Circulation

ORIGINAL RESEARCH ARTICLE

Exercise Volume Versus Intensity and the Progression of Coronary Atherosclerosis in Middle-Aged and Older Athletes: Findings From the MARC-2 Study

Vincent L. Aengevaeren, MD, PhD; Arend Mosterd, MD, PhD; Esmée A. Bakker, PhD; Thijs L. Braber, MD, PhD; Hendrik M. Nathoe, MD, PhD; Sanjay Sharma, MD; Paul D. Thompson, MD; Birgitta K. Velthuis, MD, PhD*; Thijs M.H. Eijsvogels, PhD*

BACKGROUND: Physical activity and exercise training are associated with a lower risk for coronary events. However, cross-sectional studies in middle-aged and older male athletes revealed increased coronary artery calcification (CAC) and atherosclerotic plaques, which were related to the amount and intensity of lifelong exercise. We examined the longitudinal relationship between exercise training characteristics and coronary atherosclerosis.

METHODS: Middle-aged and older men from the MARC-1 (Measuring Athlete's Risk of Cardiovascular Events 1) study were invited for follow-up in MARC-2 (Measuring Athlete's Risk of Cardiovascular Events 2) study. The prevalence and severity of CAC and plaques were determined by coronary computed tomography angiography. The volume (metabolic equivalent of task [MET] hours/week) and intensity (moderate [3 to 6 MET hours/week]; vigorous [6 to 9 MET hours/week]; and very vigorous [≥9 MET hours/week]) of exercise training were quantified during follow-up. Linear and logistic regression analyses were performed to determine the association between exercise volume/intensity and markers of coronary atherosclerosis.

RESULTS: We included 289 (age, 54 [50 to 60] years [median (Q1 to Q3)]) of the original 318 MARC-1 participants with a follow-up of 6.3±0.5 years (mean±SD). Participants exercised for 41 (25 to 57) MET hours/week during follow-up, of which 0% (0 to 19%) was at moderate intensity, 44% (0 to 84%) was at vigorous intensity, and 34% (0 to 80%) was at very vigorous intensity. Prevalence of CAC and the median CAC score increased from 52% to 71% and 1 (0 to 32) to 31 (0 to 132), respectively. Exercise volume during follow-up was not associated with changes in CAC or plaque. Vigorous intensity exercise (per 10% increase) was associated with a lesser increase in CAC score (β, −0.05 [−0.09 to −0.01]; *P*=0.02), whereas very vigorous intensity exercise was associated with a greater increase in CAC score (β, 0.05 [0.01 to 0.09] per 10%; *P*=0.01). Very vigorous exercise was also associated with increased odds of dichotomized plaque progression (adjusted odds ratio [aOR], 1.09 [1.01 to 1.18] per 10% vs 2.04 [0.93 to 4.15] for highest vs lowest very vigorous intensity tertiles, respectively), and specifically with increased calcified plaques (aOR, 1.07 [1.00 to 1.15] per 10% vs 2.09 [1.09 to 4.00] for highest vs lowest tertile, respectively).

CONCLUSIONS: Exercise intensity but not volume was associated with progression of coronary atherosclerosis during 6-year follow-up. It is intriguing that very vigorous intensity exercise was associated with greater CAC and calcified plaque progression, whereas vigorous intensity exercise was associated with less CAC progression.

Key Words: cardiomegaly ■ exercise-induced ■ coronary angiography ■ exercise ■ plaque ■ atherosclerotic

Editorial, see p XXX

*B.K. Velthius and T.M.H. Eijsvogels contributed equally.

Correspondence to: Vincent Aengevaeren, MD, PhD, Department of Physiology (392), Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Email: Vincent.Aengevaeren@radboudumc.nl

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.061173.

For Sources of Funding and Disclosures, see page XXX.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Exercise intensity, but not exercise volume, was associated with coronary atherosclerosis progression in middle-aged and older male athletes during 6 years of follow-up.
- The proportion of vigorous intensity exercise training was associated with less progression of coronary artery calcification, whereas the proportion of very vigorous intensity exercise was associated with greater progression of coronary artery calcification and atherosclerotic plaques.

What Are the Clinical Implications?

- The acceleration in coronary artery calcification attributed to very vigorous intensity exercise may reflect an increase in plaque calcification.
- The clinical relevance of this finding remains unclear, but may impact the cardiovascular risk associated with coronary atherosclerosis.
- Future studies should investigate the cardiovascular risk associated with coronary atherosclerosis in athletes and how it differs from the general population.

Nonstandard Abbreviations and Acronyms

CAC	coronary artery calcification
CCTA	coronary computed tomography angiography
CT	computed tomography
CVD	cardiovascular disease
MARC	Measuring Athletes' Risk of Cardiovascular Events
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent of task

Physical activity and exercise training are associated with a significantly lower risk of cardiovascular disease (CVD) and CVD events, with an average 30% to 40% risk reduction for the most active individuals.[1,2] Computed tomography (CT) imaging permits the measurement of coronary artery calcification (CAC), which is an indicator of coronary atherosclerotic plaque burden and the risk of future cardiovascular events.[3–5] Coronary CT angiography (CCTA) allows more detailed characterization of atherosclerotic plaques, which is also predictive of future events.[4] Previous studies indicate that coronary plaque morphology provides prognostic information beyond CAC scores, with calcified plaque being less frequently associated with CVD events compared with mixed or noncalcified plaque.[4]

Unexpectedly, emerging evidence suggests amateur athletes have increased coronary atherosclerosis compared with less active healthy controls.[6–10] Athletes more often had CAC scores ≥100 Agatston units, which was associated with their lifelong exercise volume and intensity of exercise training.[7] In the most active athletes, atherosclerotic plaque morphology appeared more often to be calcified and less mixed (ie, partially calcified).[6,8] However, previous studies were cross-sectional and could not determine whether exercise influenced the acceleration of coronary atherosclerosis and plaque morphology.

We used CAC scoring and CCTA to prospectively investigate the association between exercise volume and intensity and the progression of coronary atherosclerosis in a sizeable cohort of middle-aged and older male athletes. We hypothesized that higher volume and intensity exercise would be associated with the greatest increase in coronary atherosclerosis.

METHODS

Study Design and Population

The MARC-2 (Measuring Athletes' Risk of Cardiovascular Events 2) study, is a follow-up of the MARC-1 (Measuring Athletes' Risk of Cardiovascular Events 1) study.[11] In short, MARC-1 investigated the presence of subclinical coronary atherosclerosis in healthy, middle-aged, male amateur athletes using CT imaging. Asymptomatic middle-aged and older men (≥45 years of age) who had undergone sports medical evaluation without abnormalities were recruited between 2012 and 2014 (n=318). Men with abnormal sports medical examinations, known CVD, contrast allergy, and renal impairment were excluded. Surviving MARC-1 participants (n=314) were invited to participate in MARC-2. Data were collected between May 2019 and February 2020. For the present analysis, individuals who underwent a percutaneous coronary intervention during follow-up were excluded since CAC and plaque characteristics cannot reliably be assessed in that segment (n=2). Ethical approval was obtained from the Dutch Minister of Health, Welfare and Sport (no. 1456153-184955-PG). Participants provided written informed consent. The study was conducted according to the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Exercise Characteristics

Information regarding exercise characteristics was collected at MARC-1 and MARC-2 using a validated questionnaire.[12] Participants reported the type of sport, duration (in years) for each sport, frequency and duration of exercise sessions, and associated level of performance (recreational vs competitive). We assigned a metabolic equivalent of task (MET) for all reported sports using the Compendium of Physical Activities but used the reported level of performance (ie, performing the sport competitively at a regional level or higher) for tennis (5 vs 7.3) and swimming (8 vs 10) to choose the appropriate MET score from the Compendium since multiple options

were available.[13] In addition, running, fitness, and cycling categories were assigned MET scores based on activity type, with MET scores of 11.8 and 7.0 allocated to running and jogging, respectively. Strength training was given a MET score of 3.5 and cardio fitness received a MET score of 5.5. Different types of cycling (eg, race, mountain bike, spinning) also received specific MET scores (Table S1). We calculated the exercise volume per sport by multiplying the MET score for the specific sport by the reported exercise volume (session duration × frequency/week), months of practice per year, and total years of practice. For the current analyses, exercise volume (expressed in MET hours/week) during follow-up was used. Exercise volume is the sum of all sports activities between the baseline of MARC-1 and the follow-up assessment of MARC-2. We made tertiles of exercise volume (ie, low, medium, high) because the previously defined exercise groups (<1000, 1000 to 2000, >2000 MET min/week) did not fit the present study and would have produced skewed group distribution with 11% versus 26% versus 63% of individuals per subgroup. We also classified exercise intensity as light (<3 METs), moderate (3 to 6 METs), vigorous (6 to 9 METs), or very vigorous (≥9 METs) and calculated the percentage of exercise MET hours/week in these ranges as a proportion (%) of the total exercise volume. Since exercise in the light intensity range was negligible, with only 9 participants performing low volumes of light intensity exercise, we did not include light intensity in our analyses. Subsequently, we developed tertiles (ie, low, medium, high) based on the percentage of vigorous and very vigorous intensity exercise.

Cardiac CT

CT imaging was performed using the exact same 256-slice scanner (Philips Healthcare, The Netherlands) as in MARC-1, with electrocardiographic gating according to guidelines.[14] A noncontrast CT was acquired to calculate CAC scores (scan parameter: 120 kV, 210 mAs), which was followed by CCTA using the same protocol as in MARC-1. Participants experiencing signs of contrast reaction during baseline scan underwent only a noncontrast CT scan at follow-up (n=5). CT scans were processed on a workstation (IntelliSpace Portal; Philips Healthcare) by experienced technicians, and assessed by an experienced cardiovascular radiologist. Guidelines for interpretation and reporting of CCTA, including the 18-segment coronary artery model, were used to analyze plaque characteristics per segment.[15] The Agatston CAC score was used to quantify coronary artery calcification.[16] We quantified progression using delta CAC score (CAC score follow-up − CAC score baseline), which cannot be negative and any increase in CAC score indicates progression. CCTA was used to identify plaques not detected by noncontrast CT and to assess plaque characteristics. We classified plaques as calcified, noncalcified or mixed (ie, partially calcified) plaques. Study definitions regarding exercise and plaque characteristics are summarized in Table S2.

Statistical Analysis

All parameters were visually inspected for normality and checked for kurtosis and skewness. Continuous variables are reported as mean±SD when normally distributed or as median [interquartile range] when not. Categoric variables are presented as proportions. Participant characteristics at baseline and follow-up were compared using paired T-tests for normally distributed data and Wilcoxon signed rank tests for nonnormally distributed variables. The McNemar test was used for binary variables. Linear regression analyses were performed between exercise volume and intensity and change in CAC score and the number of plaques. CAC scores were transformed (Ln delta CAC score + 1) and analyses were adjusted for baseline confounders, CAC score or number of plaques at baseline, and time between CT scans. Binary logistic regression was used to calculate adjusted odds ratios (aORs) for the association between exercise volume and intensity and progression of plaque (dichotomized: increase/no change in number of plaques) and plaque types. All analyses were performed with exercise volume and intensity as continuous parameter and in tertiles. Exercise intensities were assessed as a proportion of MET hours/week and included separately, while adjusting for exercise volume. Additionally, we explored potential nonlinear associations using cubic spline regression analyses. We decided to adjust a priori for the following known cardiovascular risk factors at baseline: age, body mass index, systolic blood pressure, smoking (pack years), total cholesterol, family history of coronary heart disease, and use of antihypertensive, antidiabetic, and statin medications. Statistical significance was assumed at $P<0.05$. Since various analytic strategies are used to assess CAC progression, we performed multiple sensitivity analyses to include alternative methods to assess CAC progression.[17,18] For that purpose, we also calculated the delta CAC score (ie, $\sqrt{CAC\ at\ followup} - \sqrt{CAC\ at\ baseline}$) and the volume score using the squared root method, which entails removing density from the CAC score equation. We also annualized the logarithmically transformed delta CAC score and squared root CAC and volume scores instead of including follow-up time as a covariate. Statistical analyses were performed using SPSS Statistics 25 (IBM Corp, USA), except for the cubic spline regression analyses which were conducted using R software version 4.0.3.

RESULTS

A total of 291 men (age, 54 [50 to 60] years at MARC-1 baseline and 60 [56 to 66] years at follow-up) were included in MARC-2 (92% of original cohort [Figure S1]). Characteristics of MARC-1 participants that did (n=291) and did not (n=27) participate in MARC-2 were comparable (Table S3). Two participants (1%) received coronary stents before MARC-2 and were excluded from the current analyses. Five participants (2%) underwent noncontrast CT scans only in MARC-2 because of mild contrast reactions during their MARC-1 CCTAs. Two participants (1%) had (false) regression of CAC (from 1 to 0 and from 12.2 to 3.6), which was caused by a sampling error related to partial volume effect (calcium just below 130 Hounsfield units at follow-up) and unreliable measurement related to movement artefact. These individuals were not included in the delta CAC score analyses. Therefore, 287 men were included in the MARC-2 CAC analyses and 284 in the plaque analyses. Average follow-up between CT-scans was 6.3±0.5 years. Average blood pressure and use of antihypertensives and statins increased during follow-up, whereas total cholesterol

remained similar (Table 1). Six athletes quit smoking during follow-up.

Participants exercised for 41 [25 to 57] MET hours/week after MARC-1, of which a median of 0% [0 to 19%] was at moderate intensity, 44% [0 to 84%] was at vigorous intensity, and 34% [0 to 80%] was at very vigorous intensity (Figure 1). Exercise volume during follow-up was greater than the average lifelong exercise volume that was assessed upon enrollment in MARC-1 (Table S4). Hence, exercise duration, number of exercise sessions, and MET hours per week were greater at MARC-2 measurement compared with MARC-1 (Table S4). Characteristics of exercise intensity remained similar over time with the largest portion being vigorous intensity exercise followed by very vigorous intensity exercise. Characteristics of the exercise volume and vigorous and very vigorous intensity tertile groups are summarized in Tables S5, S6 and S7.

CAC was present in 151 (52%) men at baseline and increased to 205 (71%) men at follow-up. Median CAC scores increased from 1 [0 to 32] to 31 [0 to 132] (Table 2; Figure 2). CAC score categories increased over time (Table 2): CAC scores ≥100 increased from 15% to 31%, CAC scores ≥400 increased from 6% to 13%, and CAC scores ≥1000 increased from 1% to 6% at follow-up (Figure 2). At follow-up, 26% had CAC scores in the 75th MESA (Multi-Ethnic Study of Atherosclerosis) percentile or higher,[19] compared with 22% at baseline (P=0.11). Plaque prevalence increased from 64% at baseline to 83% at follow-up (Table 2; Figure 2). A total of 216 (75%) participants showed an increased number of coronary atherosclerotic plaques and had a median change in the number of plaques of 3 [1 to 5], which consisted of 1 [0 to 3] calcified plaque, 1 [0 to 2] mixed plaque, and 0 [0 to 1] noncalcified plaques. A total of 150 (52%) participants showed an increase in the number of calcified plaques: 145 (50%) showed increased mixed plaques and 105 (36%) showed increased noncalcified plaques.

We found no association between exercise volumes and CAC and plaque progression using multivariable adjusted linear (Figure 3) and logistic regression analyses (Figure 4). The proportion (%) of vigorous intensity exercise and total exercise volume correlated negatively with progression of CAC when included as continuous variables (β, −0.05 [−0.09 – −0.01] per 10%; P=0.02) and as tertiles (3rd tertile β, −0.54 [−0.90 – −0.17]; P=0.004; Figure 3), but was not significantly associated with progression of plaques (Figure 4). The proportion (%) of very vigorous exercise was positively associated with progression of CAC using linear (β, 0.05 [0.01 to 0.09] per 10%; P=0.01; Figure 3) and logistic regression analysis (β, 0.45 [0.07 to 0.82] for 3rd tertile; P=0.02; Figure 4). Very vigorous intensity exercise was not associated with the absolute increase in number of plaques (Figure 3), but was associated with plaque progression using logistic regression analyses (aOR, 1.09 [1.01 to 1.18] per 10%; P=0.04; 3rd tertile aOR, 2.04 [0.93

Table 1. Study Cohort Characteristics at Baseline and Follow-Up (n=289)

Characteristic	Baseline	Follow-up	*P* value
Age, y	53.6 (50.0–59.7)	60.0 (56.3–66.0)	<0.001
Height, cm	183 (7)	183 (7)	0.38
Weight, kg	83.0 (10.7)	83.4 (11.1)	0.18
Body mass index, kg/m^2	24.4 (23.1–26.4)	24.5 (22.9–26.6)	0.84
Body surface area, m^2	2.05 (0.15)	2.05 (0.16)	0.16
Systolic blood pressure, mmHg	128.7 (13.3)	139.4 (17.7)	<0.001
Diastolic blood pressure, mmHg	79.7 (8.5)	82.2 (8.3)	<0.001
Antihypertensive use, n (%)	20 (7)	31 (11)	0.003
Total cholesterol, mmol/L	5.4 (0.9)	5.4 (1.0)	0.73
LDL cholesterol, mmol/L	n/a	3.2 (0.9)	–
HDL cholesterol, mmol/L	n/a	1.54 (0.36)	–
Triglycerides, mmol/L	n/a	1.2 (0.9–1.8)	–
Statin use, n (%)	16 (6)	44 (15)	0.003
Glucose, mmol/L	n/a	5.0 (0.6)	–
Diabetes, n (%)	4 (1)	6 (2)	0.50
Current smoker, n (%)	15 (5)	9 (3)	0.03
Former smoker, n (%)	130 (45)	136 (47)	0.03
Never smoker, n (%)	144 (50)	144 (50)	1.00
Smoking, pack-years	0.0 (0.0–7.5)	0.0 (0.0–8.0)	0.01

Data are presented as mean (SD), n (%), or median (interquartile range). LDL indicates low-density lipoprotein; and HDL, high-density lipoprotein.

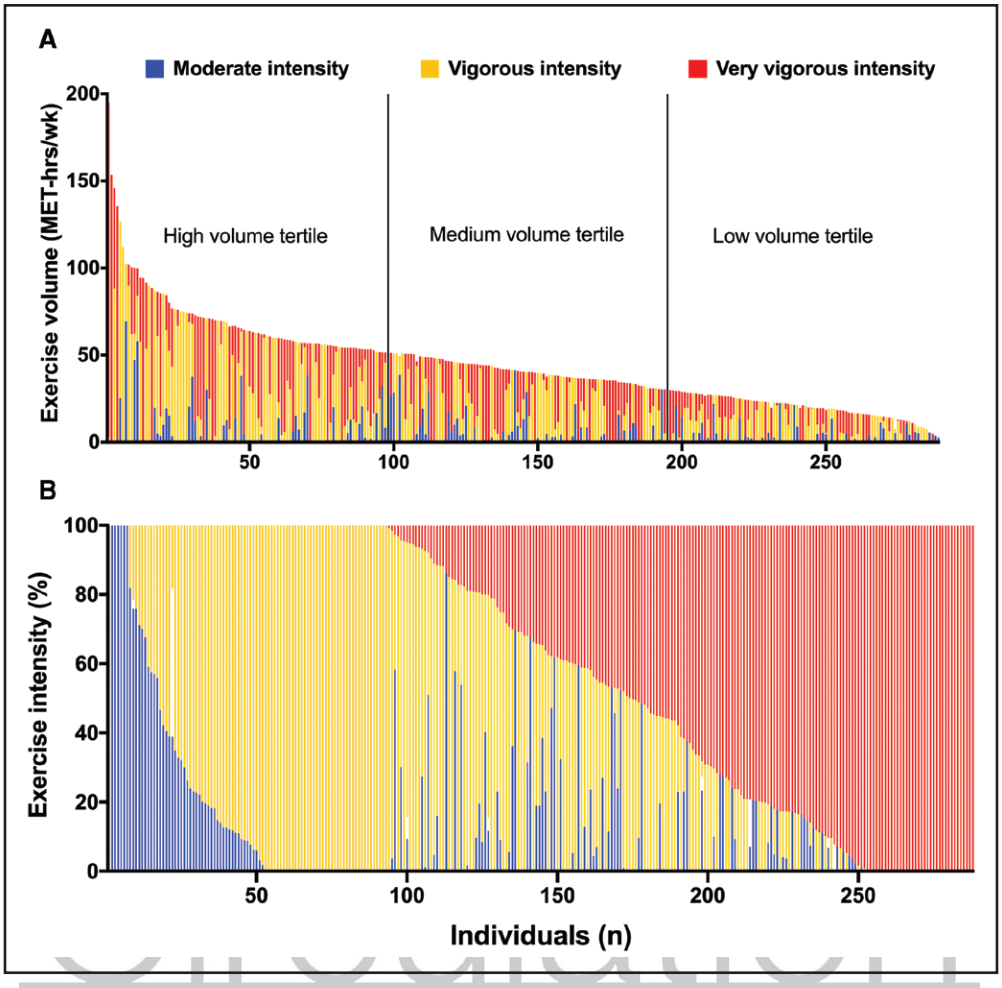

Figure 1. Exercise volume and intensity characteristics of MARC-2 participants during follow-up.
A, Distribution of exercise volume in MET h/week among participants, sorted from high to low. Each bar represents a participant in MARC-2 (n=289). The contribution of moderate, vigorous, and very vigorous intensity exercise are highlighted in blue, yellow, and red, respectively. **B,** Relative contribution of exercise intensity to total exercise volume of each participant in MARC-2, sorted from only moderate to only very vigorous exercise. The order of bars is different across panels. Missing/white bars are light intensity exercise. MARC-2 indicates Measuring Athletes' Risk of Cardiovascular Events 2 study; and MET, metabolic equivalent of task.

to 4.15]; *P*=0.06; Figure 4). This appeared to be specifically driven by an increase in calcified plaque (aOR, 1.007 [1.00 to 1.15] per 10%; *P*=0.053; 3rd tertile aOR, 2.09 [1.09 to 4.00]; *P*=0.03; Figure 4B). The absolute values are reported in Tables S8 and S9. The positive and negative value of the adjusted betas for very vigorous and vigorous intensity exercise, respectively, cannot be interpreted in isolation since these values are part of a multivariable model with 12 to 14 variables depending on the specific analysis. Since all participants either remained at CAC score 0 or had an increase in their CAC score, the increase in CAC score was lower in participants performing mainly vigorous exercise (indicated by negative beta) and greater in those performing mainly very vigorous exercise (indicated by positive beta).

Sensitivity analyses using the squared root method and annualized scores to assess CAC progression were calculated and reported in Table S10. These outcomes showed similar results as our main analyses, supporting the robustness of our findings.

Finally, cubic spline regression analyses and nonlinearity tests indicated no nonlinear associations for most analyses (*P*>0.05; data not shown), except for the association between MET hours/week and calcified plaque progression (*P*=0.048), and between both vigorous (*P*=0.01) and very vigorous intensity (*P*=0.03) and mixed plaque progression which could also be observed in the categorical data analyses (Figure 4).

DISCUSSION

We investigated progression of coronary atherosclerosis in 289 middle-aged and older male athletes using CAC scoring and CCTA and assessed its association with exercise characteristics during 6.3 years follow-up. Exercise intensity, but not volume, was associated with

Table 2. Characteristics of Coronary Atherosclerosis and Plaque at Baseline and Follow-Up

Characteristic	Baseline	Follow-Up	*P* value
Coronary atherosclerosis characteristics*			
CAC score, Agatston units	1 (0–32)	31 (0–132)	<0.001
CAC score >0, n (%)	151 (52)	205 (71)	<0.001
In those with CAC score >0			
Area, mm^2	10.5 (4.1–41.6)	26.0 (8.6–65.8)	
Density, au	2.8 (1.7–3.4)	3.0 (2.5–3.5)	
Regions of interest, n	3 (1–10)	6 (3–13)	
CAC score >100, n (%)	43 (15)	89 (31)	<0.001
CAC score >400, n (%)	18 (6)	38 (13)	<0.001
CAC score >1000, n (%)	4 (1)	17 (6)	<0.001
≥75th MESA percentile, n (%)	65 (22)	74 (26)	0.11
Presence of plaque, n (%)	184 (64)	239 (83)	<0.001
Plaque characteristics†			
Number of plaques, n	2 (1–5)	6 (2–9)	
Calcified plaques			
Presence of calcified plaques	126 (69)	184 (77)	
Number of calcified plaques	1 (0–2)	2 (1–5)	
Percentage calcified plaques	50 (0–100)	50 (15–73)	
Mixed plaques			
Presence of mixed plaques	105 (57)	175 (73)	
Number of mixed plaques	1 (0–2)	2 (0–3)	
Percentage mixed plaques	23 (0-67)	33 (0–50)	
Noncalcified plaques			
Presence of noncalcified plaques	60 (33)	124 (52)	
Number of noncalcified plaques	0 (0–1)	1 (0–1)	
Percentage noncalcified plaques	0 (0–20)	6 (0–29)	

Data is presented as n (%) or median (interquartile range). Since plaque characteristics for 2 different groups (n=184 and n=239) are described, no *P* values for within-person changes could be calculated. CAC indicates coronary artery calcification; and MESA, Multi-Ethnic Study of Atherosclerosis.

*n=289 at baseline and follow-up.

†n=184 at baseline; n=239 at follow-up.

progression of coronary atherosclerosis. Vigorous exercise was associated with less CAC progression, whereas very vigorous exercise was associated with greater progression of CAC and (mainly calcified) plaque.

Exercise Volume

We found no association between exercise volume during follow-up and progression of coronary atherosclerosis. Our previous study, MARC-1, was cross-sectional and examined the effect of 36 (27 to 42) years of exercise on coronary atherosclerosis and found that the most active athletes had higher prevalence of CAC and atherosclerotic plaques.[6] In contrast, MARC-2 assessed the additional effects of exercise on coronary atherosclerosis after only 6.3±0.5 years follow-up, which may be insufficient to find an effect of exercise volume on CAC or plaque progression. Indeed, a study in 61 recreational athletes (74% male) found no significant difference in exercise volume between individuals with or without progression of CAC (68 [33 to 122] vs 50 [34 to 82] MET hours/week; *P*=0.16) after 4.1±0.3 years of follow-up.[20] In contrast, a Korean population study categorized 25 485 young (42±6 years) Korean men and women as inactive, moderately active, and health-enhancing physically active. Moderately active was defined as ≥3 days of vigorous intensity activity for ≥20 min/day, ≥5 days of moderate intensity activity for ≥30 min/day, or ≥5 days of activities attaining ≥600 MET min/week. Health-enhancing physical activity was defined as ≥3 days of vigorous intensity activity attaining ≥1500 MET min/week or 7 days of activities attaining ≥3000 MET min/week. The latter group had a higher estimated 5-year progression of CAC during 3.0 (2.0 to 4.2) years follow-up.[21] It is also possible that exercise volume is involved in the initiation of coronary atherosclerosis, but does not

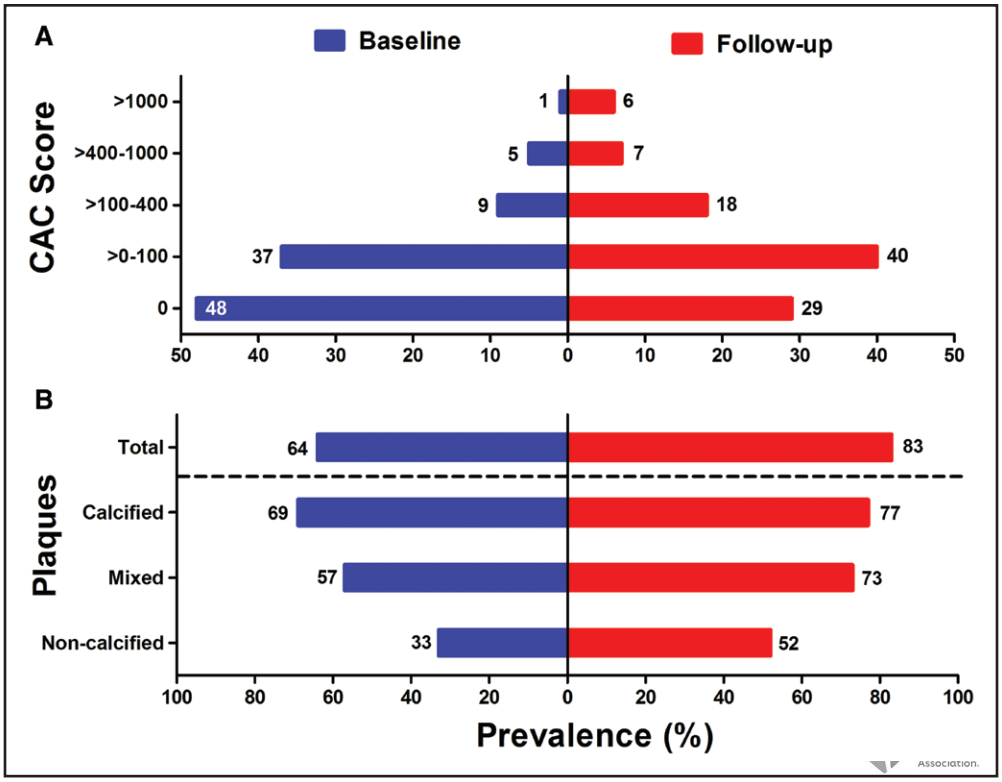

Figure 2. CAC scores and atherosclerotic plaque and plaque-type prevalence at baseline and follow-up.
A, CAC Scores. **B**, Atherosclerotic plaque. Plaque-type prevalence is calculated for individuals with plaque at baseline (n=184) and follow-up (n=239). Baseline values are from MARC-1 (Measuring Athletes' Risk of Cardiovascular Events 1) and follow-up values are from MARC-2 (Measuring Athletes' Risk of Cardiovascular Events 2).

contribute to progression. The Heinz Nixdorf recall study found that CAC score itself predicts CAC progression whereas other risk factors explain little of the variance in CAC progression.[22] Overall, the results from MARC-1 and MARC-2 suggest that exercise volume plays a role in CAC prevalence, but not in CAC progression during 6-years of follow-up.

Exercise Intensity

Previous studies investigating coronary atherosclerosis in athletes are limited by their cross-sectional design and do not address the separate roles of exercise volume versus intensity because they either compare athletes with nonathletes[8,9] or do not examine intensity and volume separately.[10,20,21] We found that vigorous exercise lowered CAC progression, whereas very vigorous exercise accelerated it. Very vigorous exercise was also associated with increased progression of (calcified) plaque. These findings align with our cross-sectional MARC-1 observation that specific exercise intensities accelerate the development of calcified plaque (seen with CAC scoring and CCTA).[6] The lower progression in the more vigorous exercise group or the increased progression in the more very vigorous intensity exercise group could not be explained by the fact that the very vigorous exercise group was older or had a higher prevalence of risk factors (Tables S5 to S7), for which we also adjusted in our analyses. Thus, our longitudinal MARC-2 observations suggest that very vigorous exercise is related to calcified plaque formation, which increases the probability that certain mechanisms contribute to the increased coronary atherosclerosis in athletes. Higher intensity exercise produces higher catecholamine levels.[23] Catecholamines are relatively stable at lower intensity exercise, but increase exponentially with higher intensity exercise.[23,24] Catecholamines increase heart rate and blood pressure, both of which increase coronary mechanical stress. Increased heart rate itself has been demonstrated to accelerate atherosclerosis probably by increasing the frequency of turbulent blood flow.[25] Catecholamines also produce long-lasting proinflammatory changes in monocytes.[26] Consequently, increases in blood pressure, heart rate, mechanical stress, disrupted laminar flow and inflammation become more likely potential mechanisms of increased coronary atherosclerosis in athletes.[7]

Exercise Type

We cannot separate the roles of exercise intensity and type of sport since most of our athletes cycled or ran, activities

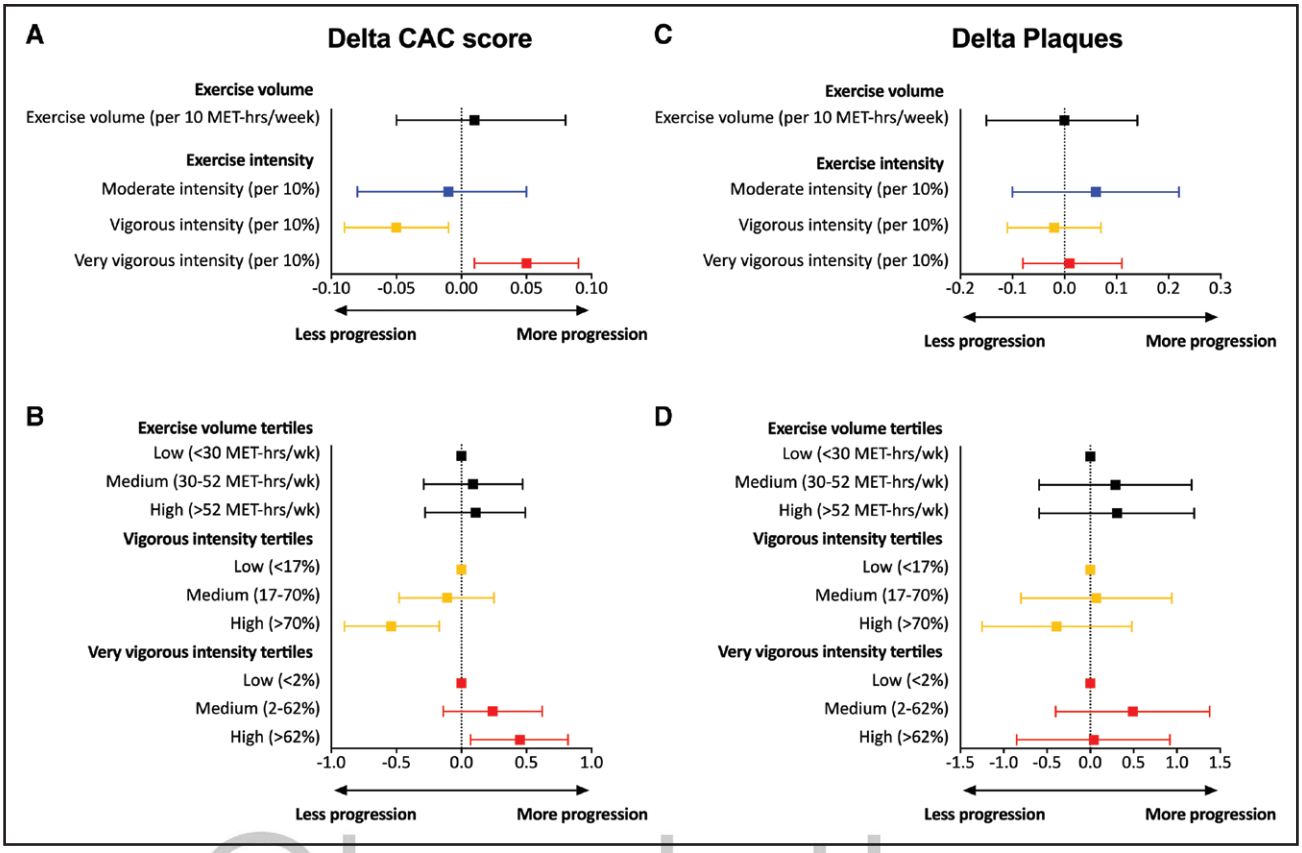

Figure 3. Association between exercise volume and intensity and progression of CAC score and change in number of plaques. **A** and **B**, Association with CAC score. **C** and **D**, Association with change in number of plaques. Adjusted betas from multivariable linear regression analyses are reported on *y* axes with 95% CI. Negative betas indicate less progression of CAC score, whereas positive betas indicate greater progression of CAC score. The models are adjusted for the following baseline confounders: age, body mass index, systolic blood pressure, use of antihypertensive, pack years smoked, total cholesterol, family history of coronary heart disease, use of statin, diabetes, time between computed tomography scans, baseline coronary artery calcification score (analyses in **A** and **B** only) and number of plaques (analyses in **C** and **D** only). The exercise intensity analyses are additionally adjusted for exercise volume during follow-up. CAC indicates coronary artery calcification; and MET, metabolic equivalent of task.

that were classified as vigorous or very vigorous, respectively (Table S1). Many athletes (71%), however, performed more than one type of sport, further obscuring the role of sport type. We previously observed that cyclists had less coronary atherosclerosis than runners, but did tend to have more calcified plaques, which we hypothesized could be attributable to differences in exercise intensity or differences in skeletal stress, bone turnover, and calcification between the 2 activities.[27] Future studies should examine differences in atherosclerosis based on exercise intensity within the separate communities of running and cycling.

Clinical Relevance

CAC and atherosclerotic plaques are strongly associated with future risk of cardiovascular events in the general and patient populations.[4,28–30] Although we and others have found an increased prevalence and severity of coronary atherosclerosis in athletes, which was associated with their lifelong exercise volume, athletes have a superior life expectancy compared with the general population.[31,32] This may partially be explained by beneficial coronary adaptations to exercise and lower risk plaque morphology.[7] The effect of very vigorous intensity exercise may mimic the effect of statins on CAC and plaque composition. Statins increase plaque calcification in some studies,[33] but decrease atheroma volume and cardiovascular risk.[34] Nevertheless, individuals in the MESA study with CAC scores >1000 had risk for a major adverse cardiovascular event of 3.4 per 100 person-years, similar to that of a secondary prevention population,[35] and 6% of our population had a CAC score >1000 on their MARC-2 evaluation. CAC scores that increase from <100 to >100 are associated with increased CVD mortality in athletes,[10] even though the absolute risk of similar CAC scores is lower with increasing physical activity[10] and cardiorespiratory fitness.[36]

Limitations

The strengths of our study are its longitudinal design and its assessment of CAC scoring and CCTA in a large

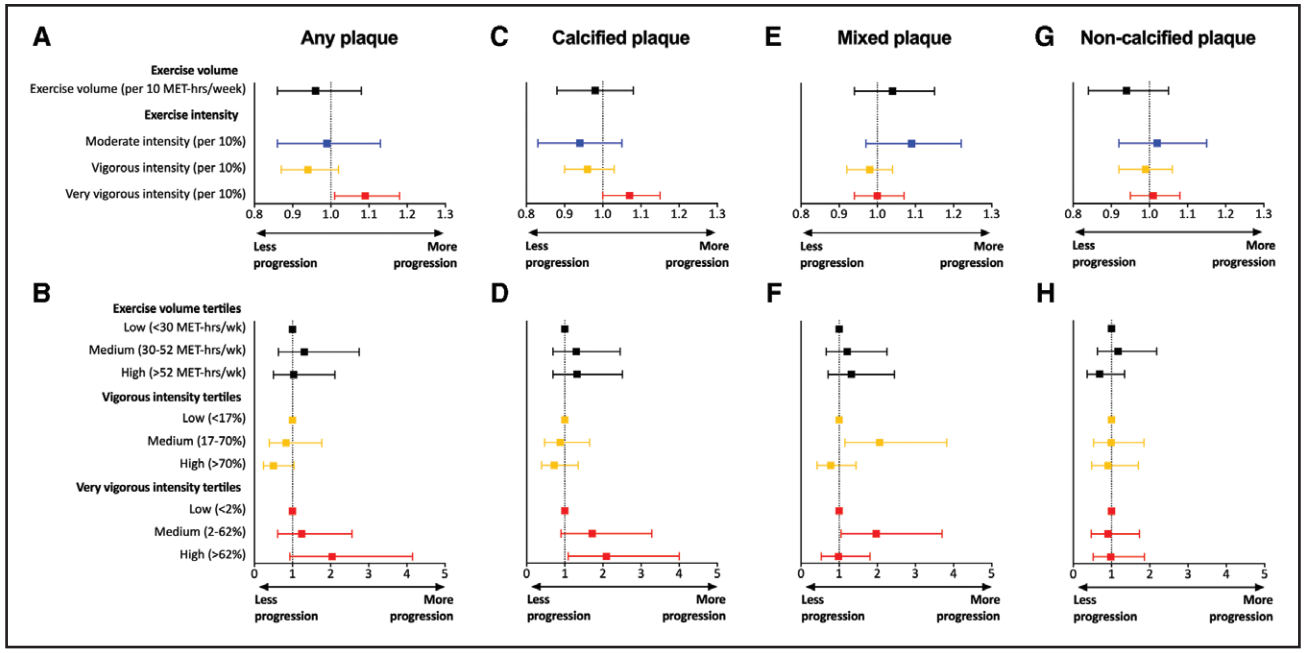

Figure 4. Association between exercise volume and intensity and plaque progression.
Association with any plaque (A and B), calcified plaque (**C** and **D**), mixed plaque (**E** and **F**), and noncalcified plaque (**G** and **H**). Plaque progression was dichotomized and defined as *yes* or *no*. Adjusted odds ratios from multivariable logistic regression analyses are reported with 95% CIs, with odds ratios <1 indicating less progression. The models are adjusted for the following baseline confounders: age, body mass index, systolic blood pressure, use of antihypertensive medication, pack-years smoked, total cholesterol, family history of coronary heart disease, use of statin, diabetes, time between computed tomography scans, and baseline number of plaques. The exercise intensity analyses are additionally adjusted for exercise volume during follow-up. MET indicates metabolic equivalent of task.

cohort of athletes. Its limitations are that participants were aware of their MARC-1 results and could have altered their lifestyle, exercise and medication regimens. Others previously showed that CAC scanning impacts risk factor control and that higher baseline CAC scores are associated with better subsequent risk factor control,[37] which may have diluted the effect of exercise. MARC-1 participants with high CAC scores and/or significant stenoses were advised to seek medical follow-up. The prevalence of statin use was increased in MARC-2, and since statins may increase CAC this could have affected the MARC-2 results. This is, however, unlikely because sensitivity analyses in MARC-2 excluding statin users did not alter the results (data not shown). Both MARC-1 and this follow-up study only included men, 99% of whom identified as White. We only included men in MARC-1 because of their higher probability of coronary atherosclerosis and risk for exercise-related cardiac arrest[19,38]; therefore, our results can be applied only to middle-aged and older White men.

Conclusions

Exercise intensity, but not volume, is associated with progression of coronary atherosclerosis in middle-aged and older male athletes during 6 years of follow-up. Progression occurred both in those exercising vigorously and those exercising very vigorously, however vigorous exercise was associated with less CAC progression, whereas very vigorous exercise was associated with greater CAC progression. This acceleration in CAC may reflect increased plaque calcification. Future studies assessing the CVD risk associated with coronary atherosclerosis in athletes are required to establish the clinical implications of these findings.

ARTICLE INFORMATION

Received June 7, 2022; accepted November17, 2022.

Affiliations

Departments of Physiology (V.L.A., E.A.B., T.M.H.E.) and Cardiology (V.L.A.), Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. Department of Cardiology, Meander Medical Center, Amersfoort, The Netherlands (A.M.). Department of Cardiology, Isala Ziekenhuis, Zwolle, The Netherlands (T.L.B.). Department of Cardiology, University Medical Center Utrecht, The Netherlands (H.M.N.). Cardiology Clinical and Academic Group, St George's University of London, United Kingdom (S.S.). Division of Cardiology, Hartford Hospital, CT (P.D.T.). Department of Radiology, University Medical Center Utrecht, The Netherlands (B.V.V.).

Sources of Funding

Drs Aengevaeren and Eijsvogels are financially supported by grants from the Dutch Heart Foundation (no. 2017T088 to V.L.A. and no. 2017T051 to T.M.H.E.). This work was also supported by the W.M. De Hoop Foundation.

Disclosures

A.M. reports serving as a consultant for Bayer, Merck, Novartis, and Pfizer; receiving speaker honoraria from Novartis. P.D.T. reports receiving research grants from the Esperion, and Norvartis; serving as a consultant for Aventis, Regeneron, Merck, Genomas, Abbvie, Sanolfi, and Pfizer; receiving speaker honoraria from Regeneron, Sanolfi, Amgen, Amarin, and Merck: owning stock in General Electric,

JA Wiley Publishing, J&J, Abbvie, Abbott, Medtronic, Serapta and Cryolife. B.K.V. reports serving as a regular speaker for Philips Healthcare. All relationships are modest. The other authors report no conflicts.

REFERENCES

1. Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the extremes: the amount of exercise to reduce cardiovascular events. *J Am Coll Cardiol*. 2016;67:316–329. doi: 10.1016/j.jacc.2015.11.034
2. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation*. 2010;122:743–752. doi: 10.1161/CIRCULATIONAHA.109.914721
3. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol*. 1998;31:126–133. doi: 10.1016/s0735-1097(97)00443-9
4. Hou ZH, Lu B, Gao Y, Jiang SL, Wang Y, Li W, Budoff MJ. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovasc Imaging*. 2012;5:990–999. doi: 10.1016/j.jcmg.2012.06.006
5. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT, Agatston A, Blumenthal RS, Nasir K. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232–2241. doi: 10.1093/eurheartj/eht508
6. Aengevaeren VL, Mosterd A, Braber TL, Prakken NHJ, Doevendans PA, Grobbee DE, Thompson PD, Eijsvogels TMH, Velthuis BK. Relationship between lifelong exercise volume and coronary atherosclerosis in athletes. *Circulation*. 2017;136:138–148. doi: 10.1161/CIRCULATIONAHA.117.027834
7. Aengevaeren VL, Mosterd A, Sharma S, Prakken NHJ, Mohlenkamp S, Thompson PD, Velthuis BK, Eijsvogels TMH. Exercise and coronary atherosclerosis: observations, explanations, relevance, and clinical management. *Circulation*. 2020;141:1338–1350. doi: 10.1161/CIRCULATIONAHA.119.044467
8. Merghani A, Maestrini V, Rosmini S, Cox AT, Dhutia H, Bastiaenan R, David S, Yeo TJ, Narain R, Malhotra A, et al. Prevalence of subclinical coronary artery disease in masters endurance athletes with a low atherosclerotic risk profile. *Circulation*. 2017;136:126–137. doi: 10.1161/CIRCULATIONAHA.116.026964
9. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, Budde T, Mann K, Barkhausen J, Heusch G, et al; Marathon Study Investigators. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J*. 2008;29:1903–1910. doi: 10.1093/eurheartj/ehn163
10. DeFina LF, Radford NB, Barlow CE, Willis BL, Leonard D, Haskell WL, Farrell SW, Pavlovic A, Abel K, Berry JD, et al. Association of all-cause and cardiovascular mortality with high levels of physical activity and concurrent coronary artery calcification. *JAMA Cardiol*. 2019;4:174–181. doi: 10.1001/jamacardio.2018.4628
11. Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Backx FJ, Grobbee DE, Rienks R, Nathoe HM, Bots ML, et al. Rationale and design of the Measuring Athlete's Risk of Cardiovascular events (MARC) study: the role of coronary CT in the cardiovascular evaluation of middle-aged sportsmen. *Neth Heart J*. 2015;23:133–138. doi: 10.1007/s12471-014-0630-0
12. Friedenreich CM, Courneya KS, Bryant HE. The lifetime total physical activity questionnaire: development and reliability. *Med Sci Sports Exerc*. 1998;30:266–274. doi: 10.1097/00005768-199802000-00015
13. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr., Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43:1575–1581. doi: 10.1249/MSS.0b013e31821ece12
14. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2009;3:190–204. doi: 10.1016/j.jcct.2009.03.004
15. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8:342–358. doi: 10.1016/j.jcct.2014.07.003
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827–832. doi: 10.1016/0735-1097(90)90282-t
17. McEvoy JW, Blaha MJ, Defilippis AP, Budoff MJ, Nasir K, Blumenthal RS, Jones SR. Coronary artery calcium progression: an important clinical measurement? A review of published reports. *J Am Coll Cardiol*. 2010;56:1613–1622. doi: 10.1016/j.jacc.2010.06.038
18. Budoff MJ, Hokanson JE, Nasir K, Shaw LJ, Kinney GL, Chow D, Demoss D, Nuguri V, Nabavi V, Ratakonda R, et al. Progression of coronary artery calcium predicts all-cause mortality. *JACC Cardiovasc Imaging*. 2010;3:1229–1236. doi: 10.1016/j.jcmg.2010.08.018
19. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2006;113:30–37. doi: 10.1161/CIRCULATIONAHA.105.580696
20. Kleiven O, Bjorkavoll-Bergseth MF, Omland T, Aakre KM, Froysa V, Erevik CB, Greve OJ, Melberg TH, Auestad B, Skadberg O, et al. Endurance exercise training volume is not associated with progression of coronary artery calcification. *Scand J Med Sci Sports*. 2020;30:1024–1032. doi: 10.1111/sms.13643
21. Sung KC, Hong YS, Lee JY, Lee SJ, Chang Y, Ryu S, Zhao D, Cho J, Guallar E, Lima JAC. Physical activity and the progression of coronary artery calcification. *Heart*. 2021;107:1710–1716. doi: 10.1136/heartjnl-2021-319346
22. Erbel R, Lehmann N, Churzidse S, Rauwolf M, Mahabadi AA, Mohlenkamp S, Moebus S, Bauer M, Kalsch H, Budde T, et al; Heinz Nixdorf Recall Study Investigators. Progression of coronary artery calcification seems to be inevitable, but predictable - results of the Heinz Nixdorf Recall (HNR) study. *Eur Heart J*. 2014;35:2960–2971. doi: 10.1093/eurheartj/ehu288
23. van de Schoor FR, Aengevaeren VL, Hopman MT, Oxborough DL, George KP, Thompson PD, Eijsvogels TM. Myocardial Fibrosis in Athletes. *Mayo Clin Proc*. 2016;91:1617–1631. doi: 10.1016/j.mayocp.2016.07.012
24. Shah AB, Bechis MZ, Brown M, Finch JM, Loomer G, Groezinger E, Weiner RB, Wasfy MM, Picard MH, Fifer MA, et al. Catecholamine response to exercise in patients with non-obstructive hypertrophic cardiomyopathy. *J Physiol*. 2019;597:1337–1346. doi: 10.1113/JP277494
25. Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. *Science*. 1984;226:180–182. doi: 10.1126/science.6484569
26. van der Heijden C, Groh L, Keating ST, Kaffa C, Noz MP, Kersten S, van Herwaarden AE, Hoischen A, Joosten LAB, Timmers H, et al. Catecholamines induce trained immunity in monocytes in vitro and in vivo. *Circ Res*. 2020;127:269–283. doi: 10.1161/CIRCRESAHA.119.315800
27. Aengevaeren VL, Mosterd A, Sharma S, Braber TL, Thompson PD, Velthuis BK, Eijsvogels TMH. Coronary atherosclerosis in athletes: exploring the role of sporting discipline. *JACC Cardiovasc Imaging*. 2019;12:1587–1589. doi: 10.1016/j.jcmg.2019.01.002
28. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JA, Rader DJ, Rubin GD, et al; American Heart Association Committee on Cardiovascular Imaging and Intervention. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. 2006;114:1761–1791. doi: 10.1161/CIRCULATIONAHA.106.178458
29. Hecht HS. Coronary artery calcium scanning: past, present, and future. *JACC Cardiovasc Imaging*. 2015;8:579–596. doi: 10.1016/j.jcmg.2015.02.006
30. Bamberg F, Sommer WH, Hoffmann V, Achenbach S, Nikolaou K, Conen D, Reiser MF, Hoffmann U, Becker CR. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. *J Am Coll Cardiol*. 2011;57:2426–2436. doi: 10.1016/j.jacc.2010.12.043
31. Garatachea N, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Emanuele E, Lucia A. Elite athletes live longer than the general population: a meta-analysis. *Mayo Clin Proc*. 2014;89:1195–1200. doi: 10.1016/j.mayocp.2014.06.004
32. Kontro TK, Sarna S, Kaprio J, Kujala UM. Mortality and health-related habits in 900 Finnish former elite athletes and their brothers. *Br J Sports Med*. 2018;52:89–95. doi: 10.1136/bjsports-2017-098206
33. van Rosendael AR, van den Hoogen IJ, Gianni U, Ma X, Tantawy SW, Bax AM, Lu Y, Andreini D, Al-Mallah MH, Budoff MJ, et al. Association of statin treatment with progression of coronary atherosclerotic plaque composition. *JAMA Cardiol*. 2021; doi: 10.1001/jamacardio.2021.3055
34. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, Tuzcu EM, Nissen SE. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol*. 2015;65:1273–1282. doi: 10.1016/j.jacc.2015.01.036

35. Peng AW, Dardari ZA, Blumenthal RS, Dzaye O, Obisesan OH, Iftekhar Uddin SM, Nasir K, Blankstein R, Budoff MJ, Bodtker Mortensen M, et al. Very high coronary artery calcium (≥1000) and association with cardiovascular disease events, non-cardiovascular disease outcomes, and mortality: results from MESA. *Circulation*. 2021;143:1571–1583. doi: 10.1161/CIRCULATIONAHA.120.050545
36. Radford NB, DeFina LF, Leonard D, Barlow CE, Willis BL, Gibbons LW, Gilchrist SC, Khera A, Levine BD. Cardiorespiratory fitness, coronary artery calcium, and cardiovascular disease events in a cohort of generally healthy middle-age men: results from the Cooper Center Longitudinal Study. *Circulation*. 2018;137:1888–1895. doi: 10.1161/CIRCULATIONAHA.117.032708
37. Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, Rana JS, Orakzai R, Hayes SW, Friedman JD, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. *J Am Coll Cardiol*. 2011;57:1622–1632. doi: 10.1016/j.jacc.2011.01.019
38. Berdowski J, de Beus MF, Blom M, Bardai A, Bots ML, Doevendans PA, Grobbee DE, Tan HL, Tijssen JG, Koster RW, et al. Exercise-related out-of-hospital cardiac arrest in the general population: incidence and prognosis. *Eur Heart J*. 2013;34:3616–3623. doi: 10.1093/eurheartj/eht401