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Year: 2024

Version: Published version

Physical fitness in male adolescents and atherosclerosis in middle age: a population-based cohort study

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjsports-2023-107663).

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Accepted 11 January 2024

ABSTRACT

Objectives To examine the associations between physical fitness in male adolescents and coronary and carotid atherosclerosis in middle age.

Methods This population-based cohort study linked physical fitness data from the Swedish Military Conscription Register during adolescence to atherosclerosis data from the Swedish CArdioPulmonary bioImage Study in middle age. Cardiorespiratory fitness was assessed using a maximal cycle-ergometer test, and knee extension muscular strength was evaluated through an isometric dynamometer. Coronary atherosclerosis was evaluated via Coronary Computed Tomography Angiography (CCTA) stenosis and Coronary Artery Calcium (CAC) scores, while carotid plaques were evaluated by ultrasound. The associations were analysed using multinomial logistic regression, adjusted (marginal) prevalences and restricted cubic splines.

Results The analysis included 8986 male adolescents (mean age 18.3 years) with a mean follow-up of 38.2 years. Physical fitness showed a reversed J-shaped association with CCTA stenosis and CAC, but no consistent association was observed for carotid plaques. After adjustments, compared with adolescents in the lowest tertile of cardiorespiratory fitness and muscular strength, those in the highest tertile had 22% (OR 0.78; 95% CI 0.61 to 0.99) and 26% (OR 0.74; 95% CI 0.58 to 0.93) lower ORs for severe (≥50%) coronary stenosis, respectively. The highest physical fitness group (high cardiorespiratory fitness and muscular strength) had 33% (OR 0.67; 95% CI 0.52 to 0.87) lower OR for severe coronary stenosis compared with those with the lowest physical fitness.

Conclusion This study supports that a combination of high cardiorespiratory fitness and high muscular strength in adolescence is associated with lower coronary atherosclerosis, particularly severe coronary stenosis, almost 40 years later.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Higher physical fitness levels, including both cardiorespiratory and muscular fitness, are associated with lower cardiovascular disease-related non-fatal and fatal events in adults. This association has also been observed for fitness during adolescence and later cardiovascular disease incidence and mortality.

⇒ No previous study has examined physical fitness in adolescence in relation to the development of coronary atherosclerosis in middle age, which may link fitness and the risk of cardiovascular events.

WHAT THIS STUDY ADDS

⇒ Our study provides novel evidence supporting that the combination of high cardiorespiratory fitness and high muscular strength in adolescence is associated with lower coronary atherosclerosis, particularly severe coronary stenosis, almost 40 years later.

⇒ These results suggest that coronary atherosclerosis is likely one of the mechanisms underlying the association between physical fitness and cardiovascular disease morbidity and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results support the clinical value of assessing both cardiorespiratory and muscular fitness for cardiovascular risk stratification.

⇒ Long-term interventions able to improve both cardiorespiratory fitness and muscular strength in adolescents could contribute to prevention of atherosclerosis in adulthood.

INTRODUCTION

Despite positive trends in the Western world during recent decades,[1 2] cardiovascular disease (CVD) remains as the leading cause of mortality worldwide.[3] Atherosclerosis, an inflammatory condition affecting all arterial regions, is the principal pathway involved in CVD.[3] Subclinical atherosclerosis, characterised by the presence of plaques in the arterial walls, is an early marker of CVD and an important predictor of future cardiovascular events.[4] Thus, identification of early modifiable risk factors is crucial for effective prevention of CVD and mortality globally.

A high level of physical fitness, including cardiorespiratory fitness and muscular strength, is considered a crucial factor in preventing CVD, cardiovascular mortality and all-cause mortality. Thus, the American Heart Association recognises cardiorespiratory fitness as a vital clinical sign[5] due to its strong association with positive cardiovascular

To cite: Herraiz-Adillo Á, Ahlqvist VH, Higueras-Fresnillo S, *et al*. *Br J Sports Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjsports-2023-107663

outcomes, including improved cardiac structure and function, reduced atherosclerosis and decreased risk of CVD and all-cause mortality.[6–10] Additionally, while the associations are less pronounced compared with cardiorespiratory fitness, increased muscular strength also exhibits beneficial effects, including lower prevalence of atherosclerosis, decreased risk of CVD and lower mortality.[11 12]

Nevertheless, despite a recent emphasis on prevention of CVD in younger individuals,[13] there is a lack of evidence on the impact of cardiorespiratory fitness in adolescence on the long-term development of atherosclerosis during late middle age. Such evidence could help to elucidate whether physical fitness early in life is related to atherosclerosis development decades later which may be of paramount importance for primary prevention of CVD. However, only one previous study has investigated the associations between physical fitness in adolescence and carotid atherosclerosis in middle age.[14] Furthermore, to the best of our knowledge, no previous study has examined associations of physical fitness in adolescence with coronary atherosclerosis later in life. In our study, Coronary Computed Tomography Angiography (CCTA), an accurate non-invasive imaging technique, enables a comprehensive assessment of the atherosclerotic burden, since CCTA allows the characterisation and quantification of both calcified and non-calcified plaques in the coronary arteries.[15 16]

Therefore, the aim of this study was to examine the association between physical fitness in male adolescents with coronary and carotid atherosclerosis in middle age, using a population-based sample and notably long follow-up.

METHODS

Study design and population

This cohort study linked information on atherosclerosis in middle age using data from the Swedish CArdioPulmonary bioImage Study (SCAPIS) (n=14 646) to information on cardiorespiratory fitness and muscular strength in male adolescents, obtained from the Swedish Military Conscription Register. Linkage of both databases, which determined our sample size (n=10 802),[17] was conducted through a personal identification number assigned to all Swedish residents at birth or on immigration. In our study, the Swedish Military Conscription Register comprised male adolescents born in Sweden between 1953 and 1968 who performed conscription between 1972 and 1987 (at ≈18 years of age). During this period, conscription was mandatory by law, except in rare circumstances, and the Swedish Military Conscription Register therefore includes 82%–92% of all Swedish men at the time of conscription.[18] SCAPIS is a collaborative project comprising six different universities in Sweden (Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå and Uppsala) aiming to predict and prevent cardiovascular and pulmonary disease. The participants included in SCAPIS were between 50 and 64 years old. Details about the SCAPIS protocol have been published elsewhere.[19]

In this study, the inclusion criteria were: (1) men <20 years old at conscription with available data on cardiorespiratory fitness, muscular strength and covariates (age, site, body mass index (BMI), duration of smoking and conscription year) and (2) available data on coronary or carotid atherosclerosis and covariates (age, site and educational status) in SCAPIS.

Online supplemental figure 1 depicts a flow chart for the study. In brief, of the 14 646 male participants included in SCAPIS, 8986 male adolescents had data on exposures, covariates and at least one of the atherosclerosis outcomes. Thus, the final sample sizes consisted of 8006, 7849 and 8934 participants for the analysis of coronary stenosis, Coronary Artery Calcium (CAC) score and carotid plaques, respectively.

Exposures at conscription

Details about cardiorespiratory fitness and muscular strength protocols have been published elsewhere.[20–22] Briefly, cardiorespiratory fitness was assessed with a maximal exercise test using an electrically braked cycle-ergometer test, provided participants had a normal ECG at rest. The conscription protocol commenced with a 5-min warm-up, during which the workload was determined based on the individual's weight. Subsequently, the workload was stepwise increased by 25 W every minute until exhaustion or incapacity to maintain the intended pedal cadence (60–70 revolutions/min). Cardiorespiratory fitness was defined as the maximal work rate achieved (in W).[23]

Three different measures were considered for muscular strength: knee extension, handgrip and elbow flexion strength (in N). Knee extension strength was considered as the main exposure since previous studies have suggested it to be the most powerful indicator of health-related muscular strength in the Swedish Military Conscription Register.[22] Strength variables were measured with an isometric dynamometer test performed at maximal contraction capacity. Knee extension and elbow flexion strength were evaluated in a sitting position with 90° flexion over the knee and elbow joint, respectively, while handgrip strength was measured by positioning the hand vertically, with 90° flexion over the elbow joint.

Atherosclerosis outcomes at SCAPIS

Coronary atherosclerosis

The detailed imaging protocol for SCAPIS has been published elsewhere.[19] Participants with a technical failure in any of the four proximal segments on the CCTA images were excluded for the analysis of coronary plaques and CAC score.[19 24]

Coronary plaques were studied through two different levels of characterisation: grade of lumen stenosis and composition of the plaques from an arterial tree level. In our study, regarding the grade of lumen stenosis, the participants were finally categorised considering the segment with the greatest amount of stenosis within the 11 clinically most relevant segments (1–3, 5–7, 9, 11–13, 17)[25] as follows: no stenosis, 1%–49% stenosis and severe (≥50%) stenosis.[19 24] The presence of a 'calcium blooming' artefact and stent were considered as 1%–49% stenosis and ≥50% stenosis, respectively. A segment involvement score was calculated as the total number of relevant coronary segments with atherosclerosis irrespective of the degree of stenosis (range 0–11).[26] Regarding composition of the plaques from an arterial tree level, coronary atherosclerosis was further characterised as: no plaque, only non-calcified plaque/s (all identified plaque/s are non-calcified), only calcified plaque/s (all identified plaque/s are calcified) and mixed composition (presence of both calcified and non-calcified segments in the arterial tree).

In addition to CCTA images, a total CAC score was obtained according to an international standard protocol[27] by adding the calcium content in each coronary artery,[28 29] and the total CAC score was divided into three categories commonly used in clinical practice as follows: 0, 1–99 and ≥100 Agatston units. Subjects with implanted stent or post coronary artery bypass grafting were not evaluated for CAC.

Carotid atherosclerosis

Carotid artery two-dimensional grey scale images were examined using a standardised protocol with a Siemens Acuson S2000 ultrasound scanner equipped with a 9L4 linear transducer (Siemens, Forchheim, Germany) and interpreted by regularly trained operators.[19] Carotid plaque was defined in accordance with the Mannheim consensus.[30] Common carotid, bulb and internal carotid arteries were examined, and participants without valid readings in both right and left carotid arteries were excluded for the analysis. Participants were classified as having either no plaque, unilateral plaque/s or bilateral carotid plaques.[31] For splines analysis, a carotid plaque score was calculated as follows: no plaque=0, unilateral plaque/s=1 and bilateral plaques=2.

Covariates

BMI at conscription was calculated as weight (kg)/height squared (m^2) obtained by standardised procedures. Years of smoking at conscription were calculated based on self-reported age of smoking initiation in SCAPIS (for those who reported previous or ongoing smoking). To account for temporal trend differences at conscription, the year of conscription (ranging from 1972 to 1987) was categorised into four distinct periods, each spanning 4 years. Educational status at SCAPIS was categorised as unfinished primary school, primary school, secondary school and university degree.

Statistical analysis

We performed a complete case analysis excluding participants without complete data on exposures (0.7% in muscular strength and 13.2% in cardiorespiratory fitness), outcomes (0.8% in carotid plaque, 4.3% in CAC and 6.1% in coronary stenosis) and any covariates (14.3%). In total, 16.8% of participants had missing values in any exposure or covariate. Three types of analyses were performed. First, the adjusted non-linear associations between quantitative exposures and atherosclerosis outcomes (summarised as scores) were evaluated trough linear regression models incorporating restricted cubic splines with four knots located at percentiles 5th, 35th, 65th and 95th.[32 33] Second, the associations between tertiles of physical fitness in adolescence and atherosclerosis outcomes (CCTA coronary stenosis, CAC score and carotid plaque) in middle age were examined through multinomial logistic regression models and adjusted (obtained by marginalisation/parametric g-formula) prevalences.[34] Third, we performed restricted cubic splines (four knots located at percentiles 5th, 35th, 65th and 95th) within multinomial logistic regression models. The analyses had increasing level of covariate control: (1) unadjusted model; (2) adjusted model (by age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription and years of smoking at conscription). We created a directed acyclic graph to illustrate the hypothesised associations of physical fitness with atherosclerosis (online supplemental figure 2). Adjusted models were further adjusted for knee extension strength in cardiorespiratory fitness and for cardiorespiratory fitness in muscular strength outcomes. Adjusted models were selected as the main analysis in splines and multinomial regressions for a better understanding of the isolated contribution of exposures on atherosclerosis outcomes without the influence of known confounders. The reference category for fitness tertiles was selected as the lowest tertile, while in multinomial models, the absence of atherosclerosis was chosen as the reference. Cut-offs for the tertiles of the different exposures are shown in table 1. Combined associations of cardiorespiratory fitness and knee extension strength were performed considering the first tertiles at the low categories, and the second and third tertiles as the high categories.

To examine the robustness of our main findings, we conducted a series of sensitivity analyses in coronary stenosis as follows: (1) including participants with data on all 18 coronary segments of the arterial tree (instead of including participants with data on the 11 most relevant segments), (2) recategorising calcium blooming as ≥50% stenosis (instead of analysing calcium blooming as 1%–49% stenosis), (3) excluding coronary segments with a stent (instead of considering stents as ≥50% stenosis), (4) excluding participants with self-reported CVD (myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, stroke or peripheral arterial disease intervention) in SCAPIS, (5) excluding presumably submaximal exercise tests (either ≤85% or ≤90% of the predicted maximal heart rate calculated as 208–(0.7×age)),[35 36] (6) further adjusting for height at conscription, (7) without adjusting for BMI at conscription and (8) without adjusting for muscular strength in cardiorespiratory fitness and without adjusting for cardiorespiratory fitness in muscular strength. Furthermore, to assess potential selection bias, we conducted multinomial logistic models that integrated inverse probability weighting to account for missing data in exposures, outcomes and the covariates used in the analysis.[37] Finally, a sensitivity analysis was conducted, incorporating quadratic and cubic terms for quantitative covariates to evaluate the presence of non-linearity in these covariates.

All statistical tests were two-sided and $p<0.05$ was considered statistically significant. Analyses were conducted using IBM-SPSS-28 (IBM Corp) and Stata V.18 (StataCorp 2021).

Equity, diversity and inclusion statement

This study uses data from the Swedish Military Conscription Register, which includes only male participants, a limitation we acknowledge in the limitations section. The SCAPIS is a population-based study that includes men and women from various birth regions. Thus, 15.6% of the male participants were born outside of Sweden. We did not impose additional restrictions related to race, ethnicity, culture, socioeconomic status or representation from marginalised groups during the study's design or data analysis.

The research team comprises a diverse group of clinical and academic researchers from different countries including both women and men (4 women and 9 men).

RESULTS

Overall, included participants had a more favourable profile in smoking status, educational status, physical fitness and atherosclerosis compared with excluded participants (online supplemental table 1).

The characteristics of the study population by tertiles of cardiorespiratory fitness and knee extension strength are presented in table 1. At conscription, the mean age of participants was 18.3 years, whereas the mean cardiorespiratory fitness and knee extension strength were 259 W and 557 N, respectively. In SCAPIS, the mean age of participants was 56.5 years (mean follow-up 38.2 years), and 52.6% and 58.8% of participants had coronary stenosis and carotid plaques, respectively.

Cardiorespiratory fitness in adolescence and atherosclerosis in middle age

The continuous (left panel) and categorical associations (right panel) of cardiorespiratory fitness in adolescence with coronary

Table 1 Descriptive characteristics of the participants in the study by tertiles of cardiorespiratory fitness and knee extension strength in adolescence

	Entire sample	Low CRF	Medium CRF	High CRF	Low strength	Medium strength	High strength
	n=8986	n=3008	n=2999	n=2979	n=3035	n=2867	n=3084
Baseline, conscription							
Age, years	18.3±0.5	18.3±0.5	18.3±0.5	18.3±0.5	18.3±0.5	18.3±0.5	18.3±0.5
Height, cm	179.7±6.5	178.0±6.5	179.8±6.2	181.4±6.3	179.1±6.6	179.8±6.4	180.3±6.5
Weight, kg	68.9±9.1	64.8±8.9	69.5±8.5	72.5±8.1	64.9±8.1	69.1±8.3	72.8±9.0
BMI, kg/m^2	21.3±2.4	20.5±2.5	21.5±2.3	22.0±2.1	20.2±2.2	21.4±2.2	22.4±2.3
Smoking at conscription							
No smoker	6451 (71.8)	1795 (59.7)	2144 (71.5)	2512 (84.3)	2059 (67.8)	2044 (71.3)	2348 (76.1)
Ex-smoker	60 (0.7)	12 (0.4)	33 (1.1)	15 (0.5)	17 (0.6)	23 (0.8)	20 (0.6)
Current	2475 (27.5)	1201 (39.9)	822 (27.4)	452 (15.2)	959 (31.6)	800 (27.9)	716 (23.2)
Cardiorespiratory fitness,* W	259.1±42.6	215.9±15.5	254.1±10.7	307.8±29.1	242.4±38.2	258.6±39.4	276.1±43.0
Extension knee strength,† N	557.0±114.1	509.5±104.1	560.5±106.7	601.5±112.2	438.7±52.7	549.8±25.3	680.2±74.9
Handgrip strength,‡ N	613.9±97.2	585.1±92.1	616.7±94.7	640.1±96.8	566.8±85.6	616.9±87.0	657.3±95.9
Elbow flexion strength,§ N	373.1±81.0	344.0±73.3	378.1±78.7	397.5±81.7	327.1±63.4	373.7±69.9	417.9±80.9
Follow-up, SCAPIS							
Follow-up, years	38.2±3.8	39.4±3.6	38.2±3.6	37.0±3.8	38.8±3.7	38.3±3.8	37.6±3.8
Age, years	56.5±3.9	57.8±3.8	56.5±3.8	55.3±3.8	57.1±3.9	56.6±3.9	55.9±3.9
BMI, kg/m^2	27.4±4.0	27.1±4.0	27.5±4.0	27.5±4.0	26.6±3.7	27.5±4.0	28.0±4.1
Educational status							
Unfinished primary school	30 (0.3)	20 (0.7)	7 (0.2)	3 (0.1)	13 (0.4)	9 (0.3)	8 (0.3)
Primary school	781 (8.7)	398 (13.2)	262 (8.7)	121 (4.1)	295 (9.7)	249 (8.7)	237 (7.7)
Secondary school	4511 (50.2)	1589 (52.8)	1531 (51.1)	1391 (46.7)	1530 (50.4)	1442 (50.3)	1539 (49.9)
University degree	3664 (40.8)	1001 (33.3)	1199 (40.0)	1464 (49.1)	1197 (39.4)	1167 (40.7)	1300 (42.2)
Coronary stenosis, n=8514							
No	4039 (47.4)	1253 (44.3)	1340 (47.3)	1446 (50.6)	1341 (47.0)	1282 (47.3)	1416 (48.0)
1%–49%	3729 (43.8)	1267 (44.8)	1249 (44.1)	1213 (42.5)	1246 (43.7)	1174 (43.3)	1309 (44.4)
≥50%	746 (8.8)	307 (10.9)	241 (8.5)	198 (6.9)	265 (9.3)	255 (9.4)	226 (7.7)
CAC score, Agatston units, n=8642							
0	4231 (49.0)	1319 (45.8)	1392 (48.4)	1520 (52.6)	1424 (48.6)	1337 (48.9)	1470 (49.4)
1–99	2999 (34.7)	1034 (35.9)	1002 (34.9)	963 (33.4)	1008 (34.4)	976 (35.7)	1015 (34.1)
≥100	1412 (16.3)	527 (18.3)	481 (16.7)	404 (14)	501 (17.1)	423 (15.5)	488 (16.4)
Carotid plaques, n=8934							
No	3690 (41.3)	1172 (39.2)	1207 (40.5)	1311 (44.2)	1182 (39.2)	1200 (42.1)	1308 (42.6)
Unilateral	2725 (30.5)	863 (28.9)	940 (31.6)	922 (31.1)	949 (31.5)	845 (29.6)	931 (30.3)
Bilateral	2519 (28.2)	953 (31.9)	831 (27.9)	735 (24.8)	882 (29.3)	808 (28.3)	829 (27.0)

Low, medium and high strength refer to knee extension strength.
All data refer to mean±SD or frequency (%).
*Tertile 1: <237 W; Tertile 2: 237–274 W; Tertile 3: ≥275 W.
†Tertile 1: <502 N; Tertile 2: 502–599 N; Tertile 3: ≥600 N.
‡Tertile 1: <570 N; Tertile 2: 570–648 N; Tertile 3: ≥649 N.
§Tertile 1: <331 N; Tertile 2: 331–399 N; Tertile 3: ≥400 N.
BMI, body mass index; CAC, coronary artery calcium; CRF, cardiorespiratory fitness; N, Newtons; SCAPIS, Swedish CArdioPulmonary bioImage Study; W, Watts.

and carotid atherosclerosis in middle age are shown in figure 1 (online supplemental tables 2 and 3 depict the ORs and adjusted prevalences for such associations). In general, splines (left panel) showed a trend towards inverse associations between cardiorespiratory fitness related to segment involvement scores and CAC scores that were more pronounced for the low range of cardiorespiratory fitness values. In adjusted models, compared with adolescents in the lowest tertile of cardiorespiratory fitness, those in the medium and highest tertiles had respectively 18% (OR 0.82; 95% CI 0.66 to 1.02) and 22% (OR 0.78; 95% CI 0.61 to 0.99) lower ORs for severe (≥50%) coronary stenosis, right panel. However, there was no clear association between tertiles of cardiorespiratory fitness and 1%–49% coronary stenosis or CAC scores. Online supplemental figure 3 depicts the multinomial logistic splines for the association between cardiorespiratory fitness (as continuous variable) and atherosclerosis indicators.

Regarding carotid atherosclerosis, a different pattern arises contrasting with coronary atherosclerosis. Compared with adolescents in the lowest tertile of cardiorespiratory fitness, those in the medium and highest tertiles had 18% (OR 1.18, 95% CI 1.04 to 1.34) and 17% (OR 1.17, 95% CI 1.02 to 1.35) higher ORs for unilateral carotid plaque/s, respectively, while there were no clear associations between cardiorespiratory fitness and bilateral carotid plaques.

Considering composition of the coronary plaques, individuals in the highest tertile of cardiorespiratory fitness had 22% (OR 0.78, 95% CI 0.61 to 0.99) lower odds of mixed composition in the arterial tree (online supplemental figure 4 and online supplemental table 4).

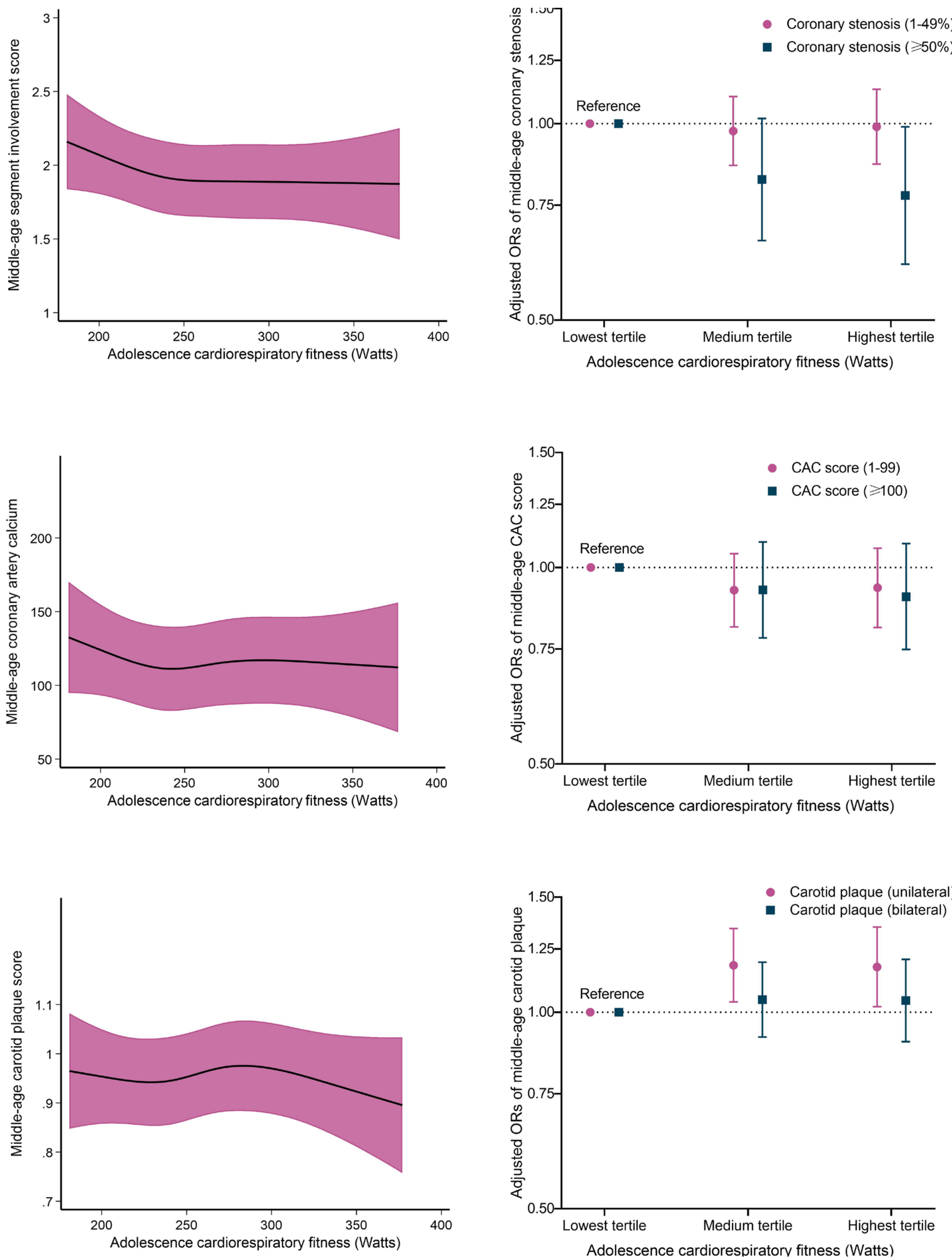

Figure 1 Associations of cardiorespiratory fitness in adolescence with coronary and carotid atherosclerosis in middle age. Left panel depicts adjusted restricted cubic splines with 95% confidence bands for the association of cardiorespiratory fitness in adolescence with segment involvement score (0–11), CAC score and carotid plaque score (0–2) in middle age. X-axes are trimmed to depict the associations for the 1st to 99th percentile of cardiorespiratory fitness values. Right panel depicts adjusted multinomial regression models with 95% CIs for the association of cardiorespiratory fitness in adolescence with coronary stenosis, CAC score and carotid plaques in middle age. Both splines and multinomial models are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription and knee extension strength. BMI, body mass index; CAC, coronary artery calcium; SCAPIS, Swedish CArdioPulmonary bioImage Study.

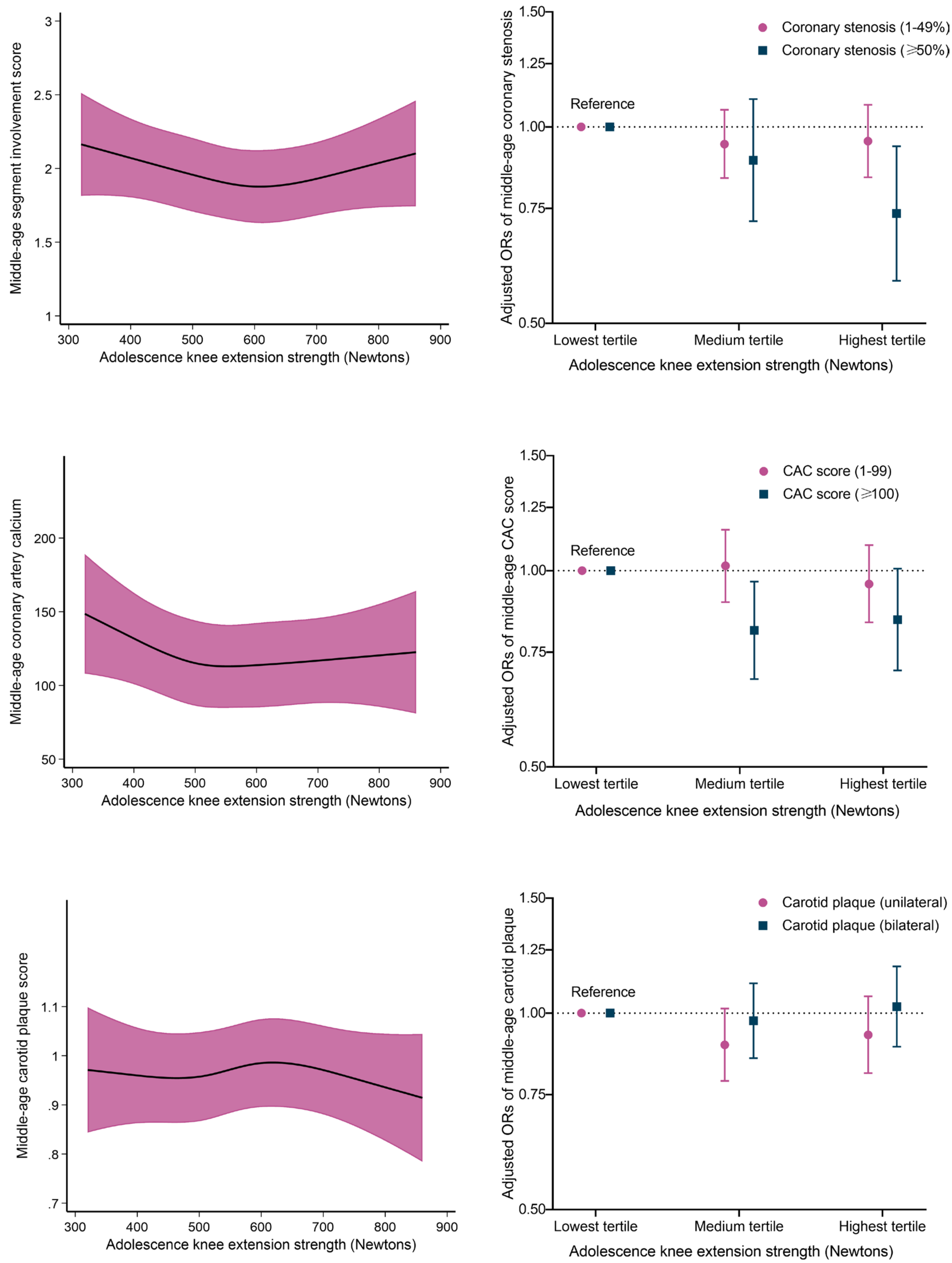

Figure 2 Associations of knee extension strength in adolescence with coronary and carotid atherosclerosis in middle age. Left panel depicts adjusted restricted cubic splines with 95% confidence bands for the association of knee extension strength in adolescence with segment involvement score (0–11), CAC score and carotid plaque score (0–2) in middle age. X-axes are trimmed to depict the associations for the 1st to 99th percentile of knee extension strength values. Right panel depicts adjusted multinomial regression models with 95% CIs for the association of knee extension strength in adolescence with coronary stenosis, CAC score and carotid plaques in middle age. Both splines and multinomial models are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription and cardiorespiratory fitness. BMI, body mass index; CAC, coronary artery calcium; SCAPIS, Swedish CArdioPulmonary bioImage Study.

Muscular strength in adolescence and atherosclerosis in middle age

Figure 2 depicts the continuous (left panel) and categorical (right panel) associations of knee extension strength in adolescence with coronary and carotid atherosclerosis in middle age (online supplemental tables 5,6 depict the ORs and adjusted prevalences for such associations). Overall, splines showed inverse associations between knee extension strength and atherosclerosis outcomes. In consonance with cardiorespiratory fitness, there was a negative association between knee extension strength and severe (≥50%) coronary stenosis in the adjusted model. When compared with the lowest tertile of knee extension strength, those in the medium and highest tertiles had 11% (OR 0.89; 95% CI 0.72 to 1.10) and 26% (OR 0.74; 95% CI 0.58 to 0.93) lower ORs for severe coronary stenosis, respectively. Regarding CAC score, adolescents in the medium and highest tertiles had 19% (OR 0.81; 95% CI 0.68 to 0.96) and 16% (OR 0.84; 95% CI 0.70 to 1.01) lower ORs for a CAC score ≥100. No clear associations were observed between knee extension strength and carotid plaques. Online supplemental figure 5 depicts the multinomial logistic splines for the association between knee muscular strength (as continuous variable) and atherosclerosis indicators.

Considering composition of the plaques, knee extension strength did not show clear associations with any types of coronary plaques (online supplemental figure 4 and online supplemental table 7).

Handgrip strength and elbow flexion strength exhibited somewhat similar, although weaker, patterns of association with coronary and carotid atherosclerosis compared with knee extension strength (online supplemental figure 6 and online supplemental tables 8,9).

Combined associations of cardiorespiratory fitness and knee extension strength in adolescence with atherosclerosis in middle age

Figure 3 depicts the combined associations of cardiorespiratory fitness and knee extension strength in adolescence with atherosclerosis in middle age, while online supplemental tables 10,11 depict the ORs and adjusted prevalences for these associations. There was a trend towards less severe (≥50%) coronary stenosis with higher levels of cardiorespiratory fitness and strength, with those in the highest physical fitness group having 33% (OR 0.67; 95% CI 0.52 to 0.87) lower OR compared with those with the lowest physical fitness. Regarding CAC score, participants in the highest physical fitness group had 24% (OR 0.76; 95% CI 0.62 to 0.93) lower OR for a CAC score ≥100 compared with those in the lowest physical fitness group. However, those in the highest physical fitness group did not have lower ORs for carotid plaques.

Sensitivity analyses

In coronary atherosclerosis, the inclusion of all coronary segments, the recategorised definition of 'calcium blooming' artefact or stent, as well as the exclusion of participants with CVD, did not significantly alter the associations between cardiorespiratory fitness and knee extension strength in relation to coronary stenosis (online supplemental table 12). In a second sensitivity analysis, the exclusion of presumably non-maximal tests generally strengthened the associations with coronary stenosis (online supplemental table 13). Further adjustment for height in adolescence generally attenuated the associations between cardiorespiratory fitness and coronary stenosis but did not influence corresponding associations with knee extension strength (online supplemental table 14). As shown in online supplemental table 15, removing the adjustment for BMI attenuated the associations of cardiorespiratory fitness and knee extension strength with coronary stenosis. Associations of cardiorespiratory fitness and knee extension strength were generally unaffected when they were not mutually adjusted for each other (online supplemental table 16). Finally, associations between cardiorespiratory fitness and atherosclerosis outcomes remained robust in the inverse probability weighting analysis (online supplemental table 17) and when incorporating quadratic and cubic terms for quantitative covariates in multinomial logistic (online supplemental tables 18,19) and linear models (data not shown).

DISCUSSION

This large population based-study showed inverse associations between cardiorespiratory fitness during adolescence and coronary atherosclerosis, particularly severe (≥50%) coronary stenosis, almost 40 years later. Furthermore, knee extension strength in adolescence showed inverse associations not only

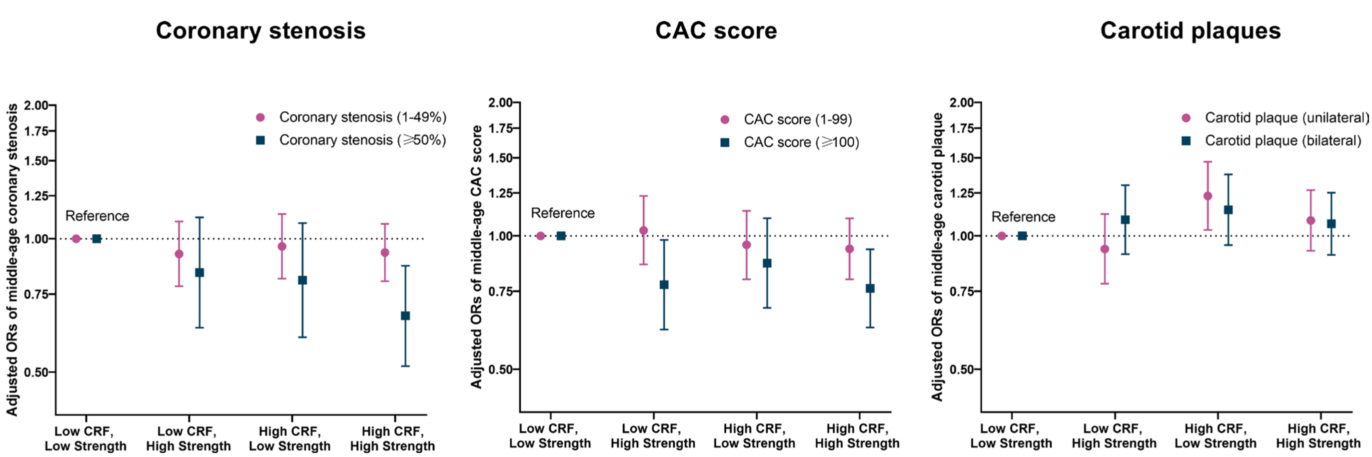

Figure 3 Combined associations of cardiorespiratory fitness and knee extension strength in adolescence with coronary stenosis, CAC score and carotid plaques in middle age. All models depict multinomial regression models with 95% CIs adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription and years of smoking at conscription. Low categories refer to the first tertile, while high categories refer to the second and third tertiles. BMI, body mass index; CAC, coronary artery calcium; CRF, cardiorespiratory fitness; Strength, knee extension muscular strength; SCAPIS: Swedish CArdioPulmonary bioImage Study.

with severe coronary stenosis but also with high CAC scores in middle age. However, neither cardiorespiratory fitness nor knee extension strength was robustly associated with the presence of bilateral carotid plaques. Finally, the combination of high cardiorespiratory fitness and knee extension strength levels was strongly associated with a lower presence of severe coronary stenosis and high CAC scores.

To the best of our knowledge, this is the first study analysing the associations between cardiorespiratory fitness in adolescence and coronary atherosclerosis in middle age measured with CCTA, an accurate non-invasive imaging technique that allows characterisation and quantification not only of calcified but also non-calcified plaques. In our study, the splines linear models suggested a somewhat reverse J-shape pattern for the association between cardiorespiratory fitness and segment involvement score, with values below 240 W (≈first tertile) associated with a worse segment involvement score. In consonance with this, in our study, after adjustments, individuals in the highest tertile of cardiorespiratory fitness had 22% lower odds of having severe coronary stenosis. Interestingly, the splines in multinomial models also supported that higher cardiorespiratory fitness associates with decreased coronary atherosclerosis. However, very high fitness levels may not confer similar protection as moderately high levels, even suggesting a potential negative effect at very high levels of cardiorespiratory fitness (around the 95th percentile). Nevertheless, wide CIs in extreme fitness values preclude definitive associations. Regarding this, it should be acknowledged that while better levels of cardiorespiratory fitness have been cross-sectionally associated with a lower risk of coronary calcification,[38] certain populations with very high levels of cardiorespiratory fitness such as endurance athletes seem to have an increased burden of coronary atherosclerosis, suggesting a U-shape relationship.[38–41] Yet, the clinical significance of accelerated coronary artery atherosclerosis in athletes engaged in very high volume-intensity exercise remains unclear.[42 43] Further studies are needed in this context.

Interestingly, high cardiorespiratory fitness was associated with less prevalence of a mixed composition (presence of both calcified and non-calcified segments) in the arterial tree, which is consistent with the lack of association observed between tertiles of cardiorespiratory fitness and CAC. These findings align with previous studies that have reported lower prevalence of mixed plaques in the coronary artery among athletes[44] or individuals with high exercise volume,[41] which is of relevance given the clear association between cardiorespiratory fitness and exercise.[45] This observation may be of importance since individuals with non-calcified or mixed plaques have been associated with a worse prognosis compared with those with predominantly calcified plaques.[46 47]

In our sensitivity analyses, associations between cardiorespiratory fitness and coronary stenosis were attenuated when estimates were not adjusted for BMI at conscription. This is intriguing and could be attributed to the selected cardiorespiratory fitness test (ie, non-weight-bearing). Notably, BMI and performance in cycle-ergometer tests (measured in W) often exhibit a positive correlation,[48] possibly because higher body mass can generate more power. However, BMI is also strongly linked to atherosclerosis risk, which might account for the observed attenuation in our sensitivity analyses. Additional research on this subject is needed.

Although no previous study has explored the associations of cardiorespiratory fitness in adolescence with later coronary atherosclerosis, our findings may be compared with previous studies that have linked cardiorespiratory fitness in adulthood to CAC later in life. The CARDIA study found that high levels of cardiorespiratory fitness in young adults were associated with 41% lower odds of coronary calcification after 15 years of follow-up.[7] However, another study also based on the CARDIA cohort found that although cardiorespiratory fitness was favourably associated with cardiac structure and function, it was not associated with CAC scores approximately 27 years later.[8] Despite different levels of covariate adjustment or follow-up could partially explain these differences, the baseline level of cardiorespiratory fitness (and physical activity) could also influence the associations between cardiorespiratory fitness and CAC. In our study, despite a lack of clear association for tertiles of cardiorespiratory fitness and CAC, the observed pattern in linear and multinomial logistic regression splines in CAC was concordant with that observed for coronary stenosis, suggesting that being unfit (cardiorespiratory fitness levels below first tertile, ≈240 W) is associated with greater risk.

In previous studies, the associations between muscular strength and CVD have generally been weaker compared with those observed for cardiorespiratory fitness.[49] However, in our study, the associations with coronary stenosis for muscular strength were similar or even slightly stronger than those for cardiorespiratory fitness. In fact, knee extension strength (more than handgrip strength or elbow flexion strength) was inversely associated not only with the presence of severe coronary stenosis, but also with a high CAC score, which was not clearly associated with tertiles of cardiorespiratory fitness. These findings are consistent with our results regarding the combined associations of cardiorespiratory fitness and knee extension strength. They indicated that achieving lower odds of coronary atherosclerosis requires the simultaneous presence of acceptable levels of cardiorespiratory fitness and knee extension strength, underscoring the integrated nature of physical fitness.

Our results regarding carotid plaques are intriguing: we did not observe consistent associations between cardiorespiratory fitness and bilateral plaques, but we found an inverted U-shaped association with unilateral plaques. This is in contrast with a previous study also analysing conscripted Swedish men, which found that cardiorespiratory fitness was associated with 19% lower odds of carotid plaques at 60 years of age.[14] However, this study analysed a sample size 10 times smaller, and considered carotid plaques as a dichotomous variable (no plaque, plaque/s) instead as continuous and multinomial ones (no plaque, unilateral plaque/s, bilateral plaques) as in our study. In addition, the Cooper Center Longitudinal Study found that midlife cardiorespiratory fitness was inversely associated with carotid artery disease measured almost two decades later.[50] However, this study characterised low cardiorespiratory fitness as the first quintile and used a different definition of carotid artery disease than our study. Further studies are therefore needed to elucidate the associations of cardiorespiratory fitness in adolescence with the development of carotid plaques later in life.

Strengths and limitations

The main strength of this study was the utilisation of CCTA on a population-based scale, enabling the characterisation of calcified and non-calcified coronary plaques within a sizeable sample of the population. Furthermore, the study benefits from a young cohort that was followed up for nearly 40 years, minimising the possibility of reverse causation, as it is highly unlikely that disease in adolescence caused low physical fitness. The study is also informative of the very-long term prognostic value of cardiorespiratory fitness and muscular strength. Additionally, physical fitness was objectively assessed using standardised procedures and not self-reported.

However, some limitations should be acknowledged. First, since conscription was only mandatory for men before 2010, only male participants were included, which unfortunately does not help to reduce the gender gap in the understanding of cardiovascular risk in women. Second, physical fitness exposures and covariates were only measured in adolescence, which impedes evaluating the cumulative effect of these variables during the follow-up. Nevertheless, a meta-analysis proved that cardiorespiratory fitness and muscular strength exhibited moderate tracking from adolescence to adulthood.[51] Third, while our study is longitudinal, its observational nature limits our capacity to make strong causal conclusions. Furthermore, the absence of certain covariates related to cardiovascular risk during conscription (eg, diet, physical activity or body composition) or measurement error in confounders restrict our ability to fully account for residual confounding in our models, which limits the assessment of the isolated contribution of physical fitness to atherosclerosis. In this sense, well-designed longitudinal studies and randomised controlled trials (despite acknowledging the difficulty of conducting long-term follow-ups) are needed to corroborate or contrast our findings. Fourth, excluded participants presented a slightly different profile compared with included participants, suggesting certain selection bias. However, our sensitivity analyses, incorporating inverse probability weighting, did not change the study's conclusions. Finally, despite the use of CCTA, our study did not enable a comprehensive characterisation of coronary plaques within a segment level. This limitation arose from the absence of information regarding mixed plaques (combining calcified and non-calcified components) within individual coronary segments. Instead, we were only able to assess a mixed composition at an arterial tree level, indicating the presence of both calcified and non-calcified segments in the arterial tree. Similarly, the characterisation of carotid plaques was imperfect, as we were unable to evaluate their phenotype, number and degree of stenosis.

Conclusions and implications

Our findings support that a combination of high cardiorespiratory fitness and high muscular strength in adolescence is associated with less atherosclerosis, particularly lower prevalence of severe coronary stenosis later in life compared with those with lower fitness levels. The effect size observed was modest, yet it is known that small changes at a population level can have important clinical and public health implications. For example, the adjusted prevalence of severe coronary stenosis was 38% lower (6.9% vs 9.5%) for those with high cardiorespiratory fitness and knee extension strength compared with those with low cardiorespiratory fitness and knee extension strength, which may have relevance for future CVD risk stratification at a population level. Furthermore, the decreasing secular trends in cardiorespiratory fitness observed in the last couple of decades in many countries[13 52–54] are a cause for concern since they are expected to increase the absolute risk for atherosclerosis in the future. Indeed, adequate levels of cardiorespiratory fitness, and to a lesser extent, muscular strength, have consistently demonstrated an inverse association with CVD morbidity[49 55] and mortality.[56 57] Our findings, which establish a link between physical fitness in adolescence and atherosclerosis in middle age, contribute to the existing evidence by showing that coronary atherosclerosis can be one of the mechanisms underlying the association between physical fitness and CVD morbidity and mortality. Thus, although further well-designed studies are needed, our findings suggest that adequate physical fitness already in adolescence may reduce coronary atherosclerosis later in life.

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Acknowledgements We thank participants and staff of the Swedish Military Conscription Register and SCAPIS project for their valuable contributions.

Contributors AH-A, VHA, SH-F, KR, FBO and PH contributed to the conception and design of the study. CJÖ, KR and PH contributed to data acquisition. AH-A, SH-F, VAH and PH conducted the statistical analysis while KH, EH, MF-S, BD, CL, DB, CJÖ, KR and FBO contributed to data analysis and interpretation. AH-A, FBO and PH drafted the manuscript, which was reviewed and revised by VHA, KH, EH, MF-S, BD, SH-F, CL, DB, CJÖ and KR. All authors approved the final version of the manuscript. PH and AH-A are the guarantors of the manuscript.

Funding The main funding body of The Swedish CArdioPulmonary bioImage Study (SCAPIS) is the Swedish Heart-Lung Foundation. The study is also funded by the Knut and Alice Wallenberg Foundation, the Swedish Research Council and VINNOVA (Sweden's Innovation Agency), University of Gothenburg and Sahlgrenska University Hospital, Karolinska Institutet and Stockholm County council, Linköping University and University Hospital, Lund University and Skåne University Hospital, Umeå University and University Hospital, and Uppsala University and University Hospital. In addition, this study is supported by the Joanna Cocozza Foundation for Children's Medical Research. SH-F is supported by a Margarita Salas grant from the Autonomous University of Madrid. FBO research activity on this topic is supported by grants from the Andalusian Government (Junta de Andalucía, Plan Andaluz de Investigación, ref: P20_00124) and the Spanish Ministry of Science and Innovation (ref: PID2020-120249RB-I00).

Competing interests EH reports payments to institution from Pfizer and Amgen, small personal fees from Amgen, NovoNordisk, Bayer and AstraZeneca, small personal fee from Amarin AB for participation on advisory board. He is the co-chair of the Swedish secondary prevention registry and the national coordinator for the trials DalCore DAL301 DalGne, Regeneron R1500-CL-1643 and Aegis II/Perfuse. The remaining authors report no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Swedish Ethical Review Authority which granted ethical approval for this work (reference numbers: 2021-06408-01 and 2022-04375-02). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data underlying this article cannot be shared publicly due to legal reasons as well as the privacy of individuals that participated in the study. However, by contacting the

study organisation (www.scapis.org) or the corresponding author, information will be provided regarding the procedures for accessing data following Swedish legislation.

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Supplementary Material

Physical fitness in male adolescents and atherosclerosis in middle-age: a population-based cohort study

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Supplementary Tables

Supplementary Table 1. Descriptive characteristics of the included versus excluded participants in the study.

Supplementary Table 2. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

Supplementary Table 3. Adjusted (marginal) prevalences for the multinomial logistic regression model of cardiorespiratory fitness in adolescence and coronary and carotid atherosclerosis in middle-age.

Supplementary Table 4. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and composition of coronary segments in middle-age by different degrees of covariate control.

Supplementary Table 5. Multinomial logistic regression, associations of knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

Supplementary Table 6. Adjusted (marginal) prevalences for the multinomial logistic regression model of knee extension strength in adolescence and coronary and carotid atherosclerosis in middle-age.

Supplementary Table 7. Multinomial logistic regression, associations of knee extension strength in adolescence and composition of coronary segments in middle-age by different degrees of covariate control.

Supplementary Table 8. Multinomial logistic regression, associations of handgrip strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

Supplementary Table 9. Multinomial logistic regression, associations of elbow flexion strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

Supplementary Table 10. Combined associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores, and carotid plaques in middle-age by different degrees of covariate control.

Supplementary Table 11. Adjusted (marginal) prevalences for the combined associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores, and carotid plaques in middle-age.

Supplementary Table 12. Associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis in middle-age, sensitivity analysis.

Supplementary Table 13. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores, and carotid plaques in middle-age, sensitivity analysis of potentially submaximal tests.

Supplementary Table 14. Multinomial logistic regression, associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis with and without adjustment for height at conscription.

Supplementary Table 15. Multinomial logistic regression, associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis with and without adjustment for BMI at conscription.

Supplementary Table 16. Multinomial logistic regression, associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis with and without adjustment for knee extension strength and cardiorespiratory fitness.

Supplementary Table 17. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control, sensitivity analysis by inverse probability weighting.

Supplementary Table 18. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis considering quadratic and cubic terms in quantitative covariates.

Supplementary Table 19. Multinomial logistic regression, associations of knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis considering quadratic and cubic terms in quantitative covariates.

Supplementary Figures

Supplementary Figure 1. Flow chart of the study.

Supplementary Figure 2. Directed acyclic graph for the association between cardiorespiratory fitness and muscular strength and atherosclerosis outcomes.

Supplementary Figure 3. Multinomial logistic regression with restricted cubic splines for the associations of cardiorespiratory fitness in adolescence and atherosclerosis in middle age.

Supplementary Figure 4. Associations of cardiorespiratory fitness and knee extension strength in adolescence with composition of coronary plaques in middle age.

Supplementary Figure 5. Multinomial logistic regression with restricted cubic splines for the associations of knee extension strength in adolescence and atherosclerosis in middle age.

Supplementary Figure 6. Associations of handgrip strength and elbow flexion strength in adolescence with coronary stenosis, CAC score and carotid plaques in middle age.

Supplementary Table 1. Descriptive characteristics of the included versus excluded participants in the study.

	Included, n=8986		**Excluded,** n=5660	
	n		n	
Baseline, conscription				
Age, y	8986	18.3 ± 0.5	2127	19.1 ± 1.5
Height, cm	8986	179.7 ± 6.5	2075	179.1 ± 6.8
Weight, kg	8986	68.9 ± 9.1	2070	67.5 ± 8.7
BMI, kg/m²	8986	21.3 ± 2.4	2070	21.1 ± 3.1
Smoking at conscription	8986		1785	
No smoker		6451 (71.8)		952 (53.3)
Ex-smoker		60 (0.7)		22 (1.2)
Current		2475 (27.5)		811 (45.4)
Cardiorespiratory fitness, Watts	8986	259.1 ± 42.6	658	254.3 ± 43.2
Extension knee strength, Newtons	8986	557.0 ± 114.1	2074	544.9 ± 109.5
Handgrip strength, Newtons	8986	613.9 ± 97.2	2074	605.6 ± 96.2
Elbow flexion strength, Newtons	8986	373.1 ± 81.0	2074	371.7 ± 86.0
Follow up, SCAPIS				
Follow up, y	8986	38.2 ± 3.8	2127	42.3 ± 4.6
Age, y	8986	56.5 ± 3.9	5660	59.1 ± 4.6
BMI, kg/m²	8986	27.4 ± 4.0	5658	27.6 ± 4.0
Educational status	8986		5136	
Unfinished primary school		30 (0.3)		70 (1.4)
Primary school		781 (8.7)		612 (11.9)
Secondary school		4511 (50.2)		2360 (46.0)
University degree		3664 (40.8)		2094 (40.8)
Coronary stenosis	8514		1991	
No		4039 (47.4)		626 (31.4)
1-49%		3729 (43.8)		1058 (53.1)
≥50%		746 (8.8)		307 (15.4)
CAC score, Agatston units	8642		2121	
0		4231 (49.0)		715 (33.7)
1-99		2999 (34.7)		784 (37.0)
≥100		1412 (16.3)		622 (29.3)
Carotid plaques	8934		2264	
No		3690 (41.3)		692 (30.6)
Unilateral		2725 (30.5)		691 (30.5)
Bilateral		2519 (28.2)		881 (38.9)

BMI: body mass index, CAC: coronary artery calcium, SCAPIS: Swedish CArdioPulmonary bioImage Study. All data refer to mean ± standard deviation or frequency (%).

Supplementary Table 2. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Cardiorespiratory fitness	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis						
1-49%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.91	(0.81-1.01)	0.087	0.97	(0.86-1.10)	0.677
Highest tertile	0.82	(0.74-0.92)	<0.001	0.99	(0.87-1.13)	0.871
≥50%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.75	(0.61-0.91)	0.004	0.82	(0.66-1.02)	0.073
Highest tertile	0.58	(0.47-0.71)	<0.001	0.78	(0.61-0.99)	0.040
CAC score						
1-99						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.88	(0.78-1.00)	0.046	0.92	(0.81-1.05)	0.223
Highest tertile	0.81	(0.72-0.91)	<0.001	0.93	(0.81-1.07)	0.314
≥100						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.85	(0.73-0.99)	0.038	0.92	(0.78-1.09)	0.357
Highest tertile	0.69	(0.59-0.81)	<0.001	0.90	(0.75-1.09)	0.281
Ultrasound carotid plaque						
Unilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.06	(0.94-1.19)	0.370	1.18	(1.04-1.34)	0.012
Highest tertile	0.95	(0.85-1.08)	0.460	1.17	(1.02-1.35)	0.026
Bilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.85	(0.75-0.96)	0.008	1.04	(0.92-1.19)	0.510
Highest tertile	0.69	(0.61-0.78)	<0.001	1.04	(0.90-1.20)	0.576

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study. Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively,
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength.

Supplementary Table 3. Adjusted (marginal) prevalences for the multinomial logistic regression model of cardiorespiratory fitness in adolescence and coronary and carotid atherosclerosis in middle-age.

Cardiorespiratory fitness	Adjusted prevalence (95% CI)		Adjusted prevalence (95% CI)		Adjusted prevalence (95% CI)	
	No coronary stenosis		**1-49% coronary stenosis**		**≥50% coronary stenosis**	
Lowest tertile	47.37	(45.38-49.35)	43.84	(41.85-45.82)	8.80	(7.70-9.89)
Medium tertile	48.55	(46.70-50.39)	43.98	(42.12-45.84)	7.47	(6.49-8.45)
Highest tertile	48.42	(46.47-50.37)	44.53	(42.55-46.51)	7.05	(5.99-8.12)
	CAC score=0		**CAC score 1-99**		**CAC score ≥100**	
Lowest tertile	49.05	(47.04-51.06)	35.01	(33.05-36.96)	15.94	(14.53-17.36)
Medium tertile	50.91	(49.05-52.78)	33.68	(31.86-35.49)	15.41	(14.07-16.75)
Highest tertile	50.93	(48.96-52.91)	33.98	(32.05-35.92)	15.08	(13.62-16.55)
	No carotid plaque		**Unilateral carotid plaque/s**		**Bilateral carotid plaques**	
Lowest tertile	43.00	(41.11-44.90)	28.47	(26.74-30.20)	28.53	(26.88-30.17)
Medium tertile	40.46	(38.73-42.20)	31.56	(29.89-33.24)	27.97	(26.39-29.56)
Highest tertile	40.57	(38.74-42.40)	31.46	(29.66-33.26)	27.97	(26.21-29.73)

BMI: body mass index, CAC: coronary artery calcium, CI: confidence interval, SCAPIS: Swedish CArdioPulmonary bioImage Study.

Marginal prevalences are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength.

Supplementary Table 4. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and composition of coronary segments in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Cardiorespiratory fitness	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
Composition of coronary segments at an arterial tree level						
Only noncalcified segments						
Lowest tertile. ref.	1.00	-	-	1.00	-	-
Medium tertile	1.17	(0.83-1.65)	0.357	1.22	(0.85-1.75)	0.274
Highest tertile	1.02	(0.72-1.44)	0.916	1.07	(0.72-1.59)	0.742
Only calcified segments						
Lowest tertile. ref.	1.00	-	-	1.00	-	-
Medium tertile	0.88	(0.78-0.98)	0.026	0.96	(0.84-1.08)	0.486
Highest tertile	0.80	(0.71-0.89)	<0.001	0.98	(0.86-1.13)	0.831
Mixed composition						
Lowest tertile. ref.	1.00	-	-	1.00	-	-
Medium tertile	0.81	(0.66-0.99)	0.042	0.84	(0.68-1.05)	0.121
Highest tertile	0.63	(0.51-0.78)	<0.001	0.78	(0.61-0.99)	0.040

BMI: body mass index, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Reference categories for composition of coronary segments was “no plaque”.
Mixed composition: presence of both calcified and noncalcified segments in the arterial tree.
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength.

Supplementary Table 5. Multinomial logistic regression, associations of knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Knee extension strength	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis						
1-49%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.87-1.09)	0.592	0.94	(0.83-1.06)	0.324
Highest tertile	0.99	(0.88-1.10)	0.797	0.95	(0.84-1.08)	0.443
≥50%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.93	(0.76-1.14)	0.491	0.89	(0.72-1.10)	0.284
Highest tertile	0.77	(0.62-0.94)	0.012	0.74	(0.58-0.93)	0.012
CAC score						
1-99						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.92-1.17)	0.520	1.02	(0.89-1.15)	0.797
Highest tertile	0.98	(0.87-1.10)	0.732	0.95	(0.83-1.09)	0.502
≥100						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.87	(0.74-1.02)	0.091	0.81	(0.68-0.96)	0.016
Highest tertile	0.93	(0.80-1.09)	0.384	0.84	(0.70-1.01)	0.060
Ultrasound carotid plaque						
Unilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.88	(0.78-0.99)	0.036	0.89	(0.79-1.02)	0.086
Highest tertile	0.89	(0.79-1.00)	0.049	0.93	(0.81-1.06)	0.268
Bilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.90	(0.80-1.02)	0.106	0.97	(0.85-1.11)	0.687
Highest tertile	0.85	(0.75-0.96)	0.009	1.02	(0.89-1.18)	0.748

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study. Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness.

Supplementary Table 6. Adjusted (marginal) prevalences for the multinomial logistic regression model of knee extension strength in adolescence and coronary and carotid atherosclerosis in middle-age.

Knee extension strength	Adjusted prevalence (95% CI)		Adjusted prevalence (95% CI)		Adjusted prevalence (95% CI)	
	No coronary stenosis		**1-49% coronary stenosis**		**≥50% coronary stenosis**	
Lowest tertile	46.92	(44.99-48.85)	44.40	(42.44-46.36)	8.68	(7.56-9.79)
Medium tertile	48.52	(46.65-50.39)	43.43	(41.55-45.32)	8.05	(7.02-9.08)
Highest tertile	48.89	(46.97-50.80)	44.34	(42.42-46.27)	6.77	(5.79-7.74)
	CAC score=0		**CAC score 1-99**		**CAC score ≥100**	
Lowest tertile	49.26	(47.31-51.21)	33.71	(31.80-35.62)	17.03	(15.54-18.53)
Medium tertile	50.39	(48.49-52.29)	35.28	(33.42-37.15)	14.33	(12.99-15.66)
Highest tertile	51.22	(49.29-53.15)	33.67	(31.80-35.54)	15.11	(13.75-16.48)
	No carotid plaque		**Unilateral carotid plaque/s**		**Bilateral carotid plaques**	
Lowest tertile	40.50	(38.66-42.34)	31.81	(30.04-33.58)	27.69	(26.06-29.32)
Medium tertile	42.20	(40.42-43.98)	29.67	(28.00-31.35)	28.12	(26.51-29.74)
Highest tertile	41.21	(39.41-43.02)	29.98	(28.27-31.70)	28.81	(27.11-30.51)

BMI: body mass index, CAC: coronary artery calcium, CI: confidence interval, SCAPIS: Swedish CArdioPulmonary bioImage Study.

Marginal prevalences are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness.

Supplementary Table 7. Multinomial logistic regression, associations of knee extension strength in adolescence and composition of coronary segments in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Knee extension strength	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
Composition of coronary segments at an arterial tree level						
Only noncalcified plaques						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.95	(0.67-1.34)	0.759	0.94	(0.66-1.34)	0.740
Highest tertile	1.07	(0.77-1.48)	0.698	1.09	(0.75-1.57)	0.658
Only calcified plaques						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.98	(0.87-1.09)	0.676	0.95	(0.84-1.07)	0.375
Highest tertile	0.96	(0.85-1.07)	0.440	0.92	(0.81-1.05)	0.228
Mixed composition						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.75-1.13)	0.423	0.89	(0.71-1.10)	0.276
Highest tertile	0.88	(0.72-1.08)	0.234	0.86	(0.68-1.08)	0.191

BMI: body mass index, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Reference categories for composition of coronary segments was “no plaque”.
Mixed composition: presence of both calcified and noncalcified segments in the arterial tree.
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness.

Supplementary Table 8. Multinomial logistic regression, associations of handgrip strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Handgrip strength	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis						
1-49%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.06	(0.95-1.19)	0.283	1.01	(0.89-1.13)	0.905
Highest tertile	1.08	(0.97-1.21)	0.154	0.99	(0.88-1.12)	0.923
≥50%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.96	(0.78-1.18)	0.730	0.90	(0.72-1.11)	0.319
Highest tertile	0.91	(0.74-1.12)	0.393	0.81	(0.64-1.02)	0.069
CAC score						
1-99						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.06	(0.94-1.20)	0.330	1.01	(0.89-1.14)	0.885
Highest tertile	1.08	(0.96-1.22)	0.221	1.00	(0.87-1.14)	0.982
≥100						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.02	(0.87-1.20)	0.781	0.93	(0.78-1.10)	0.404
Highest tertile	1.08	(0.93-1.27)	0.313	0.92	(0.77-1.10)	0.382
Ultrasound carotid plaque						
Unilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.13	(1.00-1.27)	0.053	1.12	(0.99-1.27)	0.076
Highest tertile	1.04	(0.92-1.17)	0.571	1.03	(0.90-1.17)	0.704
Bilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.98	(0.87-1.12)	0.809	1.00	(0.87-1.14)	0.952
Highest tertile	1.02	(0.90-1.15)	0.760	1.05	(0.92-1.21)	0.451

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness.

Supplementary Table 9. Multinomial logistic regression, associations of elbow flexion strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Elbow flexion strength	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis						
1-49%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.13	(1.01-1.26)	0.039	1.12	(0.99-1.26)	0.068
Highest tertile	1.07	(0.96-1.19)	0.243	1.04	(0.92-1.19)	0.523
≥50%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.84-1.27)	0.729	0.99	(0.80-1.24)	0.954
Highest tertile	0.84	(0.68-1.03)	0.096	0.77	(0.60-0.97)	0.028
CAC score						
1-99						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.09	(0.96-1.23)	0.181	1.07	(0.94-1.22)	0.312
Highest tertile	1.03	(0.91-1.16)	0.646	0.99	(0.87-1.14)	0.935
≥100						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	1.19	(1.01-1.40)	0.032	1.12	(0.94-1.33)	0.201
Highest tertile	1.06	(0.91-1.24)	0.433	0.96	(0.80-1.15)	0.631
Ultrasound carotid plaque						
Unilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.87	(0.77-0.99)	0.029	0.88	(0.78-1.01)	0.062
Highest tertile	0.91	(0.81-1.03)	0.123	0.95	(0.83-1.08)	0.423
Bilateral						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.99	(0.88-1.13)	0.944	1.08	(0.94-1.23)	0.280
Highest tertile	0.92	(0.82-1.05)	0.216	1.08	(0.94-1.24)	0.293

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Reference category for CCTA stenosis. CAC score and carotid plaques: no stenosis. CAC score=0 Agatston units and no plaque, respectively.
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness.

Supplementary Table 10. Combined associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores, and carotid plaques in middle-age by different degrees of covariate control.

	Unadjusted			Adjusted		
Cardiorespiratory fitness and knee extension strength	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis						
1-49%						
Low CRF-Low strength, ref.	1.00	-	-	1.00	-	-
Low CRF-High strength	1.02	(0.87-1.20)	0.773	0.92	(0.78-1.09)	0.358
High CRF-Low strength	0.87	(0.74-1.01)	0.076	0.96	(0.81-1.14)	0.640
High CRF-High strength	0.88	(0.77-1.00)	0.045	0.93	(0.80-1.08)	0.342
≥50%						
Low CRF-Low strength, ref.	1.00	-	-	1.00	-	-
Low CRF-High strength	1.00	(0.76-1.31)	0.998	0.84	(0.63-1.12)	0.229
High CRF-Low strength	0.72	(0.54-0.95)	0.022	0.81	(0.60-1.08)	0.154
High CRF-High strength	0.64	(0.51-0.80)	<0.001	0.67	(0.52-0.87)	0.003
CAC score						
1-99						
Low CRF-Low strength, ref.	1.00	-	-	1.00	-	-
Low CRF-High strength	1.11	(0.94-1.32)	0.220	1.03	(0.86-1.23)	0.748
High CRF-Low strength	0.88	(0.74-1.04)	0.138	0.95	(0.80-1.14)	0.601
High CRF-High strength	0.90	(0.78-1.03)	0.122	0.93	(0.80-1.09)	0.402
≥100						
Low CRF-Low strength, ref.	1.00	-	-	1.00	-	-
Low CRF-High strength	0.96	(0.77-1.19)	0.682	0.78	(0.61-0.98)	0.032
High CRF-Low strength	0.76	(0.61-0.95)	0.016	0.87	(0.69-1.10)	0.235
High CRF-High strength	0.74	(0.62-0.89)	0.001	0.76	(0.62-0.93)	0.009
Ultrasound carotid plaque						
Unilateral						
Low CRF-Low strength, ref.	1.00	-	-	1.00	-	-
Low CRF-High strength	0.91	(0.76-1.09)	0.307	0.93	(0.78-1.12)	0.462
High CRF-Low strength	1.08	(0.91-1.29)	0.351	1.23	(1.03-1.47)	0.022
High CRF-High strength	0.92	(0.80-1.06)	0.258	1.08	(0.92-1.27)	0.320
Bilateral						
Low CRF-Low strength, ref.	1.00	-	-	1.00	-	-
Low CRF-High strength	1.04	(0.88-1.24)	0.620	1.09	(0.91-1.30)	0.362
High CRF-Low strength	0.88	(0.74-1.04)	0.140	1.14	(0.95-1.38)	0.148
High CRF-High strength	0.75	(0.65-0.87)	<0.001	1.06	(0.91-1.25)	0.444

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, CRF: cardiorespiratory fitness, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study, strength: knee extension strength.

Reference category for CCTA stenosis, CAC score, and carotid plaques: no stenosis, CAC score=0 Agatston units, and no plaque, respectively.

Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, and years of smoking at conscription.

Low categories in CRF and strength refer to first tertiles, while high categories refer to second and third tertiles, e.g., Low CRF-High strength refer to first tertile of CRF and second and third tertile of strength.

Supplementary Table 11. Adjusted (marginal) prevalences for the combined associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores, and carotid plaques in middle-age.

	Adjusted prevalence (95% CI)		Adjusted prevalence (95% CI)		Adjusted prevalence (95% CI)	
	No coronary stenosis		**1-49% coronary stenosis**		**≥50% coronary stenosis**	
Low CRF-Low strength	46.11	(43.36-48.86)	44.37	(41.58-47.15)	9.53	(7.89-11.16)
Low CRF-High strength	48.29	(45.62-50.96)	43.24	(40.57-45.90)	8.47	(7.04-9.91)
High CRF-Low strength	47.65	(45.06-50.25)	44.32	(41.68-46.96)	8.03	(6.55-9.51)
High CRF-High strength	48.87	(47.30-50.45)	44.22	(42.63-45.80)	6.91	(6.10-7.73)
	CAC score=0		**CAC score 1-99**		**CAC score ≥100**	
Low CRF-Low strength	48.29	(45.51-51.07)	33.83	(31.13-36.53)	17.88	(15.76-20.01)
Low CRF-High strength	49.52	(46.81-52.23)	35.98	(33.34-38.63)	14.49	(12.69-16.30)
High CRF-Low strength	50.06	(47.44-52.69)	33.63	(31.06-36.21)	16.30	(14.29-18.32)
High CRF-High strength	51.29	(49.70-52.88)	33.92	(32.37-35.47)	14.79	(13.66-15.92)
	No carotid plaque		**Unilateral carotid plaque/s**		**Bilateral carotid plaques**	
Low CRF-Low strength	42.88	(40.23-45.52)	29.71	(27.26-32.17)	27.41	(25.15-29.67)
Low CRF-High strength	42.76	(40.22-45.30)	27.64	(25.33-29.96)	29.60	(27.35-31.84)
High CRF-Low strength	38.82	(36.39-41.26)	32.97	(30.58-35.37)	28.20	(25.94-30.47)
High CRF-High strength	41.19	(39.71-42.67)	30.87	(29.44-32.30)	27.94	(26.55-29.33)

BMI: body mass index, CAC: coronary artery calcium, CI: confidence interval, CRF: cardiorespiratory fitness, OR: odds ratio, SCAPIS: Swedish CArdioPulmonary bioImage Study, strength: knee extension strength.

The marginal prevalences are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, and years of smoking at conscription.

Low categories in CRF and strength refer to first tertiles, while high categories refer to second and third tertiles, e.g., Low CRF-High strength refer to first tertile of CRF and second and third tertile of strength.

Supplementary Table 12. Associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis in middle-age, sensitivity analysis.

	Considering the 11 relevant coronary segments (Ref. analysis) n=8006			Considering all 18 coronary segments n=8006			Considering calcium blooming as ≥50% stenosis n=8006			Exclusion of participants with stents in the 11 relevant coronary segments n=7926			Exclusion of CVD n=7742		
	OR	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
Cardiorespiratory fitness															
CCTA coronary stenosis															
1-49%															
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	0.98	(0.86-1.10)	0.696	1.00	(0.88-1.13)	0.976	0.97	(0.86-1.10)	0.653	0.98	(0.86-1.11)	0.726
Highest tertile	0.99	(0.87-1.13)	0.871	0.99	(0.87-1.13)	0.899	1.01	(0.88-1.15)	0.928	0.99	(0.87-1.13)	0.859	0.99	(0.87-1.13)	0.895
≥ 50%															
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.83	(0.67-1.02)	0.079	0.80	(0.67-0.96)	0.019	0.78	(0.62-0.98)	0.030	0.79	(0.62-1.00)	0.048
Highest tertile	0.78	(0.61-0.99)	0.040	0.79	(0.62-1.00)	0.051	0.80	(0.65-0.98)	0.031	0.74	(0.58-0.96)	0.024	0.73	(0.56-0.95)	0.018
Knee extension strength															
CCTA coronary stenosis															
1-49%															
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.94	(0.83-1.06)	0.324	0.94	(0.83-1.06)	0.329	0.95	(0.84-1.08)	0.456	0.94	(0.83-1.06)	0.325	0.95	(0.84-1.07)	0.394
Highest tertile	0.95	(0.84-1.08)	0.443	0.96	(0.84-1.09)	0.486	0.96	(0.84-1.10)	0.571	0.95	(0.84-1.08)	0.429	0.96	(0.84-1.09)	0.532
≥ 50%															
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.89	(0.72-1.10)	0.284	0.89	(0.72-1.10)	0.290	0.87	(0.72-1.04)	0.128	0.86	(0.68-1.08)	0.197	0.87	(0.69-1.10)	0.253
Highest tertile	0.74	(0.58-0.93)	0.012	0.72	(0.57-0.91)	0.007	0.78	(0.64-0.95)	0.012	0.75	(0.58-0.96)	0.021	0.77	(0.60-1.00)	0.051

BMI: body mass index, CCTA: coronary computed tomographic angiography, CI: confidence interval, CVD: cardiovascular disease, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study,

Reference group: no coronary stenosis.

Except for the "All 18 coronary segments" group, all models refer to the most 11 relevant coronary segments.

CVD group refers to participants with self-reported myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, stroke, or peripheral arterial disease intervention.

All models are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, knee extension strength (for cardiorespiratory fitness) and cardiorespiratory fitness (for knee extension strength).

Supplementary Table 13. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores, and carotid plaques in middle-age, sensitivity analysis of potentially submaximal tests.

	Considering all cardiorespiratory fitness tests (Ref. analysis)			Excluding cardiorespiratory fitness tests ≤85% predicted maximal heart rate			Excluding cardiorespiratory fitness tests ≤90% predicted maximal heart rate		
	OR	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis									
	n=8006			**n=7952**			**n=7563**		
1-49%									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	0.97	(0.86-1.09)	0.586	0.97	(0.85-1.10)	0.615
Highest tertile	0.99	(0.87-1.13)	0.871	0.98	(0.85-1.11)	0.724	0.97	(0.84-1.11)	0.618
≥50%									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.81	(0.65-1.01)	0.061	0.77	(0.62-0.97)	0.023
Highest tertile	0.78	(0.61-0.99)	0.040	0.76	(0.60-0.97)	0.030	0.73	(0.57-0.94)	0.014
CAC score									
	n=7849			**n=7795**			**n=7414**		
1-99									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.81-1.05)	0.223	0.92	(0.81-1.05)	0.215	0.91	(0.80-1.04)	0.162
Highest tertile	0.93	(0.81-1.07)	0.314	0.93	(0.80-1.07)	0.286	0.89	(0.77-1.03)	0.120
≥100									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.78-1.09)	0.357	0.91	(0.77-1.08)	0.307	0.90	(0.76-1.07)	0.242
Highest tertile	0.90	(0.75-1.09)	0.281	0.89	(0.74-1.07)	0.229	0.90	(0.74-1.09)	0.278
Ultrasound carotid plaque									
	n=8934			**n=8875**			**n=8441**		
Unilateral									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.18	(1.04-1.34)	0.012	1.18	(1.03-1.34)	0.013	1.17	(1.03-1.34)	0.018
Highest tertile	1.17	(1.02-1.35)	0.026	1.17	(1.02-1.35)	0.030	1.16	(1.01-1.35)	0.039
Bilateral									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.92-1.19)	0.510	1.04	(0.91-1.19)	0.515	1.03	(0.90-1.18)	0.675
Highest tertile	1.04	(0.90-1.20)	0.576	1.04	(0.90-1.21)	0.574	1.02	(0.88-1.18)	0.809

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Reference category for CCTA stenosis, CAC score, and carotid plaques: no stenosis, CAC score=0 Agatston units, and no plaque, respectively.
Models are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength.

Supplementary Table 14. Multinomial logistic regression, associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis with and without adjustment for height at conscription.

	Cardiorespiratory fitness						Knee extension strength					
	Adjusted			Adjusted plus height at conscription			Adjusted			Adjusted plus height at conscription		
	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
CCTA coronary stenosis	**n=8006**						**n=8006**					
1-49%												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	0.99	(0.87-1.12)	0.843	0.94	(0.83-1.06)	0.324	0.94	(0.84-1.06)	0.348
Highest tertile	0.99	(0.87-1.13)	0.871	1.01	(0.89-1.16)	0.834	0.95	(0.84-1.08)	0.443	0.95	(0.84-1.08)	0.479
≥50%												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.85	(0.68-1.05)	0.131	0.89	(0.72-1.10)	0.284	0.90	(0.72-1.11)	0.319
Highest tertile	0.78	(0.61-0.99)	0.040	0.82	(0.64-1.05)	0.124	0.74	(0.58-0.93)	0.012	0.74	(0.59-0.94)	0.015
CAC score. Agatston units	**n=7849**						**n=7849**					
1-99												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.81-1.05)	0.223	0.93	(0.82-1.06)	0.299	1.02	(0.89-1.15)	0.797	1.02	(0.90-1.16)	0.764
Highest tertile	0.93	(0.81-1.07)	0.314	0.95	(0.82-1.10)	0.487	0.95	(0.83-1.09)	0.502	0.96	(0.84-1.10)	0.537
≥100												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.78-1.09)	0.357	0.93	(0.78-1.10)	0.408	0.81	(0.68-0.96)	0.016	0.81	(0.68-0.96)	0.017
Highest tertile	0.90	(0.75-1.09)	0.281	0.91	(0.76-1.11)	0.363	0.84	(0.70-1.01)	0.060	0.84	(0.70-1.01)	0.064
Ultrasound carotid plaque	**n=8934**						**n=8934**					
Unilateral												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.18	(1.04-1.34)	0.012	1.19	(1.04-1.36)	0.009	0.89	(0.79-1.02)	0.086	0.90	(0.79-1.02)	0.091
Highest tertile	1.17	(1.02-1.35)	0.026	1.19	(1.03-1.38)	0.017	0.93	(0.81-1.06)	0.268	0.93	(0.81-1.06)	0.279
Bilateral												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.92-1.19)	0.510	1.06	(0.93-1.22)	0.352	0.97	(0.85-1.11)	0.687	0.98	(0.86-1.11)	0.733
Highest tertile	1.04	(0.90-1.20)	0.576	1.08	(0.93-1.25)	0.317	1.02	(0.89-1.18)	0.748	1.03	(0.89-1.18)	0.700

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, CRF: cardiorespiratory fitness, OR: odds ratio, SCAPIS: Swedish Cardiopulmonary Bioimage Study.

Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.

Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength (for cardiorespiratory fitness) and cardiorespiratory fitness (for knee extension strength).

Adjusted model + height at conscription: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, height at conscription, and knee extension strength (for cardiorespiratory fitness) and cardiorespiratory fitness (for knee extension strength).

Supplementary Table 15. Multinomial logistic regression, associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis with and without adjustment for BMI at conscription.

	Cardiorespiratory fitness						Knee extension strength					
	Adjusted			Adjusted minus BMI at conscription			Adjusted			Adjusted minus BMI at conscription		
	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
CCTA coronary stenosis	n=8006						n=8006					
1-49%												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	1.03	(0.92-1.16)	0.603	0.94	(0.83-1.06)	0.324	1.02	(0.91-1.15)	0.730
Highest tertile	0.99	(0.87-1.13)	0.871	1.08	(0.95-1.23)	0.215	0.95	(0.84-1.08)	0.443	1.10	(0.98-1.24)	0.111
≥50%												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.90	(0.72-1.11)	0.324	0.89	(0.72-1.10)	0.284	1.02	(0.82-1.25)	0.882
Highest tertile	0.78	(0.61-0.99)	0.040	0.90	(0.70-1.14)	0.370	0.74	(0.58-0.93)	0.012	0.94	(0.75-1.18)	0.607
CAC score. Agatston units	n=7849						n=7849					
1-99												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.81-1.05)	0.223	0.97	(0.86-1.11)	0.690	1.02	(0.89-1.15)	0.797	1.09	(0.97-1.24)	0.156
Highest tertile	0.93	(0.81-1.07)	0.314	1.01	(0.88-1.16)	0.844	0.95	(0.83-1.09)	0.502	1.09	(0.96-1.24)	0.189
≥100												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.78-1.09)	0.357	1.03	(0.87-1.21)	0.766	0.81	(0.68-0.96)	0.016	0.95	(0.80-1.13)	0.564
Highest tertile	0.90	(0.75-1.09)	0.281	1.06	(0.88-1.28)	0.516	0.84	(0.70-1.01)	0.060	1.13	(0.95-1.34)	0.160
Ultrasound carotid plaque	n=8934						n=8934					
Unilateral												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.18	(1.04-1.34)	0.012	1.18	(1.04-1.34)	0.011	0.89	(0.79-1.02)	0.086	0.90	(0.79-1.02)	0.090
Highest tertile	1.17	(1.02-1.35)	0.026	1.17	(1.02-1.35)	0.023	0.93	(0.81-1.06)	0.268	0.93	(0.82-1.06)	0.285
Bilateral												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.92-1.19)	0.510	1.05	(0.92-1.19)	0.487	0.97	(0.85-1.11)	0.687	0.97	(0.85-1.11)	0.690
Highest tertile	1.04	(0.90-1.20)	0.576	1.04	(0.91-1.21)	0.543	1.02	(0.89-1.18)	0.748	1.02	(0.89-1.17)	0.722

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, SCAPIS: Swedish Cardiopulmonary Bioimage Study.

Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.

Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength (for cardiorespiratory fitness) and cardiorespiratory fitness (for knee extension strength).

Adjusted model minus BMI at conscription: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, years of smoking at conscription, and knee extension strength (for cardiorespiratory fitness) and cardiorespiratory fitness (for knee extension strength).

Supplementary Table 16. Multinomial logistic regression, associations of cardiorespiratory fitness and knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis with and without adjustment for knee extension strength and cardiorespiratory fitness.

	Cardiorespiratory fitness						Knee extension strength					
	Adjusted			Adjusted minus Knee extension strength			Adjusted			Adjusted minus Cardiorespiratory fitness		
	OR	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis	**n=8006**						**n=8006**					
1-49%												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	0.97	(0.86-1.10)	0.669	0.94	(0.83-1.06)	0.324	0.94	(0.84-1.06)	0.339
Highest tertile	0.99	(0.87-1.13)	0.871	0.99	(0.87-1.12)	0.859	0.95	(0.84-1.08)	0.443	0.96	(0.84-1.08)	0.480
≥50%												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.80	(0.65-0.99)	0.044	0.89	(0.72-1.10)	0.284	0.88	(0.71-1.09)	0.244
Highest tertile	0.78	(0.61-0.99)	0.040	0.74	(0.59-0.94)	0.014	0.74	(0.58-0.93)	0.012	0.72	(0.57-0.91)	0.006
CAC score. Agatston units	**n=7849**						**n=7849**					
1-99												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.81-1.05)	0.223	0.92	(0.81-1.05)	0.217	1.02	(0.89-1.15)	0.797	1.02	(0.90-1.15)	0.795
Highest tertile	0.93	(0.81-1.07)	0.314	0.93	(0.81-1.07)	0.297	0.95	(0.83-1.09)	0.502	0.95	(0.83-1.09)	0.494
≥100												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.78-1.09)	0.357	0.92	(0.77-1.08)	0.306	0.81	(0.68-0.96)	0.016	0.81	(0.68-0.96)	0.015
Highest tertile	0.90	(0.75-1.09)	0.281	0.89	(0.74-1.07)	0.206	0.84	(0.70-1.01)	0.060	0.84	(0.70-1.00)	0.049
Ultrasound carotid plaque	**n=8934**						**n=8934**					
Unilateral												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.18	(1.04-1.34)	0.012	1.17	(1.03-1.33)	0.015	0.89	(0.79-1.02)	0.086	0.90	(0.80-1.03)	0.122
Highest tertile	1.17	(1.02-1.35)	0.026	1.16	(1.01-1.33)	0.035	0.93	(0.81-1.06)	0.268	0.95	(0.83-1.08)	0.456
Bilateral												
Lowest tertile. ref.	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.92-1.19)	0.510	1.04	(0.91-1.19)	0.529	0.97	(0.85-1.11)	0.687	0.98	(0.86-1.11)	0.713
Highest tertile	1.04	(0.90-1.20)	0.576	1.04	(0.90-1.20)	0.609	1.02	(0.89-1.18)	0.748	1.03	(0.90-1.18)	0.685

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, SCAPIS: Swedish Cardiopulmonary Bioimage Study.

Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.

Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength (for cardiorespiratory fitness) and cardiorespiratory fitness (for knee extension strength).

Adjusted minus Knee extension strength model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, and years of smoking at conscription.

Adjusted minus Cardiorespiratory fitness model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, and years of smoking at conscription.

Supplementary Table 17. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age by different degrees of covariate control, sensitivity analysis by inverse probability weighting.

	Adjusted			Adjusted, IPW[1]		
Cardiorespiratory fitness	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis	N=8006			N=8514		
1-49%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	0.99	(0.88-1.11)	0.819
Highest tertile	0.99	(0.87-1.13)	0.871	0.99	(0.87-1.13)	0.891
≥50%						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.80	(0.65-0.98)	0.033
Highest tertile	0.78	(0.61-0.99)	0.040	0.75	(0.60-0.94)	0.013
CAC score	N=7849			N=8642		
1-99						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.81-1.05)	0.223	0.97	(0.85-1.10)	0.632
Highest tertile	0.93	(0.81-1.07)	0.314	0.91	(0.79-1.05)	0.192
≥100						
Lowest tertile, ref.	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.78-1.09)	0.357	0.93	(0.79-1.10)	0.421
Highest tertile	0.90	(0.75-1.09)	0.281	0.86	(0.71-1.03)	0.097

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively,
Adjusted model: adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength.
[1] Multinomial logistic model incorporates inverse probability weighting to account for missing data in exposures, outcomes and main analysis covariates. We used the exposure, outcome and completely observed covariates to predict missingness. Later, we used the inverse of these predictions to reweigh our main analysis (Seaman, S. R. et al. Stat Methods Med Res, 2013: 22(3), 278–295).

Supplementary Table 18. Multinomial logistic regression, associations of cardiorespiratory fitness in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis considering quadratic and cubic terms in quantitative covariates.

	Main model[1]			Quadratic[2]			Cubic[3]		
Cardiorespiratory fitness	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis									
1-49%									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.86-1.10)	0.677	0.98	(0.87-1.11)	0.737	0.98	(0.87-1.11)	0.740
Highest tertile	0.99	(0.87-1.13)	0.871	0.99	(0.87-1.14)	0.919	0.99	(0.87-1.14)	0.923
≥50%									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.82	(0.66-1.02)	0.073	0.81	(0.65-1.00)	0.054	0.81	(0.65-1.00)	0.055
Highest tertile	0.78	(0.61-0.99)	0.040	0.76	(0.59-0.97)	0.028	0.76	(0.59-0.97)	0.028
CAC score									
1-99									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.81-1.05)	0.223	0.94	(0.82-1.07)	0.336	0.94	(0.82-1.07)	0.339
Highest tertile	0.93	(0.81-1.07)	0.314	0.95	(0.82-1.10)	0.475	0.95	(0.82-1.10)	0.487
≥100									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.92	(0.78-1.09)	0.357	0.91	(0.77-1.08)	0.271	0.91	(0.77-1.08)	0.277
Highest tertile	0.90	(0.75-1.09)	0.281	0.88	(0.73-1.06)	0.181	0.88	(0.73-1.06)	0.184
Ultrasound carotid plaque									
Unilateral									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.18	(1.04-1.34)	0.012	1.16	(1.02-1.33)	0.023	1.17	(1.02-1.33)	0.022
Highest tertile	1.17	(1.02-1.35)	0.026	1.16	(1.01-1.34)	0.043	1.16	(1.00-1.34)	0.044
Bilateral									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.04	(0.92-1.19)	0.510	1.04	(0.91-1.18)	0.603	1.03	(0.91-1.18)	0.623
Highest tertile	1.04	(0.90-1.20)	0.576	1.04	(0.89-1.20)	0.630	1.03	(0.89-1.20)	0.663

BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.

Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.

[1] Adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription and knee extension strength.

[2] Adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, knee extension strength, and quadratic terms for age at conscription, age at SCAPIS, BMI at conscription, years of smoking at conscription and knee extension strength.

[3] Adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, knee extension strength, and cubic terms for age at conscription, age at SCAPIS, BMI at conscription, years of smoking at conscription and knee extension strength.

Supplementary Table 19. Multinomial logistic regression, associations of knee extension strength in adolescence and coronary stenosis, CAC scores and carotid plaques in middle-age, sensitivity analysis considering quadratic and cubic terms in quantitative covariates.

	Main model[1]			Quadratic[2]			Cubic[3]		
Knee extension strength	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**	**OR**	**(95% CI)**	**P**
CCTA coronary stenosis									
1-49%									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.94	(0.83-1.06)	0.324	0.90	(0.78-1.03)	0.131	0.91	(0.80-1.03)	0.135
Highest tertile	0.95	(0.84-1.08)	0.443	0.85	(0.69-1.06)	0.146	0.86	(0.71-1.03)	0.107
≥50%									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.89	(0.72-1.10)	0.284	0.83	(0.65-1.07)	0.153	0.84	(0.67-1.06)	0.148
Highest tertile	0.74	(0.58-0.93)	0.012	0.64	(0.42-0.97)	0.035	0.65	(0.45-0.94)	0.020
CAC score									
1-99									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	1.02	(0.89-1.15)	0.797	0.97	(0.84-1.12)	0.681	0.97	(0.85-1.12)	0.708
Highest tertile	0.95	(0.83-1.09)	0.502	0.84	(0.67-1.06)	0.141	0.83	(0.68-1.02)	0.075
≥100									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.81	(0.68-0.96)	0.016	0.75	(0.62-0.92)	0.005	0.77	(0.64-0.92)	0.005
Highest tertile	0.84	(0.70-1.01)	0.060	0.72	(0.53-0.98)	0.036	0.74	(0.57-0.97)	0.032
Ultrasound carotid plaque									
Unilateral									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.89	(0.79-1.02)	0.086	0.89	(0.77-1.03)	0.110	0.89	(0.78-1.02)	0.103
Highest tertile	0.93	(0.81-1.06)	0.268	0.93	(0.74-1.17)	0.528	0.95	(0.78-1.16)	0.603
Bilateral									
Lowest tertile, ref.	1.00	-	-	1.00	-	-	1.00	-	-
Medium tertile	0.97	(0.85-1.11)	0.687	1.02	(0.87-1.18)	0.851	1.00	(0.87-1.15)	0.995
Highest tertile	1.02	(0.89-1.18)	0.748	1.15	(0.90-1.47)	0.256	1.13	(0.91-1.40)	0.257

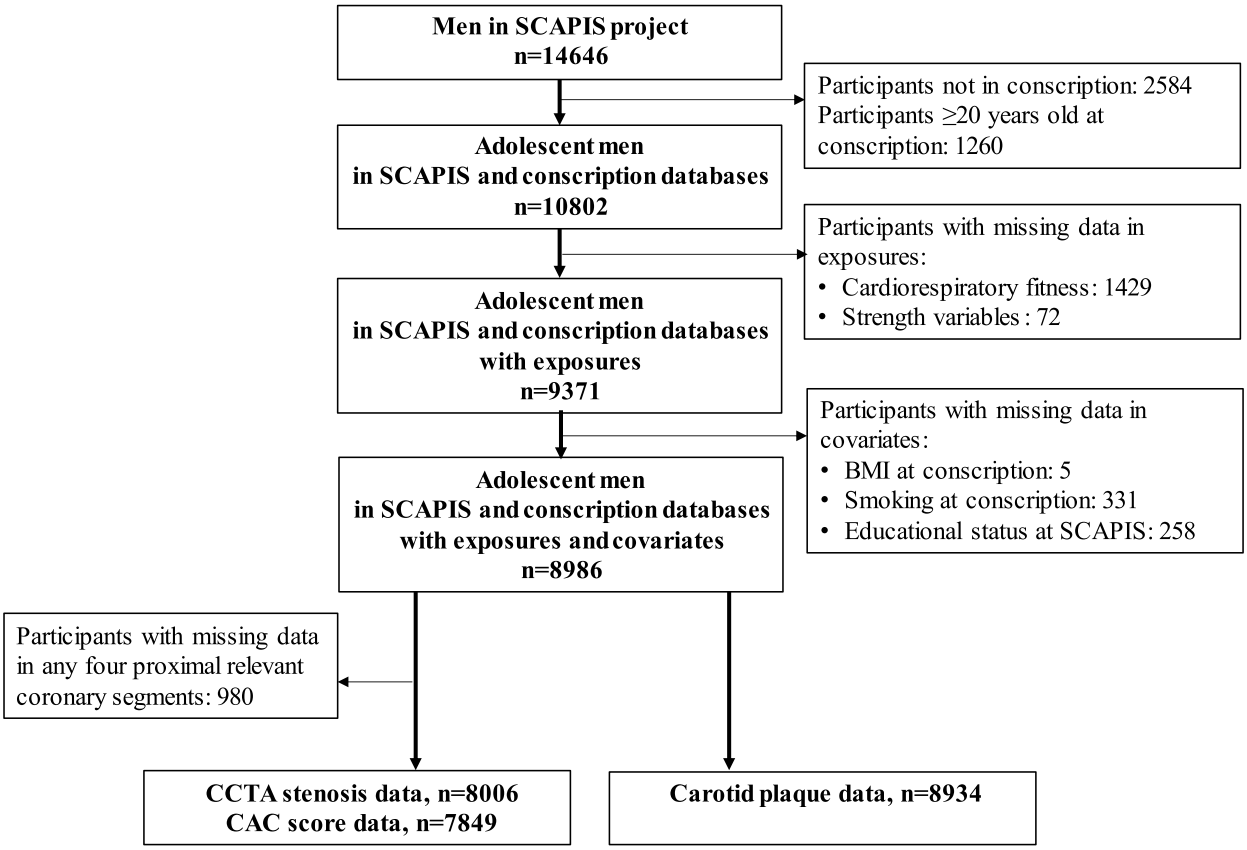
BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomographic angiography, CI: confidence interval, OR: odds ratio, ref.: reference, SCAPIS: Swedish CArdioPulmonary bioImage Study.

Reference category for CCTA stenosis, CAC score and carotid plaques: no stenosis, CAC score=0 Agatston units and no plaque, respectively.

[1] Adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription and cardiorespiratory fitness.

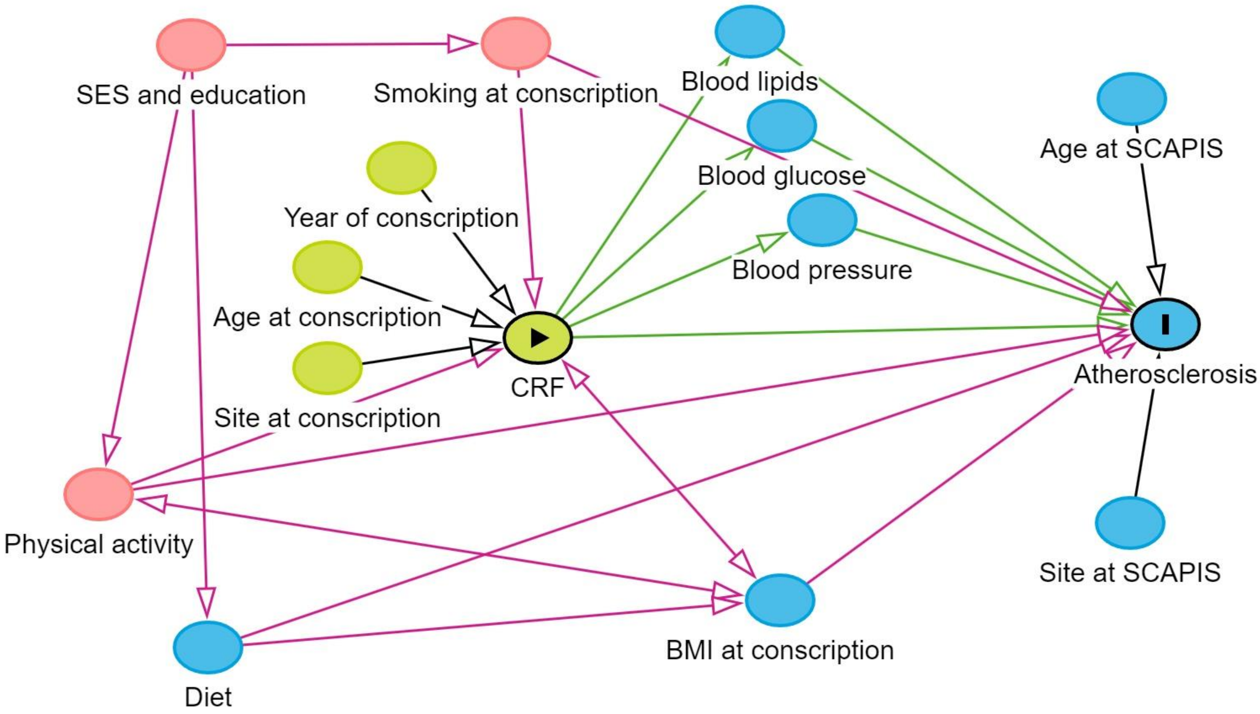
[2] Adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, cardiorespiratory fitness, and quadratic terms for age at conscription, age at SCAPIS, BMI at conscription, years of smoking at conscription and cardiorespiratory fitness.

[3] Adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, cardiorespiratory fitness, and cubic terms for age at conscription, age at SCAPIS, BMI at conscription, years of smoking at conscription and cardiorespiratory fitness.



Supplementary Figure 1. Flow chart of the study.

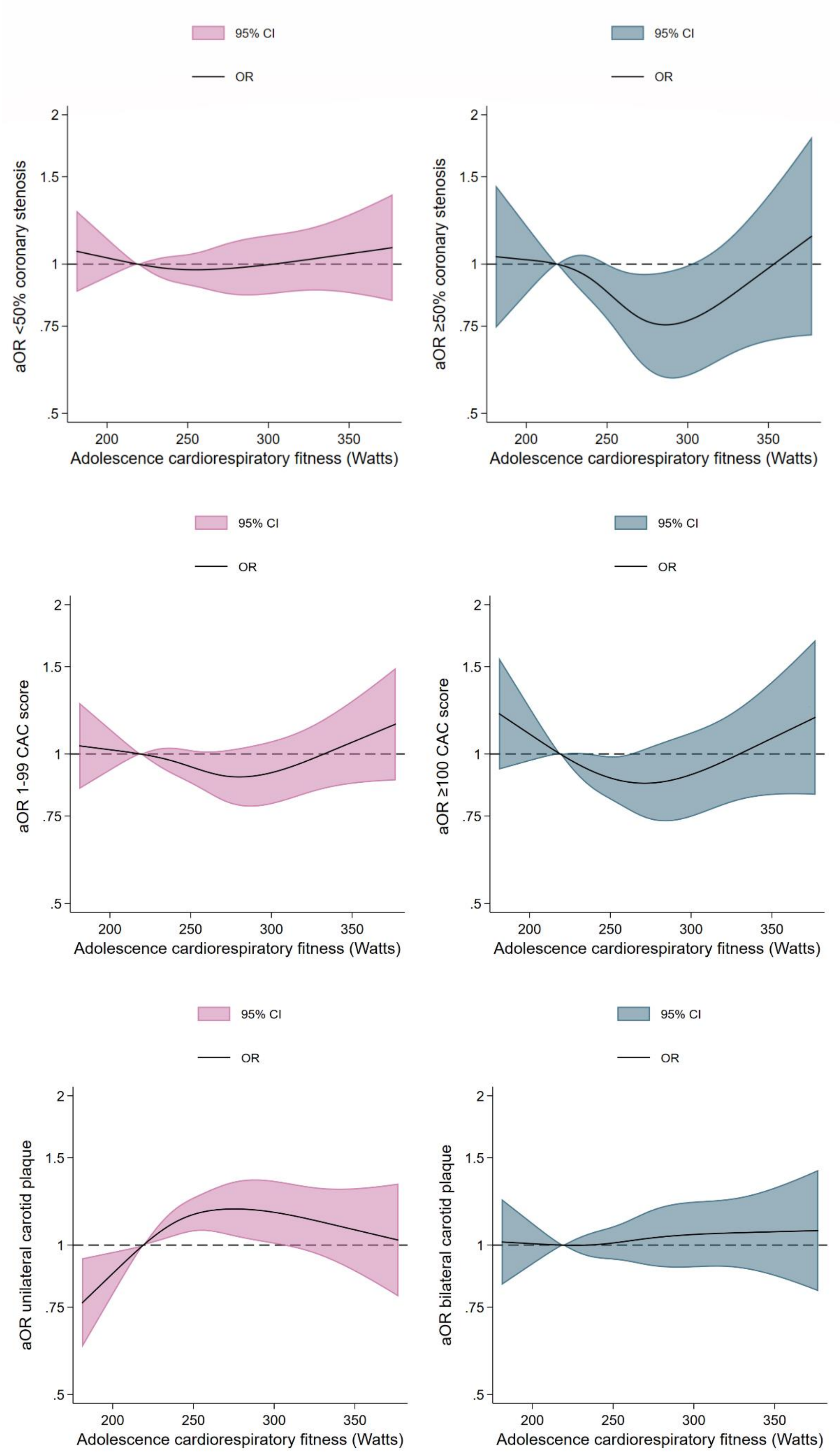
BMI: body mass index, CAC: coronary artery calcium, CCTA: coronary computed tomography angiography, SCAPIS: Swedish CArdioPulmonary bioImage Study.



Supplementary Figure 2. Directed acyclic graph for the association between cardiorespiratory fitness and muscular strength and atherosclerosis outcomes.

BMI: body mass index, CRF: cardiorespiratory fitness, SCAPIS: Swedish CArdioPulmonary bioImage Study, SES: socioeconomic status.

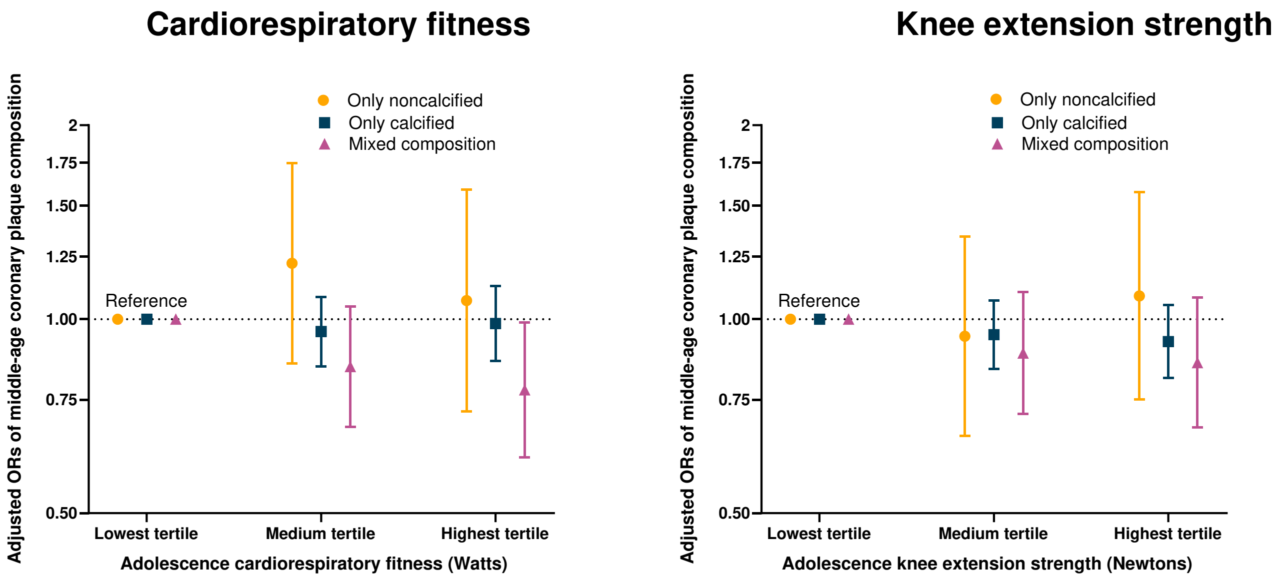
Exposure, Outcome, Ancestor of exposure, Ancestor of outcome, Ancestor of exposure *and* outcome, Causal path, Biasing path.



95% CI
OR
aOR <50% coronary stenosis
aOR ≥50% coronary stenosis
aOR 1-99 CAC score
aOR ≥100 CAC score
aOR unilateral carotid plaque
aOR bilateral carotid plaque
Adolescence cardiorespiratory fitness (Watts)

Supplementary Figure 3. Multinomial logistic regression with restricted cubic splines for the associations of cardiorespiratory fitness in adolescence and atherosclerosis in middle age.

BMI: body mass index, CAC: coronary artery calcium, OR: odds ratio, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Splines are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and knee extension strength. X-axes are trimmed at 1-99% cardiorespiratory fitness values, and the reference category is settled at the median of the first tertile (219 Watts).

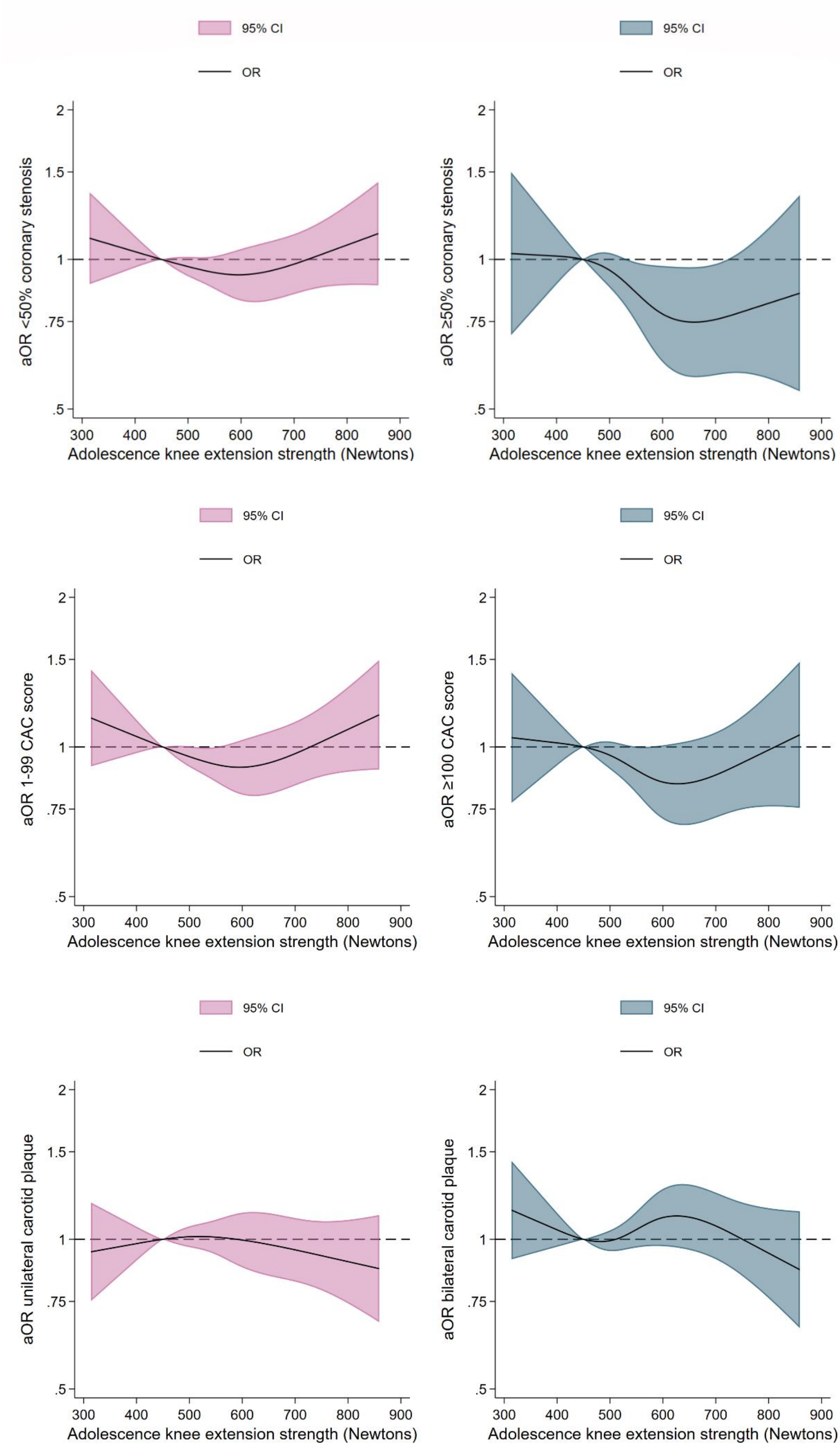


Supplementary Figure 4. Associations of cardiorespiratory fitness and knee extension strength in adolescence with composition of coronary plaques in middle age.

All models depict multinomial regression models adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, knee extension strength (for cardiorespiratory fitness analysis) and cardiorespiratory fitness (for knee extension strength analysis).

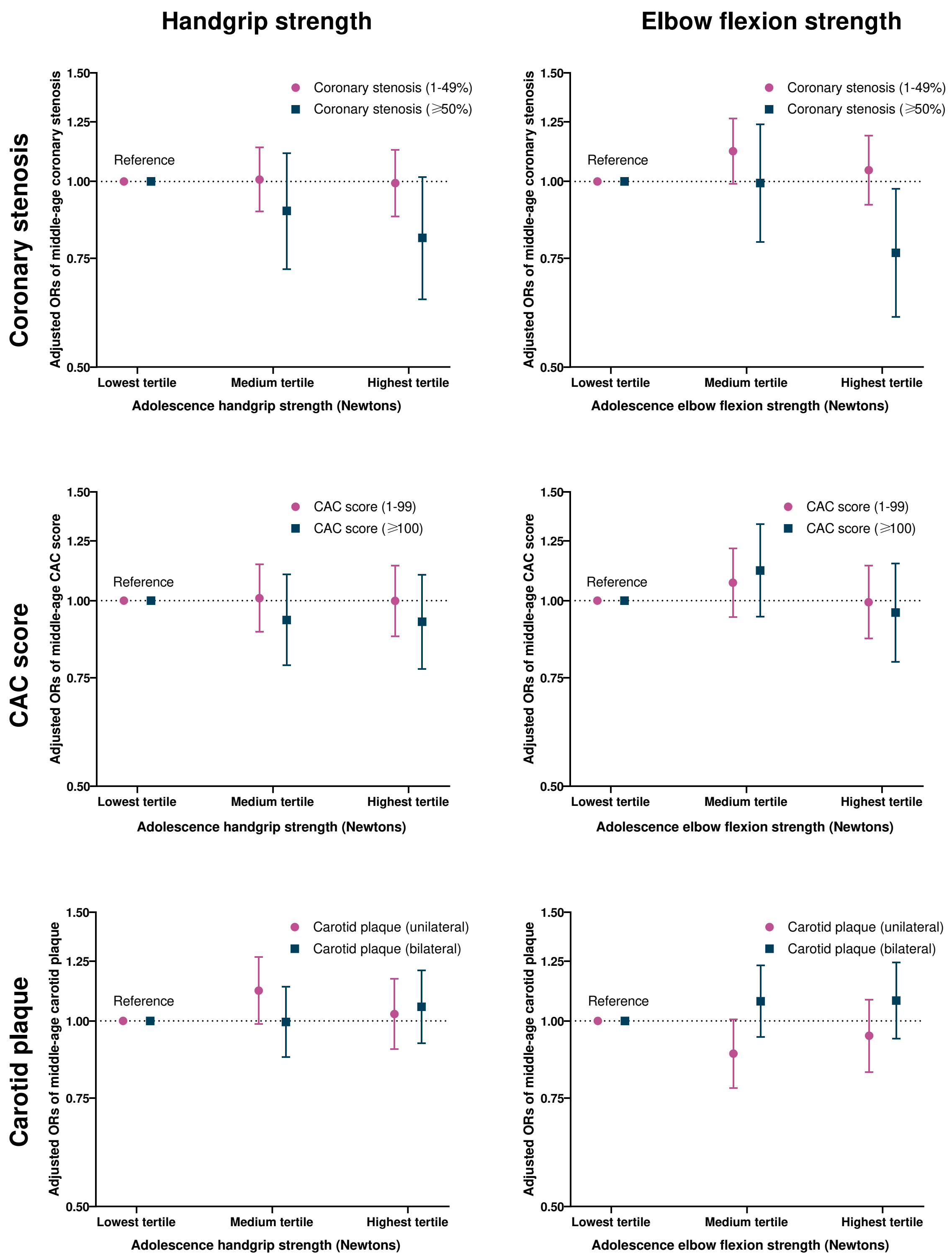
Mixed composition: presence of both calcified and noncalcified segments in the arterial tree.

BMI: body mass index, OR: odds ratio, SCAPIS: Swedish CArdioPulmonary bioImage Study.


95% CI
OR
aOR <50% coronary stenosis
aOR ≥50% coronary stenosis
aOR 1-99 CAC score
aOR ≥100 CAC score
aOR unilateral carotid plaque
aOR bilateral carotid plaque
2
1.5
1
.75
.5
300
400
500
600
700
800
900
Adolescence knee extension strength (Newtons)

Supplementary Figure 5. Multinomial logistic regression with restricted cubic splines for the associations of knee extension strength in adolescence and atherosclerosis in middle age.

BMI: body mass index, CAC: coronary artery calcium, OR: odds ratio, SCAPIS: Swedish CArdioPulmonary bioImage Study.
Splines are adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, conscription year, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness. X-axes are trimmed at 1-99% knee extension strength values, and the reference category is settled at the median of the first tertile (450 Newtons).



Supplementary Figure 6. Associations of handgrip strength and elbow flexion strength in adolescence with coronary stenosis, CAC score and carotid plaques in middle age.

All models depict multinomial regression models adjusted for age at conscription, age at SCAPIS, site in conscription, site in SCAPIS, trend year at conscription, educational status at SCAPIS, BMI at conscription, years of smoking at conscription, and cardiorespiratory fitness.

BMI: body mass index, CAC: coronary artery calcium, OR: odds ratio, SCAPIS: Swedish CArdioPulmonary bioImage Study.