.5 | Associations between OPA and 22-year mortality

Results obtained from linear hazard models are presented separately for all-cause (Table 2) and CHD mortality (Table 3). Both tables show HR with 95%CI and P values for each measure of OPA in eight different regression models: (i) unadjusted; (ii) age-adjusted; (iii) adjusted for all covariates listed in Table 1 (except cardiorespiratory fitness which is already accounted for in the relative EE exposure measures); (iv) additionally adjusted for IHD; (v) adding an IHD×OPA interaction term;

TABLE 3 Hazard ratios (HR) and 95% confidence intervals (CI) based on linear hazard modeling of the associations between occupational physical activity and 22-year CHD mortality (184 deaths) for all men (n = 1891), men without (n = 1565) and men with (n = 326) ischemic heart disease (IHD)

		Absolute energy expenditure (Unit 500 kcal/day)			Relative aerobic strain (Unit 10%)			Percent oxygen uptake reserve (Unit 10%)		
Analysis model	IHD status subgroup	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Analyses of all men										
Model 1: Unadjusted	Combined	1.12	1.05-1.21	0.002[b]	1.37	1.27-1.48	0.000[b]	1.27	1.19-1.36	0.000[b]
Model 2: Age-adjusted	Combined	1.12	1.04-1.21	0.002[b]	1.34	1.24-1.45	0.000[b]	1.25	1.17-1.34	0.000[b]
Model 3: Fully adjusted[a]	Combined	1.07	0.98-1.16	0.121	1.28	1.16-1.40	0.000[b]	1.21	1.12-1.31	0.000[b]
Model 4: Model 3 plus adjustment for IHD	Combined	1.05	0.96-1.13	0.292	1.23	1.11-1.35	0.000[b]	1.17	1.08-1.27	0.000[b]
Interaction analyses										
Model 5: Model 4 plus OPAxIHD interaction term	No IHD	1.09	0.99-1.20	0.084	1.27	1.12-1.44	0.000[b]	1.20	1.08-1.34	0.001[b]
	With IHD	1.06	0.97-1.15	0.196	1.25	1.13-1.39	0.000[b]	1.19	1.08-1.30	0.000[b]
Departure from multiplicativity (OPAxIHD)	n/a	0.97	0.93-1.01	0.146	0.98	0.95-1.02	0.389	0.99	0.97-1.02	0.488
Departure from additivity (RERI)[c]	n/a	0.04	−0.08 to 0.16	0.486	0.21	0.02-0.39	0.029[b]	0.16	0.16-0.31	0.030[b]
Stratified analyses										
Model 6: Unadjusted	No IHD	1.18	1.08-1.29	0.000[b]	1.37	1.22-1.51	0.000[b]	1.26	1.15-1.38	0.001[b]
	With IHD	0.95	0.83-1.08	0.453	1.23	1.09-1.38	0.001[b]	1.16	1.05-1.29	0.001[b]
Model 7: Age-adjusted	No IHD	1.18	1.08-1.29	0.000[b]	1.33	1.19-1.48	0.000[b]	1.24	1.13-1.36	0.001[b]
	With IHD	0.96	0.84-1.09	0.496	1.22	1.08-1.38	0.001[b]	1.16	1.05-1.29	0.005[b]
Model 8: Fully adjusted[a]	No IHD	1.14	1.03-1.26	0.008[b]	1.30	1.14-1.49	0.000[b]	1.24	1.10-1.39	0.000[b]
	With IHD	0.91	0.79-1.06	0.236	1.19	1.02-1.38	0.024[b]	1.14	1.00-1.30	0.042[b]

Kuopio IHD Risk Factor Study 1984-2011.

[a]HR adjusted for all covariates listed in Table 1 except cardio-respiratory fitness (VO_2max).

[b]$P < 0.05$.

[c]Relative excess risk due to interaction (RERI) on an additive scale using the nlcom post-estimation command in Stata: Values of 0 signal no additive interaction, >0 positive interaction, <0 negative interaction, assuming monotonicity of effects of both exposures. Note: this row shows the beta-coefficients customarily used to determine RERI (and not the exponentiated values used in other rows to denote hazard ratios).

(vi) stratified by IHD without adjustments; (vii) stratified by IHD with age adjustment; and (viii) stratified by IHD with full adjustments as in model 3. Subgroup results are presented for men without and with IHD based on interaction model 5 and, alternatively, based on stratified analyses (models 6–8).

Absolute EE per typical workday in units of 500 kcal/day shows positive associations with both all-cause and CHD mortality in crude and age-adjusted models in combined analyses of all men. However, in stratified analyses, the hazard appeared limited to men without IHD. Adjustment for all covariates attenuated the estimates, and only the association with CHD mortality remained significant (HR = 1.14, 95% CI 1.03-1.26, P = 0.008).

Relative aerobic strain measured in 10% units was positively associated with both all-cause and CHD mortality for all men in crude, age-adjusted, and fully adjusted models (models 1-4), and, for both men with and without IHD, also in interaction model 5 and crude and age-adjusted stratified analyses (models 6-7). Interactions between RAS and baseline IHD were found on the additive scale. The strongest associations between OPA and mortality after adjustment for all covariates was observed in men without baseline IHD, with each 10% increase in RAS resulting in a 15% increased instantaneous risk of all-cause mortality (HR = 1.15, 95%CI 1.07-1.24, P = 0.000) and a 30% increase in CHD mortality (HR = 1.30, 95%CI 1.14-1.49, P = 0.000). The increases among men with IHD were 11% and 19%, respectively.

Percent oxygen uptake reserve measured in 10% units was positively associated with both all-cause and CHD mortality for all men in crude, age-adjusted, and fully adjusted models (models 1-4), and, for both men with and without IHD, also in interaction model 5 and crude and adjusted stratified analyses (models 6-8). Interactions between %VO_2Res and baseline IHD were found on the additive scale.

TABLE 4 Hazard ratios (HR) and 95% confidence intervals (CI) based on linear hazard modeling of the associations between conditioning leisure time physical activity (LTPA, hours/week) and 22-year all-cause and CHD mortality (661 deaths) for all men (n = 1891), men without (n = 1565), and men with (n = 326) ischemic heart disease (IHD)

		All-cause mortality			CHD mortality		
Analysis model	**IHD status subgroup**	**HR**	**95%CI**	***P***	**HR**	**95%CI**	***P***
Analyses of all men							
Model 1: Unadjusted	Combined	0.97	0.93-1.01	0.102	0.95	0.87-1.03	0.195
Model 2: Age-adjusted	Combined	0.97	0.93-1.01	0.183	0.95	0.88-1.04	0.273
Model 2b: Age- and OPA-adjusted	Combined	1.00	0.96-1.04	0.856	1.00	0.92-1.08	0.941
Model 3: Fully adjusted[a]	Combined	1.03	0.99-1.07	0.177	1.03	0.96-1.11	0.393
Model 4: Model 3 plus adjustment for IHD	Combined	1.03	0.99-1.07	0.179	1.03	0.96-1.11	0.395
Interaction analyses							
Model 5: Model 4 plus LTPAxIHD interaction term	No IHD	0.99	0.94-1.04	0.657	0.95	0.84-1.06	0.341
	With IHD	1.11	1.05-1.18	0.001[b]	1.14	1.04-1.26	0.008[b]
Departure from multiplicativity (LTPA × IHD)	n/a	1.13	1.04-1.22	0.003[b]	1.21	1.04-1.40	0.013[b]
Departure from additivity (RERI)[c]	n/a	0.13	0.04-0.22	0.004[b]	0.31	0.07-0.55	0.011[b]
Stratified analyses							
Model 6: Unadjusted	No IHD	0.93	0.88-0.98	0.007[b]	0.88	0.78-0.99	0.034[b]
	With IHD	1.06	0.99-1.13	0.115	1.04	0.94-1.16	0.448
Model 7: Age-adjusted	No IHD	0.94	0.89-0.99	0.017[b]	0.89	0.79-1.00	0.050
	With IHD	1.05	1.01-1.10	0.028[b]	1.04	0.94-1.15	0.485
Model 7b: Age- and OPA-adjusted	No IHD	0.96	0.92-1.01	0.147	0.93	0.82-1.04	0.198
	With IHD	1.07	1.00-1.14	0.043b	1.07	0.96-1.18	0.210
Model 8: Fully adjusted[a]	No IHD	0.99	0.94-1.04	0.751	0.95	0.84-1.06	0.341
	With IHD	1.10	1.03-1.18	0.005[b]	1.14	1.04-1.26	0.008[b]

Kuopio IHD Risk Factor Study 1984-2011.

[a]HR adjusted for all covariates listed in Table 1 except cardio-respiratory fitness (VO_2max).

[b]$P < 0.05$.

[c]Relative excess risk due to interaction (RERI) on an additive scale using the nlcom post-estimation command in Stata: Values of 0 signal no additive interaction, >0 positive interaction, <0 negative interaction, assuming monotonicity of effects of both exposures. Note: this row shows the beta-coefficients customarily used to determine RERI (and not the exponentiated values used in other rows to denote hazard ratios).

The strongest associations between OPA and mortality after adjustment for all covariates was observed in men without baseline IHD, with each 10% increase in %VO_2Res resulting in a 11% increased instantaneous risk of all-cause mortality (HR = 1.11, 95%CI 1.05-1.19, P = 0.001) and a 24% increase in CHD mortality (HR = 1.24, 95%CI 1.10-1.39, $P < 0.001$). The increases among men with IHD were 8% and 14%, respectively.

Categorical measures of OPA (results not shown in tables): Finally, we report selected alternative categorical OPA measures assessed in model 8 (stratified by IHD and fully adjusted) in order to facilitate comparisons with the existing literature. For men without IHD at baseline, RAS> = 33% compared to <33% was associated with a 30% increase in risk of all-cause mortality (HR = 1.30, 95%CI 1.07-1.57, P = 0.008) and a 64% increase in risk of CHD mortality (HR = 1.64, 95% CI 1.10-2.42, P = 0.014). For men with IHD, RAS> = 33% was associated with increases of 16% in all-cause (HR = 1.16, 95%CI 0.80-1.66, P = 0.435) and 25% in CHD (HR = 1.25, 95%CI 0.71-2.19, P = 0.434) mortality risk.

3.6 | Absolute mortality risk difference by IHD subgroup

The number of excess deaths due to OPA were estimated by the difference of mortality rates and the product of these mortality rates times relative hazards from fully adjusted stratified regression models. Based on HR estimated in the fully adjusted linear model 8, a 10% increase in RAS was associated with an estimated extra 225 deaths per 100 000 person-years in men without IHD and 255 extra deaths in men with IHD. Excess CHD deaths were 190 for men without IHD and 90 for men with IHD.

3.7 | Associations between other cardiovascular risk factors and mortality

In fully adjusted models stratified by IHD, conditioning LTPA had no effect on all-cause or CHD mortality among men without IHD (HR = 0.95, 95%CI 0.84-1.06, P = 0.341 and HR = 0.99, 95%CI

0.94-1.04, $P = 0.751$, respectively). Among men with IHD, each weekly hour of LTPA was associated with a 10% increase in all-cause mortality and a 14% increase in CHD mortality (HR = 1.10, 95%CI 1.03-1.18, $P = 0.005$ and HR = 1.14, 95%CI 1.04-1.26, $P = 0.008$, respectively) (see Table 4). Other known traditional cardiovascular risk factors such as age, blood pressure, LDL-cholesterol, and smoking showed independent effects on mortality in the expected direction for all men in the fully adjusted hazard models of RAS (results not shown). Income showed no independent positive associations with mortality in these models. Alternative models adjusting for socio-economic status under varying definitions and specifications did not alter the results and conclusions (results not shown).

4 | DISCUSSION

This study found that OPA predicted all-cause and CHD mortality accounting for baseline IHD status and multiple confounders. Compared to absolute measures, relative workload measures that took individual fitness into account more strongly predicted mortality. This study also addressed several methodological issues of the extant inconsistent literature by (a) using a validated interview instrument to accurately assess OPA at baseline; (b) using continuous exposure measures; (c) using relative measures of EE taking individual cardiorespiratory fitness into account; and (d) adjusting for virtually all known biological, behavioral, and psychosocial risk factors for CVD. In addition, this study investigated possible interactions between OPA and pre-existing IHD and the impact of alternative model specifications on effect measures.

4.1 | Impact of model choice on estimates of OPA effects and interaction with baseline IHD

This study explored two basic hazard models (without and with quadratic terms, both on an exponential regression scale) and several alternative approaches to effect modification by baseline IHD (via adjustment, assessment of interaction on both additive and multiplicative scales, and stratified analyses) to examine the influence of model choice on the results. These alternatives were explored in fully adjusted models with alternative OPA measures that took 19 potentially confounding factors into account including virtually all established biological, behavioral, and psychosocial CVD risk factors. Adding a quadratic OPA term to the models did not improve model fit and, in contrast to previously published analyses of AMI incidence in this population,[29] did not lead to any substantially different risk estimates. Additional adjustment for baseline IHD (model 4) is problematic because IHD may itself be a result of (past) OPA exposure and could therefore constitute an over-adjustment leading to an underestimation of OPA effects. Also, IHD might share unmeasured common causes with both OPA and mortality, thus making it a potential collider that could introduce bias when conditioned on and be part of the confounding path between OPA and mortality when not controlled for. As expected, additional adjustment for IHD attenuated the estimates.

Relative hazards estimated for IHD subgroups from fully adjusted analyses allowing for interaction with baseline IHD (model 5) showed no subgroup difference while analyses stratified by IHD subgroup (model 8) indicated that OPA increases mortality risk more among men without baseline IHD than among men with IHD. The following reason may account for this discrepancy: Our data indicate different covariate distributions across IHD subgroups (see Table 1) and the predictive power of covariates differed between IHD subgroups (data not shown) also pointing to differences in the covariate structure between subgroups. Stratified analyses fully allow for such different covariate structures in each IHD subgroup and therefore we consider the results of stratified analyses (model 8) more valid than the estimates derived from the interaction models (model 5). However, both effect estimates for the subgroup with IHD may be biased downwards due to health-based selection as discussed below in section 4.4.

In addition, it is important to note that the reported *lower relative* hazards of RAS among men with IHD still led to *higher absolute* increments in CHD mortality (in terms of the number of excess deaths per person-year) because of their inherently higher baseline mortality risk compared to men without IHD.

Finally, fully adjusted models can be utilized to compare the magnitude of independent OPA effects with those of other traditional risk factors. For example, a 10% unit increase in RAS is comparable in magnitude to an independent age effect of 1.7 or 1.1 years among men without or with IHD, respectively (also based on fully adjusted model 8).

Interaction effects were assessed both on a multiplicative and an additive scale with results varying not only by scale, but also by type of OPA measure (absolute versus relative EE). Overall, results indicated the presence of super-additive biological interactions between relative EE measures and IHD for CHD mortality. This interaction with IHD is in alignment with the hemodynamic theory of atherosclerotic artery disease and has been expected based on previous studies of 11-year progression of atherosclerosis and of AMI incidence in this population that had shown strong interactions of the same OPA measures with IHD.[28,29] Although all investigated models represent valid analytic approaches and have been used in previous research, the different covariate structure in the IHD subgroups, the presence of interaction between some measures of OPA and baseline IHD, and the need for the development of OPA recommendations that take baseline cardiovascular health status into account together favor the utilization of models stratified by baseline IHD to estimate relative hazards for each IHD subgroup.

This study demonstrates that the choice of analytic strategies can influence the assessment of mortality risk and such choices may be in part responsible for inconsistencies in the literature. A multipronged approach exploring alternative strategies for subgroup analyses and hazard modeling together with using alternative OPA measures can increase confidence in results that appear to follow a consistent pattern across different analytic strategies.

4.2 | Improved exposure assessment and residual misclassification

To our knowledge, this is the first prospective cohort study of OPA and mortality using both *absolute and relative* measures of EE at work as exposure variables. Only our previous studies of 11-year progression of atherosclerosis and of AMI incidence in this cohort also used both absolute and relative EE measures.[28,29] Our study demonstrates that only the superior relative workload measures that take individual worker fitness into account consistently predict both CHD and all-cause mortality and do so across alternative statistical modeling approaches while the absolute measure of EE appeared to be a weaker and uncertain predictor of mortality in most models.

Our detailed exposure assessment methods that allowed for analysis of *continuous* OPA measures should also be considered an important strength of this study. The majority of cohort studies in the literature used only crude categorical measures of OPA, and the associated misclassification bias toward the null may have contributed to inconsistent results. For example, we could demonstrate that the statistically significance of effects of RAS on CHD mortality among men with IHD observed in our models with *continuous exposure measures* could not be detected when we used a *dichotomous* exposure measure (comparing the effects of RAS above and below the maximum recommended level of 33% in models fully adjusted for the same covariates as in models with continuous exposure measures; data shown in the text at the end of result section 3.5 above). The number of exposure categories and the respective cutpoints chosen can have a major influence on results. For example, among all men, the estimated fully adjusted mortality risk based on the same dichotomous RAS exposure variable appears to be much smaller (HR for RAS >33 = 1.65, 95%CI 1.20-2.27, $P = 0.002$) than the mortality risk for the same high exposure subgroup based on a trichotomized variable where the reference group is RAS <16.2 (HR for RAS >33 = 7.79, 95%CI 1.06-57.04, $P = 0.043$).

Residual exposure misclassification may still have occurred in our study because the type and duration of work activities were based on self-report data rather than on direct observations and also because the assessment of EE did not include upper-extremity work or the handling of external loads and instead was limited to the energetic costs of moving one's own body or maintaining one's body posture (sitting, standing, walking, and climbing stairs). Such activities may be occurring together with the use of hand-held equipment, material handling, carrying, lifting, and other demanding work activities not captured by our occupational interview. The relative amount of static work could thus not be determined. The ambient temperature was also not accounted for, and the average MET values assigned to work activities may also differ according to the individual body composition of fat and fat-free mass.[52] However, we have no reason to believe that this residual exposure misclassification was differential and therefore we expect any bias to be directed toward the null hypothesis of no association between OPA and mortality. In other words, we consider our observed hazard estimates to be conservative. In fact, a recent study showed that heavy lifting increased cardiovascular disease and mortality risks associated with OPA.[26] On the other hand, the nearly exclusive focus on lower-extremity activities in the computation of EE at work increases the validity of our assessments of relative EE measures that were based on the use of bicycle ergometry tests utilizing lower extremity activity for the determination of workers' maximum aerobic capacity.[53,54]

The lack of repeat relative EE measures in our study needs also to be considered as a typical limitation in this research possibly adding to a conservative misclassification bias. Development of fatal CHD is itself a long-term process related to a complex and linked series of exposures that may accumulate over an individual's life course.[55] There is limited evidence to support the assumption that some risk factors are fixed and do not alter, even over long periods of follow-up.[56] In our cohort, several indicators of OPA including occupational title, job, and repeat absolute EE measures all have been found to be rather stable over time.[28] For example, repeat absolute EE measures were available at 4- and 11-year follow-up, and these repeat measures were highly correlated (correlation coefficient 0.80 for 4-year and 0.64 for 11-year EE in kcal/day) thus limiting the extent of possible exposure misclassification. In our previous analyses of 11-year progression of carotid atherosclerosis in this cohort we found consistently stronger associations with baseline relative EE measures compared to any cumulative absolute energy expenditure measures.[28] In addition, work physiology and ergonomic principles predict that not a high absolute amount of EE alone but rather a misfit between high job-related energy demands and low worker aerobic capacity will lead to elevated blood pressure and elevated heart rates during work, the two mechanisms that constitute the central causal pathway to CVD according to the hemodynamic theory of atherosclerosis as explicated by Glagov.[57] For these reasons, we choose to focus on relative EE measures that were only available at baseline and to use only one baseline absolute EE measure in this analysis to allow comparisons between the predictive strengths of these measures. Again, any remaining exposure measurement error most likely introduced a conservative bias in the effect estimates.

4.3 | Comprehensive control for confounding and possible over-adjustment

The comprehensive adjustment for 19 potential confounders including virtually all widely accepted demographic, biological, behavioral, and psychosocial risk factors needs to be considered an important strength of this study. Specifically, there are only few studies of OPA controlling for LTPA. LTPA and some other variables could be considered both as confounders and as pathway variables, thus adjustment for them could constitute a partial over-adjustment. However, in a recent mediation analysis based on this cohort data we demonstrated that OPA predicts LTPA but LTPA does not predict incidence of CHD among these working men and therefore the effect of OPA is not being mediated by LTPA.[58] We also controlled for socioeconomic position by personal income. This could be considered an over-adjustment since most physically demanding blue-collar jobs typically generate lower income

than less physically demanding white-collar jobs. However, adjusting for all 19 covariates best reflected our goal to minimize any residual confounding even if it resulted in some over-adjustment, more conservative effect estimates, and reduction of statistical power. The list of potential confounders was also predetermined by our intent to compare results from this study of mortality with results from our previous studies of non-symptomatic atherosclerotic changes and of AMI incidence in the same study population.[28,29] In contrast to that previous study where control for these confounders changed the effects only minimally, this study showed more substantial effect attenuation, especially among men without IHD.

4.4 | Comparisons with previous study of progression of atherosclerosis: healthy worker effect

An apparent weaker mortality effect of OPA in men with IHD compared to men without IHD (in relative terms only, see above) needs to be interpreted with caution. In light of the opposite findings in our previous study on progression of non-symptomatic atherosclerosis in the same study population, our current findings for CHD mortality need to be considered the result of health-based selection of men who survived in physical demanding jobs despite their IHD. Direct comparisons with our previous studies are facilitated by the use of the same OPA measures and of multivariate models fully adjusting for the same set of potential confounders that were previously used in our study on 11-year progression of carotid atherosclerosis in this study population.[28] An alternative OPA measure of static work posture (prolonged standing at work) also increased the risk of progression of *asymptomatic* atherosclerosis predominantly among the IHD subgroup[28,59] indicating a greater vulnerability to higher workloads in men with IHD.

The consistent positive associations between relative EE and mortality are in line with previous research where both absolute and relative EE measures predicted 11-year progression of carotid atherosclerosis in both men with and without baseline IHD. However, in this study of mortality—and similarly to our study of AMI incidence[29]—only relative EE measures predicted an increased risk while absolute EE showed weaker or no effects depending on the analytic model. These diverging results within the same study sample and using the same measurements for all variables demonstrates that the choice of exposure assessment, analytic strategy, and symptomatic versus non-symptomatic CVD outcome can all be reasons for inconsistent findings in the literature.

4.5 | Observed associations between OPA and mortality: causal inference

Associations between OPA and mortality were observed in analyses of all men but were stronger for men without than for men with IHD. Irrespective of the modulating influence of hazard modeling and analytic strategies described above, we think that the weaker association in men with IHD is probably due to health-based selection and therefore a biased estimate that needs to be balanced by contradictory findings from earlier studies of asymptomatic progression of atherosclerosis in this cohort that are less vulnerable to selection bias. One needs to consider that studies of mainly pre-clinical *asymptomatic* outcomes such as progression of atherosclerosis measured as intima media thickening at a range with little if any organ perfusion consequences tend to be less prone to outcome-driven health-based selection effects than studies with clinical *symptomatic* coronary artery disease outcomes such as IHD or fatal CHD. This consideration is relevant since these fatal diseases often involve a history of painful symptoms (angina pectoris) that get triggered by strenuous physical activity, the exposure of interest. Workers with symptomatic IHD and related physical work limitations, if they can afford it, tend to leave physical demanding jobs during follow-up once symptoms occur and thus are probably underrepresented in physically demanding jobs. It is noteworthy that the physical demands in terms of EE in kcal/day changed very little for this aging workforce over the first 11 years of follow-up despite the fact that aerobic capacity declines steadily after the mid-20s.[28] Therefore, high absolute EE at work can be expected to be associated with selected relatively heart-healthy individuals or individuals with IHD of lower severity. Such "healthy worker selection effects" plague studies of incident CVD and mortality and may also have contributed to inconsistent results in the literature.

We believe that OPA increases the risk for fatal CHD and does so possibly at different degrees for both men with and without IHD depending on their level of aerobic fitness given the following considerations: (i) both absolute and relative measures of OPA predicted progression of asymptomatic carotid atherosclerosis in both men with and without IHD in this cohort; (ii) relative OPA measures were consistently positive associated with AMI, fatal CHD, and all-cause mortality in this study population; and (iii) relative measures of OPA that take individual aerobic capacity into account better capture hemodynamic stressors associated with a discrepancy of aerobic fitness and physical demands at work. Given the evidence of a strong healthy worker effect and previous findings regarding progression of atherosclerosis in this cohort, the observed weaker relative mortality risks among men with IHD are probably due to selection effects.

Other researchers have found associations between OPA, aerobic fitness, and clinical CVD outcomes.[22] However, this is the first study of OPA and fatal CHD using individualized measures of the misfit between EE demands at work and aerobic capacity of the individual worker, while also combining persons with and without pre-existing IHD in interaction analyses. A recent study using a small sample of persons with preexisting CVD suggested positive associations of high levels of OPA (and LTPA) with IHD incidence and mortality.[60] Additional research is needed to reliably quantify risks or benefits related to OPA among the growing group of aging workers with existing IHD. Therefore, the exclusion of subjects with baseline IHD, which is still the predominant practice in CVD research, should be reexamined and replaced by investigations of both persons with and without baseline IHD while also carefully examining possible heterogeneity of the associations.

4.6 | The role of leisure time physical activity

Occupational and leisure time physical activities may have opposing effects on health.[2,61] The reasons for this "paradox" are not completely understood, however, in contrast to *voluntary* leisure time activities that are typically self-paced and of lesser frequency or duration than OPA and allow for adequate rest, *mandatory* occupational activities of high frequency and duration are often paced by fixed work schedules, machines, coworkers, supervisors, or clients and may not allow for adequate rest periods. The need to work steady for many hours without exhausting oneself completely, and lack of time and facilities to change sweat-drained wet clothes may even prevent workers who can self-pace their work from engaging in sufficient short-term intense bouts of physical activity needed to achieve any beneficial cardiovascular fitness training effects. In addition, dynamic activities such as walking may be beneficial at relatively low doses during leisure but may be detrimental at relatively high doses during work, especially if they occur in combination with other work activities such as handling materials or holding tools involving considerable amounts of static work more likely to be detrimental for cardiovascular health.

Similar to our previous study on CHD incidence, conditioning LTPA had no protective effect on mortality, although early analyses of this cohort had found a protective effect of this measure of LTPA on 4-year CHD risk.[40] To the contrary, among men with IHD, conditioning LTPA was positively associated with CHD mortality risk. This contradictory finding may be explained by the fact that these previous 4-year analyses of LTPA included non-working men, and did not control for OPA. It also makes intuitive sense that EE during work averaging 2114 kcal/day, nearly six times as much than LTPA (averaging only 382 kcal/day) and about 10 times as high as current recommended levels of LTPA (about 200 kcal/week; see Table D.3. in ref.[62]) would drive the association between overall physical activity and mortality. Others have reported that LTPA is only beneficial among those with sedentary jobs.[63] A recent Belgian cohort study found detrimental effects of LTPA among persons with high levels of OPA[64] in contrast to previous reports on beneficial effects of LTPA possibly preventing detrimental effects of OPA.[65,66] These inconsistent findings warrant further exploration.[2,64] If more studies confirm the findings in these Finnish and Belgian cohorts, the current public health strategy to promote increases of LTPA may not only fail to reduce CVD and mortality among workers exposed to relatively high physical work demands but may put them at increased risk.

4.7 | Implications for prevention and medical practice

Results of this representative population-based cohort study do not indicate that detrimental effects of OPA on mortality risk are limited to excessive RAS above the recommended maximum level of 33% but instead may occur at lower levels as well. It should be noted that traditionally recommended maximum levels of relative workloads were not based on epidemiological evidence but rather on physiological measurements indicating change from aerobic to anaerobic metabolism. While recent epidemiological studies have shown that moderate and high levels of OPA are associated with an increased risk of CVD,[3] this study shows that such detrimental effects extend to CHD mortality and all-cause mortality outcomes and may occur already at levels of OPA that are below currently recommended maximum RAS levels. Additional epidemiological investigations with precise exposure assessments at work are needed to determine safe or potentially beneficial levels of OPA in terms of relative workload measures that take both individual worker fitness and type of activity into account.

Reductions of excessive relative aerobic workloads can in principal be achieved by three approaches, either alone or in combination: increase in aerobic fitness, increase in recovery time, and reduction of physical workload. Accordingly, some researchers have suggested interventions to increase cardiorespiratory fitness among workers to reduce CVD risks.[67] However, for aging workers and for workers with existing IHD or with exercise-limiting musculoskeletal disorders or other comorbidities, fitness training may not be feasible or insufficient to meet work demands. While increased LTPA may be beneficial, especially for persons with low levels of OPA, for persons with high levels of OPA, resulting fatigue may be a barrier to engage in LTPA, and LTPA may actually increase CHD risk,[64] although protective effects have also been reported.[65,66] A recent randomized workplace intervention trial among cleaners in Denmark showed that relatively few sessions of intensive aerobic exercise during paid worktime increased fitness and reduced relative workloads but also led to significant increases in both resting and 24-h ambulatory systolic blood pressure,[68,69] a key risk factor for CVD and mortality.

Primary prevention that is safe and not relying on individual workers' behavioral changes, especially among older workers with high OPA levels, may instead need to address the discrepancy of individual cardiorespiratory fitness and physical job demands by reduction of physical job demands, daily or weekly work hours, and increases of recovery time.[70,71] While automation has reduced physical workloads over the last decades for skilled workers in some industries (eg, motor vehicle production), jobs in other industries often demand higher workloads (eg, in the growing health care, hospitality, and retail sectors). In some sectors the heaviest work is performed by low wage immigrant workers who are underrepresented in national surveys and epidemiological studies (eg, custodial, construction, farm, and hotel and restaurant workers). General public health messages exclusively recommending increased physical activity may only be appropriate for the sedentary part of the working population and a subgroup of workers who participate in workplace health promotion programs. Those messages may not sufficiently address the still sizable working population performing heavy physical labor, the increasing proportion of aging workers with pre-existing chronic cardiovascular or musculoskeletal diseases or workers unlikely to receive an offer for or to participate in workplace health promotion programs. In the absence of more controlled community-based intervention trials, it is difficult to compare the effectiveness of different approaches for primary CVD prevention.

Following the precautionary principle in public health protection, the study findings may already have important implications for the practice of occupational and rehabilitative medicine even in the absence of respective intervention trials. Primary CVD prevention

efforts may benefit from a reduction of the energy demands in physically demanding jobs. Jobs in agriculture, forestry, commercial fishing, construction, manufacturing, warehousing, cleaning, or retail are at especially high risk for leading to high relative aerobic strain. Secondary and tertiary prevention efforts may be indicated for persons who do not have a sitting desk job. Occupational medicine and other occupational health professionals can assist in an individualized approach using inexpensive ambulatory heart rate monitoring during work hours to determine the ergonomic fit between individual aerobic capacity and workload. Specifically, RAS or oxygen uptake reserve should be routinely assessed in non-desk workplaces during placement of new employees as well as in the process of designing work modifications for employees returning to work after being diagnosed with CHD. Both bicycle ergometry and ambulatory ECG may be warranted for workers with CVD.[72]

Because it has been shown that percent oxygen uptake reserve is highly correlated with percent heart rate reserve (%HRR = (HRwork − HRrest)/(HRmax − HRrest) × 100%) across the aerobic fitness spectrum,[43,53] it is possible to estimate percent heart rate reserve (%HRR),[53] HR-estimated EE [HREEE], and percent oxygen uptake reserve using recently validated procedures[73] in combination with standard procedures estimating maximum heart HR based on resting HR and age.[74] It is no longer necessary to employ laboratory-based gas exchange analyses or bicycle ergometer tests to determine relevant relative EE measures of OPA.

It is best to use these relative measures of EE because they take individual differences of VO_2max into account. VO_2max has been found to differ markedly by gender, age, health status, and other factors.[75] Relative measures correlate better than absolute measures with actual cardiovascular workload, fatigue, heart rate elevations and related health consequences of aerobic strain at work as shown by others[30] and for the first time for progression of atherosclerosis,[28] AMI incidence,[29] and now both CHD and all-cause mortality in this study population.

Intervention research needs to investigate the effectiveness and efficiency of possible interventions such as fitness-inducing exercise, increase of recovery time, and reduction of work hours and/or physical job demands, especially in the growing vulnerable population of aging workers with pre-existing CVD.

5 | CONCLUSIONS

This study provides new evidence that elevated OPA in terms of relative aerobic workload (%VO_2max or %VO_2Res) predicts increased CHD and all-cause mortality in middle-aged working men, even at levels of relative aerobic workload that are below the recommended maximum. The findings further support the notion that inconsistencies in the literature on the cardiovascular health effects of OPA may be due to alternative choices of analytic strategies, exposure misclassification, health-based selection bias or healthy worker effect,[76] uncontrolled confounding,[77] and complex interactions between cardiovascular health status, cardiorespiratory fitness, and physical job demands. Worksite primary prevention of CVD and premature death requires approaches that take the individual worker CVD health status, aerobic capacity, and the energy demands of the job into account.

AUTHORS' CONTRIBUTIONS

Niklas Krause conceived this study, performed all analyses, and wrote the manuscript. Onyebuchi Arah reviewed statistical models and reviewed and edited the final manuscript draft. Jussi Kauhanen served as liaison with KIHD study data management at the University of Eastern Finland, provided access to data for this study, and reviewed the final manuscript.

ACKNOWLEDGMENTS

The authors thank Kimmo Ronkainen for managing and updating of underlying KIHD and national registry databases and provision of background information regarding respective study variables.

FUNDING

This research was partially funded by the Finnish Academy of Science through the University of Eastern Finland, and by the Center for Occupational and Environmental Health and the Southern California Education and Research Center at the University of California Los Angeles.

ETHICS APPROVAL AND INFORMED CONSENT

This secondary data analyses was exempt from human subjects institutional review. The original study was approved by the University of Eastern Finland and by the University of California.

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

ORCID

Niklas Krause http://orcid.org/0000-0002-4172-8386

REFERENCES

1. Li J, Siegrist J. Physical activity and risk of cardiovascular disease-a meta-analysis of prospective cohort studies. *Int J Environ Res Public Health*. 2012;9:391–407.
2. Krause N. Physical activity and cardiovascular mortality—disentangling the roles of work, fitness, and leisure. *Scand J Work Environ Health*. 2010;36:349–355.
3. Li J, Loerbroks A, Angerer P. Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? *Curr Opin Cardiol*. 2013;28:575–583.

4. Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med*. 2000;160:1621–1628.
5. Kannel WB, Belanger A, D'Agostino R, Israel I. Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham Study. *Am Heart J*. 1986;112:820–825.
6. Barengo NC, Hu G, Lakka TA, Pekkarinen H, Nissinen A, Tuomilehto J. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J*. 2004;25:2204–2211.
7. Autenrieth CS, Baumert J, Baumeister SE, et al. Association between domains of physical activity and all-cause, cardiovascular and cancer mortality. *Eur J Epidemiol*. 2011;26:91–99.
8. Menotti A, Puddu PE, Lanti M, Maiani G, Catasta G, Fidanza AA. Lifestyle habits and mortality from all and specific causes of death: 40-year follow-up in the Italian Rural Areas of the Seven Countries Study. *J Nutr Health Aging*. 2014;18:314–321.
9. Ferrario MM, Veronesi G, Chambless LE, et al. The contribution of major risk factors and job strain to occupational class differences in coronary heart disease incidence: the MONICA Brianza and PAMELA population-based cohorts. *J Occup Env Med*. 2011;68:717–722.
10. Franzon K, Zethelius B, Cederholm T, Kilander L. Modifiable midlife risk factors, independent aging, and survival in older men: report on long-term follow-up of the Uppsala Longitudinal Study of Adult Men cohort. *J Am Geriatric Soc*. 2015;63:877–885.
11. Johansson S, Rosengren A, Tsipogianni A, Ulvenstam G, Wiklund I, Wilhelmsen L. Physical inactivity as a risk factor for primary and secondary coronary events in Goteborg, Sweden. *Eur Heart J*. 1988;9:8–19.
12. Eaton CB, Medalie JH, Flocke SA, Zyzanski SJ, Yaari S, Goldbourt U. Self-reported physical activity predicts long-term coronary heart disease and all-cause mortalities. Twenty-one-year follow-up of the Israeli Ischemic Heart Disease Study. *Arch Fam Med*. 1995;4:323–329.
13. Besson H, Ekelund U, Brage S, et al. Relationship between subdomains of total physical activity and mortality. *Med Sci Sports Exerc*. 2008;40:1909–1915.
14. Johansson S, Rosengren A, Tsipogianni A, Ulvenstam G, Wiklund I, Wilhelmsen L. Physical inactivity as a risk factor for primary and secondary coronary events in Goteborg, Sweden. *Eur Heart J*. 1988;9:8–19.
15. Harari G, Green MS, Zelber-Sagi S. Combined association of occupational and leisure-time physical activity with all-cause and coronary heart disease mortality among a cohort of men followed-up for 22 years. *Occup Env Med*. 2015;72:617–624.
16. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. The interplay between physical activity at work and during leisure time-risk of ischemic heart disease and all-cause mortality in middle-aged Caucasian men. *Scand J Work Environ Health*. 2009;35:466–474.
17. Richard A, Martin B, Wanner M, Eichholzer M, Rohrmann S. Effects of leisure-time and occupational physical activity on total mortality risk in NHANES III according to sex, ethnicity, central obesity, and age. *J Phys Act Health*. 2015;12:184–192.
18. Kristal-Boneh E, Harari G, Melamed S, Froom P. Association of physical activity at work with mortality in Israeli industrial employees: the CORDIS study. *J Occup Environ Med*. 2000;42:127–135.
19. Stender M, Hense HW, Doring A, Keil U. Physical activity at work and cardiovascular disease risk: results from the MONICA Augsburg study. *Int J Epidemiol*. 1993;22:644–650.
20. Clays E, Lidegaard M, De Bacquer D, et al. The combined relationship of occupational and leisure-time physical activity with all-cause mortality among men, accounting for physical fitness. *Am J Epidemiol*. 2014;179:559–566.
21. Holme I, Helgeland A, Hjermann I, Leren P, Lund-Larsen PG. Physical activity at work and at leisure in relation to coronary risk factors and social class. A 4-year mortality follow-up. The Oslo study. *Acta Med Scand*. 1981;209:277–283.
22. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Physical demands at work, physical fitness, and 30-year ischaemic heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health*. 2010;36:357–365.
23. Haheim LL, Holme I, Hjermann I, Leren P. Risk factors of stroke incidence and mortality. A 12-year follow-up of the Oslo Study. *Stroke*. 1993;24:1484–1489.
24. Holtermann A, Burr H, Hansen JV, Krause N, Sogaard K, Mortensen OS. Occupational physical activity and mortality among Danish workers. *Int Arch Occup Environ Health*. 2012;85:305–310.
25. Moe B, Mork PJ, Holtermann A, Nilsen TI. Occupational physical activity, metabolic syndrome and risk of death from all causes and cardiovascular disease in the HUNT 2 cohort study. *Occup Environ Med*. 2013;70:86–90.
26. Petersen CB, Eriksen L, Tolstrup JS, Sogaard K, Gronbaek M, Holtermann A. Occupational heavy lifting and risk of ischemic heart disease and all-cause mortality. *BMC Public Health*. 2012;12:1070.
27. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Physical work demands and physical fitness in low social classes-30-year ischemic heart disease and all-cause mortality in the Copenhagen Male Study. *J Occup Environ Med*. 2011;53:1221–1227.
28. Krause N, Brand RJ, Kaplan GA, et al. Occupational physical activity, energy expenditure, and 11-year progression of carotid atherosclerosis. *Scand J Work Environ Health*. 2007;33:405–424.
29. Krause N, Brand RJ, Arah O, Kauhanen J. Ocupational physical activity and 20-year incidence of acute myocradial infarction: results from the Kuopio Ischemic Heart Disease Risk Factor Study. *Scand J Work Environ Health*. 2015;41:124–139.
30. Wu HC, Wang MJ. Determining the maximum acceptable work duration for high-intensity work. *Eur J Appl Physiol*. 2001;85:339–344.
31. Nelis M, Esko T, Mägi R, et al. Genetic structure of Europeans: a view from the North-East. *PLoS ONE*. 2009;4:e5472. https://doi.org/10.1371/journal.pone.0005472
32. Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Clin Res*. 1988;20:46–50.
33. Lakka TA, Laukkanen JA, Rauramaa R, et al. Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann Intern Med*. 2001;134:12–20.
34. Lynch J, Krause N, Kaplan GA, Tuomilehto J, Salonen JT. Workplace conditions, socioeconomic status, and the risk of mortality and acute myocardial infarction: the Kuopio Ischemic Heart Disease Risk Factor Study. *Am J Public Health*. 1997;87:617–622.
35. Rose GA, Blackburn H, Gillum RF. 1982. *Cardiovascular survey methods*. Geneva: World Health Organization.
36. Lakka TA, Salonen JT. Intra-person variability of various physical activity assessments in the kuopio ischaemic heart disease risk factor study. *Int J Epidemiol*. 1992;21:467–472.
37. Manninen P, Heliövaara M, Riihimäki H, Suomaiainen O. Physical workload and the risk of severe knee osteoarthritis. *Scand J Work Environ Health*. 2002;28:25–32.
38. Salonen JT, Lakka TA. Assessment of physical activity in population studies—validity and consistency of the methods in the Kuopio ischemic heart disease risk factor study. *Scand J Sports Sci*. 1987;9:89–95.
39. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25:71–80.
40. Lakka T, Venäläinen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med*. 1994;330:1549–1554.

41. Karpansalo M, Lakka T, Manninen P, Kauhanen J, Rauramaa R, Salonen JT. Cardiorespiratory fitness and risk of disability pension: a prospective population-based study in Finnish men. *Occup Environ Med*. 2003;60:765–769.
42. Jorgensen K. Permissible loads based on energy expenditure measurements. *Ergonomics*. 1985;28:365–369.
43. Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc*. 2001;33: S364–S369. discussion S419-20.
44. Astrand P-O, Rodahl K. *Textbook of Work Physiology, Physiological Bases of Exercise*. New York: McGraw-Hill Book Company;1986:756.
45. Lynch JW, Kaplan GA, Cohen RD. Tuomilehto J, Salonen JT. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? *Am J Epidemiol*. 1996;144:934–942.
46. Kauhanen J, Kaplan GA, Goldberg DE, Salonen R, Salonen JT. Pattern of alcohol drinking and progression of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1999;19:3001–3006.
47. Taylor HL, Jacobs DRJ, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis*. 1978;31:741–755.
48. Cox DR, Oakes D. *Analysis of Survival Data. Monographs on Statistics and Applied Probability*. London New York: Chapman & Hall; 1984: xiii;201.
49. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008:x;758.
50. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. *Am J Epidemiol*. 2009;169:756–760.
51. Kleinbaum DG. 2011. *Survival Analysis: A Self-Learning Text*. 3rd ed. New York: Springer.
52. Byrne NM, Hills AP, Hunter GR, Weinsier RL, Schutz Y. Metabolic equivalent: one size does not fit all. *J Appl Physiol*. 2005;99:1112–1119.
53. Swain DP, Leutholtz BC. Heart rate reserve is equivalent to %VO2 reserve, not to %VO2max. *Med Sci Sports Exerc*. 1997;29:410–414.
54. Aminoff T, Smolander J, Korhonen O, Louhevaara V. Prediction of acceptable physical work loads based on responses to prolonged arm and leg exercise. *Ergonomics*. 1998;41:109–120.
55. Kuh D, Ben-Shlomo Y. 1997. *A Life Course Approach to Chronic Disease Epidemiology*. New York: Oxford University Press.
56. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;150:341–353.
57. Glagov S, Giddens D, Ku D. Hemodynamics and atherosclerosis: insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med*. 1988;112:1018–1031.
58. Wang A, Arah O, Kauhanen J, Krause N. Effects of leisure-time and occupational physical activities on 20-year incidence of acute myocradial infarction: mediation and interaction. *Scand J Work Environ Health*. 2016;42:423–434.
59. Krause N, Brand RJ, Kaplan GA, Malla S, Salonen JT. *Working Posture and 11-year Progression of Carotid Atherosclerosis*. In *28th International Congress on Occupational Health*. 2006. Milan, Italy.
60. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Fitness, work and leisure-time physical activity, and ischaemic heart disease and all-cause mortality among men with pre-existing cardiovascular disease. *Scand J Work Environ Health*. 2010;36:366–372.
61. Holtermann A, Hansen JV, Burr H, Sogaard K, Sjogaard G. The health paradox of occupational and leisure-time physical activity. *Br J Sports Med*. 2012;46:291–295.
62. Committee PAGA, Physical Activity Guidelines for Advisory Committee. Wshington, DC: United States Department of Health and Human Services;2008.
63. Hu G, Jousilahti P, Borodulin K, et al. Occupational, commuting and leisure-time physical activity in relation to coronary heart disease among middle-aged Finnish men and women. *Atherosclerosis*. 2007;20:1242–1250.
64. Clays E, De Bacquer D, Janssens H, et al. The association between leisure time physical activity and coronary heart disease among men with different physical work demands: a prospective cohort study. *Eur J Epidemiol*. 2013;28:241–247.
65. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. The interplay between physical activity at work and during leisure time—risk of ischemic heart disease and all-cause mortality in middle-aged Caucasian men. *Scand J Work Environ Health*. 2009;35:466–474.
66. Holtermann A, Marott JL, Gyntelberg F, et al. Occupational and leisure time physical activity: risk of all-cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study. *BMJ Open*. 2012;2:e00556.
67. Korshøy M, Krustrup P, Jørgensen MB, et al. Cardiorespiratory fitness, cardiovascular workload and risk factors among cleaners; a cluster roandomized workstie intervention. *BMC Pbulic Health*. 2012;12:645–654.
68. Korshøj M, Krause N, Clays E, Søgaard K, Krustrup P, Holtermann A. Does aerobic exercise increase 24-hour ambulatory blood pressure among workers with high occupational physical activity?-A RCT. *Am J Hypertension*. 2017;30:444–450.
69. Korshøj M, Lidegaard M, Skotte J, et al. Does arobic exercise improve or impair cardiorespiratory fitness and health among workers with high occupational physical activity? A worksite cluster randomized controlled trial. *Scand J Work Environ Health*. 2015;41:140–152.
70. Krause N, Brand R, Kauhanen J, et al. Work time and 11-year progression of carotid atherosclerosis in middle-aged Finnish men. *Prev Chron Dis*. 2009;6:A13, 1–A13,20.
71. Wang A, Arah O, Kauhanen J, Krause N. Work Schedules and 11-year progression of carotid atherosclerosis in Finnish men. *Am J Ind Med*. 2014;58:1–13.
72. Haskell WL, Brachfeld N, Bruce RA, et al. Task Force II: determination of occupational working capacity in patients with ischemic heart disease. *J Am Coll Cardiol*. 1989;14:1025–1034.
73. Garet M, Boudet G, Montaurier C, Vermorel M, Coudert J, Chamoux A. Estimating relative physical workload using heart rate monitoring: a validation by whole-body indirect calorimetry. *Eur J Appl Physiol*. 2005;94:46–53.
74. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann. Med Exp Biol Fenn*. 1957;35:307–315.
75. Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6–75 years: a review. *Aviat Space Environ Med*. 1990;61:3–11.
76. Thompson CA, Arah OA. Selection bias modeling using observed data augmented with imputed record-level probabilities. *Ann Epidemiol*. 2014;24:747–753.
77. Arah OA. Bias analysis for uncontrolled confounding in the health sciences. *Annu Rev Public Health*. 2017;38:23–38.

How to cite this article: Krause N, Arah OA, Kauhanen J. Physical activity and 22-year all-cause and coronary heart disease mortality. *Am J Ind Med*. 2017;1–15. https://doi.org/10.1002/ajim.22756