




## Original research

## Physical activity and the progression of coronary artery calcification

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**ABSTRACT**

**Background** The association of physical activity with the development and progression of coronary artery calcium (CAC) scores has not been studied. This study aimed to evaluate the prospective association between physical activity and CAC scores in apparently healthy adults.

**Methods** Prospective cohort study of men and women free of overt cardiovascular disease who underwent comprehensive health screening examinations between 1 March 2011 and 31 December 2017. Baseline physical activity was measured using the International Physical Activity Questionnaire Short Form (IPAQ-SF) and categorised into three groups (inactive, moderately active and health-enhancing physically active (HEPA)). The primary outcome was the difference in the 5-year change in CAC scores by physical activity category at baseline.

**Results** We analysed 25 485 participants with at least two CAC score measurements. The proportions of participants who were inactive, moderately active and HEPA were 46.8%, 38.0% and 15.2%, respectively. The estimated adjusted average baseline CAC scores (95% confidence intervals) in participants who were inactive, moderately active and HEPA were 9.45 (8.76, 10.14), 10.20 (9.40, 11.00) and 12.04 (10.81, 13.26). Compared with participants who were inactive, the estimated adjusted 5-year average increases in CAC in moderately active and HEPA participants were 3.20 (0.72, 5.69) and 8.16 (4.80, 11.53). Higher physical activity was associated with faster progression of CAC scores both in participants with CAC=0 at baseline and in those with prevalent CAC.

**Conclusion** We found a positive, graded association between physical activity and the prevalence and the progression of CAC, regardless of baseline CAC scores.

**INTRODUCTION**

Physical activity is associated with a dose-dependent reduction in the risk of metabolic disease, cardiovascular events, and cardiovascular and all-cause mortality.<sup>1,2</sup> The 2018 Physical Activity Guidelines for Americans emphasise the central role of physical activity in promoting cardiovascular health and maintaining a healthy lifestyle, and recommend that adults engage in at least 150–300 minutes/week of moderate-intensity or 75–150 minutes/week of vigorous-intensity aerobic physical activity.<sup>3</sup>

While physical activity improves a wide array of cardiovascular and metabolic biomarkers,

endurance athletes were more likely to have a coronary artery calcium (CAC) score >300 Agatston units or coronary plaques compared with sedentary men with a similar risk profile.<sup>4</sup> Furthermore, men with high levels of physical activity, defined as more than 3000 metabolic equivalents of task (MET)-minutes/week (equivalent to running approximately 6.5 km/day or 350–400 min/week), had higher CAC scores compared with men with lower levels of physical activity.<sup>5</sup> It is still unclear if the higher CAC scores associated with high levels of physical activity are restricted to very high levels of activity, and how current levels of physical activity affect future CAC scores. This study was conducted to evaluate the prospective association between physical activity and CAC scores in a large cohort study of apparently healthy men and women who attended repeated health screening visits.

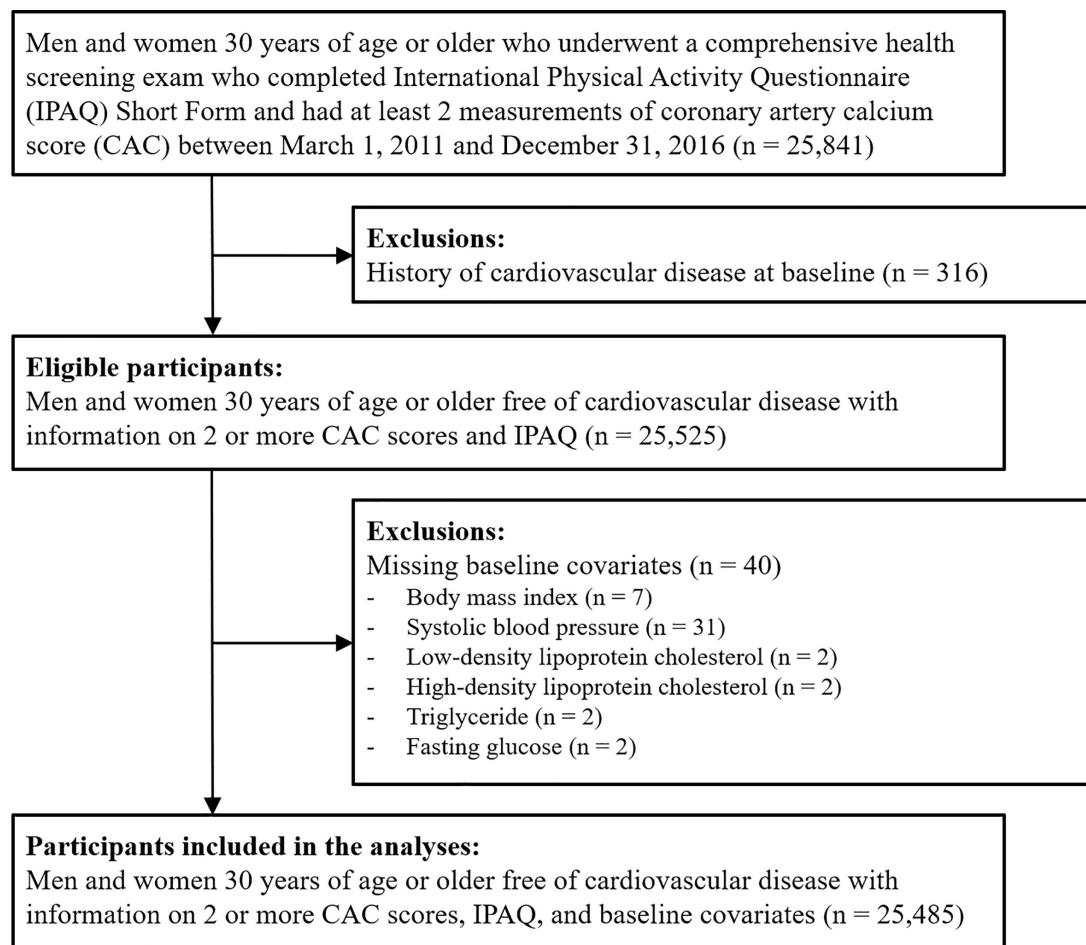
**METHODS****Study population**

The Kangbuk Samsung Health Study is a cohort of Korean men and women ≥18 years of age who underwent comprehensive health examinations annually or biennially at the two Kangbuk Samsung Hospital Total Healthcare Centers located in Seoul and Suwon, South Korea. We included men and women ≥30 years with two or more measurements of CAC score and who had completed the International Physical Activity Questionnaire Short Form questionnaire (IPAQ-SF) between 1 March 2011 and 31 December 2017 (n=25 841). In most cases, CAC scans were available as part of the screening package contracted by the employer of the participant with the health screening centre. We excluded participants with prevalent cardiovascular disease (CVD) at the time of the first CAC measurement (n=316). We then excluded participants with missing data on body mass index (BMI), systolic blood pressure (SBP), lipid levels or fasting glucose levels at baseline (n=40). The final sample included 25 485 participants (22 741 men and 2744 women; figure 1).

The Kangbuk Samsung Hospital Institutional Review Board approved the study and waived the requirement for informed consent as we only used de-identified data obtained as part of routine health screening examinations.

**Data collection**

At each screening visit, study participants filled out a questionnaire, which included questions on medical



**Figure 1** Flowchart of study participants.

history, medication use, family history, smoking habits, alcohol intake, physical activity and education level. Smoking was categorised as never, former and current smoking. Alcohol intake was categorised as none, moderate ( $\leq 20$  g/day for women,  $\leq 30$  g/day for men) and heavy drinking ( $> 20$  g/day for women,  $> 30$  g/day for men). Education level was categorised as  $\leq 12$  and  $> 12$  years of education. Family history of CVD was determined by self-report of heart disease or stroke in a first-degree relative. Prevalent CVD was identified by self-report of a physician diagnosis of coronary heart disease, other heart disease or stroke. Lipid-lowering medication use was also identified by self-report.

Anthropometric measurements were measured at each screening visit by trained medical personnel. BMI was calculated as weight divided by height squared ( $\text{kg/m}^2$ ). Hypertension was defined at the screening visit as a self-reported physician diagnosis, a self-reported use of antihypertensive medications, or a measured blood pressure  $\geq 140/90$  mmHg. Diabetes was defined as a self-reported physician diagnosis, a self-reported use of insulin or other hypoglycaemic agents, or a measured fasting serum glucose  $\geq 126$  mg/dL. Serum triglycerides, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and glucose were measured in fasting serum samples at each screening visit.

The Framingham Risk Score (FRS) for the 10-year risk of coronary events was generated using age, sex, total cholesterol, HDL-cholesterol, SBP and smoking, based on the National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III

algorithm. The FRS was then categorised as  $< 10\%$  (low risk) and  $\geq 10\%$  (moderate-to-high risk).<sup>6</sup>

### Physical activity

The self-administered questionnaire included the validated Korean version of the IPAQ-SF, which we used to measure physical activity levels. IPAQ-SF measures the duration and frequency of physical activities (moderate to vigorous, including walking) performed in any context (ie, work, home and leisure) for over 10 consecutive minutes during a 7-day period. Physical activity was then categorised into three groups: inactive, moderately active ( $\geq 3$  days of vigorous-intensity activity for  $\geq 20$  min/day,  $\geq 5$  days of moderate-intensity activity or walking for  $\geq 30$  min/day, or  $\geq 5$  days of any combination of walking and moderate- or vigorous-intensity activities attaining  $\geq 600$  MET-min/week) and health-enhancing physically active (HEPA;  $\geq 3$  days of vigorous-intensity activity attaining  $\geq 1500$  MET-min/week, or 7 days of any combination of walking, moderate- or vigorous-intensity activities attaining  $\geq 3000$  MET-min/week).<sup>7-9</sup>

### Coronary artery calcium score

We measured CAC scores with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) at both study centres. We used the same standardised protocol with 2.5 mm slice thickness, 400 ms rotation time, 120 kV tube voltage, and 124 mAS (310 mA  $\times$  0.4 s) tube current under electrocardiographically (ECG)-gated dose modulation. CAC scores were

estimated using the Agatston method.<sup>10</sup> The intraclass correlation coefficient for CAC scores was 0.99.

### Statistical analysis

P values for a linear trend in baseline participant characteristics by physical activity categories were calculated by using as predictor a continuous variable for the physical activity level (1, 2 or 3 for inactive, moderately active and HEPA, respectively) in univariable linear regression models (continuous variables) or univariable logistic regression models (dichotomous variables).

We used linear mixed models with random intercepts and slopes for follow-up time to estimate CAC scores at baseline and at 5 years as a function of baseline physical activity. The models were adjusted for age, sex, smoking, alcohol intake, education, family history of CVD, BMI, SBP, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, presence of hypertension, presence of diabetes and lipid-lowering therapy. We then estimated the 5-year change in adjusted CAC scores for each category of physical activity (inactive, moderately active and HEPA) and compared these estimates to the 5-year change in the reference category (inactive). The number of participants in the CAC 0, 1–99 and  $\geq 100$  groups after 5 years of follow-up was estimated based on the empirical Bayes estimates of random intercepts and random slopes for each individual. We performed these analyses on the progression of CAC in the entire cohort and then separately in participants with CAC  $> 0$  and CAC = 0 at baseline. Moreover, because the CAC scores are right-skewed, we performed the same analysis after transforming CAC scores into  $\log_e(\text{CAC} + 1)$ . The estimates from this model were then exponentiated to obtain the geometric means of CAC scores. In addition, we estimated the 5-year progression of CAC separately for those with CAC 1–99 and CAC  $\geq 100$  at baseline.

We further estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of coronary calcium (incident CAC  $> 0$ ) by physical activity category among participants with CAC = 0 at baseline ( $n = 20\,096$ ). Because the exact date of developing coronary calcium occurs between two screening visits, we used a parametric proportional hazards model that allows for this type of interval censoring.<sup>11</sup>

Since participants had been recruited continuously into the study since 2011, only 25.8% of participants who had undergone a CAC scan had two or more CAC measurements prior to the end of the study period. To account for potential differences between participants with a single CAC measurement and those with  $\geq 2$  CAC measurements (online supplemental appendix table 1) we performed sensitivity analysis using inverse probability weights for selection. We estimated the probability of having  $\geq 2$  CAC measurements using baseline characteristics and weighted each individual by the inverse of the predicted probability of having  $\geq 2$  CAC measurements in the analyses.

In addition, we performed the analyses stratified by age at baseline ( $< 40$  and  $\geq 40$  years), sex and FRS at baseline ( $< 10\%$  and  $\geq 10\%$ ). Lastly, using the physical activity category defined at each health examination visit, we allowed the participant's physical activity category to change over time as a time-varying exposure. To estimate the HRs for the development of CAC  $> 0$  in participants with CAC = 0 at baseline, we used pooled logistic regression to account for both time-varying exposure and interval censoring.

All statistical analyses were performed using Stata version 16.0 (StataCorp LP, College Station, TX, USA).

### RESULTS

The mean (SD) age of study participants was 42.0 (6.1) years (table 1). The proportions of participants who were inactive, moderately active and HEPA were 46.8%, 38.0% and 15.2%, respectively. Participants with higher physical activity levels were older, less likely to be current smokers, and had lower levels of total cholesterol, LDL-cholesterol and triglycerides, higher levels of HDL-cholesterol, and higher prevalence of hypertension and presence of CAC than participants with lower physical activity levels.

Participants with CAC  $> 0$  at baseline were older, were more likely to be male and current smokers, and had higher levels of traditional cardiovascular risk factors (online supplemental appendix table 2). The median (IQR) interval between the first and the last CAC measurement was 3.0 (2.0–4.2) years.

The multivariable-adjusted average CAC scores (95% CI) in participants who were inactive, moderately active and HEPA were 9.45 (8.76, 10.14), 10.20 (9.40, 11.00) and 12.04 (10.81, 13.26) at baseline (table 2). Compared with participants who were inactive, the adjusted 5-year average increases in CAC in moderately active and HEPA participants were 3.20 (0.72, 5.69) and 8.16 (4.80, 11.53). Among participants with CAC  $> 0$  at baseline ( $n = 5389$ ), the estimated differences in 5-year average increase in CAC in moderately active and HEPA participants compared with inactive participants were 7.70 (–3.72, 19.11) and 15.05 (0.56, 29.49), respectively (table 3), and among participants with CAC = 0 at baseline ( $n = 20\,096$ ), the estimated differences were 0.17 (–0.18, 0.52) and 0.32 (–0.16, 0.81), respectively (table 4). Based on our results, we estimated 800 (3.1%), 23 051 (90.5%) and 1634 (6.4%) participants would be in the CAC 0, 1–99 and  $\geq 100$  groups after 5 years of follow-up.

Among participants with CAC = 0 at baseline (median follow-up 3.1 years; maximum follow-up 6.7 years), compared with participants who were inactive, the multivariable-adjusted HR (95% CI) for developing CAC  $> 0$  in participants who were moderately active and HEPA were 1.04 (0.94, 1.15) and 1.21 (1.05, 1.38;  $p$  for trend = 0.01), respectively (Model 5, table 5).

The results did not change materially for the analyses using inverse probability weights to account for potential differences between participants with a single CAC measurement and those with  $\geq 2$  CAC measurements (online supplemental appendix tables 3–6) or when we used log-transformed CAC scores (online supplemental appendix table 7). In analysis stratified by age, sex and FRS at baseline, the positive association between physical activity and estimated difference in 5-year average increase in CAC scores was observed in participants  $\geq 40$  years ( $p < 0.001$ ), in both men and women ( $p < 0.001$  and  $p = 0.002$ ), and in both participants with FRS  $< 10\%$  and  $\geq 10\%$  ( $p = 0.009$  and  $p < 0.001$ ). The risk of developing CAC  $> 0$  was highest in the HEPA group in all subgroups except among participants  $< 40$  years (online supplemental appendix tables 8–13). When CAC  $> 0$  at baseline was further categorised into CAC 1–99 and CAC  $\geq 100$ , higher physical activity was associated with greater difference in 5-year change ( $p = 0.06$ ) among those with CAC 1–99 at baseline (online supplemental appendix table 14). However, the number of participants with CAC  $\geq 100$  was too small to provide precise estimates. The results did not change further when physical activity level was allowed to change over time (online supplemental appendix tables 15–18).

### DISCUSSION

In this large prospective study of apparently healthy men and women, physical activity was associated with a higher



## Cardiac risk factors and prevention

**Table 1** Baseline characteristics by physical activity categories

Characteristic	Overall	Inactive	Moderately active	HEPA	P for trend
n	25 485	11 920	9683	3882	
Age, years	42.0 (6.1)	41.7 (5.7)	41.7 (6.1)	43.2 (7.0)	<0.001
Men, %	89.2	87.9	91.7	87.4	0.008
Current smoker, %	35.1	36.4	35.3	30.5	<0.001
High alcohol intake, %	30.3	29.8	29.8	32.8	0.002
Higher education, %	79.9	80.2	81.7	74.1	<0.001
BMI, kg/m <sup>2</sup>	24.7 (3.1)	24.7 (3.2)	24.7 (3.0)	24.8 (3.0)	0.10
SBP, mmHg	114.3 (12.4)	113.8 (12.3)	114.5 (12.4)	115.2 (12.7)	<0.001
DBP, mmHg	74.9 (10.0)	74.8 (10.0)	75.0 (10.0)	74.7 (10.0)	0.96
Fasting glucose, mg/dL	99.5 (17.4)	99.5 (17.9)	99.4 (16.9)	99.7 (16.8)	0.60
Total cholesterol, mg/dL	204.6 (35.8)	205.8 (36.4)	204.4 (35.4)	201.6 (34.8)	<0.001
LDL-C, mg/dL	131.9 (32.5)	132.9 (32.9)	131.9 (32.4)	129.0 (31.9)	<0.001
HDL-C, mg/dL	52.6 (13.2)	51.9 (13.1)	52.5 (13.0)	55.0 (13.8)	<0.001
Triglycerides, mg/dL	123 (87–177)	129 (90–185)	122 (87–177)	109 (77–156)	<0.001
Hypertension, %	19.2	18.5	19.2	21.4	<0.001
Diabetes, %	7.0	6.9	6.9	7.8	0.10
Family history of CVD, %	15.0	14.6	15.4	15.4	0.17
Lipid-lowering therapy, %	4.6	4.5	4.6	4.8	0.73
CAC score	14.7 (75.7)	11.8 (60.8)	14.3 (71.0)	24.3 (116.9)	<0.001
CAC >0, %	21.2	19.6	21.7	25.4	<0.001
CAC 1–99, %	17.7	16.6	18.1	20.2	
CAC ≥100, %	3.4	2.8	3.5	5.0	

Values are means (SD), medians (IQR) or percentages. High alcohol intake is defined as >30 g/day for men and >20 g/day for women. Higher education is defined as college graduate or higher.

BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physically active; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation.

prevalence of CAC at baseline and with a faster progression of CAC over follow-up. The association was graded across categories of increased physical activity, and it was observed both in

participants free of CAC at baseline and in those with prevalent CAC. The association persisted after we adjusted for BMI, blood pressure and lipid levels, all potential mediators of the cardiovascular benefits of physical activity. Our findings should not be interpreted as a harmful effect of physical activity, but, rather, need to be taken into account when evaluating the progression of CAC in patients who exercise to reduce cardiovascular risk.

The cardiovascular benefits of physical activity are unquestionable.<sup>3</sup> The 2018 Physical Activity Guidelines for Americans recommend at least 150–300 minutes/week of moderate-intensity or 75–150 minutes/week of vigorous-intensity aerobic physical activity.<sup>3</sup> Regular physical activity reduces the risk of many adverse health outcomes, including mortality, CVD, diabetes, hypertension, obesity and dyslipidaemia.<sup>12–14</sup> Some health benefits occur almost immediately after physical activity and, in general, there are additional health benefits with higher levels of physical activity. For example, in a study of 130 000 participants from high-, middle- and low-income countries, higher physical activity levels were associated with lower incidence of all-cause mortality and major CVD.<sup>15</sup> In addition to the benefits of high-intensity physical activity, even small increments in physical activity are beneficial in sedentary subjects.

High levels of physical activity, however, may be associated with a higher risk of coronary artery calcification. In a meta-analysis, higher physical activity levels were associated with a higher prevalence of CAC (pooled odds ratio (OR) 1.84; 95% CI 1.41 to 2.93).<sup>16</sup> In the Coronary Artery Risk Development in Young Adults (CARDIA) study, white young adults who exercised three or more times the recommended amount in the Physical Activity Guidelines had almost twice the prevalence of

**Table 2** Five-year progression of coronary artery calcium by physical activity categories at baseline

Parameter	Inactive	Moderately active	HEPA
n	11 920	9683	3882
Mean CAC score (95% CI)			
Baseline	9.45 (8.76, 10.14)	10.20 (9.40, 11.00)	12.04 (10.81, 13.26)
Year 5	24.32 (22.54, 26.09)	28.27 (26.33, 30.20)	35.06 (31.99, 38.13)
Five-year difference (Year 5–baseline)	14.87 (13.18, 16.55)	18.07 (16.24, 19.89)	23.03 (20.11, 19.89)
Difference in mean CAC score (95% CI)			
Baseline	0 (Reference)	0.75 (–0.31, 1.81)	2.58 (1.17, 3.99)
Year 5	0 (Reference)	3.95 (1.32, 6.57)	10.75 (7.20, 14.30)
Difference in differences (Year 5–baseline)	0 (Reference)	3.20 (0.72, 5.69)	8.16 (4.80, 11.53)

Values were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, centre, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, fasting glucose, hypertension, diabetes and lipid-lowering therapy. P value for trend across International Physical Activity Questionnaire (IPAQ) categories for difference in differences was highly statistically significant ( $p<0.001$ ).

CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Table 3** Five-year progression of coronary artery calcium (CAC) by physical activity categories among participants with prevalent CAC (CAC >0) at baseline

Parameter	Inactive	Moderately active	HEPA
n	2315	2096	978
Mean CAC score (95% CI)			
Baseline	74.25 (69.11, 79.39)	76.13 (70.69, 81.58)	79.63 (72.11, 87.15)
Year 5	150.12 (140.93, 159.31)	159.70 (150.15, 169.25)	170.52 (156.67, 184.38)
Five-year difference (Year 5–baseline)	75.87 (67.92, 83.82)	83.57 (75.37, 91.77)	90.89 (78.80, 102.99)
Difference in mean CAC scores (95% CI)			
Baseline	0 (Reference)	1.88 (–5.80, 9.38)	5.38 (–3.80, 14.56)
Year 5	0 (Reference)	9.58 (–3.68, 22.83)	20.40 (3.74, 37.07)
Difference in differences (Year 5–baseline)	0 (Reference)	7.70 (–3.72, 19.11)	15.02 (0.56, 29.49)

Values were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, centre, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, fasting glucose, hypertension, diabetes and lipid-lowering therapy. P value for trend across International Physical Activity Questionnaire (IPAQ) categories for difference in differences was 0.03.

CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

CAC >0 compared with those who exercised at levels below the Guidelines (OR 1.80; 95% CI 1.21 to 2.67).<sup>17</sup> Older adults in the highest tertile of self-reported physical activity in the Whitehall II study also had a higher prevalence of CAC compared with those in the lowest tertile of physical activity<sup>18</sup> and, among athletes, the most active group (>2000 MET-min/week) had a higher prevalence of CAC >0 and higher CAC scores compared with the least active group (<1000 MET-min/week).<sup>19</sup> Finally, in the Coopers Clinic Study, there was only a modest and non-statistically significant association between physical activity levels

**Table 4** Five-year progression of coronary artery calcium (CAC) by physical activity categories among participants with no CAC (CAC=0) at baseline

Parameter	Inactive	Moderately active	HEPA
n	9605	7587	2904
Mean CAC score at 5 years (95% CI)	1.32 (1.09, 1.55)	1.49 (1.23, 1.75)	1.64 (1.21, 2.06)
Difference in mean CAC scores at 5 years (95% CI)	0 (Reference)	0.17 (–0.18, 0.52)	0.32 (–0.16, 0.81)

Values were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, centre, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, fasting glucose, hypertension, diabetes and lipid-lowering therapy. P value for trend across International Physical Activity Questionnaire (IPAQ) categories for difference in differences 0.16.

CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Table 5** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC) (CAC >0) among participants with no coronary calcium (CAC=0) at baseline

Model	Inactive	Moderately active	HEPA	P for trend
n	9605	7587	2904	
Model 1	Reference	1.00 (0.90, 1.11)	1.12 (0.98, 1.28)	0.18
Model 2	Reference	1.00 (0.91, 1.11)	1.13 (0.99, 1.30)	0.13
Model 3	Reference	1.04 (0.93, 1.15)	1.19 (1.04, 1.37)	0.02
Model 4	Reference	1.04 (0.94, 1.15)	1.21 (1.05, 1.38)	0.01
Model 5	Reference	1.04 (0.94, 1.15)	1.21 (1.05, 1.38)	0.01

Model 1: adjusted for age, sex and centre. Model 2: Model 1 + smoking, alcohol, education and family history of cardiovascular disease. Model 3: Model 2 + body mass index, systolic blood pressure, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides and fasting glucose. Model 4: Model 3 + history of diabetes and history of hypertension. Model 5: Model 4 + lipid-lowering therapy.

CAC, coronary artery calcium; HEPA, health-enhancing physically active.

and CAC scores  $\geq 400$ , but physical activity was still inversely associated with all-cause mortality, particularly in the subgroup of participants with CAC scores  $\geq 400$  at baseline.<sup>20 21</sup>

A possible mechanism underlying this association is that physical activity may increase coronary atherosclerosis. Potential pathways include mechanical stress and vessel wall injury of coronary arteries,<sup>22</sup> physiological responses during exercise, such as increased blood pressure,<sup>23</sup> increased parathyroid hormone levels<sup>24</sup> and changes in coronary haemodynamics and inflammation.<sup>25</sup> In addition, other factors, such as diet, vitamins and minerals, may change with physical activity.<sup>26</sup>

The second possibility is that physical activity may increase CAC scores without increasing CVD risk. The standard Agatston CAC scores are calculated as a combination of calcium density and the volume of plaque burden. Higher calcium density, which suggests more stable, calcified plaque, produces a higher CAC score, however, it is associated with lower CVD risk.<sup>10</sup> In the Multi-Ethnic Study of Atherosclerosis, when CAC volume and density were analysed separately, recreational physical activity was positively associated with CAC density but not with CAC volume after controlling for CAC density. However, higher levels of recreational physical activity were inversely associated with incident CVD independent of CAC density and volume, possibly through stabilisation of coronary plaques.<sup>27</sup> Moreover, in a study of healthy athletes, more active participants had a more benign plaque composition with fewer mixed plaques and more often only calcified plaques, also suggesting that exercise may contribute to the stabilisation of atherosclerotic plaques.<sup>19</sup>

In general, progression of CAC scores is associated with a higher risk of CVD among individuals with CAC=0 and those with CAC >0.<sup>28</sup> Moreover, the absence of detectable CAC is a strong negative predictor of CVD,<sup>29</sup> whereas the presence of any CAC, even at very low levels, is associated with an increased risk of CVD.<sup>30</sup> However, considering the undeniable protective effect of physical activity on CVD, the positive relationship between physical activity with CAC progression should be interpreted with caution as the complex interplay between physical activity, CAC progression and subsequent CVD risk remains largely unknown.

In most previous studies the association of physical activity and CAC scores had been evaluated in cross-sectional analyses. Our study provides evidence that participants with higher levels of physical activity at baseline not only have higher CAC scores, but are more likely to develop CAC in the future. In our analysis, the positive association of physical activity with progression of

CAC was graded across categories of physical activity and was not restricted to participants with extreme levels of physical activity. This association may be clinically relevant, as patients who increase their exercise levels for CVD prevention may be discouraged by increasing CAC scores, despite the unquestionable beneficial effects of physical activity on morbidity and mortality. Increasing CAC score, however, may be an indication of stabilising atherosclerotic plaque and warrants careful interpretation.

There are several limitations to consider in the interpretation of our findings. First, physical activity was measured by a self-reported questionnaire and we did not have an objective assessment of physical activity. While we used a validated questionnaire for assessing physical activity, it is still subject to substantial measurement error, most likely overestimating physical activity levels. Misclassification in physical activity, however, is likely non-differential with respect to CAC scores and will tend to underestimate observed associations. Second, we could not evaluate the association between physical activity and CAC levels with incident cardiovascular events as the information was not available. This association is likely complex and will require long-term follow-up of large cohorts. Third, we did not have information on CAC density or volume in our dataset. A more refined measurement of CAC will provide a better understanding of the association between physical activity, CAC progression and subsequent CVD risk. Fourth, as an observational study, we may not have fully accounted for the baseline differences in the participant characteristics and the potential for residual confounding remains. Finally, our study population was comprised of apparently healthy, low-risk, young to middle-aged Korean men and women, and our findings may not generalise to other risk or race/ethnicity groups.

In conclusion, we identified a positive, graded association between physical activity with the prevalence and the progression of coronary calcium scores. Although the implications of a positive association between physical activity and CAC in terms of cardiovascular events need to be established in future studies, our findings do not question the well-established cardiovascular benefits of physical activity. Patients and physicians, however, need to consider that engaging in physical activity may accelerate the progression of coronary calcium, possibly due to plaque healing, stabilisation and calcification.

## Key messages

### What is already known about this subject?

- While physical activity improves a wide array of cardiovascular and metabolic biomarkers, the association between physical activity and progression of coronary artery calcium (CAC) scores is unclear.

### What does this study add?

- The estimated adjusted 5-year increase in CAC was higher in participants engaged in moderate physical activity or health-enhancing physical activity compared with those who were inactive. The progression of CAC was faster with higher physical activity.

### How might this impact on clinical practice?

- Engaging in physical activity may accelerate the progression of CAC, possibly due to plaque healing, stabilisation and calcification.

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**Appendix Table 1.** Baseline characteristics by number of CAC measurements (n = 98,780)

	1 measurement	≥ 2 measurements	P-value
Number	73,295	25,485	
Age	41.8 (8.2)	42.0 (6.1)	0.009
Men, %	71.5	89.2	< 0.001
Physical activity, %			< 0.001
Inactive	49.4	46.8	
Moderately active	35.0	38.0	
HEPA	15.7	15.2	
Current smoker, %	26.1	35.1	< 0.001
High alcohol intake, %	23.5	30.3	< 0.001
BMI, kg/m <sup>2</sup>	24.2 (3.3)	24.7 (3.1)	< 0.001
Higher education, %	78.3	79.8	< 0.001
SBP, mmHg	111.7 (12.5)	114.3 (12.4)	< 0.001
DBP, mmHg	72.4 (9.8)	74.9 (10.0)	< 0.001
Fasting glucose, mg/dl	97.2 (15.7)	99.5 (17.4)	< 0.001
Total cholesterol, mg/dl	197.8 (34.2)	204.6 (35.8)	< 0.001
LDL-C, mg/dl	127.6 (31.8)	131.9 (32.5)	< 0.001
HDL-C, mg/dl	55.7 (14.6)	52.6 (13.2)	< 0.001
Triglycerides, mg/dl	106 (75-156)	123 (87-177)	< 0.001
Hypertension, %	15.0	19.2	< 0.001
Diabetes, %	5.4	7.0	< 0.001
Family history of CVD, %	12.4	15.0	< 0.001
Lipid lowering therapy, %	4.0	4.6	< 0.001
CAC > 0, %	10.5	21.2	< 0.001
CAC 1 – 99, %	8.6	17.7	
CAC ≥ 100, %	1.9	3.4	

Numbers in the Table are mean (standard deviation), median (interquartile range), or percentages.

Abbreviations: BMI, body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physically active; LDL-C, low-density lipoprotein cholesterol; and SBP: systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.



**Appendix Table 2.** Baseline characteristics by coronary artery calcification categories at baseline (n = 25,485).

	CAC = 0	CAC 1 – 99	CAC ≥ 100
Number	20,096	4,522	867
Age	41.0 (5.5)	45.1 (6.4)	48.4 (7.5)
Men, %	87.4	95.7	97.0
Physical activity, %			
Inactive	47.8	43.8	38.4
Moderately active	37.8	38.8	39.2
HEPA	14.5	17.3	22.4
Current smoker, %	33.8	39.5	41.1
High alcohol intake, %	28.2	37.3	39.9
BMI, kg/m <sup>2</sup>	24.6 (3.1)	25.3 (3.0)	25.5 (3.0)
Higher education, %	79.6	80.9	78.9
SBP, mmHg	113.5 (12.2)	116.7 (12.6)	118.3 (12.6)
DBP, mmHg	74.1 (9.9)	77.5 (10.0)	78.3 (10.0)
Fasting glucose, mg/dl	98.2 (15.3)	103.4 (21.7)	108.5 (28.3)
Total cholesterol, mg/dl	203.0 (34.9)	211.2 (38.1)	207.4 (40.2)
LDL-C, mg/dl	130.4 (31.9)	138.5 (34.1)	134.5 (35.7)
HDL-C, mg/dl	53.1 (13.4)	50.7 (12.5)	50.9 (13.1)
Triglycerides, mg/dl	119 (84-172)	137 (98-196)	135 (98-197)
Hypertension, %	15.4	30.9	45.8
Diabetes, %	5.1	12.9	20.9
Family history of CVD, %	14.4	17.3	17.9
Lipid-lowering therapy, %	3.3	8.2	16.6

Numbers in the Table are mean (standard deviation), median (interquartile range), or percentages.

Abbreviations: BMI, body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP: systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.

All variables evaluated were statistically different by coronary artery calcification categories at baseline (*P*-value < 0.001).

**Appendix Table 3.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA
Number	48,111	35,305	15,364
Mean CAC score (95% CI)			
Baseline	8.79 (7.75, 9.83)	10.96 (9.53, 12.39)	15.66 (12.53, 18.78)
Year 5	22.78 (20.75, 24.81)	28.09 (25.61, 30.56)	37.80 (32.65, 42.96)
5-year difference (Year 5 – baseline)	13.99 (12.68, 15.30)	17.13 (15.65, 18.61)	22.15 (19.26, 25.04)
Difference in mean CAC score (95% CI)			
Baseline	Reference	2.17 (0.35, 3.99)	6.86 (3.40, 10.33)
Year 5	Reference	5.31 (2.06, 8.57)	15.03 (9.32, 20.74)
Difference in differences (Year 5 – baseline)	Reference	3.14 (1.16, 5.12)	8.16 (4.99, 11.34)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant ( $P < 0.001$ ).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 4.** 5-year progression of coronary artery calcium (CAC) by physical activity categories among participants with prevalent CAC (CAC > 0) at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA
Number	5,565	4,895	2,629
Mean CAC score (95% CI)			
Baseline	67.70 (61.03, 74.38)	73.37 (66.12, 80.43)	86.99 (74.41, 99.57)
Year 5	142.43 (130.21, 154.65)	156.15 (144.06, 168.23)	180.11 (155.43, 204.80)
5-year difference (Year 5 – baseline)	74.73 (67.29, 82.17)	82.77 (76.03, 89.52)	93.13 (77.13, 109.13)
Difference in mean CAC scores (95% CI)			
Baseline	Reference	5.67 (-2.35, 13.69)	19.29 (6.01, 32.56)
Year 5	Reference	13.72 (-2.00, 29.44)	37.68 (11.03, 64.34)
Difference in differences (Year 5 – baseline)	Reference	8.05 (-1.98, 18.07)	18.40 (0.77, 36.02)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was 0.02.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 5.** 5-year progression of coronary artery calcium (CAC) by physical activity categories among participants with no CAC (CAC = 0) at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA
Number	42,546	30,410	12,735
Mean CAC score at 5 years (95% CI)	1.34 (1.15, 1.53)	1.50 (1.22, 1.78)	1.68 (1.13, 2.23)
Difference in mean CAC scores at 5 years (95% CI)	Reference	0.17 (-0.16, 0.51)	0.36 (-0.22, 0.94)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences 0.16.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 6.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA	P for trend
Number	49,486	35,713	14,995	
Model 1	Reference	1.02 (0.85, 1.21)	1.13 (0.91, 1.41)	0.33
Model 2	Reference	1.02 (0.86, 1.21)	1.13 (0.91, 1.41)	0.33
Model 3	Reference	1.05 (0.88, 1.24)	1.17 (0.94, 1.46)	0.19
Model 4	Reference	1.05 (0.88, 1.24)	1.18 (0.95, 1.47)	0.17
Model 5	Reference	1.05 (0.89, 1.24)	1.18 (0.95, 1.47)	0.16

Model 1: adjusted for age, sex, and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.



**Appendix Table 7.** 5-year progression in the geometric mean of coronary artery calcium (CAC) by physical activity categories.

	<b>Inactive</b>	<b>Moderately active</b>	<b>HEPA</b>
Number	48,111	35,305	15,364
Geometric mean CAC score (95% CI)			
Baseline	0.64 (0.60, 0.68)	0.75 (0.70, 0.80)	0.86 (0.78, 0.94)
Year 5	1.43 (1.36, 1.51)	1.67 (1.58, 1.76)	2.01 (1.85, 2.17)
5-year difference (Year 5 – baseline)	0.80 (0.74, 0.85)	0.92 (0.86, 0.98)	1.15 (1.03, 1.26)
Difference in geometric mean CAC score (95% CI)			
Baseline	Reference	0.11 (0.05, 0.17)	0.22 (0.13, 0.31)
Year 5	Reference	0.24 (0.12, 0.35)	0.57 (0.40, 0.75)
Difference in differences (Year 5 – baseline)	Reference	0.13 (0.14, 0.21)	0.35 (0.22, 0.48)

Values in the Table were estimated from a random intercept and random slope mixed model for  $\log_e(\text{CAC score} + 1)$  adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. The estimates were then exponentiated to obtain the geometric means of CAC scores at 5-years and the 5-year change. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant ( $P < 0.001$ ). Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 8.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by age.

	Inactive	Moderately active	HEPA
<b>Age &lt; 40</b>			
Number	4,288	3,573	1,127
Mean CAC score (95% CI)			
Baseline	3.12 (2.25, 3.98)	3.71 (2.74, 4.69)	3.07 (1.46, 4.68)
Year 5	9.81 (8.28, 11.33)	10.51 (8.85, 12.18)	9.54 (6.63, 12.45)
5-year difference (Year 5 – baseline)	6.69 (5.31, 8.07)	6.80 (5.32, 8.28)	6.47 (3.82, 9.13)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	0.60 (-0.61, 1.80)	-0.05 (-1.82, 1.73)
Year 5	0 (reference)	0.70 (-1.49, 2.91)	-0.26 (-3.52, 2.99)
Difference in differences (Year 5 – baseline)	0 (reference)	0.11 (-1.91, 2.14)	-0.22 (-3.21, 2.78)
<b>Age ≥ 40</b>			
Number	7,632	6,110	2,755
Mean CAC score (95% CI)			
Baseline	9.74 (7.45, 12.02)	13.31 (10.76, 15.85)	23.41 (19.72, 27.09)
Year 5	29.54 (26.35, 32.73)	38.17 (34.65, 41.69)	52.64 (47.45, 57.82)
5-year difference (Year 5 – baseline)	19.81 (17.26, 22.35)	24.86 (22.08, 27.65)	29.23 (25.05, 33.40)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	3.57 (0.30, 6.84)	13.67 (9.42, 17.93)
Year 5	0 (reference)	8.63 (3.99, 13.27)	23.09 (17.07, 29.12)
Difference in differences (Year 5 – baseline)	0 (reference)	5.06 (1.28, 8.83)	9.42 (4.53, 14.31)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was not significant in age < 40 group (*P* = 0.95) but statistically significant on age ≥ 40 group (*P* < 0.001).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 9.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline by age.

	Inactive	Moderately active	HEPA	P for trend
<b>Age &lt; 40</b>				
Number	3,883	3,228	1,020	
Model 1	Reference	0.94 (0.78, 1.13)	1.08 (0.83, 1.40)	0.88
Model 2	Reference	0.94 (0.78, 1.13)	1.09 (0.83, 1.42)	0.84
Model 3	Reference	0.95 (0.79, 1.15)	1.14 (0.88, 1.49)	0.59
Model 4	Reference	0.96 (0.80, 1.16)	1.14 (0.88, 1.49)	0.56
Model 5	Reference	0.96 (0.80, 1.16)	1.13 (0.87, 1.48)	0.59
<b>Age ≥ 40</b>				
Number	5,722	4,359	1,884	
Model 1	Reference	1.03 (0.91, 1.16)	1.20 (1.03, 1.40)	0.04
Model 2	Reference	1.03 (0.91, 1.16)	1.19 (1.02, 1.39)	0.05
Model 3	Reference	1.07 (0.94, 1.21)	1.26 (1.08, 1.47)	0.006
Model 4	Reference	1.07 (0.95, 1.21)	1.27 (1.09, 1.49)	0.005
Model 5	Reference	1.07 (0.95, 1.21)	1.27 (1.09, 1.49)	0.004

Model 1: adjusted for sex and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 10.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by sex.

	Inactive	Moderately active	HEPA
<b>Men</b>			
Number	10,472	8,875	3,394
Mean CAC score (95% CI)			
Baseline	10.11 (8.42, 11.80)	12.70 (10.89, 14.52)	18.30 (15.45, 21.16)
Year 5	26.41 (24.08, 28.74)	31.41 (28.93, 33.90)	42.34 (38.36, 46.33)
5-year difference (Year 5 – baseline)	16.30 (14.44, 18.16)	18.71 (16.74, 20.68)	24.04 (20.81, 27.27)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	2.59 (0.23, 4.95)	8.19 (4.94, 11.45)
Year 5	0 (reference)	5.00 (1.68, 8.32)	15.93 (11.36, 20.51)
Difference in differences (Year 5 – baseline)	0 (reference)	2.41 (-0.30, 5.12)	7.74 (4.04, 11.46)
<b>Women</b>			
Number	1,448	808	488
Mean CAC score (95% CI)			
Baseline	1.47 (-0.85, 3.78)	3.13 (0.23, 6.04)	1.57 (-2.06, 5.21)
Year 5	4.61 (1.58, 7.63)	9.97 (6.08, 13.86)	10.39 (5.47, 15.31)
5-year difference (Year 5 – baseline)	3.14 (1.14, 5.14)	6.83 (4.17, 9.50)	8.82 (5.41, 12.23)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	1.67 (-1.55, 4.89)	0.11 (-3.75, 3.97)
Year 5	0 (reference)	5.36 (0.80, 9.92)	5.78 (0.34, 11.23)
Difference in differences (Year 5 – baseline)	0 (reference)	3.69 (0.36, 7.02)	5.68 (1.72, 9.63)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant for both subgroups ( $P < 0.001$  and  $P = 0.002$  in men and women, respectively).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.



**Appendix Table 11.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline by sex.

	Inactive	Moderately active	HEPA	P for trend
<b>Men</b>				
Number	8,256	6,848	2,467	
Model 1	Reference	1.00 (0.90, 1.11)	1.11 (0.97, 1.28)	0.18
Model 2	Reference	1.01 (0.91, 1.12)	1.13 (0.98, 1.30)	0.13
Model 3	Reference	1.04 (0.94, 1.15)	1.19 (1.34, 1.37)	0.02
Model 4	Reference	1.04 (0.94, 1.16)	1.20 (1.05, 1.38)	0.02
Model 5	Reference	1.04 (0.94, 1.16)	1.20 (1.05, 1.38)	0.02
<b>Women</b>				
Number	1,349	739	437	
Model 1	Reference	0.92 (0.53, 1.60)	1.18 (0.65, 2.14)	0.72
Model 2	Reference	0.93 (0.54, 1.61)	1.20 (0.66, 2.17)	0.68
Model 3	Reference	0.95 (0.55, 1.65)	1.23 (0.68, 2.22)	0.60
Model 4	Reference	0.93 (0.54, 1.61)	1.24 (0.69, 2.25)	0.59
Model 5	Reference	0.94 (0.54, 1.63)	1.24 (0.69, 2.25)	0.57

Model 1: adjusted for age and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 12.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by Framingham Risk Score.

	Inactive	Moderately active	HEPA
<b>FRS &lt; 10%</b>			
Number	9,457	7,642	2,969
Mean CAC score (95% CI)			
Baseline	10.85 (9.18, 12.53)	12.34 (10.48, 14.19)	12.18 (9.25, 15.11)
Year 5	20.88 (18.54, 23.23)	24.11 (21.54, 26.68)	27.16 (23.04, 31.27)
5-year difference (Year 5 – baseline)	10.03 (8.12, 11.94)	11.78 (9.71, 13.84)	14.98 (11.62, 18.33)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	1.48 (-0.95, 3.92)	1.33 (-2.01, 4.67)
Year 5	0 (reference)	3.23 (-0.21, 6.66)	6.27 (1.56, 10.99)
Difference in differences (Year 5 – baseline)	0 (reference)	1.75 (-1.07, 4.56)	4.95 (1.09, 8.81)
<b>FRS ≥ 10%</b>			
Number	1,815	1,454	601
Mean CAC score (95% CI)			
Baseline	15.75 (11.52, 19.99)	21.75 (17.14, 26.35)	57.20 (50.40, 64.00)
Year 5	59.60 (53.88, 65.31)	75.82 (69.56, 82.08)	121.67 (112.11, 131.22)
5-year difference (Year 5 – baseline)	43.84 (39.40, 48.28)	54.08 (49.17, 58.99)	64.47 (56.73, 72.21)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	5.99 (0.44, 11.54)	41.44 (33.99, 48.90)
Year 5	0 (reference)	16.22 (8.25, 24.20)	62.07 (51.33, 72.81)
Difference in differences (Year 5 – baseline)	0 (reference)	10.24 (3.61, 16.86)	20.62 (11.70, 29.55)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant for both subgroups ( $P = 0.009$  and  $P < 0.001$  in FRS < 10% and FRS ≥ 10% group, respectively).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 13.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline by Framingham Risk Score.

	Inactive	Moderately active	HEPA	P for trend
<b>FRS &lt; 10%</b>				
Number	8,000	6,323	2,386	
Model 1	Reference	0.99 (0.87, 1.11)	1.17 (1.00, 1.36)	0.18
Model 2	Reference	0.98 (0.87, 1.11)	1.16 (0.99, 1.35)	0.21
Model 3	Reference	1.00 (0.88, 1.13)	1.18 (1.01, 1.38)	0.11
Model 4	Reference	1.00 (0.89, 1.13)	1.19 (1.01, 1.39)	0.11
Model 5	Reference	1.00 (0.89, 1.13)	1.19 (1.01, 1.39)	0.10
<b>FRS ≥ 10%</b>				
Number	1,058	785	267	
Model 1	Reference	1.10 (0.89, 1.37)	1.17 (0.87, 1.56)	0.06
Model 2	Reference	1.11 (0.89, 1.37)	1.20 (0.90, 1.61)	0.05
Model 3	Reference	1.15 (0.93, 1.43)	1.26 (0.94, 1.69)	0.05
Model 4	Reference	1.16 (0.93, 1.43)	1.32 (0.98, 1.77)	0.04
Model 5	Reference	1.16 (0.93, 1.44)	1.31 (0.97, 1.75)	0.04

Model 1: adjusted for age, sex, and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 14.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by CAC scores.

	Inactive	Moderately active	HEPA
<b>CAC 1–99</b>			
Number	1,982	1,756	784
Mean CAC score (95% CI)			
Baseline	19.43 (17.92, 20.94)	19.86 (18.27, 21.44)	20.55 (18.42, 22.67)
Year 5	64.47 (61.08, 67.85)	67.36 (63.80, 70.91)	71.20 (65.95, 76.45)
5-year difference (Year 5 – baseline)	45.04 (41.83, 48.24)	47.50 (44.14, 50.86)	50.66 (45.58, 55.73)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	0.43 (-1.26, 2.11)	1.12 (-1.08, 3.32)
Year 5	0 (reference)	2.89 (-1.81, 7.57)	6.74 (0.65, 12.82)
Difference in differences (Year 5 – baseline)	0 (reference)	2.46 (-2.18, 7.10)	5.62 (-0.38, 11.63)
<b>CAC ≥ 100</b>			
Number	333	340	194
Mean CAC score (95% CI)			
Baseline	168.45 (119.42, 217.48)	184.76 (134.99, 234.53)	239.68 (179.27, 300.08)
Year 5	432.32 (367.96, 396.68)	467.49 (402.97, 532.01)	487.85 (407.72, 567.98)
5-year difference (Year 5 – baseline)	263.87 (217.66, 310.07)	282.73 (237.11, 328.34)	248.17 (189.70, 306.65)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	16.31 (-29.30, 61.92)	74.23 (16.64, 125.81)
Year 5	0 (reference)	35.17 (-39.00, 109.35)	55.53 (-31.02, 142.09)
Difference in differences (Year 5 – baseline)	0 (reference)	18.86 (-46.07, 83.79)	-15.69 (-90.22, 58.84)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-values for trend across IPAQ categories for difference in differences were not statistically significant (*P* = 0.06 and *P* = 0.78 in CAC 1–99 and CAC ≥ 100 group, respectively).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.



**Appendix Table 15.** 5-year progression of coronary artery calcium (CAC) by time-varying physical activity categories at baseline.

	Inactive	Moderately active	HEPA
Mean CAC score (95% CI)			
Baseline	10.23 (9.02, 11.45)	10.28 (9.01, 11.55)	11.30 (9.65, 12.96)
Year 5	24.42 (22.65, 26.20)	27.82 (25.98, 29.65)	35.83 (33.29, 38.37)
5-year difference (Year 5 – baseline)	14.19 (12.50, 15.88)	17.54 (15.72, 19.35)	24.53 (21.68, 27.38)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	0.05 (-1.11, 1.20)	1.07 (-0.54, 2.67)
Year 5	0 (reference)	3.39 (1.42, 5.36)	11.41 (8.74, 14.08)
Difference in differences (Year 5 – baseline)	0 (reference)	3.35 (0.88, 5.82)	10.34 (7.03, 13.66)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant ( $P < 0.001$ ).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 16.** 5-year progression of coronary artery calcium (CAC) by time-varying physical activity categories among participants with prevalent CAC (CAC > 0) at baseline.

	Inactive	Moderately active	HEPA
Mean CAC score (95% CI)			
Baseline	73.62 (68.33, 78.91)	73.45 (68.14, 78.76)	76.68 (70.43, 82.92)
Year 5	149.08 (141.25, 156.91)	154.33 (146.60, 162.05)	170.87 (161.33, 180.41)
5-year difference (Year 5 – baseline)	75.47 (68.18, 82.75)	80.88 (73.63, 88.12)	94.19 (83.91, 104.48)
Difference in mean CAC scores (95% CI)			
Baseline	0 (reference)	-0.17 (-4.36, 4.03)	3.06 (-2.54, 8.66)
Year 5	0 (reference)	5.24 (-1.60, 12.08)	21.79 (12.56, 31.01)
Difference in differences (Year 5 – baseline)	0 (reference)	5.41 (-3.53, 14.35)	18.73 (6.82, 30.63)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was 0.003.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 17.** 5-year progression of coronary artery calcium (CAC) by time-varying physical activity categories among participants with no CAC (CAC = 0) at baseline.

	Inactive	Moderately active	HEPA
Mean CAC score at 5 years (95% CI)	1.18 (0.97, 1.38)	1.74 (1.52, 1.95)	1.82 (1.51, 2.12)
Difference in mean CAC scores at 5 years (95% CI)	0 (reference)	0.56 (0.33, 0.79)	0.67 (0.32, 1.02)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was < 0.001.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 18.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) by time-varying physical activity categories among participants with no coronary calcium (CAC = 0) at baseline.

	Inactive	Moderately active	HEPA	P for trend
Model 1	Reference	0.87 (0.78, 0.96)	0.98 (0.85, 1.12)	0.18
Model 2	Reference	0.92 (0.83, 1.02)	0.98 (0.85, 1.13)	0.41
Model 3	Reference	1.01 (0.91, 1.12)	1.15 (1.00, 1.33)	0.11
Model 4	Reference	1.03 (0.92, 1.14)	1.17 (1.01, 1.35)	0.06
Model 5	Reference	1.03 (0.92, 1.14)	1.17 (1.01, 1.36)	0.06
Model 6	Reference	1.02 (0.91, 1.13)	1.17 (1.01, 1.35)	0.08

Model 1: adjusted for age, sex, and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy. Model 6: Model 5 + time difference.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 1.** Baseline characteristics by number of CAC measurements (n = 98,780)

	1 measurement	≥ 2 measurements	P-value
Number	73,295	25,485	
Age	41.8 (8.2)	42.0 (6.1)	0.009
Men, %	71.5	89.2	< 0.001
Physical activity, %			< 0.001
Inactive	49.4	46.8	
Moderately active	35.0	38.0	
HEPA	15.7	15.2	
Current smoker, %	26.1	35.1	< 0.001
High alcohol intake, %	23.5	30.3	< 0.001
BMI, kg/m <sup>2</sup>	24.2 (3.3)	24.7 (3.1)	< 0.001
Higher education, %	78.3	79.8	< 0.001
SBP, mmHg	111.7 (12.5)	114.3 (12.4)	< 0.001
DBP, mmHg	72.4 (9.8)	74.9 (10.0)	< 0.001
Fasting glucose, mg/dl	97.2 (15.7)	99.5 (17.4)	< 0.001
Total cholesterol, mg/dl	197.8 (34.2)	204.6 (35.8)	< 0.001
LDL-C, mg/dl	127.6 (31.8)	131.9 (32.5)	< 0.001
HDL-C, mg/dl	55.7 (14.6)	52.6 (13.2)	< 0.001
Triglycerides, mg/dl	106 (75-156)	123 (87-177)	< 0.001
Hypertension, %	15.0	19.2	< 0.001
Diabetes, %	5.4	7.0	< 0.001
Family history of CVD, %	12.4	15.0	< 0.001
Lipid lowering therapy, %	4.0	4.6	< 0.001
CAC > 0, %	10.5	21.2	< 0.001
CAC 1 – 99, %	8.6	17.7	
CAC ≥ 100, %	1.9	3.4	

Numbers in the Table are mean (standard deviation), median (interquartile range), or percentages.

Abbreviations: BMI, body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physically active; LDL-C, low-density lipoprotein cholesterol; and SBP: systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.



**Appendix Table 2.** Baseline characteristics by coronary artery calcification categories at baseline (n = 25,485).

	CAC = 0	CAC 1 – 99	CAC ≥ 100
Number	20,096	4,522	867
Age	41.0 (5.5)	45.1 (6.4)	48.4 (7.5)
Men, %	87.4	95.7	97.0
Physical activity, %			
Inactive	47.8	43.8	38.4
Moderately active	37.8	38.8	39.2
HEPA	14.5	17.3	22.4
Current smoker, %	33.8	39.5	41.1
High alcohol intake, %	28.2	37.3	39.9
BMI, kg/m <sup>2</sup>	24.6 (3.1)	25.3 (3.0)	25.5 (3.0)
Higher education, %	79.6	80.9	78.9
SBP, mmHg	113.5 (12.2)	116.7 (12.6)	118.3 (12.6)
DBP, mmHg	74.1 (9.9)	77.5 (10.0)	78.3 (10.0)
Fasting glucose, mg/dl	98.2 (15.3)	103.4 (21.7)	108.5 (28.3)
Total cholesterol, mg/dl	203.0 (34.9)	211.2 (38.1)	207.4 (40.2)
LDL-C, mg/dl	130.4 (31.9)	138.5 (34.1)	134.5 (35.7)
HDL-C, mg/dl	53.1 (13.4)	50.7 (12.5)	50.9 (13.1)
Triglycerides, mg/dl	119 (84-172)	137 (98-196)	135 (98-197)
Hypertension, %	15.4	30.9	45.8
Diabetes, %	5.1	12.9	20.9
Family history of CVD, %	14.4	17.3	17.9
Lipid-lowering therapy, %	3.3	8.2	16.6

Numbers in the Table are mean (standard deviation), median (interquartile range), or percentages.

Abbreviations: BMI, body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP: systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.

All variables evaluated were statistically different by coronary artery calcification categories at baseline (*P*-value < 0.001).

**Appendix Table 3.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA
Number	48,111	35,305	15,364
Mean CAC score (95% CI)			
Baseline	8.79 (7.75, 9.83)	10.96 (9.53, 12.39)	15.66 (12.53, 18.78)
Year 5	22.78 (20.75, 24.81)	28.09 (25.61, 30.56)	37.80 (32.65, 42.96)
5-year difference (Year 5 – baseline)	13.99 (12.68, 15.30)	17.13 (15.65, 18.61)	22.15 (19.26, 25.04)
Difference in mean CAC score (95% CI)			
Baseline	Reference	2.17 (0.35, 3.99)	6.86 (3.40, 10.33)
Year 5	Reference	5.31 (2.06, 8.57)	15.03 (9.32, 20.74)
Difference in differences (Year 5 – baseline)	Reference	3.14 (1.16, 5.12)	8.16 (4.99, 11.34)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant ( $P < 0.001$ ).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 4.** 5-year progression of coronary artery calcium (CAC) by physical activity categories among participants with prevalent CAC (CAC > 0) at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA
Number	5,565	4,895	2,629
Mean CAC score (95% CI)			
Baseline	67.70 (61.03, 74.38)	73.37 (66.12, 80.43)	86.99 (74.41, 99.57)
Year 5	142.43 (130.21, 154.65)	156.15 (144.06, 168.23)	180.11 (155.43, 204.80)
5-year difference (Year 5 – baseline)	74.73 (67.29, 82.17)	82.77 (76.03, 89.52)	93.13 (77.13, 109.13)
Difference in mean CAC scores (95% CI)			
Baseline	Reference	5.67 (-2.35, 13.69)	19.29 (6.01, 32.56)
Year 5	Reference	13.72 (-2.00, 29.44)	37.68 (11.03, 64.34)
Difference in differences (Year 5 – baseline)	Reference	8.05 (-1.98, 18.07)	18.40 (0.77, 36.02)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was 0.02.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 5.** 5-year progression of coronary artery calcium (CAC) by physical activity categories among participants with no CAC (CAC = 0) at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA
Number	42,546	30,410	12,735
Mean CAC score at 5 years (95% CI)	1.34 (1.15, 1.53)	1.50 (1.22, 1.78)	1.68 (1.13, 2.23)
Difference in mean CAC scores at 5 years (95% CI)	Reference	0.17 (-0.16, 0.51)	0.36 (-0.22, 0.94)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences 0.16.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 6.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline, adjusted for inverse probability weights.

	Inactive	Moderately active	HEPA	P for trend
Number	49,486	35,713	14,995	
Model 1	Reference	1.02 (0.85, 1.21)	1.13 (0.91, 1.41)	0.33
Model 2	Reference	1.02 (0.86, 1.21)	1.13 (0.91, 1.41)	0.33
Model 3	Reference	1.05 (0.88, 1.24)	1.17 (0.94, 1.46)	0.19
Model 4	Reference	1.05 (0.88, 1.24)	1.18 (0.95, 1.47)	0.17
Model 5	Reference	1.05 (0.89, 1.24)	1.18 (0.95, 1.47)	0.16

Model 1: adjusted for age, sex, and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 7.** 5-year progression in the geometric mean of coronary artery calcium (CAC) by physical activity categories.

	<b>Inactive</b>	<b>Moderately active</b>	<b>HEPA</b>
Number	48,111	35,305	15,364
Geometric mean CAC score (95% CI)			
Baseline	0.64 (0.60, 0.68)	0.75 (0.70, 0.80)	0.86 (0.78, 0.94)
Year 5	1.43 (1.36, 1.51)	1.67 (1.58, 1.76)	2.01 (1.85, 2.17)
5-year difference (Year 5 – baseline)	0.80 (0.74, 0.85)	0.92 (0.86, 0.98)	1.15 (1.03, 1.26)
Difference in geometric mean CAC score (95% CI)			
Baseline	Reference	0.11 (0.05, 0.17)	0.22 (0.13, 0.31)
Year 5	Reference	0.24 (0.12, 0.35)	0.57 (0.40, 0.75)
Difference in differences (Year 5 – baseline)	Reference	0.13 (0.14, 0.21)	0.35 (0.22, 0.48)

Values in the Table were estimated from a random intercept and random slope mixed model for  $\log_e(\text{CAC score} + 1)$  adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. The estimates were then exponentiated to obtain the geometric means of CAC scores at 5-years and the 5-year change. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant ( $P < 0.001$ ). Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 8.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by age.

	Inactive	Moderately active	HEPA
<b>Age &lt; 40</b>			
Number	4,288	3,573	1,127
Mean CAC score (95% CI)			
Baseline	3.12 (2.25, 3.98)	3.71 (2.74, 4.69)	3.07 (1.46, 4.68)
Year 5	9.81 (8.28, 11.33)	10.51 (8.85, 12.18)	9.54 (6.63, 12.45)
5-year difference (Year 5 – baseline)	6.69 (5.31, 8.07)	6.80 (5.32, 8.28)	6.47 (3.82, 9.13)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	0.60 (-0.61, 1.80)	-0.05 (-1.82, 1.73)
Year 5	0 (reference)	0.70 (-1.49, 2.91)	-0.26 (-3.52, 2.99)
Difference in differences (Year 5 – baseline)	0 (reference)	0.11 (-1.91, 2.14)	-0.22 (-3.21, 2.78)
<b>Age ≥ 40</b>			
Number	7,632	6,110	2,755
Mean CAC score (95% CI)			
Baseline	9.74 (7.45, 12.02)	13.31 (10.76, 15.85)	23.41 (19.72, 27.09)
Year 5	29.54 (26.35, 32.73)	38.17 (34.65, 41.69)	52.64 (47.45, 57.82)
5-year difference (Year 5 – baseline)	19.81 (17.26, 22.35)	24.86 (22.08, 27.65)	29.23 (25.05, 33.40)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	3.57 (0.30, 6.84)	13.67 (9.42, 17.93)
Year 5	0 (reference)	8.63 (3.99, 13.27)	23.09 (17.07, 29.12)
Difference in differences (Year 5 – baseline)	0 (reference)	5.06 (1.28, 8.83)	9.42 (4.53, 14.31)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was not significant in age < 40 group (*P* = 0.95) but statistically significant on age ≥ 40 group (*P* < 0.001).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.



**Appendix Table 9.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline by age.

	Inactive	Moderately active	HEPA	P for trend
<b>Age &lt; 40</b>				
Number	3,883	3,228	1,020	
Model 1	Reference	0.94 (0.78, 1.13)	1.08 (0.83, 1.40)	0.88
Model 2	Reference	0.94 (0.78, 1.13)	1.09 (0.83, 1.42)	0.84
Model 3	Reference	0.95 (0.79, 1.15)	1.14 (0.88, 1.49)	0.59
Model 4	Reference	0.96 (0.80, 1.16)	1.14 (0.88, 1.49)	0.56
Model 5	Reference	0.96 (0.80, 1.16)	1.13 (0.87, 1.48)	0.59
<b>Age ≥ 40</b>				
Number	5,722	4,359	1,884	
Model 1	Reference	1.03 (0.91, 1.16)	1.20 (1.03, 1.40)	0.04
Model 2	Reference	1.03 (0.91, 1.16)	1.19 (1.02, 1.39)	0.05
Model 3	Reference	1.07 (0.94, 1.21)	1.26 (1.08, 1.47)	0.006
Model 4	Reference	1.07 (0.95, 1.21)	1.27 (1.09, 1.49)	0.005
Model 5	Reference	1.07 (0.95, 1.21)	1.27 (1.09, 1.49)	0.004

Model 1: adjusted for sex and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 10.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by sex.

	Inactive	Moderately active	HEPA
<b>Men</b>			
Number	10,472	8,875	3,394
Mean CAC score (95% CI)			
Baseline	10.11 (8.42, 11.80)	12.70 (10.89, 14.52)	18.30 (15.45, 21.16)
Year 5	26.41 (24.08, 28.74)	31.41 (28.93, 33.90)	42.34 (38.36, 46.33)
5-year difference (Year 5 – baseline)	16.30 (14.44, 18.16)	18.71 (16.74, 20.68)	24.04 (20.81, 27.27)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	2.59 (0.23, 4.95)	8.19 (4.94, 11.45)
Year 5	0 (reference)	5.00 (1.68, 8.32)	15.93 (11.36, 20.51)
Difference in differences (Year 5 – baseline)	0 (reference)	2.41 (-0.30, 5.12)	7.74 (4.04, 11.46)
<b>Women</b>			
Number	1,448	808	488
Mean CAC score (95% CI)			
Baseline	1.47 (-0.85, 3.78)	3.13 (0.23, 6.04)	1.57 (-2.06, 5.21)
Year 5	4.61 (1.58, 7.63)	9.97 (6.08, 13.86)	10.39 (5.47, 15.31)
5-year difference (Year 5 – baseline)	3.14 (1.14, 5.14)	6.83 (4.17, 9.50)	8.82 (5.41, 12.23)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	1.67 (-1.55, 4.89)	0.11 (-3.75, 3.97)
Year 5	0 (reference)	5.36 (0.80, 9.92)	5.78 (0.34, 11.23)
Difference in differences (Year 5 – baseline)	0 (reference)	3.69 (0.36, 7.02)	5.68 (1.72, 9.63)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant for both subgroups ( $P < 0.001$  and  $P = 0.002$  in men and women, respectively).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 11.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline by sex.

	Inactive	Moderately active	HEPA	P for trend
<b>Men</b>				
Number	8,256	6,848	2,467	
Model 1	Reference	1.00 (0.90, 1.11)	1.11 (0.97, 1.28)	0.18
Model 2	Reference	1.01 (0.91, 1.12)	1.13 (0.98, 1.30)	0.13
Model 3	Reference	1.04 (0.94, 1.15)	1.19 (1.34, 1.37)	0.02
Model 4	Reference	1.04 (0.94, 1.16)	1.20 (1.05, 1.38)	0.02
Model 5	Reference	1.04 (0.94, 1.16)	1.20 (1.05, 1.38)	0.02
<b>Women</b>				
Number	1,349	739	437	
Model 1	Reference	0.92 (0.53, 1.60)	1.18 (0.65, 2.14)	0.72
Model 2	Reference	0.93 (0.54, 1.61)	1.20 (0.66, 2.17)	0.68
Model 3	Reference	0.95 (0.55, 1.65)	1.23 (0.68, 2.22)	0.60
Model 4	Reference	0.93 (0.54, 1.61)	1.24 (0.69, 2.25)	0.59
Model 5	Reference	0.94 (0.54, 1.63)	1.24 (0.69, 2.25)	0.57

Model 1: adjusted for age and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 12.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by Framingham Risk Score.

	Inactive	Moderately active	HEPA
<b>FRS &lt; 10%</b>			
Number	9,457	7,642	2,969
Mean CAC score (95% CI)			
Baseline	10.85 (9.18, 12.53)	12.34 (10.48, 14.19)	12.18 (9.25, 15.11)
Year 5	20.88 (18.54, 23.23)	24.11 (21.54, 26.68)	27.16 (23.04, 31.27)
5-year difference (Year 5 – baseline)	10.03 (8.12, 11.94)	11.78 (9.71, 13.84)	14.98 (11.62, 18.33)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	1.48 (-0.95, 3.92)	1.33 (-2.01, 4.67)
Year 5	0 (reference)	3.23 (-0.21, 6.66)	6.27 (1.56, 10.99)
Difference in differences (Year 5 – baseline)	0 (reference)	1.75 (-1.07, 4.56)	4.95 (1.09, 8.81)
<b>FRS ≥ 10%</b>			
Number	1,815	1,454	601
Mean CAC score (95% CI)			
Baseline	15.75 (11.52, 19.99)	21.75 (17.14, 26.35)	57.20 (50.40, 64.00)
Year 5	59.60 (53.88, 65.31)	75.82 (69.56, 82.08)	121.67 (112.11, 131.22)
5-year difference (Year 5 – baseline)	43.84 (39.40, 48.28)	54.08 (49.17, 58.99)	64.47 (56.73, 72.21)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	5.99 (0.44, 11.54)	41.44 (33.99, 48.90)
Year 5	0 (reference)	16.22 (8.25, 24.20)	62.07 (51.33, 72.81)
Difference in differences (Year 5 – baseline)	0 (reference)	10.24 (3.61, 16.86)	20.62 (11.70, 29.55)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant for both subgroups ( $P = 0.009$  and  $P < 0.001$  in FRS < 10% and FRS ≥ 10% group, respectively).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 13.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) in participants with no coronary calcium (CAC = 0) at baseline by Framingham Risk Score.

	Inactive	Moderately active	HEPA	P for trend
<b>FRS &lt; 10%</b>				
Number	8,000	6,323	2,386	
Model 1	Reference	0.99 (0.87, 1.11)	1.17 (1.00, 1.36)	0.18
Model 2	Reference	0.98 (0.87, 1.11)	1.16 (0.99, 1.35)	0.21
Model 3	Reference	1.00 (0.88, 1.13)	1.18 (1.01, 1.38)	0.11
Model 4	Reference	1.00 (0.89, 1.13)	1.19 (1.01, 1.39)	0.11
Model 5	Reference	1.00 (0.89, 1.13)	1.19 (1.01, 1.39)	0.10
<b>FRS ≥ 10%</b>				
Number	1,058	785	267	
Model 1	Reference	1.10 (0.89, 1.37)	1.17 (0.87, 1.56)	0.06
Model 2	Reference	1.11 (0.89, 1.37)	1.20 (0.90, 1.61)	0.05
Model 3	Reference	1.15 (0.93, 1.43)	1.26 (0.94, 1.69)	0.05
Model 4	Reference	1.16 (0.93, 1.43)	1.32 (0.98, 1.77)	0.04
Model 5	Reference	1.16 (0.93, 1.44)	1.31 (0.97, 1.75)	0.04

Model 1: adjusted for age, sex, and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.

**Appendix Table 14.** 5-year progression of coronary artery calcium (CAC) by physical activity categories at baseline by CAC scores.

	Inactive	Moderately active	HEPA
<b>CAC 1–99</b>			
Number	1,982	1,756	784
Mean CAC score (95% CI)			
Baseline	19.43 (17.92, 20.94)	19.86 (18.27, 21.44)	20.55 (18.42, 22.67)
Year 5	64.47 (61.08, 67.85)	67.36 (63.80, 70.91)	71.20 (65.95, 76.45)
5-year difference (Year 5 – baseline)	45.04 (41.83, 48.24)	47.50 (44.14, 50.86)	50.66 (45.58, 55.73)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	0.43 (-1.26, 2.11)	1.12 (-1.08, 3.32)
Year 5	0 (reference)	2.89 (-1.81, 7.57)	6.74 (0.65, 12.82)
Difference in differences (Year 5 – baseline)	0 (reference)	2.46 (-2.18, 7.10)	5.62 (-0.38, 11.63)
<b>CAC ≥ 100</b>			
Number	333	340	194
Mean CAC score (95% CI)			
Baseline	168.45 (119.42, 217.48)	184.76 (134.99, 234.53)	239.68 (179.27, 300.08)
Year 5	432.32 (367.96, 396.68)	467.49 (402.97, 532.01)	487.85 (407.72, 567.98)
5-year difference (Year 5 – baseline)	263.87 (217.66, 310.07)	282.73 (237.11, 328.34)	248.17 (189.70, 306.65)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	16.31 (-29.30, 61.92)	74.23 (16.64, 125.81)
Year 5	0 (reference)	35.17 (-39.00, 109.35)	55.53 (-31.02, 142.09)
Difference in differences (Year 5 – baseline)	0 (reference)	18.86 (-46.07, 83.79)	-15.69 (-90.22, 58.84)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-values for trend across IPAQ categories for difference in differences were not statistically significant (*P* = 0.06 and *P* = 0.78 in CAC 1–99 and CAC ≥ 100 group, respectively).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.



**Appendix Table 15.** 5-year progression of coronary artery calcium (CAC) by time-varying physical activity categories at baseline.

	Inactive	Moderately active	HEPA
Mean CAC score (95% CI)			
Baseline	10.23 (9.02, 11.45)	10.28 (9.01, 11.55)	11.30 (9.65, 12.96)
Year 5	24.42 (22.65, 26.20)	27.82 (25.98, 29.65)	35.83 (33.29, 38.37)
5-year difference (Year 5 – baseline)	14.19 (12.50, 15.88)	17.54 (15.72, 19.35)	24.53 (21.68, 27.38)
Difference in mean CAC score (95% CI)			
Baseline	0 (reference)	0.05 (-1.11, 1.20)	1.07 (-0.54, 2.67)
Year 5	0 (reference)	3.39 (1.42, 5.36)	11.41 (8.74, 14.08)
Difference in differences (Year 5 – baseline)	0 (reference)	3.35 (0.88, 5.82)	10.34 (7.03, 13.66)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was highly statistically significant ( $P < 0.001$ ).

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 16.** 5-year progression of coronary artery calcium (CAC) by time-varying physical activity categories among participants with prevalent CAC (CAC > 0) at baseline.

	Inactive	Moderately active	HEPA
Mean CAC score (95% CI)			
Baseline	73.62 (68.33, 78.91)	73.45 (68.14, 78.76)	76.68 (70.43, 82.92)
Year 5	149.08 (141.25, 156.91)	154.33 (146.60, 162.05)	170.87 (161.33, 180.41)
5-year difference (Year 5 – baseline)	75.47 (68.18, 82.75)	80.88 (73.63, 88.12)	94.19 (83.91, 104.48)
Difference in mean CAC scores (95% CI)			
Baseline	0 (reference)	-0.17 (-4.36, 4.03)	3.06 (-2.54, 8.66)
Year 5	0 (reference)	5.24 (-1.60, 12.08)	21.79 (12.56, 31.01)
Difference in differences (Year 5 – baseline)	0 (reference)	5.41 (-3.53, 14.35)	18.73 (6.82, 30.63)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was 0.003.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 17.** 5-year progression of coronary artery calcium (CAC) by time-varying physical activity categories among participants with no CAC (CAC = 0) at baseline.

	Inactive	Moderately active	HEPA
Mean CAC score at 5 years (95% CI)	1.18 (0.97, 1.38)	1.74 (1.52, 1.95)	1.82 (1.51, 2.12)
Difference in mean CAC scores at 5 years (95% CI)	0 (reference)	0.56 (0.33, 0.79)	0.67 (0.32, 1.02)

Values in the Table were estimated from a random intercept and random slope mixed model for CAC score adjusted for baseline age, sex, center, smoking, alcohol intake, education, family history of cardiovascular disease, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting glucose, hypertension, diabetes, and lipid lowering therapy. *P*-value for trend across IPAQ categories for difference in differences was < 0.001.

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; HEPA, health-enhancing physically active.

**Appendix Table 18.** Hazard ratios (95% confidence intervals) for the development of coronary artery calcium (CAC > 0) by time-varying physical activity categories among participants with no coronary calcium (CAC = 0) at baseline.

	Inactive	Moderately active	HEPA	P for trend
Model 1	Reference	0.87 (0.78, 0.96)	0.98 (0.85, 1.12)	0.18
Model 2	Reference	0.92 (0.83, 1.02)	0.98 (0.85, 1.13)	0.41
Model 3	Reference	1.01 (0.91, 1.12)	1.15 (1.00, 1.33)	0.11
Model 4	Reference	1.03 (0.92, 1.14)	1.17 (1.01, 1.35)	0.06
Model 5	Reference	1.03 (0.92, 1.14)	1.17 (1.01, 1.36)	0.06
Model 6	Reference	1.02 (0.91, 1.13)	1.17 (1.01, 1.35)	0.08

Model 1: adjusted for age, sex, and center; Model 2: Model 1 + smoking, alcohol, education, and family history of cardiovascular disease; Model 3: Model 2 + body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and fasting glucose; Model 4: Model 3 + history of diabetes, and history of hypertension; and Model 5: Model 4 + lipid lowering therapy. Model 6: Model 5 + time difference.

Abbreviations: CAC, coronary artery calcium; HEPA, health-enhancing physically active.