Relationship Between Lifelong Exercise Volume and Coronary Atherosclerosis in Athletes

Editorial, see p 149

BACKGROUND: Higher levels of physical activity are associated with a lower risk of cardiovascular events. Nevertheless, there is debate on the dose-response relationship of exercise and cardiovascular disease outcomes and whether high volumes of exercise may accelerate coronary atherosclerosis. We aimed to determine the relationship between lifelong exercise volumes and coronary atherosclerosis.

METHODS: Middle-aged men engaged in competitive or recreational leisure sports underwent a noncontrast and contrast-enhanced computed tomography scan to assess coronary artery calcification (CAC) and plaque characteristics. Participants reported lifelong exercise history patterns. Exercise volumes were multiplied by metabolic equivalent of task (MET) scores to calculate MET-minutes per week. Participants' activity was categorized as <1000, 1000 to 2000, or >2000 MET-min/wk.

RESULTS: A total of 284 men (age, 55±7 years) were included. CAC was present in 150 of 284 participants (53%) with a median CAC score of 35.8 (interquartile range, 9.3–145.8). Athletes with a lifelong exercise volume >2000 MET-min/wk (n=75) had a significantly higher CAC score (9.4 [interquartile range, 0–60.9] versus 0 [interquartile range, 0–43.5]; *P*=0.02) and prevalence of CAC (68%; adjusted odds ratio [$OR_{adjusted}$]=3.2; 95% confidence interval [CI], 1.6–6.6) and plaque (77%; $OR_{adjusted}$=3.3; 95% CI, 1.6–7.1) compared with <1000 MET-min/wk (n=88; 43% and 56%, respectively). Very vigorous intensity exercise (≥9 MET) was associated with CAC ($OR_{adjusted}$=1.47; 95% CI, 1.14–1.91) and plaque ($OR_{adjusted}$=1.56; 95% CI, 1.17–2.08). Among participants with CAC>0, there was no difference in CAC score (*P*=0.20), area (*P*=0.21), density (*P*=0.25), and regions of interest (*P*=0.20) across exercise volume groups. Among participants with plaque, the most active group (>2000 MET-min/wk) had a lower prevalence of mixed plaques (48% versus 69%; $OR_{adjusted}$=0.35; 95% CI, 0.15–0.85) and more often had only calcified plaques (38% versus 16%; $OR_{adjusted}$=3.57; 95% CI, 1.28–9.97) compared with the least active group (<1000 MET-min/wk).

CONCLUSIONS: Participants in the >2000 MET-min/wk group had a higher prevalence of CAC and atherosclerotic plaques. The most active group, however, had a more benign composition of plaques, with fewer mixed plaques and more often only calcified plaques. These observations may explain the increased longevity typical of endurance athletes despite the presence of more coronary atherosclerotic plaque in the most active participants.

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Sources of Funding, see page 146

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Clinical Perspective

What Is New?

- This study improves our understanding of coronary atherosclerosis in middle-aged athletes by analyzing coronary artery calcification and atherosclerotic plaque characteristics with contrast-enhanced computed tomography in relation to the amount of lifelong exercise.
- Athletes with a high lifelong exercise volume are more likely to have coronary atherosclerosis, but the most active athletes have a more benign composition of atherosclerotic plaques, that is, less mixed and more often only calcified plaques.

What Are the Clinical Implications?

- Physically active individuals may have substantial, asymptomatic coronary atherosclerosis.
- We showed substantial coronary artery calcification and plaque in very active athletes, which is associated with an increased risk of cardiac events.
- Because the atherosclerotic plaque types had a more benign composition in the most active athletes, long-term follow-up of athletes needs to show whether atherosclerotic burden in athletes confers a risk similar to that in the general population.
- Future studies unraveling the mechanisms leading to higher coronary artery calcification and plaque prevalence in very active athletes are warranted.

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, accounting for >17 million deaths per year.[1] Atherosclerotic coronary artery disease is the main cause of CVD morbidity and mortality. Computed tomography (CT) imaging allows assessment of coronary risk because the extent of coronary artery calcification (CAC) is an indicator of the atherosclerotic plaque burden of the coronaries and the risk of future cardiovascular events.[2,3] Furthermore, CT coronary angiography (CTCA) allows assessment and characterization of atherosclerotic plaques, which significantly determine risk estimation.[3]

Higher levels of physical activity are associated with a lower risk of cardiovascular events,[4,5] and elite athletes live longer than the general population.[6] Nevertheless, there is debate about the dose-response relationship of exercise and CVD outcomes[7,8] and whether high volumes of exercise may accelerate coronary atherosclerosis.[9–11] The relationship between physical activity and coronary atherosclerosis has been studied since 1960, when a postmortem study found a similar degree of coronary atherosclerosis in sedentary and active men.[12] Although a recent German study found no difference in CAC scores between marathon runners (n=108) and age-matched control subjects (n=864), the athletes had significantly higher CAC scores compared with the control subjects (n=216) who were matched for both age and CVD risk factors.[13] This contrasts with other observational studies that found either no association[14–16] or an inverse relationship[17,18] between physical activity or fitness and CAC. Prior studies did not examine participants exposed to high volumes of exercise training for a prolonged period of time. Therefore, the question remains whether extreme exercise exposure accelerates the development of coronary artery atherosclerosis and calcification.

This study sought to determine the relationship between high volumes of exercise and CT-guided assessment of CAC and atherosclerotic plaque characteristics. Others have shown that a CAC area is directly associated with CVD risk but that increased density of CAC is inversely associated with CVD risk.[19] Moreover, the type of plaque is important for the risk of cardiac events,[3] with a lower risk attributed to calcified plaques compared with noncalcified and mixed plaques. We hypothesized that athletes who performed more lifelong exercise would demonstrate similar or higher CAC scores but with a greater CAC density compared with athletes performing lower lifelong exercise volumes. We also expected athletes with the highest exercise volume to have more low-risk calcified plaques instead of noncalcified and mixed plaques. The enhanced plaque calcification may offset the increased CAC score and contribute to the superior life expectancy of athletes compared with their less active peers.

METHODS

Study Population

This is an analysis of the MARC study (Measuring Athlete's Risk of Cardiovascular Events). The rationale and design of MARC have been published previously.[20] Men ≥45 years of age were eligible if they were asymptomatic, engaged in competitive or recreational leisure sports, were free of known CVD, and had undergone a sports medical examination with bicycle exercise ECG that revealed no abnormalities, according to the responsible physician. We included only men because of their higher probability of coronary atherosclerosis and risk of exercise-related cardiac arrest than women.[21,22] Regional sports physicians assisted with recruiting potential participants by providing a flyer detailing the MARC study to athletes who underwent a sports medical examination for comprehensive assessment of exercise tolerance. In the Netherlands, athletes often visit a sports physician either to improve their training patterns by determining their fitness (VO_2max), (an)aerobic threshold, peak heart rate, and peak load (Watts) or to gain reassurance that they can participate in sports safely. There was therefore no referral or medical condition underlying the examination in MARC participants. Exclusion criteria were an abnormal sports medical examination according to the responsible physician, known coronary artery disease, contrast allergy, and renal impairment. The

medical ethics committee approved the study, and all participants provided written informed consent before participation. The study was conducted according to the Declaration of Helsinki. Baseline characteristics were obtained during the sports medical examination.

Lifelong Exercise Volume

Participants reported their lifelong exercise history, including type of sport, year started and stopped, numbers of days a week and months per year, duration of the sessions, and level at which they performed for every sport. We assigned a metabolic equivalent of task (MET) for all reported sports.[23] We calculated the exercise volume per sport by multiplying the MET score for the specific sport with the reported exercise volume (session duration×frequency/week), months of practice per year, and total years of practice. The lifelong exercise volume represents the sum of all sports activities between age 12 and the age at study participation and was expressed in MET-hours per week. We also calculated the average lifetime exercise exposure in MET-hours per week and MET-minutes per week by dividing the total lifetime exercise volume by age at participation minus 12 for average exercise volume per year and then divided this number by 52 for average exercise volume per week (MET-hours/week). MET-minutes per week were calculated from MET-hours per week multiplied by 60. On the basis of the international physical activity recommendation that individuals perform 500 to 1000 MET-min/wk of exercise,[24] we assigned study participants to a lifelong exercise volume group of <1000, 1000 to 2000, or >2000 MET-min/wk. Moreover, we classified per individual the sport with the most lifelong hours as the dominant sport. Finally, we classified exercise as light (<3 MET), moderate (3–6 MET), vigorous (6–9 MET), or very vigorous (≥ 9 MET) intensity and calculated the average lifetime hours per week of exercise in the specific intensity ranges.

Cardiac CT

Participants underwent a low-dose cardiac CT with a 256-slice CT scanner (Philips Healthcare, Best, the Netherlands) with electrocardiographic gating according to guidelines.[25] A noncontrast CT was acquired to calculate the CAC score (scan parameters: 120 kV and 60 mAs), followed by CTCA. The total average radiation dose was 3.9±0.9 mSv (1.0±0.4 mSv for CAC score and 3.0±1.2 mSv for CTCA). CT scans were processed on a workstation (IntelliSpace Portal, Philips Healthcare) by experienced technicians and assessed by 2 experienced cardiac radiologists who were blinded to the sports medical examination findings and exercise levels. The American Heart Association–modified 16-segment coronary artery model was used to analyze plaque and CAC characteristics per segment.[26,27]

CAC and Plaque Characteristics

The Agatston CAC score was constructed by multiplying the calcified area (millimeters squared) of each plaque by 1, 2, 3, or 4, depending on the density of the plaque, based on Hounsfield units (HU), and summing up all CT slices.[28] Calcified areas are included in the score when the plaque density was >130 HU. Calcified areas received a density score of 1 when density was between 130 and 200 HU, 2 for 200 to 300 HU, 3 for 300 to 400 HU, and 4 for >400 HU. The number of calcified areas is indicated by the regions of interest. CAC scores were dichotomized (CAC=0 and CAC>0) and categorized (0, >0–100, and >100). CTCA was used to segment CAC, to assess the characteristics of plaques identified by the noncontrast CT scan, and to identify plaques with calcification levels below the Hounsfield threshold (<130 HU). We divided plaques into calcified, noncalcified, mixed <130 HU (detected with CTCA but not with CAC scoring), and mixed >130 HU (detected with CTCA and CAC scoring) plaques.

Data Analysis

All parameters were visually inspected for normality and checked for kurtosis and skewness. Continuous variables were reported as mean±SD when normally distributed or as median (interquartile range) when not normally distributed, and categorical variables were presented as proportions. We used *t* tests to compare continuous variables between individuals with CAC=0 and those with CAC>0 when data were normally distributed. Mann-Whitney *U* tests were used to compare the characteristics of the CAC=0 versus CAC>0 groups when data were not normally distributed. Pearson χ^2 tests were used to compare categorical variables. One-way ANOVA with Bonferroni post hoc tests was used to compare participant characteristics between the lifelong exercise volume groups (<1000, 1000–2000, >2000 MET-min/wk) when data were normally distributed, and Kruskal-Wallis 1-way ANOVA tests were used when data were not normally distributed. Two-way repeated measures ANOVA was performed to describe the distribution of lifelong exercise patterns per group across age per decade. Binary logistic regression was used to calculate unadjusted and adjusted odds ratios (ORs) for the association between exercise characteristics (volume, intensity, sport type) and CAC, coronary atherosclerosis, and plaque type presence. Furthermore, we decided a priori to adjust for the following known cardiovascular risk factors: body mass index, systolic blood pressure, smoking, use of antihypertensive, cholesterol, and family history of coronary heart disease. In addition, we made a model in which we adjusted for use of statins and diabetes mellitus because these factors are known to influence coronary atherosclerosis.[29,30] Moreover, to explore a potential nonlinear relationship between lifetime exercise volume (MET-hours per week) and CAC or plaque, we performed restricted cubic spline regression analyses. The knots were placed at the 5th, 50th, and 95th percentiles.[31,32] We performed a test for nonlinearity, which compares models with the cubic spline terms and models with only the linear terms using the likelihood ratio test. Finally, we explored the association between lifetime exercise volume and CAC characteristics for only those participants with CAC>0 and the association between exercise characteristics (volume, intensity, sport type) and plaque characteristics for participants with any coronary atherosclerosis only. Statistical significance was assumed at a value of $P<0.05$. Statistical analyses were performed with SPSS Statistics 21 (IBM Corp, Armonk, NY). The cubic spline regression analysis was conducted with SAS software, version 9.3 (SAS, Cary, NC).

RESULTS

A total of 284 participants from the original study population of n=318 (100% white) were included because 27 athletes did not return the lifelong exercise questionnaire and 7 athletes returned an incomplete questionnaire. CAC characteristics were not different between included and excluded athletes (data not shown). Frequency of the sports activities and the dominant sports are summarized in Table I in the online-only Data Supplement. Mean±SD age of the study population was 55.0±6.5 years; 150 of the 284 participants (53%) had CAC with a median CAC score of 35.8 (9.3–145.8). Average lifetime exercise volume was 2.9 h/wk (1.9–4.4 h/wk), resulting in 1356 MET-min/wk (851–2030 MET-min/wk; Table II in the online-only Data Supplement). Subject characteristics of each exercise volume group are summarized in Table 1.

Athletes with CAC were older, had higher systolic and diastolic blood pressures and higher total cholesterol concentrations, more frequently used statins, more often were former smokers, and more often had a positive family history for coronary heart disease compared with athletes without CAC (Table II in the online-only Data Supplement). Athletes with CAC were also more physically active during their lifetime compared with athletes without CAC, as evidenced by more years of exercise, exercise sessions per week, hours per week, MET-minutes per week, and subsequently more lifetime MET-hours. Logistic regression analyses confirmed the association between lifetime exercise volume (MET-hours/week) and CAC presence, with $OR_{adjusted}$=1.02 for CAC>0 per MET-hour per week (Table 2). Specifically, only very-vigorous-intensity exercise (hours per week) was associated with CAC presence, with $OR_{adjusted}$=1.47 (95% CI, 1.14–1.91).

Figure 1 provides an overview of lifelong exercise patterns for each exercise volume group. CAC was more common in athletes with higher lifelong exercise volumes (Table 1). Athletes performing >2000 MET-min/wk more frequently had CAC>0 (68%) compared with the <1000 MET-min/wk group (43%; Table 1 and Figure 2A). CAC scores (9.4 [0–60.9] versus 0 [0–43.5]; *P*=0.019), CAC area (4.3 [0–20.3] versus 0 [0–16.8]; *P*=0.025), and number of regions of interest (2 [2–5] versus 0 [0–3]; *P*=0.014) were all significantly higher in the >2000 versus <1000 MET-min/wk group. We also found an increase in CAC score categories (*P*=0.006) across the exercise volume groups (Figure 2A). Unadjusted (OR=2.80; 95% CI, 1.47–5.32) and multivariable-adjusted (OR=3.20; 95% CI, 1.56–6.57) logistic regression analyses demonstrated a significantly higher CAC prevalence in the >2000 versus <1000 MET-min/wk group (Table 2). However, there were no significant differences in CAC score (*P*=0.20), area (*P*=0.21), density (*P*=0.25), and regions of interest (*P*=0.20) across exercise volume groups when analyses were repeated only in participants with CAC>0 (Table III in the online-only Data Supplement). In addition, analysis of CAC location revealed no differences in the presence of CAC within each coronary vessel and in proximal versus distal segments (Table III in the online-only Data Supplement). Analysis of coronary atherosclerosis characteristics (Table IV in the online-only Data Supplement) showed significantly higher plaque prevalence (calcified, noncalcified, mixed <130 HU, or mixed >130HU) in the most active group (77%) versus the least active group (56%; Figure 2B). Unadjusted (OR=2.72; 95% CI, 1.37–5.39) and (OR=3.35; 95% CI, 1.57–7.14) multivariable-adjusted logistic regression analyses confirmed these observations and demonstrated a significantly higher coronary atherosclerosis prevalence in the >2000 versus <1000 MET-min/wk group (Table 3). In addition, prevalence of plaque appears to be specifically associated with hours of very-vigorous-intensity exercise ($OR_{adjusted}$=1.56; 95% CI, 1.17–2.08), whereas hours of moderate- and vigorous-intensity exercise did not affect plaque prevalence. In participants with coronary atherosclerosis, a lower prevalence of mixed plaques was observed in the most active (48%) versus least active group (69%; Figure 3A), with $OR_{adjusted}$=0.35 (95% CI, 0.15–0.85). A difference in the prevalence of mixed plaques <130 HU was responsible for this finding (43% in <1000 MET-min/wk, 33% in 1000–2000 MET-min/wk, and 21% in >2000 MET-min/wk group; *P*=0.046) because no differences were observed in the prevalence of mixed plaques >130 HU across exercise volume groups (41%, 49%, and 40%, respectively; *P*=0.47). The lower prevalence of mixed plaques in the highest exercise volume group appears to be largely mediated by hours of vigorous-intensity exercise ($OR_{adjusted}$=0.83; 95% CI, 0.71–0.98), whereas moderate and very vigorous intensity did not affect plaque morphology. When considering dominant plaque types (only calcified, only noncalcified, or only mixed plaques), we observed that the most active group significantly more often had only calcified plaques compared with the least active group ($OR_{adjusted}$=3.57; 95% CI, 1.28–9.97; Figure 3B). Other types of plaque dominance (including mixed plaques <130 HU and >130 HU) did not significantly differ across exercise volume groups (*P*>0.05). Exercise intensity was also not related to plaque dominance. Analysis of coronary atherosclerosis location revealed no differences in the presence of plaques within each coronary vessel and in proximal versus distal segments (Table IV in the online-only Data Supplement).

Finally, the test for nonlinearity for cubic spline regression was nonsignificant for presence of CAC (*P*=0.48) and presence of plaque (*P*=0.29), indicating that there was no nonlinear relationship with lifelong exercise volumes.

Table 1. Comparison of Participant and Coronary Artery Calcification Characteristics Across Exercise Volume Groups

	Lifelong Exercise Volume, MET-min/wk			
	<1000 (n=88)	1000–2000 (n=121)	>2000 (n=75)	*P* Value
Participant characteristics				
Age, y	54.4 (6.1)	54.8 (6.3)	55.9 (6.9)	0.35
Systolic blood pressure, mm Hg	128 (11)	130 (15)	129 (12)	0.63
Diastolic blood pressure, mm Hg	80 (8)	80 (9)	80 (8)	0.82
Height, cm	183 (7)	183 (6)	181 (7)	0.11
Weight, kg	84 (11)	83 (10)	80 (9)†	0.029*
Body mass index, kg/m^2	25.3 (2.9)	24.8 (2.8)	24.5 (2.3)	0.14
Body surface area, m^2	2.06 (0.16)	2.05 (0.14)	2.00 (0.13) †	0.025*
Exercise tolerance, W	298 (44)	319 (47)†	321 (48)†	0.001*
Total cholesterol, mmol/L	5.36 (0.87)	5.31 (0.88)	5.44 (0.96)	0.63
Statin, n (%)	6 (7)	2 (2)	7 (9)	0.048*
Current smokers, n (%)	7 (8)	5 (4)	2 (3)	0.26
Former smoker, n (%)	32 (36)	43 (36)	33 (44)	0.46
Never smoker, n (%)	49 (56)	73 (60)	40 (53)	0.60
Smoking, pack-y	0 (0–8)	0 (0–7)	0 (0–8)	0.81
Antihypertensive, n (%)	7 (8)	7 (6)	6 (8)	0.78
Diabetes mellitus, n (%)	1 (1)	1 (1)	2 (3)	0.55
Family history of coronary heart disease, n (%)	29 (33)	35 (29)	25 (33)	0.75
CAC characteristics				
CAC, Agatston units	0 (0–43.5)	0.8 (0–26.5)	9.4 (0–60.9)†‡	0.019*
CAC=0, n (%)	50 (57)	60 (50)	24 (32)	0.005*
Area, mm^2	0 (0–16.81)	0.8 (0–10.8)	4.3 (0–20.3)†	0.025*
Density, AU	3.0 (1.9–3.5)	2.6 (1.6–3.2)	3.0 (2.0–3.4)	0.25
Regions of interest, n	0 (0–3)	1 (0–3)	2 (2–5) †‡	0.014*
Lifelong exercise characteristics				
Years of exercise§	27 (13–37)	36 (30–41)†	40 (35–47)†‡	<0.001*
Sessions/wk, n	0.9 (0.7-1.4)	2.1 (1.7–2.5)†	3.3 (2.7–4.5)†‡	<0.001*
Duration/session, h	1.4 (1.1–1.8)	1.4 (1.2–1.7)	1.7 (1.5–2.0)†‡	<0.001*
Exercise duration/wk, h	1.5 (0.9-1.9)	3.0 (2.4–3.6)†	5.7 (4.6–7.3)†‡	<0.001*
MET-minutes per week, AU	669 (405–802)	1443 (1189–1672)†	2724 (2295–3526)†‡	<0.001*
MET-hours per week, AU	11.2 (6.7–13.4)	24.1 (19.8–27.9)†	45.4 (38.2–58.8)†‡	<0.001*
Light intensity, %	0 (0-0)	0 (0-0)	0 (0-0)	0.47
Moderate intensity, %	11 (0–39)	6 (0–23)	0 (0–14)†	0.035*
Vigorous intensity, %	52 (21–89)	56 (22–86)	67 (32–87)	0.66
Very vigorous intensity, %	2 (0–50)	18 (0–53)	23 (3–54)†	0.036*
Lifetime MET-h, AU	24 257 (13 541–30 410)	52 280 (42 458–61 098)†	104 208 (81 539–137 010)†‡	<0.001*

AU indicates arbitrary units; CAC, coronary artery calcification; and MET, metabolic equivalent of task. Data are presented as mean (SD), n (%), or median (interquartile range).

*P<0.05.

†Pairwise comparison, significantly different from <1000 MET-min/wk.

‡Pairwise comparison, significantly different from 1000 to 2000 MET-min/wk.

§Since age 12 years.

DISCUSSION

This study provides new insights into the association between lifelong exercise volumes and coronary atherosclerosis. On the basis of the noncontrast CT scan, we found that participants with CAC>0 had a higher lifelong exercise volume compared with participants with CAC=0. Logistic regression showed an $OR_{adjusted}$

Table 2. Unadjusted and Multivariable-Adjusted Associations Between Lifelong Exercise Volumes and Presence of CAC (CAC>0)

	Unadjusted		Model 1*		Model 2†		Model 3‡	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Presence of CAC								
MET-hours per week	1.02 (1.01–1.04)	0.003	1.02 (1.00–1.04)	0.014	1.02 (1.01–1.04)	0.012	1.02 (1.01–1.04)	0.006
Exercise intensity, h/wk								
Moderate	1.09 (0.88–1.37)	0.43	1.06 (0.84–1.33)	0.65	1.01 (0.79–1.30)	0.91	1.03 (0.80–1.32)	0.81
Vigorous	1.16 (1.01–1.32)	0.031	1.12 (0.97–1.28)	0.13	1.12 (0.97–1.29)	0.13	1.13 (0.97–1.31)	0.12
Very vigorous	1.35 (1.06–1.71)	0.014	1.35 (1.06–1.72)	0.016	1.41 (1.10–1.81)	0.008	1.47 (1.14–1.91)	0.003
Exercise volume groups, MET-min/wk								
<1000	Reference		Reference		Reference		Reference	
1000–2000	1.34 (0.77–2.32)	0.30	1.33 (0.75–2.35)	0.33	1.45 (0.80–2.63)	0.22	1.62 (0.88–2.97)	0.12
>2000	2.80 (1.47–5.32)	0.002	2.69 (1.38–5.23)	0.004	2.93 (1.46–5.86)	0.002	3.20 (1.56–6.57)	0.001

CAC indicates coronary artery calcification; CI, confidence interval; MET, metabolic equivalent of task; and OR, odds ratio. Each exposure (exercise volume and exercise intensity) was entered separately into the different models.

*Adjusted for age.

†Also adjusted for body mass index, systolic blood pressure, ever smoked, use of antihypertensives, total cholesterol, and family history of coronary heart disease.

‡Also adjusted for use of statin and diabetes mellitus.

of 1.02 per MET-hour per week and $OR_{adjusted}$=3.20 for >2000 versus <1000 MET-min/wk for the prevalence of CAC>0. CTCA confirmed our CAC data in that we found that the most active group had a significantly higher prevalence of any type of plaque. However, among individuals with coronary atherosclerosis, a lower prevalence of mixed plaques and a higher prevalence of only calcified plaques were observed in the most versus least active athletes. Interestingly, very-vigorous-intensity exercise was associated with CAC and plaque presence, and vigorous-intensity exercise was associated with reduced prevalence of mixed plaques. These findings suggest that athletes with the highest exercise volumes more often have CAC and atherosclerotic plaques, but their plaques are of a more benign composition.

Accelerated CAC

Athletes in the most active group show a higher prevalence of CAC and higher CAC scores. This is in agreement with a previous study that showed higher CAC scores in German marathon runners when they were matched for age and risk factors with control subjects.[13] A major limitation of that study was that the history of the subjects' cardiovascular risk factors was unknown.

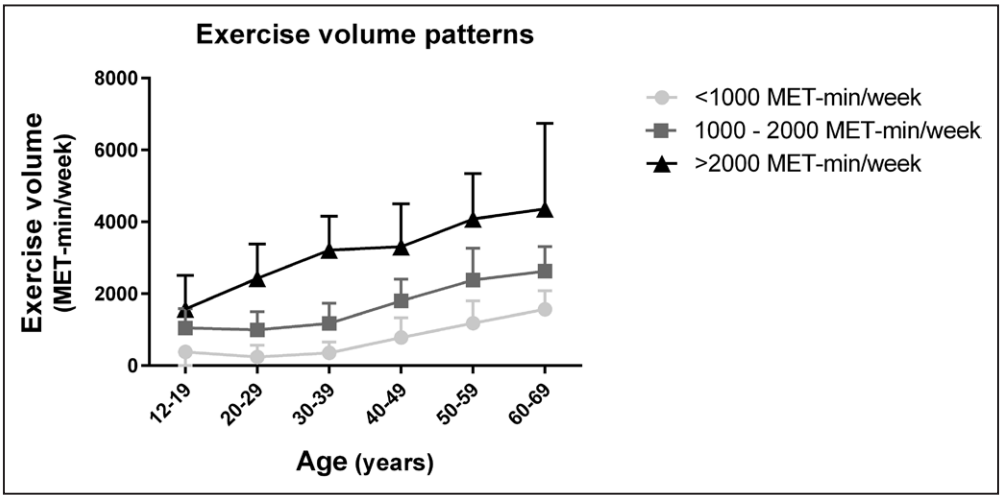

Figure 1. Patterns of exercise volumes per decade.
A gradual age-related increase in exercise volume was found in each exercise volume group (<1000, 1000–2000, >2000 MET-min/wk). Data were averaged per decade and available for all participants (n=284) for decades between age 12 and 50. For decade 50 to 60 years (n=192) and 60 to 70 years (n=64), data were available in a subgroup only. MET indicates metabolic equivalent of task.

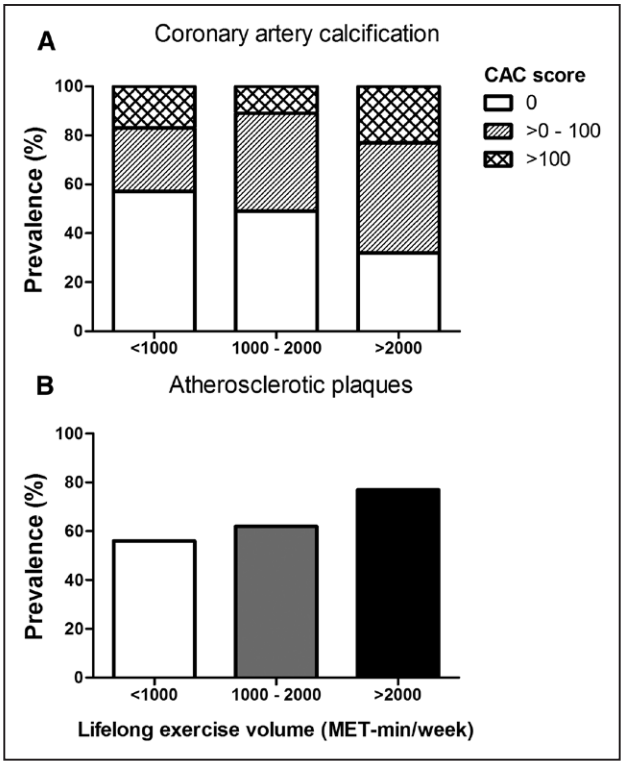

Figure 2. Prevalence of coronary artery calcification (CAC) and atherosclerotic plaques across lifelong exercise volume groups.

Data were derived from computed tomography (CT) and CT coronary angiography scans for assessment of CAC and atherosclerotic plaques (n=284). **A**, Comparison of CAC score categories across exercise volume groups. A significant difference in CAC score categories (*P*=0.006) was found across exercise volume groups, with higher CAC scores in the >2000 MET-min/wk group. The >2000 MET-min/wk group had an adjusted odds ratio of 3.2 (95% confidence interval [CI], 1.6–6.6) for CAC scores >0 compared with the <1000 MET-min/wk group. **B**, Significant increase of atherosclerotic plaque prevalence across exercise volume groups (*P*=0.013) with an adjusted odds ratio of 3.3 (95% CI, 1.6–7.1) for the presence of plaque for the >2000– compared with the <1000 MET-min/wk group. MET indicates metabolic equivalent of task.

Participants could have recently become runners and reduced their risk factors; however, that would not undo the lifelong process of atherosclerosis. Support for this hypothesis is that 52% of the runners were former smokers. We quantified lifelong exercise patterns to account for changes in exercise volume throughout the lifetime (Figure 1) and therefore can determine the dose-response relationships between exercise exposure and coronary atherosclerosis more accurately. Athletes in the least active group performed an equivalent of ≈1 h/wk of running throughout their entire lives (669 MET-min/wk [405–802 MET-min/wk]), whereas athletes in the most active group performed an equivalent of ≈4 h/wk of running (2724 MET-min/wk [2295–3526 MET-min/wk]). Our findings support a consistent pattern of an increased prevalence of CAC and CAC scores in athletes with high exercise volumes.

CAC and Plaque Characteristics

Atherosclerotic plaque characteristics can differ, which has an important effect on the risk of cardiac events. The CAC score is a multiplication of area and density, whereby an increase in area increases the risk of cardiovascular events and an increase in density lowers the risk of cardiovascular events.[19] We hypothesized that athletes would have similar or higher CAC scores because of a higher density of their plaques. Analysis in participants with CAC>0 showed that there was no difference in density across exercise volume groups. These findings emphasize that CAC characteristics (ie, area, density, regions of interest, and location) were comparable between exercise volume groups, despite a higher CAC prevalence in the most active athletes.

Our CTCA data revealed additional information on plaque composition. Among participants with plaques, we found a lower prevalence of mixed plaques and a higher prevalence of only calcified plaques in the >2000 MET-min/wk group. A previous study estimated the 3-year probability of major adverse cardiac events at 6% for calcified plaques, 23% for noncalcified plaques, and 38% for mixed plaques in a cohort of patients suspected of having coronary artery disease.[3] Therefore, plaque composition (fewer mixed, more only calcified) seems to be more benign in the most active athletes, which is supported by the lower prevalence of CVD in athletes[4,5] and the superior life expectancy of elite athletes.[6]

Influence of Exercise Intensity

We found a significant association between hours of very-vigorous-intensity exercise and presence of CAC and plaque and an inverse association between vigorous exercise intensity and presence of mixed plaque. These observations are in line with findings from previous studies because extreme exercise appears to be related to cardiac troponin release,[33] myocardial fibrosis,[34] and atrial fibrillation.[35] It is therefore possible that it is not the duration of exercise that is most important in the development of coronary atherosclerosis but the intensity of exercise. In contrast, epidemiological studies have shown that vigorous-intensity exercise is associated with greater risk reductions in all-cause and cardiovascular mortality compared with moderate-intensity exercise.[36,37] Alternatively, exercise intensity may be a proxy for overall lifelong exercise volume because the most active exercisers (>2000 MET-min/wk) reported the highest volume of very-vigorous-intensity exercise. Future (animal) studies exploring the mechanisms of

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Table 3. Unadjusted and Multivariable-Adjusted Associations Between Lifelong Exercise Volumes and Computed Tomography Coronary Angiography Evidence of Coronary Atherosclerosis

	Unadjusted		Model 1*		Model 2†		Model 3‡	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Presence of plaque								
MET-hours per week	1.02 (1.00–1.03)	0.021	1.02 (1.00–1.03)	0.06	1.02 (1.00–1.04)	0.033	1.02 (1.00–1.04)	0.015
Exercise intensity, h/wk								
Moderate	1.11 (0.86–1.43)	0.41	1.08 (0.84–1.39)	0.56	1.05 (0.81–1.38)	0.70	1.07 (0.81–1.40)	0.64
Vigorous	1.10 (0.96–1.26)	0.18	1.06 (0.92–1.23)	0.40	1.08 (0.93–1.26)	0.33	1.08 (0.93–1.27)	0.32
Very vigorous	1.38 (1.06–1.80)	0.015	1.38 (1.06–1.79)	0.017	1.46 (1.11–1.92)	0.007	1.56 (1.17–2.08)	0.002
Exercise volume groups, MET-min/wk								
<1000	Reference		Reference		Reference		Reference	
1000–2000	1.30 (0.74–2.27)	0.36	1.28 (0.73–2.27)	0.39	1.49 (0.81–2.71)	0.20	1.62 (0.88–2.99)	0.12
>2000	2.72 (1.37–5.39)	0.004	2.60 (1.29–5.24)	0.007	2.99 (1.44–6.23)	0.003	3.35 (1.57–7.14)	0.002

CI indicates confidence interval; MET, metabolic equivalent of task; and OR, odds ratio. Each exposure (exercise volume and exercise intensity) was entered separately into the different models.

*Adjusted for age.

†Also adjusted for body mass index, systolic blood pressure, ever smoked, use of antihypertensives, total cholesterol, and family history of coronary heart disease.

‡Also adjusted for use of statin and diabetes mellitus.

CAC and plaque development after exposure to different exercise intensities are therefore needed.

Potential Underlying Mechanisms

The underlying mechanisms for the higher prevalence of CAC/plaque and its increased calcification in athletes with the highest exercise volume and intensity are unknown. Hypotheses for the potential underlying mechanisms include increased exposure to flexing of the coronary arteries at high heart rates with disruption of laminar blood flow, high blood pressures during exercise, increased levels of parathyroid hormone resulting from their exercise training, or hypomagnesemia. Flexing of the coronary arteries during exercise may increase mechanical stress on the vessel wall and disturb flow patterns,[38] potentially accelerating atherosclerosis.[39] High blood pressure accelerates CAC,[30] and high blood pressures during exercise may have an influence on atherosclerosis when individuals are exposed for a substantial amount of time. Exercise is known to increase parathyroid hormone immediately after exercise,[40] and this might promote coronary calcification. Higher levels of parathyroid hormone correlate with increased risk of atherosclerotic disease as assessed by whole-body magnetic resonance imaging.[41] Alternatively, magnesium levels could also contribute to the increased CAC scores in athletes because magnesium

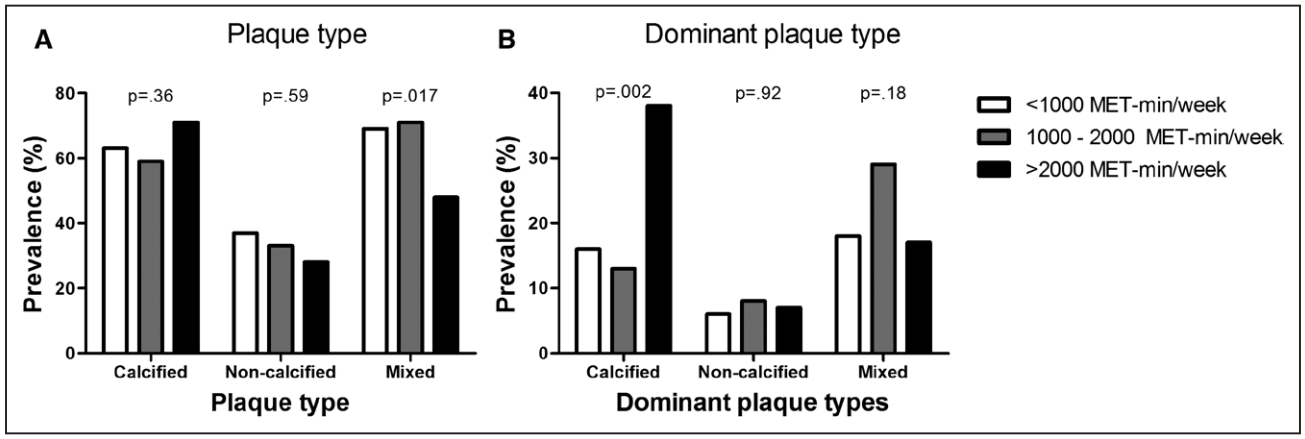

Figure 3. Plaque characteristics across the lifelong exercise volume groups in participants with computed tomography coronary angiography evidence of coronary atherosclerosis (n=182).

The >2000 MET-min/wk group had fewer mixed plaques (**A**) and more often only calcified plaques (**B**). These data suggest that plaque morphology is different across exercise volume groups, which may translate to a lower risk for major adverse cardiac events for the most active exercisers, despite their higher prevalence of coronary atherosclerosis. MET indicates metabolic equivalent of task.

levels are inversely related to CAC[42] and athletes may[43] have low magnesium levels. In conclusion, future studies are warranted to confirm which mechanisms are responsible for the higher CAC/plaque prevalence in the most active athletes.

Clinical Relevance

Although active athletes have more CAC and plaque, they have fewer mixed plaques and more often have only calcified plaques. The combination of these plaque types results in a lower risk profile for future CVD. However, the difference between CAC=0 and CAC>0 is significant, with estimated 3-year probabilities of major adverse cardiac events of 2.1% for CAC score of 0, 13% for a CAC score between 1 and 100, 16% for CAC score between 101 and 400, and 34% for a CAC score >400.[3] Higher CAC categories were also associated with a higher event rate (CAC<100, 1 of 69 [1%]; CAC 100 to <400, 3 of 25 [12%]; and CAC >400, 3 of 14 [21%]; *P*=0.002) in German marathoners after 6.2 years of follow-up.[44] It is therefore prudent to aggressively manage atherosclerotic risk factors in athletes with high CAC scores, for example, starting with statins. Higher CAC scores may indicate higher risk in athletes, but it is likely that the athlete's risk is not similar to that of the general population. Exercise training increases coronary blood flow by increasing arteriolar diameters and/or density and improves vasomotor reactivity of the coronary resistance arteries.[45] Therefore, beneficial vascular adaptations such as an improved coronary flow reserve[46,47] may also allow athletes to better deal with coronary stenoses and to experience fewer symptoms and events than the general population with a similar plaque burden. Follow-up studies focused on clinical outcomes are warranted to adequately advise athletes and to minimize their risk for future cardiovascular events.

Limitations

Limitations of this study include a potential recall bias because we requested the participants' lifelong historical exercise pattern. However, these athletes were dedicated exercisers who could remember their lifelong exercise activity very well, and only 7 (2%) of the exercise questionnaires were incomplete. In addition, recall bias should affect all athletes in our cohort in the same way. This was an observational study; therefore, we cannot exclude the possibility of residual confounding (eg, from diet or alcohol intake). Furthermore, we included only recreational and competitive athletes and did not include a control group from the general population. Therefore, we cannot make any comparisons with nonathletes. Moreover, we included only men, so our results cannot be translated to women, and follow-up research in female athletes is needed to allow sex-specific risk estimation and counseling. Finally, we included only white men in the MARC study. Because race is known to affect CAC distribution,[22] findings from our study cannot be directly extrapolated to athletes of other races.

Recent studies demonstrated that the use of statins can promote calcification of atherosclerotic plaques.[29,48] Therefore, we also analyzed the data excluding participants using statins. This did not materially alter our results, so we did not exclude these participants. Because diabetes mellitus can accelerate atherosclerosis,[30] we also analyzed the data excluding participants with diabetes mellitus. This also did not alter our results, so we chose not to exclude these participants.

A strength of our study is how we measured exercise volume. We chose to record lifelong exercise patterns because atherosclerosis is also a lifelong process.[49] We included only sports activities, so physical activity in other domains (work, commuting, gardening, household activities) was not included. Unfortunately, this reduces the comparability of our exercise volumes with other studies. Another strength of this study is the combined use of both noncontrast CT and CTCA to compare both CAC and otherwise undetected atherosclerotic plaques.

Conclusions

In this study of middle-aged men engaged in competitive or recreational leisure sports, participants in the >2000–MET-min/wk group had a higher prevalence of CAC and atherosclerotic plaques. The most active group, however, had a more benign composition of plaques, with fewer mixed plaques and more often only calcified plaques. These observations may explain the increased longevity typical of endurance athletes despite the presence of more coronary atherosclerosis in the most active participants.

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DISCLOSURES

Dr Mosterd reports serving as a consultant for Bayer, Merck, Novartis, and Pfizer and receiving speaker honoraria from

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FOOTNOTES

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