

BMJ Open Accelerometer derived physical activity and subclinical coronary and carotid atherosclerosis: cross-sectional analyses in 22 703 middle-aged men and women in the SCAPIS study

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ABSTRACT

Objectives The aim included investigation of the associations between sedentary (SED), low-intensity physical activity (LIPA), moderate-to-vigorous intensity PA (MVPA) and the prevalence of subclinical atherosclerosis in both coronaries and carotids and the estimated difference in prevalence by theoretical reallocation of time in different PA behaviours.

Design Cross-sectional.

Setting Multisite study at university hospitals.

Participants A total of 22 670 participants without cardiovascular disease (51% women, 57.4 years, SD 4.3) from the population-based Swedish CardioPulmonary bioImage study were included. SED, LIPA and MVPA were assessed by hip-worn accelerometer.

Primary and secondary outcomes Any and significant subclinical coronary atherosclerosis (CA), Coronary Artery Calcium Score (CACS) and carotid atherosclerosis (CarA) were derived from imaging data from coronary CT angiography and carotid ultrasound.

Results High daily SED (>70% ≈10.5 hours/day) associated with a higher OR 1.44 (95% CI 1.09 to 1.91), for significant CA, and with lower OR 0.77 (95% CI 0.63 to 0.95), for significant CarA. High LIPA (>55% ≈8 hours/day) associated with lower OR for significant CA 0.70 (95% CI 0.51 to 0.96), and CACS, 0.71 (95% CI 0.51 to 0.97), but with higher OR for CarA 1.41 (95% CI 1.12 to 1.76). MVPA above reference level, >2% ≈20 min/day, associated with lower OR for significant CA (OR range 0.61–0.67), CACS (OR range 0.71–0.75) and CarA (OR range 0.72–0.79). Theoretical replacement of 30 min of SED into an equal amount of MVPA associated with lower OR for significant CA, especially in participants with high SED 0.84 (95% CI 0.76 to 0.96) or low MVPA 0.51 (0.36 to 0.73).

Conclusions MVPA was associated with a lower risk for significant atherosclerosis in both coronaries and carotids, while the association varied in strength and direction for SED and LIPA, respectively. If causal, clinical implications

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Strengths include the large population-based sample with state-of-the-art methods for both exposures (accelerometer-derived activity pattern) and outcomes (subclinical coronary and carotid atherosclerosis derived from imaging data).
- ⇒ This enables detailed analyses of the associations between sedentary and physical activity of different intensities, and prevalence of any and significant atherosclerosis in different vascular beds.
- ⇒ However, the cross-sectional design of the study prevents any causal inference and we cannot rule out reverse causality.
- ⇒ We have no information on any genetic contribution to the associations.

include avoiding high levels of daily SED and low levels of MVPA to reduce the risk of developing significant subclinical atherosclerosis.

BACKGROUND

Both regular physical activity (PA) and limited time spent in sedentary (SED) are related to maintained cardiovascular health and lower cardiovascular disease (CVD) risk.¹ Positive effects of PA on CVD risk factors and inflammation may lead to slower progression of atherosclerosis, the main underlying cause of CVD. However, less is known regarding the relation between PA pattern and subclinical atherosclerosis, where the few studies available mainly have studied carotid intima-media thickness (IMT) and coronary artery calcification (CAC), showing inconsistent

findings.^{2–7} Potential reasons for this include small sample sizes^{2 4 7} and the use of self-reported measures of SED and PA,^{5–7} which are prone to recall bias and large measurement errors.⁸ In contrast, device-based measurements may provide more reliable quantifications of PA patterns, and may in addition enable valid estimation of the theoretical effect of reallocating time spent in one PA behaviour at the expense of time in another (as each day is fixed to 24 hours) on subclinical atherosclerosis. This has previously been studied for metabolic risk factors^{9 10} or CVD incidence,^{11 12} but not for subclinical atherosclerosis. A deeper understanding of these associations would add significant knowledge to the current understanding and may have important clinical applications for counselling and tailored preventive interventions in the future.

Therefore, we aimed to investigate (a) the associations between SED and PA of different intensities, and the prevalence of any and significant subclinical coronary atherosclerosis (CA), Coronary Artery Calcium Score (CACS) and carotid atherosclerosis (CarA), (b) any interaction on the associations by sex, waist circumference, perceived stress and the other PA variables and (c) the estimated difference in prevalence of subclinical atherosclerosis by theoretical reallocation of time in different PA behaviours, by using hip-worn accelerometry data.

METHODS

Data were obtained from the Swedish CARDioPulmonary bioImage study (SCAPIS), which is a large prospective observational cohort study of randomly selected participants from the general population. The SCAPIS baseline data collection was carried out between 2013 and 2018 as a multicentre study at six Swedish university hospitals. Each site aimed to recruit 5000 individuals from the respective municipality areas using sex and age (50 to ≤54, 55 to ≤59 and 60 to ≤64 years) stratified random selection. Participants visited the test site on two to three occasions within 2 weeks, depending on local logistic arrangements. All examinations were performed by experienced nurses, biomedical analysts and readers according to the standard operating procedures established for each examination. In total, 59 909 men and women were invited to the SCAPIS study, of which 30 154 (50.3%) participated. The SCAPIS study and design have previously been described.¹³ In the present study, no separate power calculation was made, hence all participants from the baseline data collection that had valid accelerometer and outcomes data were included.

Assessment of SED behaviour and PA

Tri-axial accelerometers, ActiGraph model GT3X, wGT3X+and wGT3X-BT (ActiGraph LLC, Pensacola, Florida, USA) were used. The outcome from the different models has previously been shown to be comparable,¹⁴ as all raw data recordings from the three different models were extracted as ActiGraph vector magnitude counts using the ActiLife algorithm which truncates the

acceleration to 2.13g regardless model.¹⁵ Participants were instructed to wear the accelerometer in an elastic belt over the right hip during all waking hours for 7 days, except during water-based activities. The accelerometer recorded raw data (sample rate 30 Hz) from three axes. ActiLife V.6.13.3 was used to initialise the accelerometers, download and process the collected raw data combined into a resulting vector extracted as 60 s epochs using a low-frequency extension filter, and expressed in counts per minute (cpm). Non-wear time was defined as 60 or more consecutive minutes with no movement (0 cpm), with allowance for a maximum of 2 min of counts between 0 and 199 cpm. Wear time was calculated as 24 hours minus non-wear time. Participants with a minimum of 600 min of valid daily wear time for at least 4 days were included.¹⁶ SED was defined as <200 cpm,¹⁷ low-intensity PA (LIPA) as 200–2689 cpm and moderate-to-vigorous intensity PA (MVPA) as ≥2690.¹⁸ As daily wear time varied between study participants above the minimum of 600 min per day, SED as well as LIPA and MVPA are presented as percentages of daily wear time in the main analyses. For the isothermal substitution models, minutes per day were used.

Assessment of atherosclerosis in carotid and coronary arteries

Assessment of coronary and CarA has been previously described.^{13 19} Briefly, dual-source CT scanners (SOMATOM Definition Flash, Siemens Healthineers Germany) were used at all sites. For CAC images, ECG-gated non-contrast CT at 120 kV was performed and CACS was estimated according to Agatston.²⁰ Coronary CT angiography (CCTA) was performed at 100 or 120 kV using five different protocols and iohexol (350 mg I/mL; GE Healthcare) was administered at a dose of 325 mg I/kg body weight. The CCTA image datasets were assessed at each site by well-trained readers who classified coronary artery segments as having signs of atherosclerosis or not and a segment involvement score (SIS, ie, number of segments with atherosclerosis) was calculated. CarA was assessed by using a Siemens Acuson S2000 ultrasound scanner equipped with a 9L4 linear transducer (both from Siemens Healthineers, Erlangen, Germany) and atherosclerotic plaques in the common carotid artery, bulb or in the internal carotid artery fulfilling the Mannheim consensus²¹ were identified. In our analyses, the outcomes were dichotomised as (1) SIS>0 'any CA', (2) SIS≥4 'significant CA', (3) CACS>0 'any CAC', (4) CACS≥100 'significant CAC', (5) carotid plaque on one side 'any CarA' and (6) carotid plaques on both sides 'significant CarA'.

Other measurements

Waist circumference was measured in a horizontal plane around the abdomen at the level of the iliac crest. Highest educational attainment, smoking habits and perceived stress were self-reported (see questions in online supplemental text). The 10-item screening tool Alcohol Use

Disorders Identification Test (AUDIT) was used to assess alcohol habits.²² Diet habits were evaluated using an Anti-Inflammatory Diet Index score.²³ Family history of CVD was self-reported as the participant's father or mother had suffered from a myocardial infarction or stroke before 60 and 65 years of age, respectively.

Patient and public involvement

No patient was involved.

Statistical analysis

The association between %SED, %LIPA and %MVPA on a continuous scale, and any and significant CA, CACS and CarA, were analysed using generalised linear model with a Gaussian link function and natural cubic splines. Knots were set at 40%, 55% and 70% for SED, at 25%, 40% and 55% for LIPA, and at 2%, 5% and 8% for MVPA. Knots were chosen to provide an equal range of exposure to be able to study any dose-response relationship. Reference levels were set as the mean of percent spent in each PA group of participants below the lowest knot; SED reference was set to 35%, LIPA reference to 22% and MVPA reference to 1.5%. Further, the percent of wear time spent in SED, LIPA and MVPA were analysed after categorisation into five groups based on the highest and lowest knots used (with the addition of two cut-points in between). ORs with 95% CIs for any and significant CA, CACS and CarA were calculated using binary logistic regression modelling. Median wear time in the study population (894 min per day) was used to convert the percent of wear time into minutes per day. Covariates included in the multivariable-adjusted models were chosen according to a prespecified working model (online supplemental figure 1) and included those variables identified as covariates or confounders (not mediators). Adjustment of study site as a random effect did not change the result. To test for interaction on the associations by sex, waist circumference, perceived stress and % in SED or MVPA, an interaction term was included in the model. Significant interaction(s) were defined as $p < 0.05$ and adjusted for repeated measurements, using a false discovery rate of 5%.

To examine the theoretical effect on prevalent atherosclerosis of replacing time in SED, LIPA and MVPA, with time in any of the other PA-related behaviours, we used the isothermal substitution method.²⁴ All PA variables (in daily minutes), except the variable to be substituted, were entered into the models simultaneously along with a total wear time variable and covariates. By including the total wear time variable, time is isothermal and hence the regression estimate, OR with 95% CI, for each variable in the model reflects the effect of substituting 30 minute of time in one PA behaviour with the equal amount of time in another specific activity behaviour. We additionally analysed SED time substitution with equal amounts of LIPA and MVPA in 1 min, 5 min, 10 min and 60 min bouts, respectively. Statistical analyses were performed by using SPSS (V.27, SPSS) and R with Tidyverse and Splines

package (R core Team 2022, R Foundation for Statistical Computing, Vienna, Austria. V.4.2.1).

RESULTS

Of the 30 154 participants in SCAPIS, a total of 22 670 (51.1% women, mean age of 57.4 SD 4.3 years) without known CVD and self-reported chest pain or discomfort during physical effort were included in the present analyses (for specific drop-out, see online supplemental figure 2). A total of 41%, 40% and 54% of the participants displayed any CA, CACS and CarA, respectively, with 11%, 11% and 24% having significant CA, CACS and CarA, respectively. Participants with any or significant CA or CACS were more often men, older, with higher waist circumference, more prevalent self-reported family history of CVD, lower educational level, higher probability of alcohol abuse, lower reported anti-inflammatory diet habits, and less self-reported perceived stress (table 1 and online supplemental table 1). Similar differences between participants with and without any or significant CarA were present, however, less pronounced.

Higher SED was associated with higher OR for significant CA, but lower OR for both any and significant CarA after multivariable adjustment (figure 1). Those with the most time spent SED ($>70\%$, ≈ 10.5 hours/day) had a higher risk for significant CA (OR (95% CI): 1.44 (1.09 to 1.91)), and a lower risk for significant CarA (0.77 (0.63 to 0.95)) (table 2). Accordingly, higher LIPA was associated with a lower risk for significant CA and CACS and a higher risk for both any and significant CarA (figure 1). High LIPA ($>55\%$, ≈ 8 hours/day) associated with lower OR for significant CA 0.70 (0.51 to 0.96) and CACS 0.71 (0.51 to 0.97), but with higher OR for significant CarA 1.41 (1.12 to 1.76) (table 2). MVPA above reference level ($>2\%$, ≈ 20 min/day) was associated with lower OR for any as well as significant CA, CACS and CarA (figure 1), with the OR range for significant CA being 0.61–0.67, for CACS OR_{range} = 0.71–0.75 and for CarA OR_{range} = 0.72–0.79 (table 2).

The interactions between %SED and sex ($p=0.045$), %LIPA and sex ($p=0.021$) and %SED and %MVPA ($p=0.032$) for significant CA (online supplemental table 2) did not remain significant after adjustment for a false discovery rate of 5% ($p_{\text{Limit}}=0.0014$).

Theoretical replacement of 30 min of SED time with LIPA and MVPA resulted in a 2%, 0.98 (0.96–1.00) and 3%, 0.97 (0.92–1.02), respectively, lower OR of having significant CA (table 3). In participants with high SED time (≥ 9 hours/day) substitution of 30 min of SED time with MVPA was associated with a 16% lower OR for significant CA 0.84 (0.76–0.96). In participants with low levels of MVPA (<35 min/day), theoretically substituting 30 min of SED time or LIPA with MVPA was associated with lower OR for all three outcomes (OR range 0.51–0.69).

Table 1	Study characteristics in relation to the prevalence of significant CA, CACS and CarA	Significant CA (SIS≥4)		Significant CACS (≥100)		Significant CarA (≥2)	
		Yes	No	Yes	No	Yes	No
	Prevalence, % (n)	11% (2602)	89% (20 068)	11% (2553)	89% (20 117)	24% (5470)	76% (17 200)
	Sex, men (N=22 670)	78% (2032)	45% (9056)	75% (1920)	46% (9168)	59% (3240)	46% (7848)
	Age, years (N=22 670)	59.4 (4.1)	57.2 (4.3)	59.5 (4.0)	57.1 (4.3)	58.6 (4.2)	57.0 (4.3)
	Waist circumference, ≥88 cm women, ≥102 cm men (N=22 665)	50% (1307)	42% (8428)	49% (1256)	42% (8479)	44% (2394)	43% (7341)
	Family history of CVD, yes (N=22 063)	15% (365)	10% (2051)	14% (355)	11% (2061)	12% (648)	11% (1768)
	Educational level, university degree (N=22 063)	39% (973)	48% (9286)	40% (974)	47% (9285)	43% (2276)	48% (7983)
	Smoking habits, regularly (N=21 840)	12% (291)	6% (1232)	11% (266)	6% (1257)	11% (558)	6% (965)
	Alcohol habits, AUDIT score* (N=19 950)	4.9 (3.5)	4.0 (2.9)	4.9 (3.6)	4.0 (2.8)	4.4 (3.2)	4.0 (2.8)
	Diet habits, AIDI score† (N=22 670)	5.5 (1.7)	5.6 (1.8)	5.5 (1.7)	5.6 (1.8)	5.6 (1.7)	5.6 (1.8)
	Perceived stress, several periods/permanent last year or longer (N=21 849)	16% (399)	20% (3975)	16% (390)	21% (3984)	19% (971)	20% (3403)
	Sedentary, % of daily wear time (N=22 670)	55 (10)	54 (10)	55 (10)	54 (10)	54 (10)	54 (10)
	LIPA, % of daily wear time (N=22 670)	38 (9)	40 (9)	39 (9)	40 (9)	40 (9)	40 (9)
	MVPA, % of daily wear time (N=22 670)	6 (4)	6 (3)	6 (4)	6 (3)	6 (3)	6 (3)
Data presented as percentages (n) or mean (SD).							
*Range 0–40. The higher score, the higher probability of alcohol abuse.							
†Range 0–16. The higher score, the higher probability of an anti-inflammatory diet.							
AIDI, Anti-Inflammatory Diet Index; AUDIT, Alcohol Use Disorders Identification Test; CA, coronary atherosclerosis; CACS, Coronary Artery Calcium Scoring; CarA, carotid atherosclerosis; CVD, cardiovascular disease; LIPA, low-intensity physical activity; MVPA, moderate-to-vigorous physical activity; SIS, Segment Involvement Score.							

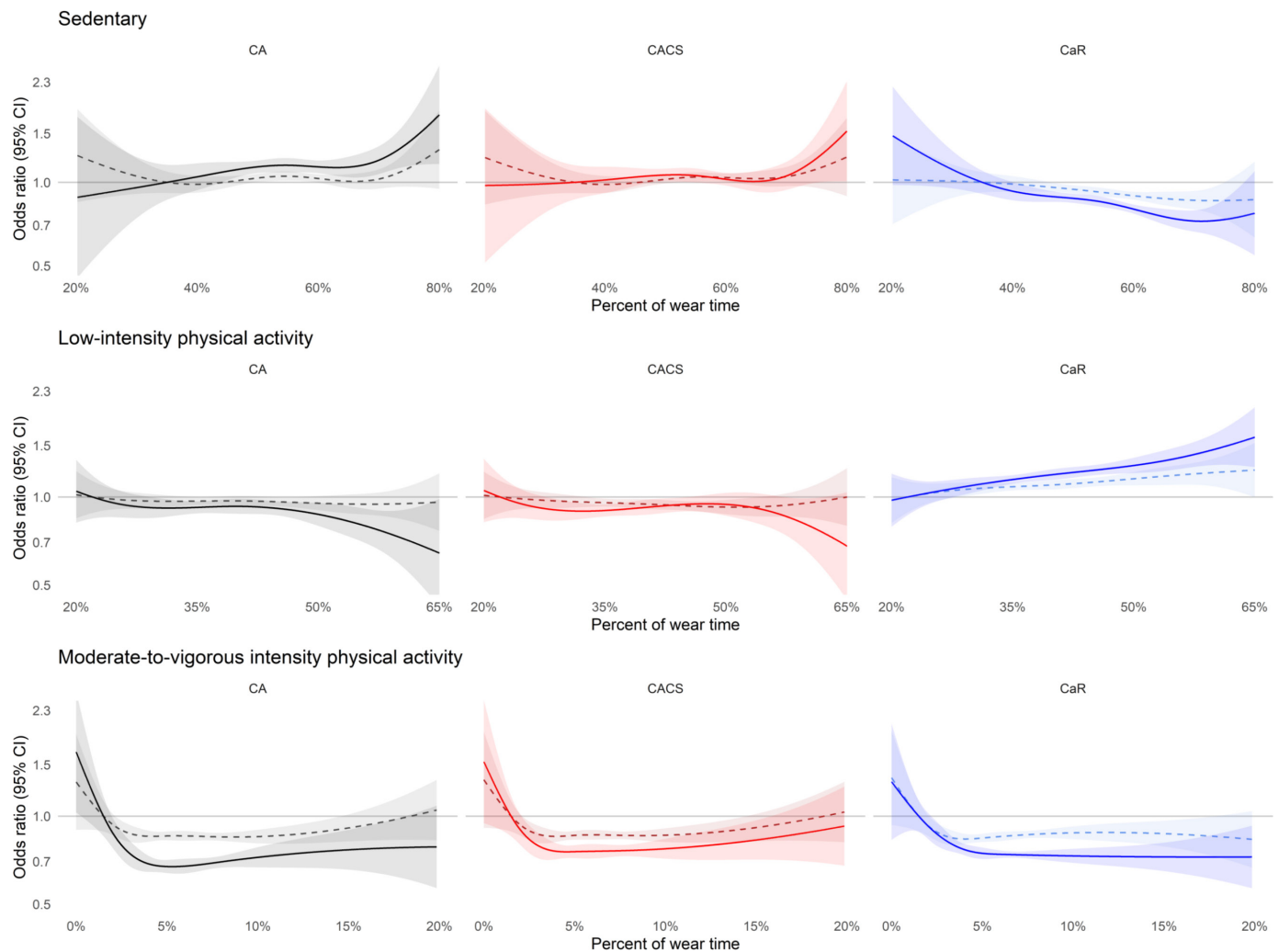


Figure 1 Association between any and significant CA, CACS and CaR with the exposures. OR with 95% CI for any (dashed lines) and significant (solid lines) CA, CACS and CaR with percentage of wear time spent in (A) SED, (B) LIPA and (C) MVPA. Reference levels are set to 35% for SED, 22% for LIPA and 1.5% for MVPA. Adjusted for sex, age, wear time, SCAPIS site, family history of CVD, educational level, perceived stress, smoking, alcohol, diet and percentage of moderate-to-vigorous physical activity. For visual reasons, y-axis values were restricted to the above range, leaving outliers ($n \leq 30$) out in each analysis. CA, coronary atherosclerosis; CACS, Coronary Artery Calcium Score; CaR, carotid atherosclerosis; CVD, cardiovascular disease; LIPA, low-intensity physical activity; MVPA, moderate-to-vigorous physical activity; SCAPIS, Swedish CardioPulmonary Biolmage Study; SED, sedentary.

In participants with high SED time (≥ 9 hours/day), reallocating SED time with an equal amount of time in LIPA was related to lower OR in a stepwise-like fashion, from 1 min (OR 0.998 (95% CI 0.996 to 1.00)) to 60 min amount of time (0.90 (95% CI 0.79 to 1.02)). A similar pattern was seen for MVPA, from 1 min (0.994 (95% CI 0.990 to 0.998)) to 60 min (0.71 (95% CI 0.55 to 0.91) (figure 2).

DISCUSSION

Key findings in this large, population-based sample of men and women without known CVD were (1): participants with the highest SED time had 44% higher OR for significant CA compared with those with low daily time in SED, (2) participants with MVPA above reference level had 21%–39% lower OR for significant CA, CAC and

CarA compared with reference and (3) theoretical substitution of time spent in SED to equal amount of time spent in MVPA was associated with lower risk of significant CA, with the greatest effect in those with high SED time or with low levels of MVPA.

The association between self-reported SED, PA and subclinical atherosclerosis has previously been studied.^{5–7} In the MESA study, self-reported PA in MET-hours/week was not reliably associated with the amount of either IMT or CAC ($n=6482$ adults, 45–84 years).⁵ Follow-up examinations after 2–5 years on the progression of CAC and ankle-brachial index in participants with no CAC at baseline, revealed that only vigorous PA and intentional exercise were significantly related to the progression of CAC and ankle-brachial index, respectively.⁶ This rather weak association between PA patterns and measurements

Table 2 OR with 95% CI for any and significant CA, CACS and CarA in relation to groups of wear time spent in SED, LIPA and MVPA, with minimal (model 1) and multivariable (model 2) adjustment

Minimal adjustment analyses, model 1 (N=22670)						Multivariable adjustment analyses, model 2 (N=19440)					
SED % of daily wear time											
	Any CA	Any CACS	Any CarA	Any CA	Any CACS	Any CarA		Any CA	Any CACS	Any CarA	
<40%	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	<40%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
40%–50%	0.99 (0.89–1.10)	1.02 (0.91–1.14)	0.95 (0.86–1.06)	1.00 (0.89–1.13)	1.04 (0.92–1.18)	0.98 (0.87–1.10)	40%–50%	0.99 (0.89–1.10)	1.00 (0.89–1.13)	1.04 (0.92–1.18)	0.98 (0.87–1.10)
50%–60%	0.98 (0.88–1.09)	0.99 (0.90–1.10)	0.91 (0.83–1.01)	1.04 (0.92–1.17)	1.05 (0.93–1.19)	0.94 (0.84–1.06)	50%–60%	0.99 (0.88–1.09)	1.04 (0.92–1.17)	1.05 (0.93–1.19)	0.94 (0.84–1.06)
60%–70%	0.99 (0.89–1.10)	1.02 (0.92–1.14)	0.87 (0.79–0.97)	1.03 (0.90–1.17)	1.08 (0.94–1.23)	0.88 (0.78–1.00)	60%–70%	0.99 (0.89–1.10)	1.03 (0.90–1.17)	1.08 (0.94–1.23)	0.88 (0.78–1.00)
>70%	1.04 (0.89–1.22)	1.01 (0.86–1.19)	0.94 (0.80–1.10)	1.04 (0.86–1.25)	1.05 (0.87–1.28)	0.86 (0.80–1.15)	>70%	1.04 (0.89–1.22)	1.04 (0.86–1.25)	1.05 (0.87–1.28)	0.86 (0.80–1.15)
	Significant CA	Significant CACS	Significant CarA	Significant CA	Significant CACS	Significant CarA		Significant CA	Significant CACS	Significant CACS	Significant CarA
<40%	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	<40%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
40%–50%	1.14 (0.96–1.37)	0.99 (0.83–1.17)	0.89 (0.79–1.00)	1.18 (0.96–1.45)	1.02 (0.84–1.24)	0.87 (0.77–1.00)	40%–50%	1.14 (0.96–1.37)	0.99 (0.83–1.17)	1.02 (0.84–1.24)	0.87 (0.77–1.00)
50%–60%	1.15 (0.97–1.36)	1.02 (0.87–1.20)	0.87 (0.78–0.97)	1.21 (0.99–1.48)	1.07 (0.88–1.30)	0.84 (0.74–0.96)	50%–60%	1.15 (0.97–1.36)	1.02 (0.87–1.20)	1.07 (0.88–1.30)	0.84 (0.74–0.96)
60%–70%	1.11 (0.93–1.33)	0.92 (0.78–1.10)	0.78 (0.69–0.88)	1.17 (0.94–1.45)	0.98 (0.79–1.21)	0.74 (0.64–0.85)	60%–70%	1.11 (0.93–1.33)	0.92 (0.78–1.10)	0.98 (0.79–1.21)	0.74 (0.64–0.85)
>70%	1.36 (1.08–1.72)	1.12 (0.89–1.41)	0.84 (0.71–1.00)	1.44 (1.09–1.91)	1.16 (0.87–1.53)	0.77 (0.63–0.95)	>70%	1.36 (1.08–1.72)	1.12 (0.89–1.41)	1.16 (0.87–1.53)	0.77 (0.63–0.95)
LIPA % of daily wear time											
	Any CA	Any CACS	Any CarA	Any CA	Any CACS	Any CarA		Any CA	Any CACS	Any CarA	
<25%	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	<25%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25%–35%	0.98 (0.85–1.14)	1.00 (0.86–1.16)	1.02 (0.89–1.18)	1.01 (0.86–1.18)	1.01 (0.86–1.18)	1.05 (0.90–1.23)	25%–35%	0.98 (0.85–1.14)	1.00 (0.86–1.16)	1.01 (0.86–1.18)	1.05 (0.90–1.23)
35%–45%	1.00 (0.86–1.15)	1.01 (0.87–1.16)	1.09 (0.95–1.26)	1.00 (0.86–1.17)	0.98 (0.84–1.15)	1.14 (0.98–1.33)	35%–45%	1.00 (0.86–1.15)	1.01 (0.87–1.16)	1.00 (0.86–1.17)	1.14 (0.98–1.33)
45%–55%	1.04 (0.89–1.20)	1.05 (0.90–1.22)	1.15 (1.00–1.34)	1.00 (0.85–1.18)	0.98 (0.83–1.16)	1.14 (0.97–1.34)	45%–55%	1.04 (0.89–1.20)	1.05 (0.90–1.22)	1.00 (0.85–1.18)	1.14 (0.97–1.34)
>55%	1.01 (0.84–1.22)	1.02 (0.85–1.23)	1.25 (1.05–1.49)	0.98 (0.80–1.21)	0.97 (0.79–1.20)	1.24 (1.02–1.51)	>55%	1.01 (0.84–1.22)	1.02 (0.85–1.23)	0.98 (0.80–1.21)	1.24 (1.02–1.51)
	Significant CA	Significant CACS	Significant CarA	Significant CA	Significant CACS	Significant CarA		Significant CA	Significant CACS	Significant CACS	Significant CarA
<25%	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	<25%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25%–35%	0.88 (0.72–1.07)	0.80 (0.66–0.98)	1.00 (0.85–1.17)	0.89 (0.72–1.11)	0.85 (0.68–1.06)	1.06 (0.89–1.27)	25%–35%	0.88 (0.72–1.07)	0.80 (0.66–0.98)	0.85 (0.68–1.06)	1.06 (0.89–1.27)
35%–45%	0.94 (0.78–1.14)	0.90 (0.74–1.09)	1.11 (0.95–1.31)	0.91 (0.73–1.13)	0.88 (0.71–1.09)	1.19 (1.00–1.42)	35%–45%	0.94 (0.78–1.14)	0.90 (0.74–1.09)	0.88 (0.71–1.09)	1.19 (1.00–1.42)
45%–55%	0.93 (0.76–1.15)	0.95 (0.78–1.17)	1.20 (1.01–1.41)	0.88 (0.70–1.11)	0.95 (0.75–1.20)	1.24 (1.03–1.49)	45%–55%	0.93 (0.76–1.15)	0.95 (0.78–1.17)	0.88 (0.70–1.11)	1.24 (1.03–1.49)
>55%	0.78 (0.59–1.03)	0.78 (0.59–1.03)	1.36 (1.12–1.67)	0.70 (0.51–0.96)	0.71 (0.51–0.97)	1.41 (1.12–1.76)	>55%	0.78 (0.59–1.03)	0.78 (0.59–1.03)	0.70 (0.51–0.96)	1.41 (1.12–1.76)
MVPA % of daily wear time											
	Any CA	Any CACS	Any CarA	Any CA	Any CACS	Any CarA		Any CA	Any CACS	Any CarA	
<2%	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	<2%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2%–4%	0.85 (0.74–0.98)	0.86 (0.75–1.00)	0.91 (0.79–1.05)	0.91 (0.77–1.07)	0.88 (0.75–1.04)	0.91 (0.77–1.07)	2%–4%	0.85 (0.74–0.98)	0.86 (0.75–1.00)	0.91 (0.79–1.05)	0.91 (0.77–1.07)
4%–6%	0.77 (0.67–0.89)	0.80 (0.70–0.92)	0.82 (0.71–0.94)	0.88 (0.75–1.03)	0.88 (0.74–1.03)	0.84 (0.72–0.99)	4%–6%	0.77 (0.67–0.89)	0.80 (0.70–0.92)	0.82 (0.71–0.94)	0.84 (0.72–0.99)
6%–8%	0.74 (0.64–0.86)	0.76 (0.66–0.88)	0.85 (0.74–0.98)	0.89 (0.75–1.05)	0.88 (0.74–1.04)	0.92 (0.78–1.08)	6%–8%	0.74 (0.64–0.86)	0.76 (0.66–0.88)	0.85 (0.74–0.98)	0.92 (0.78–1.08)

Continued

Table 2 Continued

	Minimal adjustment analyses, model 1 (N=22670)			Multivariable adjustment analyses, model 2 (N=19440)		
>8%	0.74 (0.64–0.85)	0.76 (0.66–0.88)	0.86 (0.74–0.98)	0.87 (0.74–1.04)	0.87 (0.73–1.03)	0.92 (0.78–1.08)
	Significant CA	Significant CACS	Significant CarA	Significant CA	Significant CACS	Significant CarA
<2%	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2%–4%	0.62 (0.52–0.75)	0.70 (0.58–0.84)	0.77 (0.66–0.90)	0.67 (0.54–0.83)	0.75 (0.60–0.93)	0.79 (0.66–0.94)
4%–6%	0.57 (0.47–0.68)	0.61 (0.51–0.73)	0.74 (0.64–0.86)	0.67 (0.55–0.84)	0.71 (0.58–0.89)	0.78 (0.66–0.92)
6%–8%	0.49 (0.40–0.59)	0.57 (0.47–0.69)	0.70 (0.60–0.81)	0.61 (0.49–0.76)	0.71 (0.56–0.89)	0.74 (0.62–0.88)
>8%	0.53 (0.44–0.64)	0.62 (0.51–0.75)	0.71 (0.61–0.82)	0.67 (0.53–0.84)	0.74 (0.59–0.93)	0.72 (0.61–0.87)

Model 1, adjusted for sex, age and wear time.
 Model 2, model 1+SCAPIS site, family history of CVD, educational level, perceived stress, smoking, alcohol, diet and % in MVPA (for SED and LIPA), and % in SED (for MVPA).
 CA, coronary atherosclerosis; CACS, Coronary Artery Calcium Scoring; CarA, carotid atherosclerosis; CVD, cardiovascular disease; LIPA, low-intensity physical activity; MVPA, moderate-to-vigorous physical activity; SCAPIS, Swedish CardioPulmonary BioImage Study; SED, sedentary.

of atherosclerosis may be caused by the poor validity of self-reported PA.⁸

Using accelerometry, in young-to-middle-aged healthy men and women (n=614, mean age 44 years), IMT in common and internal carotid arteries was positively associated with the SED/LIPA ratio, and negatively associated to the average intensity of PA in cross-sectional analyses.²⁵ Investigating IMT progression in common carotid arteries, participants with more vigorous PA at baseline had a slower progression over 3 years. In middle-aged⁴ and older³ participants, a wide range of measures of vascular structure, function and subclinical vascular disease (IMT, central and peripheral augmentation index, distensibility coefficient, plaque presence and pulse wave velocity) showed significant beneficial associations with both LIPA and MVPA and inverse association with SED. However, in a previous study in healthy subjects (mean age 66 years), no evident association was seen between SED, LIPA, MVPA and CACS.²

The present finding of significant differences in the prevalence of significant CA by theoretically reallocating 30 min of SED or LIPA into MVPA or adverse effects of adding 30 min of SED time at the expense of MVPA, helps to explain findings from previous studies.^{11 12} Among 87498 participants, substituting 20 min/day of any behaviour into a similar amount of time of MVPA was associated with 9% lower CVD incidence risk over median 6.2 years of follow-up.¹² Conversely, reallocation of 1 hour/day into more SED is associated with a 5% increased risk. Similarly, in 3319 participants (mean age 68.9 years), substitution of 10 min/day of SED into MVPA was associated with 8% lower CVD risk over mean time 6.2 years follow-up, while the converse reallocation of 10 min/day from MVPA to SED associates with a 14% higher risk.¹¹ However, both studies above used wrist-worn accelerometry data, compared with hip-worn accelerometry in the present study.

Interestingly, we found different associations between SED and the coronary and carotid vascular beds. While there was a significant trend with a higher risk of CA with higher SED, there was simultaneously a lower risk of CarA. Some possible explanations for these findings exist. For one, we know from earlier studies that there are differences regarding the relative importance of various risk factors as well as in plaque characteristics between the carotids and the coronaries.^{26 27} For example, cholesterol appears more important risk factor for coronary artery disease whereas hypertension is more strongly associated with stroke. Also, perivascular adipose tissue surrounding the coronary arteries is presented a risk factor of CVD, but not for the carotids, which could affect the results of plaque morphology between the two vascular systems.^{27 28} Furthermore, significant CA and significant CarA in this study represent different severity of subclinical atherosclerosis in coronaries and carotids, respectively. This is supported by stronger associations of CA and CACS with traditional risk factors in the present study (table 1), where the associations between CarA and the same risk

Table 3 OR (95% CI) according to isotemporal substitution for significant CA, CACS and CarA when replacing 30 min in SED as well as in LIPA and MVPA with an equal amount of time in another physical activity behaviour (above), and after stratification for time spent in SED and MVPA (below)

	Substitution of 30min SED		Substitution of 30min LIPA		Substitution of 30min MVPA	
	SED to LIPA	SED to MVPA	LIPA to SED	LIPA to MVPA	MVPA to SED	MVPA to LIPA
Significant CA	0.98 (0.96–1.00)	0.97 (0.92–1.02)	1.02 (1.00–1.04)	0.99 (0.93–1.04)	1.03 (0.98–1.09)	1.01 (0.96–1.07)
Significant CACS	0.99 (0.97–1.01)	0.99 (0.94–1.04)	1.01 (0.99–1.03)	1.00 (0.94–1.05)	1.01 (0.96–1.06)	1.00 (0.95–1.06)
Significant CarA	1.03 (1.02–1.04)	0.98 (0.95–1.02)	0.97 (0.96–0.98)	0.95 (0.91–0.99)	1.02 (0.98–1.06)	1.05 (1.01–1.09)
Significant CA						
Low/Moderate SED (Gr1–Gr3, <9 hours/day*)	0.97 (0.94–1.00)	0.98 (0.93–1.04)	1.03 (1.00–1.06)	1.01 (0.95–1.07)	1.02 (0.96–1.08)	0.99 (0.93–1.05)
High SED (Gr4–Gr5, ≥9 hours/day)	0.95 (0.89–1.01)	0.84 (0.76–0.96)	1.06 (0.99–1.12)	0.89 (0.78–1.02)	1.19 (1.05–1.35)	1.12 (0.98–1.28)
Significant CA						
Low MVPA (Gr1–Gr2, <35 min/day†)	0.98 (0.94–1.01)	0.51 (0.36–0.73)	1.02 (0.99–1.06)	0.53 (0.37–0.75)	1.95 (1.37–2.77)	1.90 (1.33–2.72)
Mod/high MVPA (Gr1–Gr2, ≥35 min/day)	0.99 (0.97–1.01)	1.02 (0.96–1.08)	1.01 (0.99–1.04)	1.03 (0.96–1.11)	0.98 (0.92–1.04)	0.97 (0.90–1.04)
Significant CACS						
Low/moderate SED (Gr1–Gr3, <9 hours/day*)	0.99 (0.96–1.01)	0.99 (0.93–1.05)	1.01 (0.99–1.04)	1.00 (0.94–1.06)	1.01 (0.96–1.07)	1.00 (0.94–1.06)
High SED (Gr4–Gr5, ≥9 hours/day)	0.95 (0.89–1.01)	0.92 (0.81–1.05)	1.05 (0.99–1.12)	0.97 (0.85–1.11)	1.09 (0.96–1.23)	1.03 (0.90–1.18)
Significant CACS						
Low MVPA (Gr1–Gr2, <35 min/day†)	0.99 (0.96–1.03)	0.69 (0.48–0.98)	1.01 (0.97–1.04)	0.69 (0.48–0.99)	1.46 (1.02–2.07)	1.45 (1.01–2.07)
Mod/high MVPA (Gr1–Gr2, ≥35 min/day)	1.00 (0.97–1.02)	1.03 (0.97–1.10)	1.00 (0.98–1.03)	1.04 (0.97–1.11)	0.97 (0.91–1.03)	0.96 (0.90–1.03)
Significant CarA						
Low/moderate SED (Gr1–Gr3, <9 hours/day*)	1.03 (1.01–1.05)	0.99 (0.95–1.03)	0.97 (0.95–0.99)	0.96 (0.92–1.00)	1.01 (0.97–1.06)	1.04 (1.00–1.09)
High SED (Gr4–Gr5, ≥9 hours/day)	1.00 (0.95–1.05)	0.92 (0.84–1.01)	1.00 (0.95–1.05)	0.92 (0.83–1.02)	1.09 (0.99–1.20)	1.09 (0.98–1.20)
Significant CarA						
Low MVPA (Gr1–Gr2, <35 min/day†)	1.03 (1.01–1.06)	0.60 (0.46–0.78)	0.97 (0.94–0.99)	0.58 (0.44–0.76)	1.67 (1.27–2.18)	1.72 (1.31–2.26)
Mod/high MVPA (Gr1–Gr2, ≥35 min/day)	1.03 (1.02–1.05)	1.01 (0.96–1.05)	0.97 (0.95–0.99)	0.98 (0.93–1.03)	0.99 (0.95–1.04)	1.02 (0.97–1.08)

Adjusted for sex, age, wear time, SCAPIS site, family history of CVD, educational level, perceived stress, smoking, alcohol and diet.
 *calculated using cut-point for sedentary Gr 4 (60% of wear time), multiplied with median wear time (894 min/day), equals approximately 540 minutes/day or 9 hours/day.
 †calculated using cut-point for MVPA Gr 2 (4% of wear time), multiplied with median wear time (894 min/day), equals approximately 35 min/day.
 CA, coronary atherosclerosis; CACS, Coronary Artery Calcium Score; CarA, carotid atherosclerosis; CVD, cardiovascular disease; Gr, Group; LIPA, low-intensity physical activity; MVPA, moderate-to-vigorous physical activity; SCAPIS, Swedish CardioPulmonary BioImage Study; SED, sedentary.

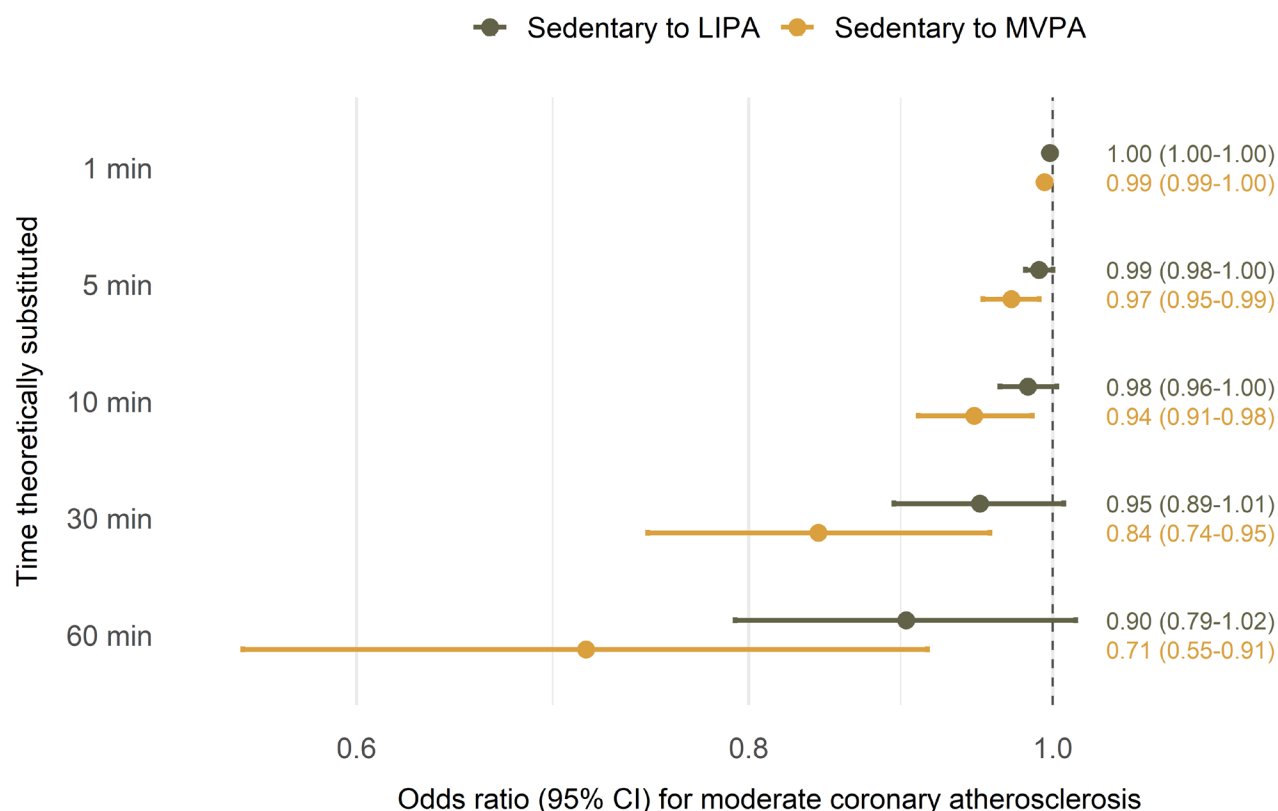


Figure 2 Theoretical substitution of sedentary time with LIPA and MVPA for significant CA. OR (95% CI) according to isotemporal substitution for significant CA in participants with high sedentary time (≈ 9 hours per day) when replacing sedentary time with LIPA or MVPA of different amounts of time. Adjusted for sex, age, wear time, SCAPIS site, family history of CVD, educational level, perceived stress, smoking, alcohol and diet. CA, coronary atherosclerosis; CVD, cardiovascular disease; LIPA, low-intensity physical activity; MVPA, moderate-to-vigorous physical activity; SCAPIS, Swedish CardioPulmonary BiImage Study.

factors are less pronounced. Second, there may be factors still unadjusted for in the analyses. For example, variations in which daily context SED and PA are accumulated may be of importance. It has been suggested that high occupational PA may have adverse health effects as well as contribute to an increased risk for CVD²⁹ due to more unfavourable characteristics (long duration, insufficient recovery, restricted movement and body position etc) compared with leisure time PA.³⁰ A third possible explanation is methodological. The definition used for carotid plaque in SCAPIS is a focal thickening of the intima, which relies on the visual detection of plaque usually located in the bulb area. In obese subjects (which are in general more SED in this study population³¹), proper visualisation of the bulb is often more difficult than visualisation of the far wall of the common carotid artery. Plaques in the bulb area might, therefore, be underestimated in obese individuals.³²

Although the present study only includes cross-sectional analyses, some potential mechanisms for the main results can be discussed. Higher PA and lower levels of SED time have been beneficially related to several common cardiovascular risk factors including inflammation, insulin resistance and hypertension. This may

contribute to a slower progression of subclinical atherosclerosis and plaque formation. In addition, in analyses of asymptomatic patients, those with greater PA and higher intensity of PA had a lower prevalence of intraplaque haemorrhage, which makes plaques more unstable and often precedes an acute ischaemic event.³³ Similarly, participants reporting higher levels of SED had a higher prevalence of intraplaque haemorrhage. Hence, PA may be linked to not only plaque prevalence but also plaque morphology and stability in individuals with prevalent atherosclerosis. Though, it has previously been proposed that exercise training actually may increase CAC, but that acceleration of CAC by exercise training may induce denser and/or more stable plaques and in a later stage, lower CVD risk.^{34 35}

Limitations in the present study included the use of hip-worn accelerometer analyses of only SED behaviour (and not sitting/standing/lying), inability to detect load-bearing, upper-limb activities and water-based activities, as well as an underestimation of PA during some activities, for example, cycling. The choice of wear time algorithm may constitute a limitation, as it may have affected the absolute values of time spent in lower intensities, but only to a limited degree affected the relations between

PA and atherosclerosis. Due to stringent safety criteria, including the use of low-dose radiation and strict risk management, the exclusion rate was rather high. Caution must be applied when extrapolating the present results to women and men outside the ages of the study participants. The observational and so far, cross-sectional design of the SCAPIS study limits any definitive causal inferences. Future studies may focus on understanding any diverse association between occupational and leisure time PA and CVD risk, as well as potential interaction with educational level.

CONCLUSION

In this large population-based study using device-based measurements of SED and PA, we found associations between MVPA and lower risk for significant atherosclerosis in both coronaries and carotids. However, the associations varied in strength and also in direction for SED and LIPA, respectively. Whether this finding indicates different pathophysiological pathways of PA patterns in different vascular beds or is a result of residual confounding is not possible to determine in this cross-sectional study. Nevertheless, substituting SED time with PA, particularly in the least active individuals, was associated with a lower risk of subclinical atherosclerosis in both settings. If these findings are causal, clinical implications include avoiding high levels of daily SED and low levels of MVPA to reduce subclinical atherosclerosis severity.

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