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Occupational physical activity predicts baseline and 8-year progression of carotid atherosclerosis among women

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Abstract

Introduction: Recent reviews link higher levels of occupational physical activity (OPA) to cardiovascular disease (CVD). However, the evidence for women is inconsistent and studies of activity-limiting symptomatic CVD are prone to healthy worker survivor effect. To address these limitations, this study investigated OPA effects on asymptomatic carotid artery intima–media thickness (IMT) among women.

Methods: Participants include 905 women from the population-based Kuopio Ischemic Heart Disease Risk Factor Study with baseline (1998–2001) data on self-reported OPA and sonographic measurement of IMT. Linear mixed models with adjustment for 15 potential confounders estimated and compared mean baseline IMT and 8-year IMT progression for five levels of self-reported OPA. Analyses stratified by cardiovascular health and retirement status were planned because strong interactions between preexisting CVD and OPA intensity have previously been reported.

Results: Light standing work, moderately heavy active work, and heavy or very heavy physical work were all consistently associated with greater baseline IMT and 8-year IMT progression than light sitting work. The greatest baseline IMT was observed for heavy or very heavy physical work (1.21 mm), and the greatest 8-year IMT progression for light standing work and moderately heavy active work (both 0.13 mm), 30% above sitting work (0.10 mm). Stratified analyses showed that these differences were driven by much stronger OPA effects among women with baseline carotid artery stenosis. Retired women experienced slower IMT progression than those working at baseline.

Conclusions: Higher levels of OPA predict higher baseline IMT and 8-year IMT progression, especially among women with baseline stenosis.

KEYWORDS

atherosclerosis, cardiovascular diseases, cardiovascular mortality, epidemiology, occupational health and safety, physical strain at work, population-based, prevention of cardiovascular disease, prospective study, strenuousness of physical work, women, work environment

1 | INTRODUCTION

Recent studies, primarily among men, linked prolonged standing and high levels of occupational physical activity (OPA) with elevated risks of cardiovascular diseases (CVD)[1–3] and mortality.[4–6] Previous studies among women report positive,[2,7] no,[8] or negative associations.[9] One longevity study reported inconsistent results across sexes: while longevity decreased with increased OPA in both sexes, this effect was reversed among men after adjustment for education, income, ethnicity, smoking, and cardiovascular health. No such reversal was observed for women, instead the detrimental effects of high OPA increased after confounder adjustment.[10] In general, OPA levels are higher for men, and sex segregation appears in jobs with high OPA.[11] Even within the same occupational title, women may experience lower levels of OPA than men.[12] Due to these exposure differences across sex, results from male or mixed populations may not apply to women. Moreover, established sex-differences in age at first CVD diagnosis[13] potentially underestimate female risk in studies with short follow-up. High levels of standing work and OPA intensity predict accelerated progression of 4- and 11-year intima–media thickness (IMT) among men in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), especially among those with carotid stenosis or ischemic heart disease (IHD).[14,15] These findings await replication among women.

IMT is an established marker of atherosclerosis,[16] and risk factor for CVD.[17,18] IMT is measured noninvasively and even large stenotic carotid IMT increases usually remain asymptomatic. Therefore, studies of IMT are less prone to selection bias, than studies of symptomatic CVD causing activity-related pain (e.g., angina pectoris) that triggers selection out of physically demanding jobs, leading to underestimation of adverse health effects of high OPA (healthy worker survivor effect).[19] Prolonged periods of standing work or high OPA lead to increases of concurrent working and 24-hour heart rates (HR).[20] OPA is also positively associated with ambulatory blood pressure (BP) during work, leisure, and sleep.[21] Resting and ambulatory 24-hour HR and BP are independent risk factors for CVD[20] via their hemodynamic forces that lead to adverse changes in the arterial wall giving rise to inflammatory processes manifesting as progression in IMT and arteriosclerotic changes.[22] Considering previously mentioned sex-differences, this study aimed to investigate a hypothesized positive relation between OPA and IMT progression, especially among women with carotid stenosis or IHD.[14,15]

2 | METHODS

2.1 | Study design and population

This population-based prospective cohort study of Finnish women, aged 62.2 years old (SD 7.0) at baseline, included questionnaires (self-administered), blood samples, anthropometric, IMT, and resting BP measures, performed during baseline (1998–2001), and follow-up (2005–2008).[23] Inclusion criteria were actively working at baseline or within the last year before baseline, answering the OPA exposure question and a baseline IMT measure This analysis was approved by the University of Eastern Finland and the regional data protection authority for Zealand, Denmark (REG-082-2020). The protocol for the collection of data was approved by the Research Ethics Committee of the University of Kuopio, Finland.[23]

2.2 | Exposure assessment

OPA was assessed by one question (including additional text): “Estimate how much you move at your work and how physically disturbing your present/last work is/was?” with six response categories*: light sitting work (mainly beside a table or behind a similar setting); other sitting work (mainly seated, but I handle large quantities of light materials); light standing work (mainly stand up work free of heavy work motions); moderately heavy active work (mainly moving labor, where I carry many light materials or average heavy units or walk many stairs, or walk long distances);*

heavy physical work (mainly a stand up job, with regular handling of average heavy units, or occasional lifting of heavy units, dig, etc., *but in between sit or stand); very heavy physical work (mainly continuous handling of heavy labor functions)*. As only 51 women reported "very heavy physical work", this category was collapsed with "heavy physical work" for analyses.

2.3 | Outcome assessment

Carotid artery IMT, a surrogate measure of atherosclerosis,[24] was measured at baseline and 8-year follow-up, at approximately 100 sites along a 1.0–1.5 cm section of both the left and right common carotid artery, below the carotid bulb, using high-resolution B-mode ultrasonography.[24] The mean of the maximum IMT values separately determined in the right and left artery was used for analyses.

2.4 | Assessment of potential confounders

The same covariates as described previously among KIHD men[15] were evaluated as potential confounders: age; biological: blood glucose, fibrinogen, HDL and LDL cholesterol, body mass index (BMI), systolic BP (SBP), use of antihypertensive, and lipid-lowering drugs; behavioral: alcohol, smoking, and conditioning leisure time physical activity (LTPA); occupational: mental strain at work, coworker and supervisor support; socioeconomic: personal income.

2.5 | Assessment of potential effect modifiers

Baseline cardiovascular health and retirement status were assessed as follows:

Stenosis: at least 20% lumen reduction in one or both carotid arteries, classified by a physician blinded to other measures.[24]

IHD: history of myocardial infarction or angina pectoris, use of anti-angina medication, or positive findings of angina according to the London School of Hygiene cardiovascular questionnaire.[25]

Hypertension: resting BP ≥140/90 mmHg and/or use of antihypertensive medication, and/or self-reported physician diagnosis.

Retirement status was assessed by survey and dichotomized into non-retiree (*employed full-time; less than 5 days/week; part-time; under forced vacation—temporarily laid off; unemployed; partly retired*) and retiree (*early retired; disability retired or retired; retired on a pension (without disability); for some other reason not working*).

2.6 | Statistical analyses

Study population characteristics are described by mean, standard deviation (SD), and range for continuous variables and by frequencies and percentages (%) for categorical variables. Multivariable mixed effect linear regression models with repeat observations of IMT, random intercept, and time-slope were used to jointly estimate and compare mean baseline IMT and 8-year IMT for each OPA category.

To ensure comparability with previously reported effects of working posture[14] and OPA intensity on progression of IMT among KIHD men,[15] the same confounders were forced into incrementally adjusted regression models. Additional factors known to be associated with both OPA and IMT[26] (education, civil status, menopause, diabetes, shift work, and weekly work hours) were individually assessed for their impact on OPA effect estimates in regression models fully adjusted for the above variables. None of these changed the OPA effect on IMT by ≥±0.001 mm and were therefore not included in the analyses.

Final analyses were incrementally adjusted for age (Model 1); age and biological factors: blood glucose, fibrinogen, HDL and LDL cholesterol, BMI, SBP, use of antihypertensive, and lipid-lowering drugs (Model 2); additional adjustment for behavioral factors: alcohol, smoking, and LTPA (Model 3); occupational factors: mental strain at work, supervisor, and coworker support at work (Model 4); and socioeconomic factors: personal income (Model 5). Because of missing values in several possibly confounding baseline variables (blood glucose $n=1$, fibrinogen $n=7$, LDL cholesterol $n=4$, HDL cholesterol $n=3$, mental strain at work $n=211$, social support at work $n=182$, and personal income $n=76$) the results of the above analyses were based on combining 20 sets of results—using Rubin's rule—each from a set of data where the missing values were stochastically imputed.[27] These imputations were performed using the method of chained equations using, beyond the above mentioned variables featuring missing data, baseline age, BMI, personal and partner's educational level, personal and partner's retirement status, civil status, shift work, financial security, self-reported health, IHD, stenosis, hypertension, and IMT.

Modifying effects of baseline cardiovascular health (IHD, stenosis, and hypertension) and retirement status were examined in models using interaction product terms with OPA. Analyses stratified by IHD and stenosis were planned to address previously reported strong interactions with prolonged standing at work and OPA intensity.[14,15] In addition, potential modifying effects of hypertension were explored to address proposed limited or altered physiologic responses to LTPA among individuals with hypertension or using antihypertensive medication.[28] Analyses stratified by hypertension included adjustment for SBP and use of antihypertensive medication to account for assumed differential OPA effects on IMT across different initial levels of SBP within each subgroup. Finally, as it is unknown, if and how long OPA effects persist after retirement, or if they are reversible, a sensitivity analysis stratified by retirement status addressed this in two differently defined potential OPA effect washout periods.

All statistical analyses were performed with statistical software SAS, version 9.4 (SAS Institute).

3 | RESULTS

Of 920 KIHD women, 15 were excluded due to missing information on OPA ($n=14$) or IMT ($n=1$). Of the remaining 905 women, 619 participated in repeated ultrasound examinations after an average of 7.8 (SD 0.8) years. Of the 286 not participating in the repeated ultrasound examination 17 died, 65 were severely ill, 134 did not wish to participate in the follow-up, 37 could not be reached, and 33 were not eligible for follow-up due to missing data (Figure 1).

3.1 | Characteristics of the study population

Participants were 53–72 years old at baseline and 61–80 years old at follow-up. At baseline, 36% had stenosis, 27% had IHD, 68% were hypertensive, and 64% were retired (Table 1).

3.2 | Effects of occupational physical activity on baseline IMT and 8-year IMT change

Fully adjusted baseline IMT and 8-year IMT progression were lowest for light or other sitting work and highest for light standing, moderately heavy active, or heavy or very heavy physical work (Figure 2). Specifically, fully adjusted 8-year IMT changes associated with light standing work (0.130 mm, 95% CI 0.093–0.166) and moderately heavy active work (0.127 mm, 95% CI 0.104–0.150) were larger (22% and 19%) than changes associated with light sitting work (0.107 mm, 95% CI 0.070–0.144) (Table S2). Crude estimates of baseline and 8-year IMT were slightly lower than adjusted estimates indicating little and only negative confounding by traditional CVD risk factors leading if at all to slight *under*estimation of effects in insufficiently adjusted models Tables S1 and S2.

3.3 | Effects of occupational physical activity on baseline IMT and 8-year IMT change by baseline cardiovascular health and retirement status

Interaction terms in fully adjusted models indicate that OPA effects on both baseline and 8-year IMT change were likely modified by baseline stenosis ($p<0.01$) and IHD ($p=0.13$), but neither retirement status ($p=0.26$) nor hypertension ($p=0.73$). The actual presence, magnitude, and direction of effect modification was assessed by stratified analyses (Figure 3; Tables S3–S5).

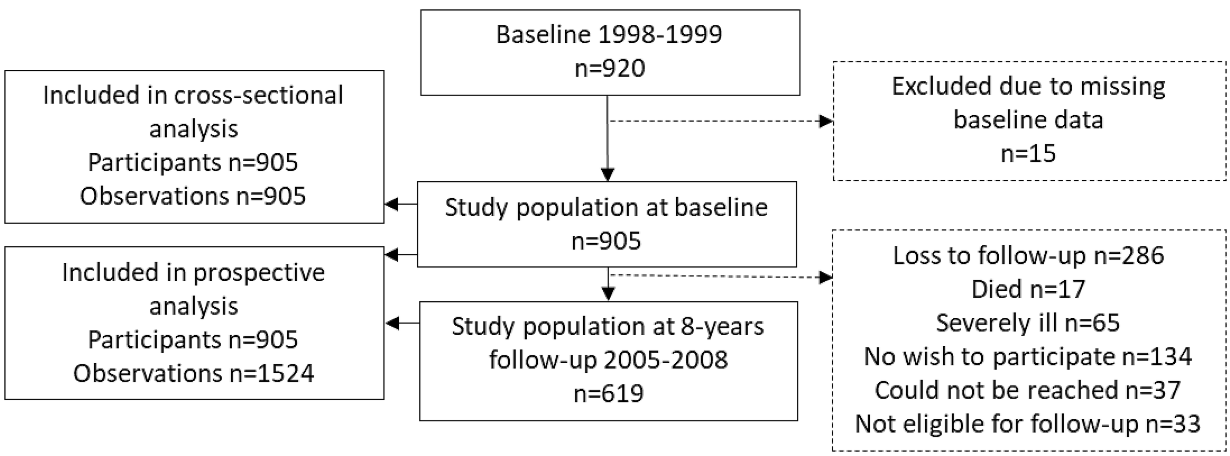


FIGURE 1 Flow of the participants at the two time points for data collection.

3.4 | Effect modification by stenosis

Compared to women without stenosis, OPA effects on baseline IMT among workers with stenosis were substantially (0.155–0.225 mm) stronger and increased stepwise from light sitting (1.260 mm) and other sitting (1.269 mm) to light standing (1.308 mm), moderately heavy active (1.348 mm) and heavy or very heavy physical work (1.319 mm) (Figure 3A; Table S3). 8-year IMT progression was smaller among workers with stenosis, in this group changes associated with light standing (0.124 mm, 95% CI 0.055–0.192) and moderately heavy active work (0.096 mm, 95% CI 0.043–0.149) were 254% and 174% greater than the change in light sitting work (0.035 mm, 95% CI −0.048 to 0.118) (Figure 3A; Table S4). The estimated difference in 8-year IMT progression between light sitting and light standing work was 89 times greater with stenosis (0.089 mm) compared to no stenosis (0.001 mm); the respective differences between light sitting and moderately heavy active or heavy or very heavy physical work were about six times greater with stenosis versus no stenosis (0.011 vs. 0.061 and −0.005 vs. 0.031 mm) (Figure 3A; Table S4).

3.5 | Effect modification by ischemic heart disease

Compared to workers without IHD, OPA effects on baseline IMT among workers with IHD were stronger (0.024–0.079 mm) and increased stepwise from light sitting (1.184 mm) to other sitting (1.219 mm), light standing (1.258 mm), and moderately heavy active (1.256 mm), except for heavy or very heavy physical work (1.190 mm) (Figure 3B; Table S3). OPA effects on 8-year IMT change were about 0.02 mm stronger for light sitting and moderately heavy work among workers with IHD, while the differences between light sitting work and higher OPA categories varied in direction (Figure 3B; Table S4).

3.6 | Effect modification by hypertension

Compared to normotensive workers, OPA effects on baseline IMT among workers with hypertension were less strong (0.011–0.040 mm) for sitting, but stronger (0.026–0.076 mm) for light standing and heavier OPA categories and increased stepwise from light sitting (1.183 mm) and other sitting (1.185 mm), to light standing (1.242 mm), and moderately heavy active (1.221 mm) and heavy or very heavy physical work (1.238 mm) (Figure 3C; Table S3). Eight-year IMT changes across hypertension status show no consistent pattern and differences between light sitting work and higher levels of OPA appear to be greater among normotensives and declining with increasing OPA levels. In contrast, normotensives, showed IMT progressions especially among those reporting heavy or very heavy physical work (0.183 mm) or light standing work (0.147 mm), corresponding to 169% and 116% greater IMT changes than associated with light sitting work (0.068 mm) (Figure 3C; Table S4). The estimated 8-year IMT change differences between light sitting and the remaining OPA categories were positive for normotensives but negative for hypertensives (Figure 3C; Table S4).

3.7 | Effect modification by retirement

Retirees and non-retirees showed similar baseline IMT levels, except for retirees exposed to light standing work (1.239 vs. 1.148 mm) and non-retirees exposed to heavy or very heavy physical work (1.252 vs. 1.195 mm) (Figure 3D; Table S5). Retirees reporting moderately heavy active (0.125 mm, 95% CI 0.097–0.153) or light standing work (0.116 mm, 95% CI 0.069–0.164) showed the greatest IMT progressions, corresponding to 33%–23% greater progression than light sitting work (0.094 mm, 95% CI 0.044–0.145). Among non-retirees, light standing (0.148 mm, 95% CI 0.090–0.205) or moderately heavy active work (0.137 mm, 95% CI 0.096–0.178) showed the greatest 8-year IMT changes, corresponding to a 12%–21% greater progression than light sitting work (0.122 mm, 95% CI 0.067–0.176) (Figure 3D, Table S5).

An exploratory analysis including only those not being retired at both baseline and 8-year follow-up ($n=64$) showed lower baseline IMT values across all OPA categories (Table S5) compared to the entire population (model 1, Table S1). Eight-year IMT progression was overall larger in this subgroup, compared with the entire population (Model 1, Table S2), or non-retirees at baseline. Those exposed to moderately heavy active work progressed faster than those exposed to light sitting work, results for other comparisons were relatively minor (see Table S5).

4 | DISCUSSION

4.1 | Summary of findings

OPA was positively associated with both baseline IMT and IMT progression. Specifically, light standing, moderately heavy active, and heavy or very heavy physical work had the strongest effects on baseline IMT and, with the exception of heavy or very heavy physical work, also on 8-year IMT progression.

TABLE 1 Characteristics of the study sample by levels of occupational physical activity.

	Light sitting work (*n* = 124)		Other sitting work (*n* = 126)		Light standing work (*n* = 134)	
	Mean (SD)	***n* [%]**	**Mean (SD)**	***n* [%]**	**Mean (SD)**	***n* [%]**
Age (years)	62.2 (7.0)		63.0 (6.4)		63.8 (6.5)	
53–56		40 [32.0]		28 [22.2]		28 [20.9]
59–62		31 [24.8]		37 [29.4]		29 [21.6]
64–68		22 [17.6]		32 [25.4]		39 [29.1]
71–73		32 [25.6]		29 [23.0]		38 [28.4]
Biological factors						
Blood glucose (mmol/l)	5.0 (1.1)		4.9 (0.5)		5.1 (1.3)	
Plasma fibrinogen (g/l)	3.1 (0.6)		3.2 (0.6)		3.2 (0.7)	
LDL cholesterol (mmol/l)	3.7 (1.0)		3.8 (1.1)		3.6 (0.9)	
HDL cholesterol (mmol/l)	1.4 (0.3)		1.3 (0.3)		1.4 (0.3)	
Body mass index (kg/m^2)	27.3 (5.2)		27.7 (4.7)		27.7 (5.2)	
Body mass index ≥ 30 kg/m^2		32 [25.6]		39 [31.0]		37 [27.6]
Systolic blood pressure (mmHg)	135.8 (16.6)		136.7 (15.3)		138.4 (18.1)	
Systolic blood pressure ≥ 140 mmHg		48 [38.4]		50 [39.7]		62 [46.3]
Using antihypertensive drugs		41 [32.8]		57 [45.2]		56 [41.8]
Using lipid-lowering drugs		6 [4.8]		5 [4.0]		4 [3.0]
Behavioral factors						
Alcohol consumption (g/week)	27.8 (47.2)		21.5 (31.1)		26.8 (51.5)	
Smoking						
Currently smoking		13 [10.4]		15 [11.9]		13 [9.7]
Former smoker		34 [27.2]		27 [21.4]		18 [13.4]
Never smoked		78 [62.4]		84 [66.7]		103 [76.9]
Yearly hours of conditioning LTPA (with average intensity 6 METS) (hours/year)	200.2 (282.9)		170.5 (151.5)		166.5 (155.0)	
Psychoscial job factors						
Mental strain at work (the higher the more strain)	10.6 (5.8)		12.4 (6.1)		10.0 (5.5)	
Social support at work (the higher the more support)	7.1 (2.6)		7.4 (2.6)		7.4 (2.5)	
Socioeconomic factors						
Personal income (in 1000 Finnish Marks)	100.7 (492.0)		935.7 (544.7)		982.6 (514.4)	
Effect modifiers						
Carotid artery stenosis		38 [30.7]		37 [29.4]		65 [48.5]
Ischemic heart disease		27 [21.6]		37 [29.4]		30 [22.4]
Hypertension		77 [61.6]		87 [69.1]		88 [65.7]
Retired		58 [72.5]		58 [65.2]		58 [59.2]

Moderately heavy active work ($n = 318$)		Heavy or very heavy physical work ($n = 203$)		All participants ($n = 905$)	
Mean (SD)	*n* [%]	Mean (SD)	*n* [%]	Mean (SD)	*n* [%]
63.3 (6.4)		63.2 (6.5)		63.6 (6.5)	
	72 [22.6]		46 [22.7]		214 [23.6]
	77 [24.2]		55 [27.1]		229 [25.3]
	92 [28.9]		53 [26.1]		238 [26.3]
	77 [24.2]		49 [24.1]		225 [24.8]
5.2 (1.3)		5.1 (1.0)		5.1 (1.1)	
3.2 (0.6)		3.3 (0.5)		3.2 (0.6)	
3.7 (0.9)		3.8 (0.9)		3.7 (0.9)	
1.3 (0.3)		1.3 (0.3)		1.4 (0.3)	
28.5 (4.9)		29.6 (5.3)		28.4 (5.1)	
	100 [31.5]		90 [44.3]		298 [32.9]
137.2 (17.2)		138.3 (18.4)		137.4 (17.3)	
	122 [38.4]		79 [38.9]		361 [39.9]
	143 [45.0]		100 [49.3]		397 [43.8]
	16 [5.0]		14 [6.9]		45 [5.0]
13.8 (29.6)		14.4 (32.8)		18.9 (37.6)	
	21 [6.7]		23 [11.3]		85 [9.4]
	46 [14.6]		18 [8.9]		143 [15.8]
	248 [78.7]		162 [79.8]		675 [74.8]
181.5 (180.7)		186.1 (199.8)		181.4 (195.3)	
13.0 (6.6)		13.8 (7.2)		12.2 (6.5)	
7.2 (2.3)		6.6 (2.8)		7.2 (2.6)	
740.6 (371.4)		618.4 (482.4)		814.1 (486.4)	
	106 [33.4]		78 [38.4]		324 [35.8]
	83 [26.1]		72 [35.5]		249 [27.5]
	212 [66.7]		145 [71.4]		609 [67.2]
	151 [62.1]		110 [63.2]		435 [63.6]

(Continues)

TABLE 1 (Continued)

	Light sitting work ($n=124$)		Other sitting work ($n=126$)		Light standing work ($n=134$)	
	Mean (SD)	n [%]	Mean (SD)	n [%]	Mean (SD)	n [%]
Additional factors						
Educational level						
Part of elementary school		0		5 [4.0]		7 [5.2]
Elementary school and/ or part of junior high		15 [12.0]		20 [15.9]		38 [28.4]
Elementary school and vocational school		33 [26.4]		40 [31.8]		37 [27.6]
Junior high and/or senior high		18 [14.4]		14 [11.1]		2 [1.5]
Junior high and vocational school		29 [23.2]		26 [20.6]		17 [12.7]
Senior high graduate		2 [1.6]		3 [2.4]		1 [0.8]
Senior high and nonacademic degree		15 [12.0]		9 [7.1]		14 [10.5]
Academic degree		13 [10.4]		9 [7.1]		18 [13.4]
Weekly work hours	37.8 (7.7)		37.9 (7.3)		38.3 (11.2)	
Premenopause		6 [4.8]		2 [1.6]		4 [3.0]
Menopause		47 [37.6]		61 [48.4]		74 [55.2]
Menopause with hormone treatment		72 [57.6]		63 [50.0]		56 [41.8]
Outcomes						
Intima–media thickness (mm) at baseline	1.1 (0.2)		1.2 (0.3)		1.2 (0.3)	
Intima–media thickness (mm) at follow-up	1.2 (0.2)		1.2 (0.2)		1.3 (0.3)	
Observed 8-year change in intima–media thickness from baseline to follow-up (mm)	0.1 (0.2)		0.1 (0.2)		0.1 (0.2)	
Follow-up time (years)	7.8 (0.8)		7.9 (0.7)		7.9 (0.8)	
Drop-outs during follow-up time (number of participants)		37 [29.8]		33 [26.2]		46 [34.3]

Note: Kuopio Ischemic Heart Disease Risk Factor Study, 1998–2008 ($n=905$).

Stratified analyses were performed to identify possible high-risk worker populations, and to generate empirical data that will be needed for the development of future individualized physical activity guidelines considering those with preexisting CVD. Effects of higher OPA categories were consistently stronger among workers with stenosis, IHD, or hypertension for baseline IMT, but varied for 8-year IMT progression among those with IHD or hypertension. Retirees had slower progression of IMT compared to non-retirees.

4.2 | Magnitude, significance and precision of observed OPA effects

Average baseline IMT was 1.16 mm (SD 0.27 mm) and the minimum 0.64 mm. Eight-year IMT changes averaged 0.11 mm, and differences between OPA categories ranged between 0.02 and 0.09 mm. Absolute differences of ≥0.01 mm are biological relevant due to the known cross-sectional association with an 11% increased coronary heart disease (CHD) risk in men[24] and 0.2 mm

Moderately heavy active work (*n* = 318)		Heavy or very heavy physical work (*n* = 203)		All participants (*n* = 905)	
Mean (SD)	*n* [%]	Mean (SD)	*n* [%]	Mean (SD)	*n* [%]
	16 [5.0]		40 [19.7]		68 [7.5]
	124 [39.0]		79 [38.9]		276 [30.5]
	133 [41.8]		71 [35.0]		314 [34.7]
	6 [1.9]		7 [3.5]		47 [5.2]
	27 [8.5]		6 [3.0]		105 [11.6]
	1 [0.3]		0		7 [0.8]
	7 [2.2]		0		45 [5.0]
	4 [1.3]		0		44 [4.9]
43.6 (13.4)		50.4 (19.4)		42.8 (14.3)	
	14 [4.4]		15 [7.4]		41 [4.5]
	184 [57.9]		119 [58.6]		485 [53.5]
	120 [37.7]		69 [34.0]		380 [41.9]
1.2 (0.3)		1.2 (0.4)		1.2 (0.3)	
1.3 (0.3)		1.3 (0.2)		1.3 (0.3)	
0.1 (0.2)		0.1 (0.2)		0.1 (0.3)	
7.9 (0.7)		7.7 (0.6)		7.8 (0.7)	
	96 [30.2]		74 [36.5]		286 [31.6]

prospectively increased risk for CHD (24% men, 42% women) and stroke (28% women).[29,30] Thus, the majority of the reported 8-year IMT progressions and differences between OPA categories are considered of clinical, occupational, and public health relevance. Based on this effect estimation, spread of confidence intervals across zero values, and consistency of observations, these study results indicate that light standing work and higher levels of OPA are positively—and stronger than sitting work—associated with both baseline IMT and IMT progression, especially in women with baseline stenosis.

4.3 | Comparison with other studies

The ARIC study investigated OPA effects on IMT among women without CVD, and found a negative cross-sectional association; however, women with CVD were excluded from that study.[31] In contrast, occupational standing

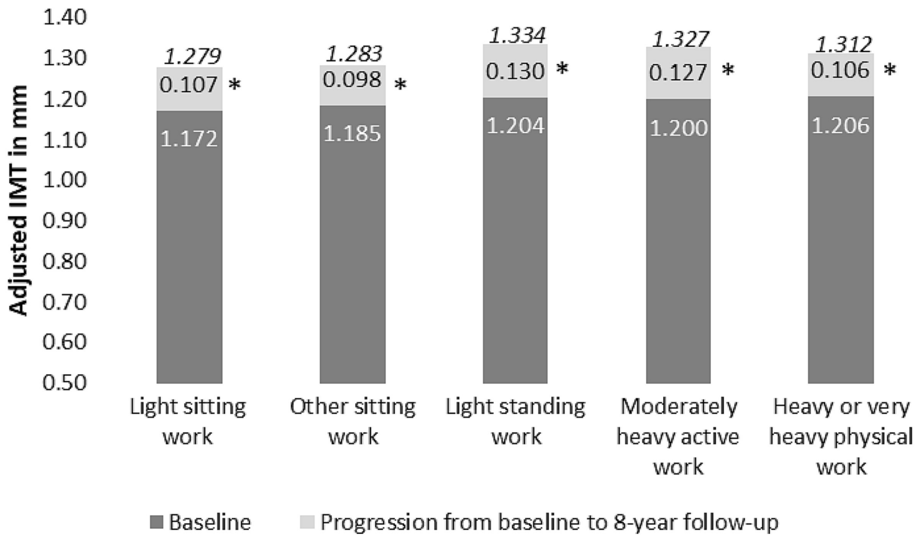
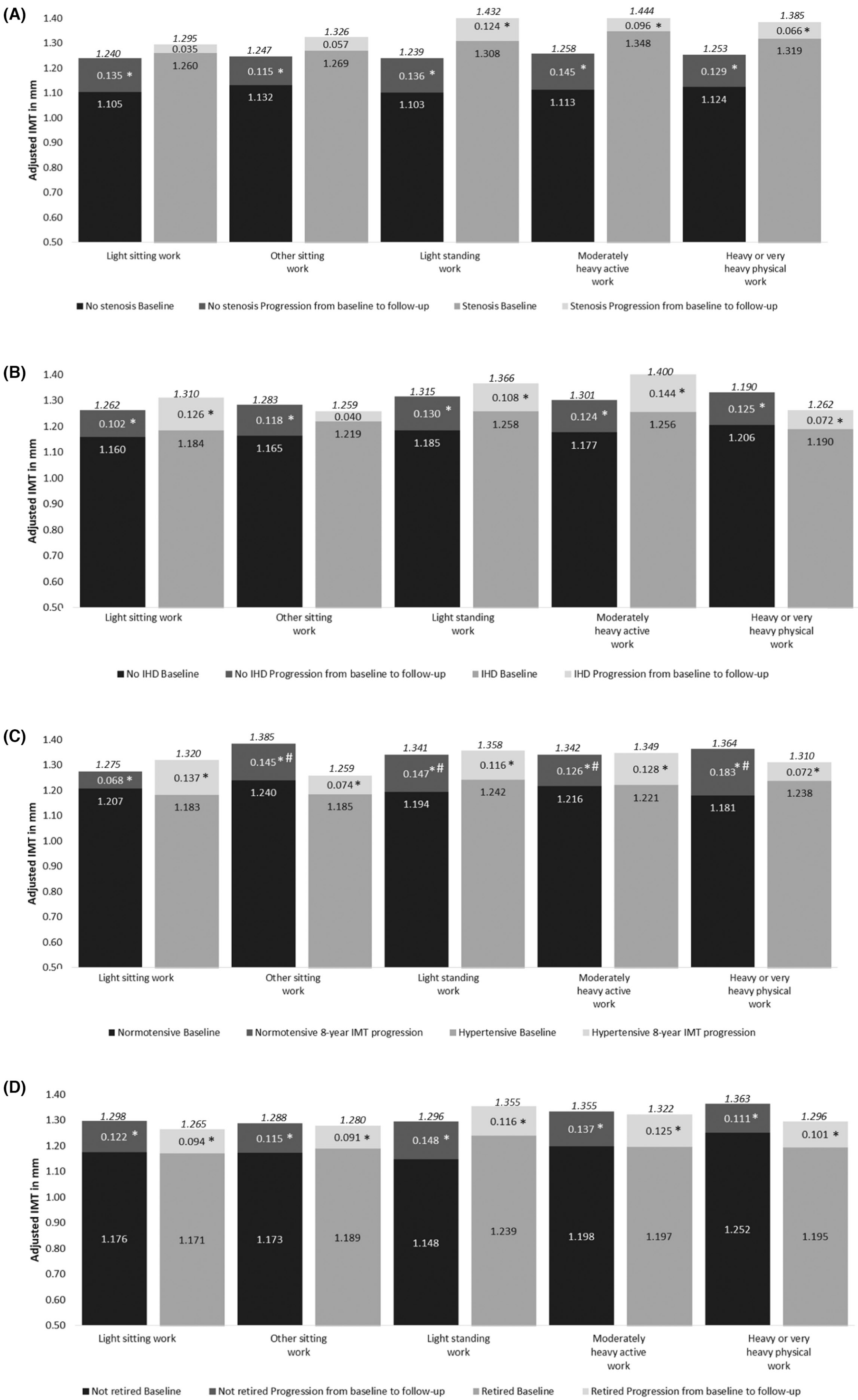


FIGURE 2 Estimated baseline intima–media thickness (IMT), 8-year IMT change, and total adjusted IMT at 8-year follow-up in mm (*total in italics*), by occupational physical activity. Results from mixed effects linear regression models fully adjusted for age, blood glucose, fibrinogen, HDL and LDL cholesterol, BMI, systolic blood pressure, use of antihypertensive and lipid-lowering drugs, use of alcohol and tobacco, leisure time physical activity, mental strain at work, supervisor and coworker support at work, and personal income. * indicates a statistically significant ($p < 0.05$) within group IMT progression, no statistical differences between group (reference group: light sitting) in IMT progression were seen.

predicted 4-year IMT progression, and OPA intensity predicted 11-year IMT progression in men, especially among those with stenosis, IHD, or 60+ years old.[14,15] This new study of KIHD women confirms similar positive associations between OPA and IMT including strongest effects with stenosis, but results were overall less precise and partially inconsistent for those with IHD and hypertension. While outcome and covariate data were gathered with nearly identical methods as in the male KIHD population, OPA intensity exposure among women was less accurately measured by one categorical variable, and in contrast to continuous measures in men, and without any duration, repeated measures, or accounting for cardiorespiratory fitness in relative measures of aerobic strain. Those continuous relative aerobic workload measures yielded the strongest IMT and CVD effects among men. In addition, sex-differences in terms of (i) actual exposure or its reporting,[11,12,32] (ii) more retirees among the older female cohort diluting OPA effects (Figure 3D; Table S5), (iii) sex-based selection in and out of heavy work potentially amplified by (iv) delayed onset of atherosclerosis and symptomatic CVD in women are likely to lead to underestimation of OPA effects among women.[29] In addition, dependence between repeated IMT measures was accounted for in mixed effect analyses used in the female cohort. For all these reasons, lower precision of effect estimates and slightly different patterns of IHD effect modification are probably more a reflection of methodological differences than of underlying physiological difference between men and women. Stronger unfavorable hemodynamic responses to upright positions have been reported for men,[33] while, with the exception of a potential premenopausal hormonal cardioprotective effect, women could also be more vulnerable to adverse OPA effects because of generally lower hemoglobin and cardiorespiratory fitness levels requiring higher efforts in cardiac output to handle an identical workload.

Our overall study findings are consistent with other recent epidemiological studies linking standing work and high OPA levels with CVD. Compared to mostly sitting work, mostly standing work and high-intensity OPA were associated with 51% and 60% increased risks for transitory ischemic attacks among women in the US Sister Study.[2] A recent prospective study of Canadian workers utilizing an

FIGURE 3 Estimated baseline intima–media thickness (IMT), 8-year change, and total IMT at 8-year follow-up in mm (*total in italics*), by occupation physical activity. Stratified by baseline (A) carotid artery stenosis, (B) ischemic heart disease, (C) hypertension, and (D) retirement status—results from mixed effects linear regression models fully adjusted for age, level of blood glucose, fibrinogen, HDL and LDL cholesterol, BMI, systolic blood pressure, use of antihypertensive and lipid-lowering drugs, use of alcohol and tobacco and level of leisure time physical activity, mental strain at work and supervisor and coworker support at work, and personal income. * indicates a statistical significant ($p < 0.05$) within group IMT progression, # indicates a statistical significant ($p < 0.05$) between group (reference group: light sitting) IMT progression.


(A)
Adjusted IMT in mm
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
1.240
0.135 *
1.105
1.295
0.035
1.260
1.247
0.115 *
1.132
1.326
0.057
1.269
1.239
0.136 *
1.103
1.432
0.124 *
1.308
1.258
0.145 *
1.113
1.444
0.096 *
1.348
1.253
0.129 *
1.124
1.385
0.066 *
1.319
Light sitting work
Other sitting work
Light standing work
Moderately heavy active work
Heavy or very heavy physical work
No stenosis Baseline
No stenosis Progression from baseline to follow-up
Stenosis Baseline
Stenosis Progression from baseline to follow-up
(B)
Adjusted IMT in mm
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
1.262
0.102 *
1.160
1.310
0.126 *
1.184
1.283
0.118 *
1.165
1.259
0.040
1.219
1.315
0.130 *
1.185
1.366
0.108 *
1.258
1.301
0.124 *
1.177
1.400
0.144 *
1.256
1.190
0.125 *
1.206
1.262
0.072 *
1.190
Light sitting work
Other sitting work
Light standing work
Moderately heavy active work
Heavy or very heavy physical work
No IHD Baseline
No IHD Progression from baseline to follow-up
IHD Baseline
IHD Progression from baseline to follow-up
(C)
Adjusted IMT in mm
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
1.275
0.068 *
1.207
1.320
0.137 *
1.183
1.385
0.145 * #
1.240
1.259
0.074 *
1.185
1.341
0.147 * #
1.194
1.358
0.116 *
1.242
1.342
0.126 * #
1.216
1.349
0.128 *
1.221
1.364
0.183 * #
1.181
1.310
0.072 *
1.238
Light sitting work
Other sitting work
Light standing work
Moderately heavy active work
Heavy or very heavy physical work
Normotensive Baseline
Normotensive 8-year IMT progression
Hypertensive Baseline
Hypertensive 8-year IMT progression
(D)
Adjusted IMT in mm
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
1.298
0.122 *
1.176
1.265
0.094 *
1.171
1.288
0.115 *
1.173
1.280
0.091 *
1.189
1.296
0.148 *
1.148
1.355
0.116 *
1.239
1.355
0.137 *
1.198
1.322
0.125 *
1.197
1.363
0.111 *
1.252
1.296
0.101 *
1.195
Light sitting work
Other sitting work
Light standing work
Moderately heavy active work
Heavy or very heavy physical work
Not retired Baseline
Not retired Progression from baseline to follow-up
Retired Baseline
Retired Progression from baseline to follow-up

objective job OPA exposure matrix showed a doubled risk of acute myocardial infarction for workers mostly standing at work compared to those mostly sitting.[1] Contrary, there is also epidemiologic evidence for prolonged sitting as a CVD risk factor. However, most studies have been based on leisure-time or all-day measures of sitting in general populations that contain large segments of nonworkers whose occupational "baseline" exposures were assumed to be zero and thereby inflated the chronic health risks associated with sitting work and physical inactivity.[34] Two recent meta-analysis reported a 25% and 15% increased CHD risk for high levels of OPA.[6,35] CHD outcomes are characterized by preceding activity-related angina pectoris and are especially vulnerable to healthy worker survivor effect. Furthermore, most of the reviewed studies and the review methodology itself used only crude categorical OPA exposure measures (high vs. low) increasing the risk of conservative exposure misclassification bias.

The result of women with heavy or very heavy physical work showing the highest IMT baseline levels, but not the highest 8-year IMT progression, except in the normotensive, can be best explained by the so-called healthy worker survivor effect,[19] describing the migration of workers from physically demanding jobs to less strenuous jobs. As cardiorespiratory fitness and health declines with age, aging workers, who may also experience chronic fatigue or activity-related cardiorespiratory symptoms such as chest pain and dyspnea, tend to retire early or migrate to less strenuous jobs. This may lead to an accumulation of workers with CVD in sedentary jobs and healthy survivors in very heavy jobs, which can lead to a dilution of risks or even spurious protective effects for high OPA exposure. Thus, the healthy worker survivor effect[19] could explain the high IMT progression and total 8-year IMT among hypertensives exposed to light sitting work. Similar patterns of increased risk for standing work and higher OPA intensity, combined with attenuated risks in the highest OPA category (heavy manual labor), were also observed for incident cerebrovascular diseases among US women.[2]

4.4 | Biological plausibility

Prolonged standing alone is associated with increased hydrostatic pressure and venous pooling, reducing plasma volume and compensatory increases in heart rate and blood pressure,[36] resulting in increased intravascular turbulence and suboptimal shear stress, leading to endothelial injury and inflammation in the arterial wall and IMT progression.[22] Similarly, higher OPA intensities also increase heart rate and blood pressure during work and even after work[37] triggering the same pathophysiological mechanisms and are established independent risk factors for CVD.[38] The Northern Manhattan Study showed that such traditional CVD risk factors act more strongly on areas with preexisting plaque.[39] These observations were confirmed in previous epidemiological studies among men[14,15] and in this study among women showing positive interactions of OPA with stenosis and accelerated IMT progression.

4.5 | Methodological considerations

4.5.1 | Exposure assessment and misclassification bias

OPA was only measured at baseline but OPA may have changed during follow-up due to changes in employment or job tasks. In fact, 36% of the women retired during follow-up, and as expected under our hypothesis, stratified analyses showed lower IMT progression among retirees compared to non-retirees. The lack of repeated OPA measurements did not allow us to calculate an average or cumulative OPA exposure measure that could take the varying duration of exposure during follow-up into account. Another limitation is the self-reported OPA by questionnaire, as accelerometry has been shown to be more accurate than questionnaires.[40] Future studies should also estimate the relative intensities of OPA by using ambulatory HR measures to calculate percent heart rate reserve, taking cardiorespiratory fitness into account.[14,37] However, our OPA questionnaire assessed six rank-ordered OPA categories with specific interpretable descriptors capturing the dimensions of both work posture and intensity. Women's average age was 63 years and 64% were retired at baseline and nearly 75% by follow-up. Retirees had lower IMT values at follow-up than those who continued working until follow-up, which probably diluted OPA effects, especially as those with CVD retired earlier: 78% versus 67% were hypertensive, 48% versus 23% had IHD, and 49% versus 37% had stenosis. Future studies should consider complete job histories and repeated measures of OPA, if feasible collected by wearable monitors. The IMT outcome measure as an non-symptomatic early indicator of atherosclerosis and CVD and objectively measured via validated and highly accurate ultrasound,[41] is an important strength of this study.

4.5.2 | Control for confounding

This study controlled for established biomedical and behavioral cardiovascular disease risk factors, several psychosocial job factors, and for socioeconomic status. All covariates were assessed with state-of-the-art-instruments and most of them analyzed on a precise continuous scale. Moreover, incremental adjustments for these 15 confounding variables increased detrimental OPA effects on IMT and IMT change indicating that elimination of residual confounding would not attenuate, but rather further increase effect estimates.

4.5.3 | Perspectives

Evaluations of IMT could be an early screening tool and indicator of severity of asymptomatic atherosclerosis, guiding clinicians and occupational health practitioners to initiate preventive efforts before the worker may develop clinically manifested symptomatic CVD. However, interventions targeting traditional CVD risk factors would be of limited value, given that they explain less than 30% of IMT variance[39] and about 66% of that proportion is explained by age and sex that are non-modifiable risk factors. Therefore, the usefulness of IMT, beyond risk prediction, for targeting early interventions in vulnerable populations, depends on the identification of nontraditional or new genetic and environmental risk factors of IMT.[39] Prolonged occupational standing and high OPA are two such emerging IMT risk factors.

As the workforce is aging[42] and medical treatment of CVD and potentially fatal cardiac events is improving, the proportion of workers with predisposing CVD will continue to increase and thus the potential impact of OPA and respective prevention efforts. Therefore, future studies and interventions should not exclude workers with CVD but instead perform analyses stratified by CVD status, to be able to determine risk modification by CVD status, for developing better targeted vocational rehabilitation and preventive initiatives.

Data from the Eurostat 2015 survey (https://www.eurofound.europa.eu/surveys/european-working-conditions-surveys/sixth-european-working-conditions-survey-2015) show that 20% of European workers stand during the majority of their working time, and 30% are exposed to at least moderate physical efforts at work. Therefore, knowledge regarding the impact on cardiovascular health from these occupational exposures is essential not only for improvement of CVD risk prediction and adequate patient counseling, but also for the developing of safe work-rest schedules, guidance in the planning and distribution of work postures, work tasks, work schedules, job rotation, or job transfers. For example, the traditionally practice in occupational health to transfer workers with IHD from physically demanding to "light standing" work may need to be replaced by the provision of light sitting work.

5 | CONCLUSION

Light standing work and higher levels of OPA intensity are positively—and stronger than sedentary work—associated with both baseline IMT and IMT progression, especially in workers with baseline carotid artery stenosis. Retirees, independent of OPA, showed lower IMT progressions than non-retirees.

AUTHOR CONTRIBUTIONS

Acquisition of data (JK), initial idea, and funding for the study (MK, KA, OSM, NK), drafting analysis plan (MK, KA, NK), analyzing data (MK), statistical guidance (VS, NK), interpretation of results (MK, KA, OSM, VS, NK), drafting manuscript (MK, NK), commenting and approval of manuscript (MK, KA, OSM, VS, JK, NK).

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from University of Kuopio but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the University of Eastern Finland.

PATIENT CONSENT STATEMENT

All participants gave an informed written consent to participate.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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