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

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## 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

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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).

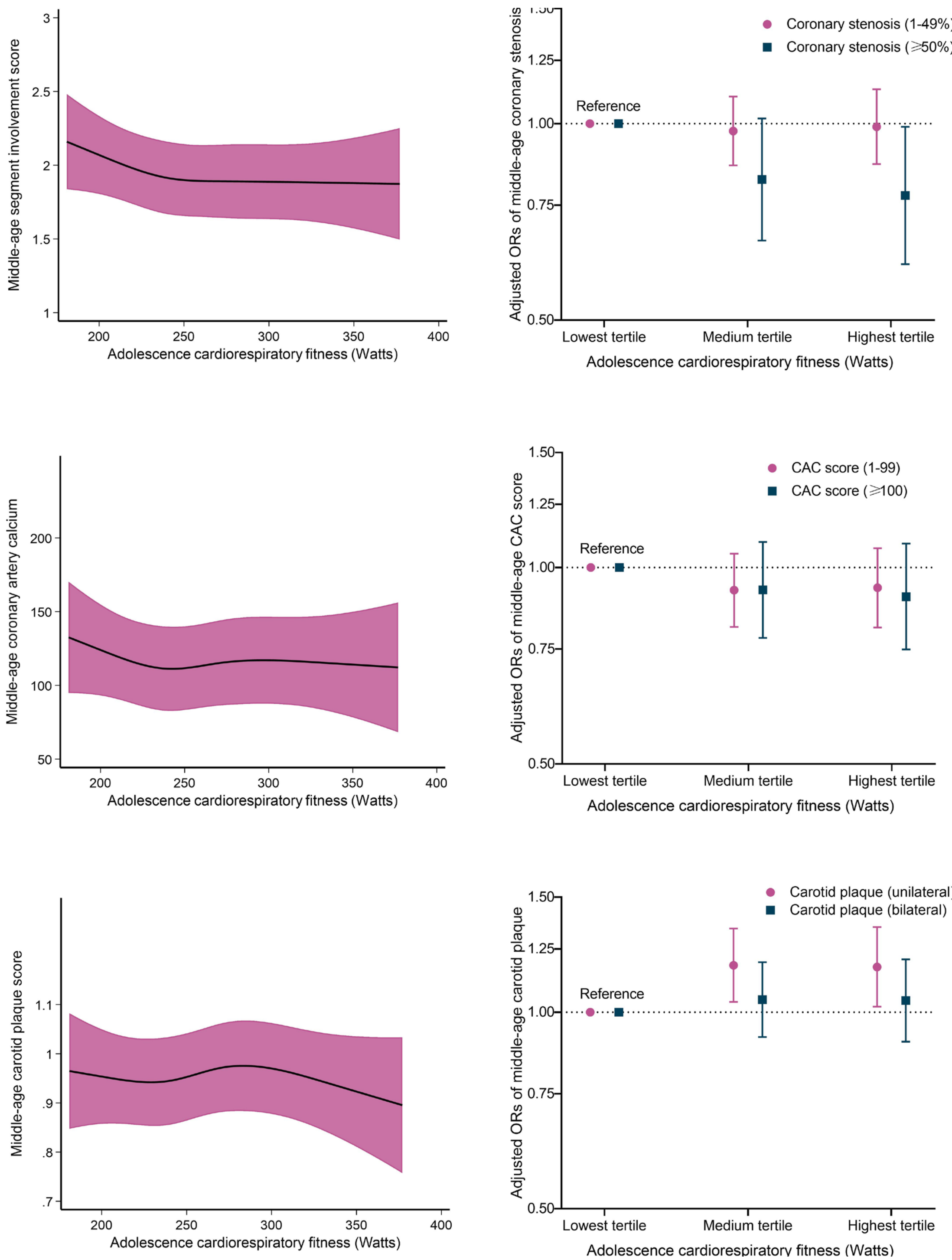


**Figure 1** Associations of cardiorespiratory fitness in adolescence with coronary and carotid atherosclerosis in middle age. Left panel depicts adjusted restricted cubic splines with 95% confidence bands for the association of cardiorespiratory fitness in adolescence with segment involvement score (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.

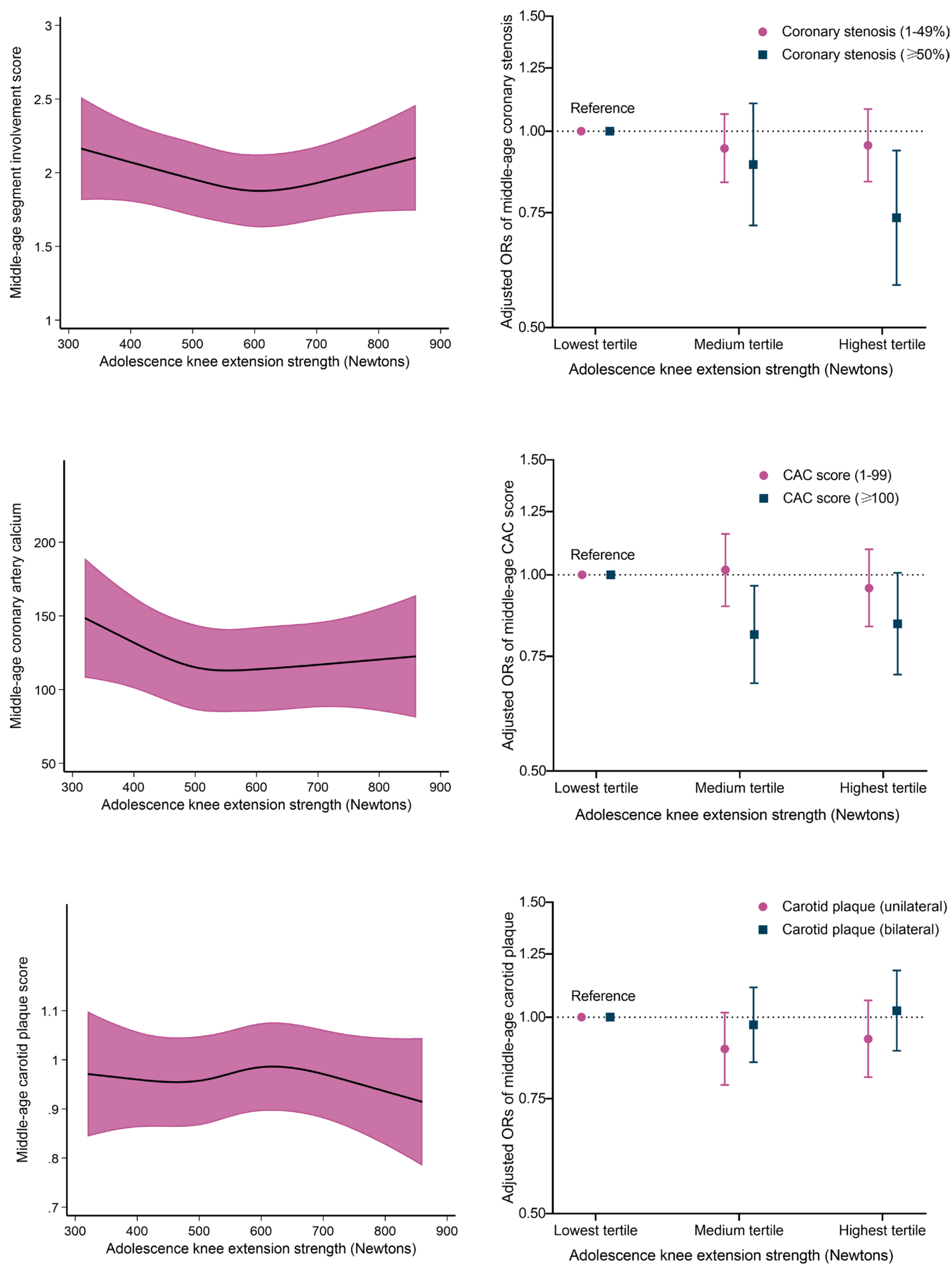


**Figure 2** Associations of knee extension strength in adolescence with coronary and carotid atherosclerosis in middle age. Left panel depicts adjusted restricted cubic splines with 95% confidence bands for the association of knee extension strength in adolescence with segment involvement score (0–11), 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

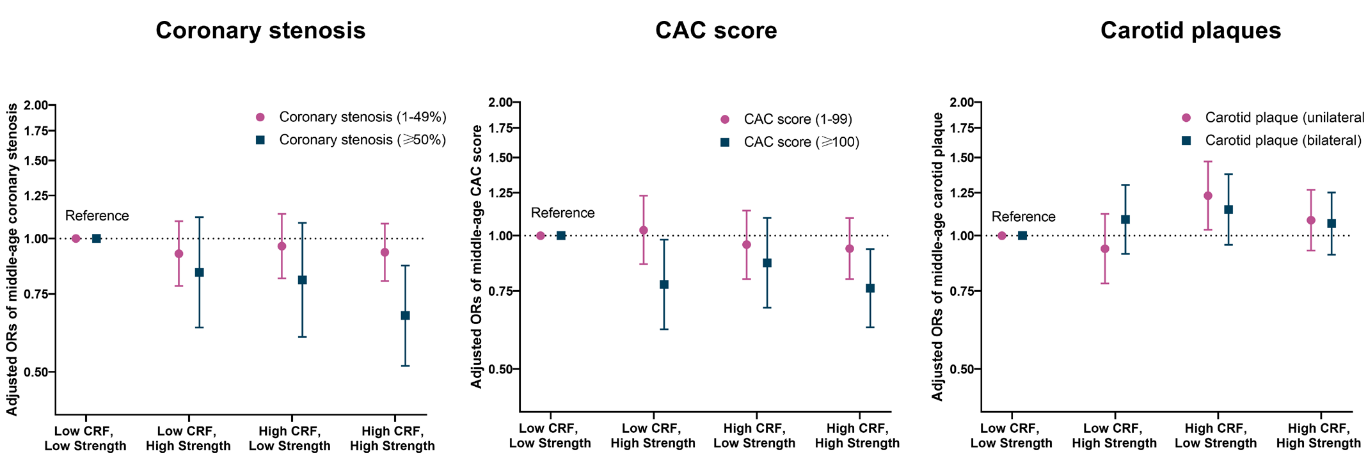


**Figure 3** Combined associations of cardiorespiratory fitness and knee extension strength in adolescence with coronary stenosis, CAC score and carotid plaques in middle age. All models depict multinomial regression models with 95% CIs adjusted for age at conscription, age at SCAPIS, site in conscription, 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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