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**Aengevaeren, VL, Mosterd, A, Braber, TL, Prakken, NHJ, Doevendans, PA, Grobbee, DE, Thompson, PD, Eijsvogels, TMH and Velthuis, BK**

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### Article

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1 **The Relationship Between Lifelong Exercise Volume and Coronary Atherosclerosis in Athletes**

2 Aengevaeren, Lifelong exercise and coronary atherosclerosis

3

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**Word Count: 3926**

**Word Count Abstract: 325**

**Total Number of Tables: 3**

**Total Number of Figures: 3**

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1 **ABSTRACT**

2 **Background.** Higher levels of physical activity are associated with a lower risk of cardiovascular  
3 events. Nevertheless, there is debate on the dose-response relationship of exercise and CVD  
4 outcomes and whether high volumes of exercise may accelerate coronary atherosclerosis. We  
5 aimed to determine the relationship between lifelong exercise volumes and coronary  
6 atherosclerosis.

7 **Methods.** Middle aged men engaged in competitive or recreational leisure sports underwent a  
8 non-contrast and contrast-enhanced computed tomography scan to assess coronary artery  
9 calcification (CAC) and plaque characteristics. Participants reported lifelong exercise history  
10 patterns. Exercise volumes were multiplied by Metabolic Equivalent of Task (MET) scores to  
11 calculate MET-min/week. Participants were categorized as <1000 MET-min/week, 1000-2000  
12 MET-min/week or >2000 MET-min/week.

13 **Results.** 284 men (55±7 years) were included. CAC was present in 150/284 (53%) participants with  
14 a median CAC score of 35.8 [9.3-145.8). Athletes with a lifelong exercise volume >2000 MET-  
15 min/week (n=75) had a significantly higher CAC score (9.4 [0-60.9] versus 0 [0-43.5], p=.02) and  
16 prevalence of CAC (68%,OR<sub>adjusted</sub>=3.2 (95%CI: 1.6-6.6)) and plaque (77%, OR<sub>adjusted</sub>=3.3 (95%CI:  
17 1.6-7.1)) compared to <1000 MET-min/week (n=88, 43% and 56% respectively). Very vigorous  
18 intensity exercise (≥9 METs) was associated with CAC (OR<sub>adjusted</sub>=1.47 (95%CI: 1.14-1.91)) and  
19 plaque (OR<sub>adjusted</sub>=1.56 (95%CI: 1.17-2.08)). Among participants with CAC>0, there was no  
20 difference in CAC score (p=.20), area (p=.21), density (p=.25) and regions of interest (p=.20) across  
21 exercise volume groups. Among participants with plaque, the most active group (>2000 MET-  
22 min/week) had a lower prevalence of mixed plaques (48% versus 69%, OR<sub>adjusted</sub>=0.35 (95%CI:

1 0.15-0.85) and more often had only calcified plaques (38% versus 16%,  $OR_{adjusted}=3.57$  (95%CI:  
2 1.28-9.97)) compared to the least active group (<1000 MET-min/week).

3 **Conclusions.** Participants in the >2000 MET-min/week group had a higher prevalence of CAC and  
4 atherosclerotic plaques. The most active group did however have a more benign composition of  
5 plaques, with fewer mixed plaques and more often only calcified plaques. These observations  
6 may explain the increased longevity typical of endurance athletes despite the presence of more  
7 coronary atherosclerotic plaque in the most active participants.

8  
9 Keywords: coronary atherosclerosis; coronary artery calcium; exercise; coronary computed  
10 tomography angiography

1 **CLINICAL PERSPECTIVE**

2 **What is new:**

- 3 - This study improves understanding of coronary atherosclerosis in middle-aged athletes by  
4 analyzing CAC and atherosclerotic plaque characteristics with contrast-enhanced CT in  
5 relation to lifelong exercise.
- 6 - Athletes with a high lifelong exercise volume are more likely to have coronary  
7 atherosclerosis, but the most active athletes have a more benign composition of  
8 atherosclerotic plaques, i.e. less mixed and more often only calcified plaques.

9 **What are the clinical implications:**

- 10 - Physically active persons may have substantial, asymptomatic, coronary atherosclerosis.
- 11 - We showed substantial CAC and plaque in very active athletes, which is associated with  
12 an increased risk of cardiac events.
- 13 - As the atherosclerotic plaque types had a more benign composition, long-term follow-up  
14 of athletes needs to show whether atherosclerotic burden in athletes confers a similar risk  
15 as in the general population.
- 16 - Future studies unravelling the mechanisms leading to higher CAC and plaque prevalence  
17 in very active athletes are warranted.

18

## 1 INTRODUCTION

2 Cardiovascular diseases (CVD) are the leading cause of death worldwide, accounting for >17  
3 million deaths per year<sup>1</sup>. Atherosclerotic coronary artery disease is the main cause of CVD  
4 morbidity and mortality. Computed tomography (CT) imaging allows assessment of coronary risk  
5 since the extent of coronary artery calcification (CAC) is an indicator of the coronaries'  
6 atherosclerotic plaque burden and the risk of future cardiovascular events<sup>2, 3</sup>. Furthermore,  
7 coronary angiography (CTCA) allows assessment and characterization of atherosclerotic plaques,  
8 which significantly determines risk estimation<sup>3</sup>.

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

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

12

## 13 **METHODS**

### 14 ***Study population***

15 This is an analysis of the Measuring Athlete’s Risk of Cardiovascular Events (MARC) study, whose  
16 rationale and design have been published previously<sup>20</sup>. Men aged 45 years or older were eligible  
17 if they were asymptomatic, engaged in competitive or recreational leisure sports, were free of  
18 known CVD and had undergone a sports medical examination with bicycle exercise ECG that  
19 revealed no abnormalities, according to the responsible physician. We included only men because  
20 of their higher probability of coronary atherosclerosis and risk of exercise related cardiac arrest  
21 than women<sup>21, 22</sup>. Regional sports physicians assisted with recruiting potential participants, as  
22 they provided a flyer detailing the MARC study to athletes that underwent a sports medical



1 examination for comprehensive assessment of exercise tolerance. In the Netherlands, athletes  
2 often visit a sports physician either to improve their training patterns by determining their fitness  
3 (VO2 max), (an)aerobic threshold, peak heart rate and peak load (Watt) or to gain reassurance  
4 that they can sport safely. There was therefore no referral or medical condition underlying the  
5 examination in MARC participants. Exclusion criteria were 1) an abnormal sports medical  
6 examination according to the responsible physician, 2) known coronary artery disease, 3) contrast  
7 allergy and 4) renal impairment. The medical ethics committee approved the study and all  
8 participants provided written informed consent before participation. The study was conducted  
9 according to the Declaration of Helsinki. Baseline characteristics were obtained during the sports  
10 medical examination.

11

### 12 ***Lifelong exercise volume***

13 Participants reported their lifelong exercise history including type of sport, year started and  
14 stopped, numbers of days a week, months per year, duration of the sessions and the level at  
15 which they performed for every sport. We assigned a metabolic equivalent of task (MET) for all  
16 reported sports<sup>23</sup>. We calculated the exercise volume per sport by multiplying the MET score for  
17 the specific sport with the reported exercise volume (session duration \* frequency/week),  
18 months of practice per year and total years of practice. The lifelong exercise volume represents  
19 the sum of all sports activities between age 12 and the age at study participation and was  
20 expressed in MET-hours/week. We also calculated the average lifetime exercise exposure in MET-  
21 hours/week and MET-min/week by dividing the total lifetime exercise volume by age at  
22 participation minus 12 for average exercise volume per year and then divided this number by 52

1 for average exercise volume per week (MET-hours/week). MET-min/week was calculated from  
2 MET-hours/week multiplied by 60. Based on the international physical activity recommendation  
3 that individuals perform 500 to 1000 MET-min/week of exercise<sup>24</sup>, we assigned study participants  
4 to a lifelong exercise volume group of <1000, 1000-2000 or >2000 MET-min/week. Moreover, we  
5 classified per individual the sport with the most lifelong hours as the dominant sport. Finally, we  
6 classified exercise as light (<3 MET), moderate (3-6 MET), vigorous (6-9 MET) or very vigorous ( $\geq$   
7 9 MET) intensity and calculated the average lifetime hours/week of exercise in the specific  
8 intensity ranges.

9

### 10 ***Cardiac Computed Tomography***

11 Participants underwent a low dose cardiac CT using a 256-slice CT scanner (Philips Healthcare,  
12 Best, The Netherlands) with electrocardiographic gating according to guidelines<sup>25</sup>. A non-contrast  
13 CT was acquired to calculate the CAC score (scan parameters 120 kV, 60mAs), followed by CTCA.  
14 The total average radiation dose was  $3.9\pm 0.9$  mSv ( $1.0\pm 0.4$  mSv for CAC score and  $3.0\pm 1.2$  mSv  
15 for CTCA). CT scans were processed on a workstation (IntelliSpace Portal, Philips Healthcare) by  
16 experienced technicians, and assessed by two experienced cardiac radiologists who were blinded  
17 to the sports medical examination findings and exercise levels. The American Heart Association  
18 modified 16-segment coronary artery model was used to analyze plaque and CAC characteristics  
19 per segment<sup>26, 27</sup>.

20

### 21 ***Coronary Artery Calcification and plaque characteristics***

1 The Agatston CAC score was constructed by multiplying the calcified area ( $\text{mm}^2$ ) of each plaque  
2 by 1,2,3 or 4 depending on the density of the plaque based on Hounsfield Units (HU), and  
3 summing up all CT slices<sup>28</sup>. Calcified areas are included in the score when the plaque density was  
4 above 130 Hounsfield Units (HU). Calcified areas received a density score of 1 when density was  
5 between 130 – 200 HU, 2 = 200 – 300 HU, 3 = 300 – 400 and 4 = >400 HU. The number of calcified  
6 areas are indicated by the regions of interest. CAC scores were dichotomized (CAC=0 and CAC>0)  
7 and categorized (0, >0 – 100 and >100). CTCA was used to segment CAC, assess plaque  
8 characteristics of plaques identified by the non-contrast CT scan and for the identification of  
9 plaques with calcification levels below the Hounsfield (<130 HU) threshold. We divided plaques  
10 into 1) calcified, 2) non-calcified, 3) mixed <130HU (detected with CTCA but not with CAC scoring)  
11 and 4) mixed >130 HU (detected with CTCA and CAC scoring) plaques.

12

### 13 **Data analysis**

14 All parameters were visually inspected for normality and checked for kurtosis and skewness.  
15 Continuous variables were reported as mean $\pm$ SD when normally distributed or as median  
16 [interquartile range] when not normally distributed and categorical variables were presented as  
17 proportions. T-tests were used to compare continuous variables between individuals with CAC=0  
18 *versus* CAC>0 when data were normally distributed. Mann-Whitney U tests were used to compare  
19 the characteristics of the CAC=0 *versus* CAC>0 groups when data were not normally distributed.  
20 Pearson Chi-Square tests were used to compare categorical variables. One-way ANOVA with  
21 Bonferroni post-hoc tests were used to compare participant characteristics between the lifelong  
22 exercise volume groups (<1000 / 1000-2000 / >2000 MET-min/week) when data was normally

1 distributed, and Kruskal-Wallis 1-way ANOVA tests were used when data were not normally  
2 distributed. Two-way repeated measures ANOVA was performed to describe the distribution of  
3 lifelong exercise patterns per group across age per decade. Binary logistic regression was used to  
4 calculate unadjusted and adjusted odds ratio's (ORs) for the association between exercise  
5 characteristics (volume / intensity / sport type) and CAC, coronary atherosclerosis and plaque  
6 type presence. Furthermore, we decided a priori to adjust for the following known cardiovascular  
7 risk factors: body mass index, systolic blood pressure, smoking, use of antihypertensive,  
8 cholesterol and family history of coronary heart disease. Additionally, we made a model in which  
9 we also adjusted for use of statins and diabetes, because these factors are known to influence  
10 coronary atherosclerosis<sup>29, 30</sup>. Moreover, to explore a potential non-linear relationship between  
11 lifetime exercise volume (MET-hours/week) and CAC or plaque, we performed restricted cubic  
12 spline regression analyses. The knots were placed at the 5th, 50th and 95th percentile<sup>31, 32</sup>. We  
13 performed a test for non-linearity, which compares models with the cubic spline terms and  
14 models with only the linear terms using the likelihood ratio test. Finally, we explored the  
15 association between lifetime exercise volume and CAC characteristics for only those participants  
16 with CAC>0, and the association between exercise characteristics (volume / intensity / sport type)  
17 and plaque characteristics for participants with any coronary atherosclerosis only. Statistical  
18 significance was assumed at p<0.05. Statistical analyses were performed using SPSS Statistics 21  
19 (IBM Corp, Armonk, NY, USA). The cubic spline regression analysis was conducted using SAS  
20 software, version 9.3 (SAS, Cary, NC, USA).

21

## 22 **RESULTS**

1 A total of 284 participants from the original study population of n=318 (100% Caucasian) were  
2 included because 27 athletes did not return the lifelong exercise questionnaire and 7 athletes  
3 returned an incomplete questionnaire. CAC characteristics were not different between included  
4 and excluded athletes (data not shown). Frequency of the sports activities and dominant sports  
5 are summarized in **Supplemental Table 1**. Mean age ( $\pm$ SD) of the study population was 55.0 $\pm$ 6.5  
6 years, 150 of the 284 participants (53%) had CAC with a median CAC score of 35.8 [9.3-145.8].  
7 Average lifetime exercise volume was 2.9 [1.9-4.4] hours/week, resulting in 1356 [851-2030] MET-  
8 min/week (**Supplemental Table 2**).

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

19 **Figure 1** provides an overview of lifelong exercise patterns for each exercise  
20 volume group. CAC was more common in athletes with higher lifelong exercise volumes (**Table**  
21 **1**). Athletes performing >2000 MET-min/week more frequently had CAC>0 (68%) as compared to  
22 the <1000 MET-min/week group (43%, **Table 1, Figure 2 Panel A**). CAC scores (9.4 [0-60.9] vs. 0

1 [0-43.5],  $p=.019$ ), CAC area (4.3 [0-20.3] vs. 0 [0-16.8],  $p=.025$ ) and number of regions of interest  
2 (2 [2-5] vs. 0 [0-3],  $p=.014$ ) were all significantly higher in the >2000 MET-min/week *versus* <1000  
3 MET-min/week group. We also found an increase in CAC score categories ( $p=.006$ ) across the  
4 exercise volume groups (**Figure 2 Panel A**). Unadjusted (OR=2.80 (95%CI: 1.47 – 5.32)) and  
5 multivariable adjusted logistic regression analyses (OR=3.20 (95%CI: 1.56 – 6.57)) demonstrated  
6 a significantly higher CAC prevalence in >2000 MET-min/week *versus* <1000 MET-min/week  
7 (**Table 2**). However, there were no significant differences in CAC score ( $p=.20$ ), area ( $p=.21$ ),  
8 density ( $p=.25$ ), and regions of interest ( $p=.20$ ) across exercise volume groups when analyses were  
9 repeated only in participants with CAC>0 (**Supplemental Table 3**). Also, analysis of CAC location  
10 revealed no differences in the presence of CAC within each coronary vessel and in proximal *versus*  
11 distal segments (**Supplemental Table 3**). Analysis of coronary atherosclerosis characteristics  
12 (**Supplemental Table 4**) showed significant higher plaque prevalence (either calcified, non-  
13 calcified, mixed <130 HU or mixed >130HU) in the most active group (77%) *versus* the least active  
14 group (56%, **Figure 2 Panel B**). Unadjusted (OR=2.72 (95%CI: 1.37 – 5.39)) and multivariable  
15 adjusted logistic regression analyses (OR=3.35 (95%CI: 1.57 – 7.14)) confirmed these observations  
16 and demonstrated a significantly higher coronary atherosclerosis prevalence in >2000 MET-  
17 min/week *versus* <1000 MET-min/week (**Table 3**). Also prevalence of plaque appears to be  
18 specifically associated with hours of very vigorous intensity exercise (OR<sub>adjusted</sub>=1.56 (95%CI: 1.17  
19 – 2.08)), whereas hours of moderate and vigorous intensity exercise did not impact plaque  
20 prevalence. In participants with coronary atherosclerosis, a lower prevalence of mixed plaques  
21 was observed in the most active (48%) *versus* least active group (69%, **Figure 3 Panel A**) with  
22 OR<sub>adjusted</sub>=0.35 (95%CI: 0.15 – 0.85). A difference in the prevalence of mixed plaques <130 HU was

1 responsible for this finding (43% in <1000 MET-min/week, 33% in 1000-2000 MET-min/week and  
2 21% in >2000 MET-min/week group,  $p=.046$ ) as no differences were observed in the prevalence  
3 of mixed plaques >130 HU across exercise volume groups (41%, 49% and 40% respectively,  $p=.47$ ).  
4 The lower prevalence of mixed plaques in the highest exercise volume group appears to be largely  
5 mediated by hours of vigorous intensity exercise ( $OR_{adjusted}=0.83$ , 95%CI: 0.71 – 0.98), whereas  
6 moderate and very vigorous intensity did not impact plaque morphology. When considering  
7 dominant plaque types (either only calcified, only non-calcified or only mixed plaques), we  
8 observed that the most active group had significantly more often only calcified plaques compared  
9 to the least active group ( $OR_{adjusted}=3.57$  (95%CI: 1.28 – 9.97), **Figure 3 Panel B**). Other types of  
10 plaque dominance (including mixed plaques <130 HU and >130 HU) did not significantly differ  
11 across exercise volume groups ( $p>.05$ ). Exercise intensity was also not related to plaque  
12 dominance. Analysis of coronary atherosclerosis location revealed no differences in the presence  
13 of plaques within each coronary vessel and in proximal *versus* distal segments (**Supplemental**  
14 **Table 4**).

15 Finally, the test for non-linearity for cubic spline regression was non-significant for  
16 presence of CAC ( $p=.48$ ) and presence of plaque ( $p=.29$ ), indicating that there was no non-linear  
17 relationship with lifelong exercise volumes.

18

## 19 **DISCUSSION**

20 This study provides new insights in the association between lifelong exercise volumes and  
21 coronary atherosclerosis. Based on the non-contrast CT-scan, we found that participants with  
22 CAC>0 had a higher lifelong exercise volume compared to participants with CAC=0. Logistic

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

10

### 11 ***Accelerated Coronary Artery Calcification***

12 Athletes in the most active group show a higher prevalence of CAC and higher CAC scores. This is  
13 in agreement with a previous study, which showed higher CAC scores in German marathon  
14 runners when they were matched for age and risk factors with controls<sup>13</sup>. A major limitation of  
15 that study was that the history of the subjects' cardiovascular risk factors was unknown.  
16 Participants could have recently become runners and reduced their risk factors, however that  
17 would not undo the lifelong process of atherosclerosis. Support for this hypothesis is that 52% of  
18 the runners were former smokers. We quantified lifelong exercise patterns to account for  
19 changes in exercise volume throughout the lifetime (**Figure 1**) and therefore can determine the  
20 dose-response relationships between exercise exposure and coronary atherosclerosis more  
21 accurately. Athletes in the least active group performed an equivalent of ~1 hour/week of running  
22 throughout their entire lives (669 [405-802] MET-min/week), whereas athletes in the most active



1 group performed an equivalent of ~4 hours/week of running (2724 [2295-3526] MET-min/week).  
2 Our findings support a consistent pattern of an increased prevalence of CAC and CAC scores in  
3 athletes with high exercise volumes.

4

#### 5 ***CAC and plaque characteristics***

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

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

22

## 1 ***Influence of Exercise Intensity***

2 We found a significant association between hours of very vigorous intensity exercise and  
3 presence of CAC and plaque, and an inverse association between vigorous exercise intensity and  
4 presence of mixed plaque. These observations are in line with findings from previous studies as  
5 extreme exercise appears to be related to cardiac troponin release<sup>33</sup>, myocardial fibrosis<sup>34</sup>, and  
6 atrial fibrillation<sup>35</sup>. It is therefore possible that not the duration of exercise is most important in  
7 the development of coronary atherosclerosis, but specifically the intensity of exercise. In contrast,  
8 epidemiological studies have shown that vigorous intensity exercise is associated with greater risk  
9 reductions in all-cause and cardiovascular mortality compared to moderate intensity exercise<sup>36</sup>,  
10 <sup>37</sup>. Alternatively, exercise intensity may be a proxy for overall lifelong exercise volume as the most  
11 active exercisers (>2000 MET-min/week) reported the highest volume of very vigorous intensity  
12 exercise. Future (animal) studies exploring the mechanisms of CAC and plaque development  
13 following exposure to different exercise intensities are therefore needed.

14

## 15 ***Potential Underlying Mechanisms***

16 The underlying mechanisms for the higher prevalence of CAC/plaque and its increased  
17 calcification in athletes with the highest exercise volume and intensity are unknown. Hypotheses  
18 for the potential underlying mechanisms include increased exposure to: 1) flexing of the coronary  
19 arteries at high heart rates with disruption of laminar blood flow, 2) high blood pressures during  
20 exercise, 3) increased levels of parathyroid hormone (PTH) due to their exercise training or 4)  
21 hypomagnesemia. Flexing of the coronary arteries during exercise may increase mechanical stress  
22 on the vessel wall and disturb flow patterns<sup>38</sup>, potentially accelerating atherosclerosis<sup>39</sup>. High

1 blood pressure accelerates coronary artery calcification<sup>30</sup> and high blood pressures during  
2 exercise may have an influence on atherosclerosis when individuals are exposed for a substantial  
3 amount of time. Exercise is known to acutely increase PTH after exercise<sup>40</sup> and this might promote  
4 coronary calcification. Higher levels of PTH correlate with increased risk of atherosclerotic disease  
5 as assessed by whole body magnetic resonance imaging<sup>41</sup>. Alternatively, magnesium levels could  
6 also contribute to the increased CAC scores in athletes since magnesium levels are inversely  
7 related to CAC<sup>42</sup> and athletes may<sup>43</sup> have low magnesium levels. In conclusion, future studies are  
8 warranted to confirm which mechanisms are responsible for the higher CAC / plaque prevalence  
9 in the most active athletes.

10

### 11 ***Clinical relevance***

12 Although active athletes have more CAC and plaque, they have fewer mixed plaques and more  
13 often have only calcified plaques. The combination of these plaque types results in a lower risk  
14 profile for future CVD. However, the difference between CAC=0 and CAC>0 is significant, with  
15 estimated 3-year probabilities of major adverse cardiac events of 2.1% for CAC score=0; 13% for  
16 a CAC score between 1 to 100; 16% for CAC score between 101 and 400; and 34% for a CAC score  
17 above 400<sup>3</sup>. Higher CAC categories were also associated with a higher event rate (CAC <100: 1/69  
18 (1%); CAC 100 to <400: 3/25 (12%); and CAC >400: 3/14 (21%), p=.002) in German marathoners  
19 after 6.2 years of follow-up<sup>44</sup>. It is therefore prudent to aggressively manage atherosclerotic risk  
20 factors in athletes with high CAC scores, e.g. start with statins. Higher CAC scores may indicate  
21 higher risk in athletes, however it is likely that the athlete's risk is not similar to that of the general  
22 population. Exercise training increases coronary blood flow by increasing arteriolar diameters

1 and/or density and improves vasomotor reactivity of the coronary resistance arteries<sup>45</sup>.  
2 Therefore, beneficial vascular adaptations such as an improved coronary flow reserve<sup>46, 47</sup> may  
3 also allow athletes to better deal with coronary stenoses and experience fewer symptoms and  
4 events than the general population with a similar plaque burden. Follow-up studies focussed on  
5 clinical outcomes are warranted, to adequately advice athletes and minimalize their risk for future  
6 cardiovascular events.

7

### 8 ***Limitations***

9 Limitations of this study include a potential recall bias as we requested the participants' lifelong  
10 historical exercise pattern. However, these athletes were dedicated exercisers who could  
11 remember their lifelong exercise activity very well and only 7 (2%) of the exercise questionnaires  
12 were incomplete. In addition, recall bias should affect all athletes in our cohort in the same way.  
13 This was an observational study and therefore we cannot exclude the possibility of residual  
14 confounding (from e.g. diet or alcohol intake). Furthermore, we only included recreational and  
15 competitive athletes and did not include a control group from the general population. Therefore,  
16 we cannot make any comparisons with non-athletes. Moreover, we only included men, so our  
17 results cannot be translated to women and follow-up research in female athletes is needed to  
18 allow sex-specific risk-estimation and counselling. Finally, we included only Caucasian men in the  
19 MARC study. As race is known to impact CAC distribution<sup>22</sup>, findings from our study cannot be  
20 directly extrapolated to athletes of other races.

21 Recent studies demonstrated that the use of statins can promote calcification of  
22 atherosclerotic plaques<sup>29, 48</sup>. Therefore, we also analyzed the data excluding participants using

1 statins. This did not materially alter our results so we did not exclude these participants. Diabetes  
2 can accelerate atherosclerosis<sup>30</sup> so we also analyzed the data excluding participants with  
3 diabetes. This also did not alter our results so we chose not to exclude these participants.

4 A strength of our study is how we measured exercise volume. We chose to record lifelong  
5 exercise patterns as atherosclerosis is also a lifelong process<sup>49</sup>. We only included sports activities,  
6 so physical activity in other domains were not included (work, commuting, gardening, household  
7 activities). Unfortunately, this reduces the comparability of our exercise volumes with other  
8 studies. Another strength of this study is the combined use of both non-contrast CT and CTCA, to  
9 compare both CAC and otherwise non-detected atherosclerotic plaques.

10

## 11 **Conclusion**

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

18

19 **Sources of funding:** This work was supported by a grant from Sportcor, a Dutch national registry  
20 of sudden cardiac arrest in athletes, the Foundations 'Wetenschappelijk Onderzoek Hart- en  
21 Vaatziekten' and 'Bijstand Meander Medical Center' Amersfoort, the Röntgen Foundation  
22 Utrecht and Philips Healthcare. The funders had no role in study design, data collection and

1 analysis, decision to publish, or preparation of the manuscript. V.L.A is financially supported by a  
2 grant from the Radboud Institute for Health Sciences. T.M.H.E is supported by a Horizon 2020  
3 grant from the European Commission (Marie Skłodowska-Curie Fellowship 655502).

4

5 **Disclosures:** V.L.A., T.L.B., N.H.J.P., P.A.D. and T.M.H.E. have no relationships or conflicts to  
6 disclose. A.M. reports serving as a consultant for Bayer, Merck, Novartis, and Pfizer; receiving  
7 speaker honoraria from Novartis. D.E.G. reports receiving research grants from Roche, Pfizer,  
8 Novartis. P.D.T. reports receiving research grants from the Amarin, Esperion, Regeneron, Sanofi,  
9 and Pfizer; serving as a consultant for Aventis, Regeneron, Merck, Genomas, Abbvie, Sanofi, and  
10 Pfizer; receiving speaker honoraria from Regeneron, Sanofi, Amgen, Amarin, and Merck: owning  
11 stock in General Electric, JA Wiley Publishing, J&J, Abbvie, Abbott, Medtronic, Serapta and  
12 Cryolife. B.K.V. reports serving as a regular speaker for Philips Healthcare. All relationships are  
13 modest.

14

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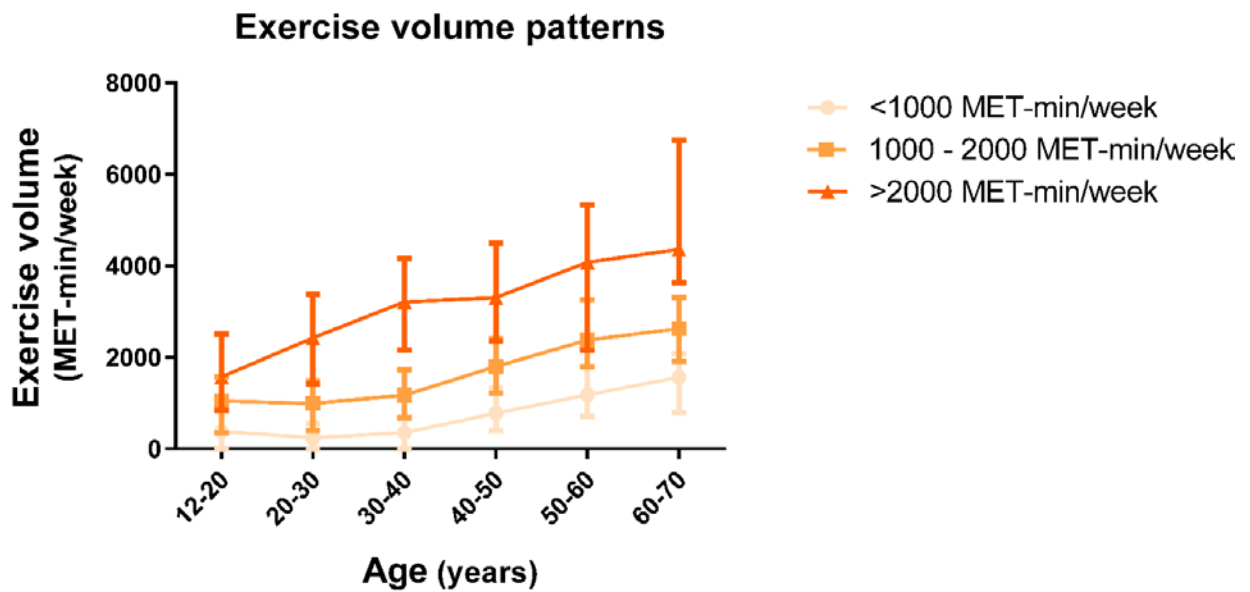
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- 13
- 14

1 **FIGURE LEGENDS**

2 **Figure 1. Patterns of exercise volumes per decade.** A gradual age-related increase in exercise  
3 volume was found in each exercise volume group (<1000 / 1000-2000 / >2000 MET-min/week).  
4 Data was averaged per decade and available for all participants (n=284) for decades between age  
5 12 and 50. For decade 50-60 (n=192) and 60-70 (n=64), data was available in a subgroup only.

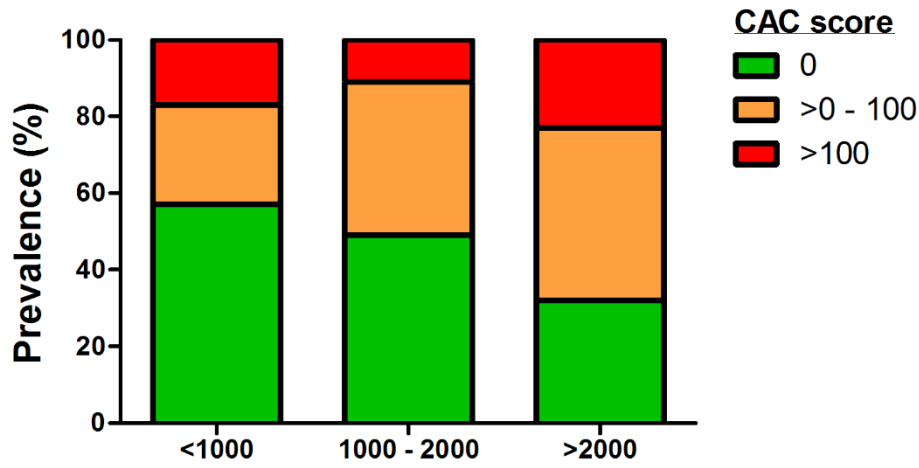
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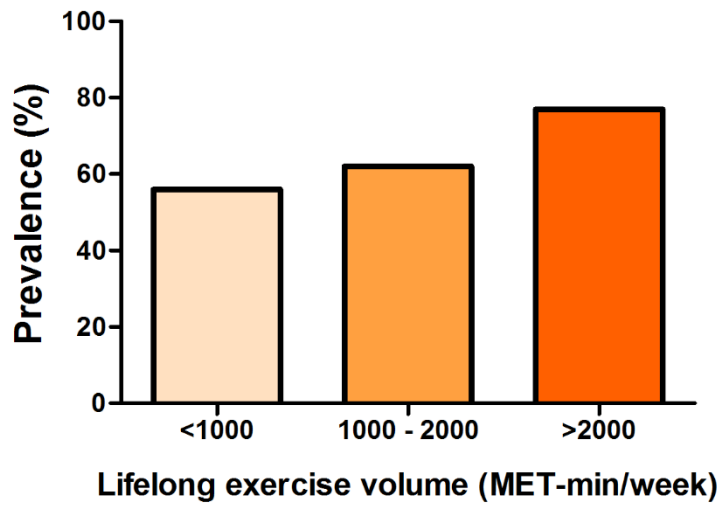
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1 **Figure 2. Prevalence of coronary artery calcification and atherosclerotic plaques across lifelong**  
2 **exercise volume groups.** Data were derived from CT and CTCA scans for assessment of CAC and  
3 atherosclerotic plaques (n=284). **Panel A** shows a comparison of CAC score categories across  
4 exercise volume groups. A significant difference in CAC score categories ( $p=.006$ ) was found  
5 across exercise volume groups, with higher CAC scores in the >2000 MET-min/week group. The  
6 >2000 MET-min/week group had an adjusted odds ratio of 3.2 (95%CI: 1.6-6.6) for CAC scores >0  
7 compared to the <1000 MET-min/week group. **Panel B** shows a significant increase of  
8 atherosclerotic plaque prevalence across exercise volume groups ( $p=.013$ ) with an adjusted odds  
9 ratio of 3.3 (95%CI: 1.6-7.1) for presence of plaque for the >2000 MET-min/week compared to  
10 the <1000 MET-min/week group. CAC = coronary artery calcification; CT = computed tomography;  
11 CTCA = computed tomography coronary angiography; MET = metabolic equivalent of task.  
12

**A. Coronary artery calcification**

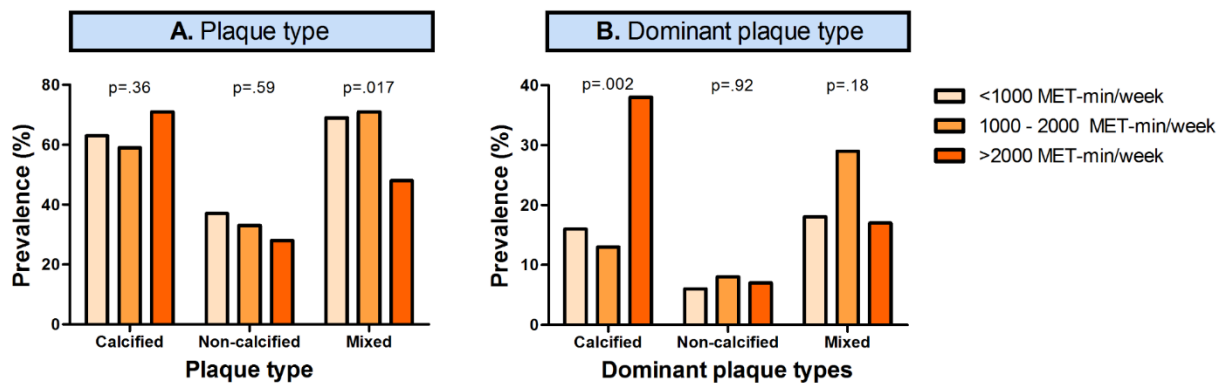


**B. Atherosclerotic plaques**





1 **Figure 3. Plaque characteristics across the lifelong exercise volume groups in participants with**  
 2 **CTCA evidence of coronary atherosclerosis (n=182).** The >2000 MET-min/week group had fewer  
 3 mixed plaques (**panel A**) and more often only calcified plaques (**panel B**). These data suggest that  
 4 plaque morphology is different across exercise volume groups, which may translate to a lower  
 5 risk for major adverse cardiac events for the most active exercisers, despite their higher  
 6 prevalence of coronary atherosclerosis. CAC = coronary artery calcification; CTCA = computed  
 7 tomography coronary angiography; MET = metabolic equivalent of task.  
 8



9

- 1 **Table 1.** A comparison of participant and coronary artery calcification characteristics across
- 2 exercise volume groups.

	Lifelong exercise volume (MET-min/week)			P-value
	<1000	1000-2000	>2000	
	(n=88)	(n=121)	(n=75)	
<b>Participant characteristics</b>				
Age, years	54.4 (6.1)	54.8 (6.3)	55.9 (6.9)	.35
Systolic BP, mmHg	128 (11)	130 (15)	129 (12)	.63
Diastolic BP, mmHg	80 (8)	80 (9)	80 (8)	.82
Height, cm	183 (7)	183 (6)	181 (7)	.11
Weight, kg	84 (11)	83 (10)	80 (9) <sup>†</sup>	.029*
BMI, kg/m <sup>2</sup>	25.3 (2.9)	24.8 (2.8)	24.5 (2.3)	.14
BSA, m <sup>2</sup>	2.06 (.16)	2.05 (.14)	2.00 (.13) <sup>†</sup>	.025*
Exercise tolerance, Watt	298 (44)	319 (47) <sup>†</sup>	321 (48) <sup>†</sup>	.001*
Total Cholesterol, mmol/l	5.36 (.87)	5.31 (.88)	5.44 (.96)	.63
Statin, n (%)	6 (7%)	2 (2%)	7 (9%)	.048*
Current smokers, n (%)	7 (8%)	5 (4%)	2 (3%)	.26
Former smoker, n (%)	32 (36%)	43 (36%)	33 (44%)	.46
Never smoker, n (%)	49 (56%)	73 (60%)	40 (53%)	.60
Pack years of smoking, n	0 [0-8]	0 [0-7]	0 [0-8]	.81
Antihypertensive, n (%)	7 (8%)	7 (6%)	6 (8%)	.78

Diabetes, n (%)	1 (1%)	1 (1%)	2 (3%)	.55
Family history of CHD, n (%)	29 (33%)	35 (29%)	25 (33%)	.75
<b>CAC Characteristics</b>				
CAC, Agatston Units	0 [0-43.5]	.8 [0-26.5]	9.4 [0-60.9] <sup>††</sup>	.019*
CAC=0, n (%)	50 (57%)	60 (50%)	24 (32%)	.005*
Area, mm <sup>2</sup>	0 [0-16.81]	.8 [0-10.8]	4.3 [0-20.3] <sup>†</sup>	.025*
Density, au	3.0 [1.9-3.5]	2.6 [1.6-3.2]	3.0 [2.0-3.4]	.25
Regions of interest, n	0 [0-3]	1 [0-3]	2 [2-5] <sup>††</sup>	.014*
<b>Lifelong Exercise Characteristics</b>				
Years of exercise <sup>§</sup> , n	27 [13-37]	36 [30-41] <sup>†</sup>	40 [35-47] <sup>††</sup>	<.001*
Sessions/week, n	0.9 [.7-1.4]	2.1 [1.7-2.5] <sup>†</sup>	3.3 [2.7-4.5] <sup>††</sup>	<.001*
Duration/session, hrs	1.4 [1.1-1.8]	1.4 [1.2-1.7]	1.7 [1.5-2.0] <sup>††</sup>	<.001*
Exercise duration/week, hrs	1.5 [.9-1.9]	3.0 [2.4-3.6] <sup>†</sup>	5.7 [4.6-7.3] <sup>††</sup>	<.001*
MET-min/week, au	669 [405-802]	1443 [1189-1672] <sup>†</sup>	2724 [2295-3526] <sup>††</sup>	<.001*
MET-hours/week, au	11.2 [6.7-13.4]	24.1 [19.8-27.9] <sup>†</sup>	45.4 [38.2-58.8] <sup>††</sup>	<.001*
Light intensity, (%)	0 [0-0]	0 [0-0]	0 [0-0]	.47
Moderate intensity, (%)	11 [0-39]	6 [0-23]	0 [0-14] <sup>†</sup>	.035*
Vigorous intensity, (%)	52 [21-89]	56 [22-86]	67 [32-87]	.66
Very vigorous intensity, %	2 [0-50]	18 [0-53]	23 [3-54] <sup>†</sup>	.036*
Lifetime MET-hours, au	24257 [13541- 30410]	52280 [42458- 61098] <sup>†</sup>	104208 [81539- 137010] <sup>††</sup>	<.001*

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Au, arbitrary units; BMI, body mass index; BP, Blood pressure; BSA, body surface area; CAC, coronary artery calcification; CHD, coronary heart disease; MET, Metabolic Equivalent of Task. Data is presented as mean (SD), n (%) or median [interquartile range]. \* = P-value <.05. † = pairwise comparison, significantly different from <1000 MET-min/week. ‡ = pairwise comparison, significantly different from 1000-2000 MET-min/week. § = since age 12.

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**Table 2.** Unadjusted and multivariable-adjusted associations between lifelong exercise volumes and presence of coronary artery calcification (CAC>0).

	Unadjusted		Model 1*		Model 2†		Model 3‡	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
<b>Presence of CAC</b>								
MET-hrs/week	1.02 (1.01 – 1.04)	.003	1.02 (1.00 – 1.04)	.014	1.02 (1.01 – 1.04)	.012	1.02 (1.01 – 1.04)	.006
<b>Exercise intensity</b>								
Moderate intensity (hrs/week)	1.09 (0.88 – 1.37)	.43	1.06 (0.84 – 1.33)	.65	1.01 (0.79 – 1.30)	.91	1.03 (0.80 – 1.32)	.81
Vigorous intensity (hrs/week)	1.16 (1.01 – 1.32)	.031	1.12 (0.97 – 1.28)	.13	1.12 (0.97 – 1.29)	.13	1.13 (0.97 – 1.31)	.12
Very vigorous intensity (hrs/week)	1.35 (1.06 – 1.71)	.014	1.35 (1.06 – 1.72)	.016	1.41 (1.10 – 1.81)	.008	1.47 (1.14 – 1.91)	.003

<i>Exercise volume groups</i>								
<1000	Reference		Reference		Reference		Reference	
MET-min/week								
1000 – 2000	1.34	.30	1.33	.33	1.45	.22	1.62	.12
MET-min/week	(0.77 – 2.32)		(0.75 – 2.35)		(0.80 – 2.63)		(.88 – 2.97)	
>2000	2.80	.002	2.69	.004	2.93	.002	3.20	.001
MET-min/week	(1.47 – 5.32)		(1.38 – 5.23)		(1.46 – 5.86)		(1.56 – 6.57)	

MET, Metabolic Equivalent of Task. Each exposure (exercise volume and exercise intensity) was entered separately into the different models. \* Adjusted for age. † Additionally adjusted for body mass index, systolic blood pressure, ever smoked, use of antihypertensive, total cholesterol and family history of coronary heart disease. ‡ Additionally adjusted for use of statin and diabetes.

**Table 3.** Unadjusted and multivariable-adjusted associations between lifelong exercise volumes and CTCA evidence of coronary atherosclerosis.

	Unadjusted		<i>Model 1</i> <sup>*</sup>		<i>Model 2</i> <sup>†</sup>		<i>Model 3</i> <sup>‡</sup>	
	<i>Odds Ratio</i> <i>(95% CI)</i>	<i>P-value</i>	<i>Odds Ratio</i> <i>(95% CI)</i>	<i>P-value</i>	<i>Odds Ratio</i> <i>(95% CI)</i>	<i>P-value</i>	<i>Odds Ratio</i> <i>(95% CI)</i>	<i>P-value</i>
<b><i>Presence of plaque</i></b>								
MET-hrs/week	1.02 (1.00 – 1.03)	.021	1.02 (1.00 – 1.03)	.06	1.02 (1.00 – 1.04)	.033	1.02 (1.00 – 1.04)	.015
<b><i>Exercise intensity</i></b>								
Moderate intensity (hrs/week)	1.11 (0.86 – 1.43)	.41	1.08 (0.84 – 1.39)	.56	1.05 (0.81 – 1.38)	.70	1.07 (0.81 – 1.40)	.64
Vigorous intensity (hrs/week)	1.10 (0.96 – 1.26)	.18	1.06 (0.92 – 1.23)	.40	1.08 (0.93 – 1.26)	.33	1.08 (0.93 – 1.27)	.32
Very vigorous intensity (hrs/week)	1.38 (1.06 – 1.80)	.015	1.38 (1.06 – 1.79)	.017	1.46 (1.11 – 1.92)	.007	1.56 (1.17 – 2.08)	.002

<i>Exercise volume groups</i>								
<1000 MET-min/week	Reference		Reference		Reference		Reference	
1000 – 2000 MET-min/week	1.30 (0.74 – 2.27)	.36	1.28 (0.73 – 2.27)	.39	1.49 (0.81 – 2.71)	.20	1.62 (.88 – 2.99)	.12
>2000 MET-min/week	2.72 (1.37 – 5.39)	.004	2.60 (1.29 – 5.24)	.007	2.99 (1.44 – 6.23)	.003	3.35 (1.57 – 7.14)	.002

MET, Metabolic Equivalent of Task. Each exposure (exercise volume and exercise intensity) was entered separately into the different models. \* Adjusted for age. † Additionally adjusted for body mass index, systolic blood pressure, ever smoked, use of antihypertensive, total cholesterol and family history of coronary heart disease. ‡ Additionally adjusted for use of statin and diabetes.



**Supplemental Table 1.** Frequency of sports participation

Type of sport	Frequency (%)		MET-score*
	Total	Dominant sport	
Athletics	41 (14%)	10 (4%)	6.7
Badminton	14 (5%)	1 (0%)	5.5
Baseball	4 (1%)	1 (0%)	5
Basketball	18 (6%)	2 (1%)	6.5
Bowling	1 (0%)	1 (0%)	3
Boxing	4 (1%)	0 (0%)	8.7
Cycling	169 (60%)	81 (29%)	6.8/7.5/8.5/10
Dancing	2 (1%)	0 (0%)	5
Diving	2 (1%)	0 (0%)	7
Fitness/health club/strength	54 (19%)	13 (5%)	3.5/4.5/5.5/7.3/7.8
Golf/cricket	12 (4%)	6 (2%)	4.8
Gymnastics	13 (5%)	1 (0%)	3.8/6
Handball	8 (3%)	2 (1%)	8
Hockey	36 (13%)	11 (4%)	7.8

Horse riding	6 (2%)	2 (1%)	5.5
Judo/Karate/Jujutsu	20 (7%)	1 (0%)	5.3
Korfball	7 (3%)	2 (1%)	6.5
Motor cross	5 (2%)	0 (0%)	4
Mountain climbing	2 (1%)	1 (0%)	6.6
Paragliding	2 (1%)	0 (0%)	1.8
Rowing	21 (7%)	4 (1%)	9.2
Rugby	4 (1%)	2 (1%)	6.3/8.3
Running	158 (56%)	72 (25%)	6/7/9.3/11.8
Sailing/windsurfing	8 (3%)	3 (1%)	3/4.5/5
Shooting sport	1 (0%)	1 (0%)	4.3
(Water) Skiing/snowboard	9 (3%)	1 (0%)	5.3/6
Soccer	109 (38%)	29 (10%)	7
(Inline) Speed skating	35 (12%)	1 (0%)	7.5/9
Squash	8 (3%)	1 (0%)	9.7
Swimming	28 (10%)	3 (1%)	8/10
Table tennis	10 (4%)	2 (1%)	4

Tennis	78 (28%)	10 (4%)	5/7.3
Triathlon	12 (4%)	5 (2%)	9.8
Ultimate Frisbee	2 (1%)	0 (0%)	8
Volleyball	22 (8%)	3 (1%)	4/6
Walking	6 (2%)	2 (1%)	4.3
Water polo	17 (6%)	10 (4%)	10

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MET: Metabolic Equivalent of Task; \*MET-score can differ based on level of competition and specific type of sport (e.g. cycling can be racing/spinning/touring/etc.)

**Supplemental Table 2.** Participant characteristics of the total study population as well as athletes with and without coronary artery calcification.

	<b>Total population (n=284)</b>	<b>Without CAC (n=134)</b>	<b>With CAC (n=150)</b>	<b>P-value</b>
<b>Participant Characteristics</b>				
Age, years	55.0 (6.5)	53.2 (5.7)	56.6 (6.8)	<.001*
Systolic BP, mmHg	129 (13)	127 (13)	131 (13)	.003*
Diastolic BP, mmHg	80 (8)	79 (8)	81 (8)	.033*
Height, cm	182 (7)	183 (7)	182 (6)	.35
Weight, kg	83 (10)	82 (10)	83 (10)	.66
BMI, kg/m <sup>2</sup>	24.9 (2.7)	24.7 (2.6)	25.1 (2.8)	.22
BSA, m <sup>2</sup>	2.04 (.14)	2.04 (.14)	2.04 (.14)	.98
Exercise tolerance, Watt	313 (47)	313 (45)	313 (50)	.96
Total cholesterol, mmol/l	5.4 (0.9)	5.2 (0.9)	5.5 (0.9)	.004*
Statin, n (%)	15 (5%)	1 (1%)	14 (9%)	.001*
Current smokers, n (%)	14 (5%)	8 (6%)	6 (4%)	.44
Former smoker, n (%)	108 (38%)	42 (31%)	66 (44%)	.03*
Never smoker, n (%)	162 (57%)	84 (63%)	78 (52%)	.07
Pack years of smoking, n	0 [0-8]	0 [0-7]	0 [0-8]	.21
Antihypertensive, n (%)	20 (7%)	6 (5%)	14 (9%)	.11
Diabetes, n (%)	4 (1%)	2 (2%)	2 (1%)	.91
Family history of CHD, n (%)	89 (31%)	34 (25%)	55 (37%)	.041*

<b>CAC Characteristics</b>				
CAC, Agatston Units	.9 [0-42.1]	-	35.8 [9.3-145.8]	-
Area, mm <sup>2</sup>	.9 [0-15.0]	-	13.0 [4.5-44.1]	-
Density, au	2.8 [1.8-3.4]	-	2.8 [1.8-3.4]	-
Regions of interest, n	1 [1-4]	-	3 [1-10]	-
<b>Lifelong Exercise Characteristics</b>				
Years of exercise training <sup>†</sup> , n	36 [27-42]	35 [23-39]	37 [31-45]	<.001*
Sessions/week, n	1.9 [1.3-2.8]	1.8 [1.2-2.6]	2.0 [1.5-3.0]	.019*
Duration/session, hrs	1.5 [1.2-1.8]	1.5 [1.2-1.8]	1.5 [1.3-1.8]	.20
Exercise duration/week, hrs	2.9 [1.9-4.4]	2.6 [1.7-3.8]	3.1 [2.1-4.7]	.012*
MET-min/week, au	1356 [851-2030]	1225 [749-1782]	1528 [997-2248]	.003*
MET-hours/week, au	22.6 [14.2-33.8]	20.4 [12.48-29.7]	25.5 [16.6-37.5]	.003*
Light intensity, (%)	0 [0-0]	0 [0-0]	0 [0-0]	.18
Moderate intensity, (%)	4 [0-27]	4 [0-24]	6 [0-31]	.58
Vigorous intensity, (%)	59 [23-87]	66 [27-90]	55 [20-82]	.19
Very vigorous intensity, %	16 [0-53]	13 [0-51]	19 [0-54]	.39
Lifetime MET-hours, au	50290 [32431-76462]	41526 [26716-65149]	56259 [34682-89679]	<.001*

Au, arbitrary units; BMI, body mass index; BP, Blood pressure; BSA, body surface area; CAC, coronary artery calcification; CHD, coronary heart disease; MET, Metabolic Equivalent of Task. Data is presented as mean (SD), n (%) or median [interquartile range]. \* = P-value < .05. † = since age 12.

**Supplemental Table 3.** A comparison of participant and coronary artery calcification (CAC) characteristics across exercise volume groups in participants with CAC>0.

	Lifelong exercise volume (MET-min/week)			P-value
	<1000	1000-2000	>2000	
	(n=38)	(n=61)	(n=51)	
CAC, Agatston Units	69.6 [13.8-331.5]	24.1 [6.5-85.5]	39.2 [8.4-159.0]	.20
Area, mm <sup>2</sup>	22.0 [7.8-99.3]	10.5 [3.7-30.0]	12.4 [4.1-53.0]	.21
Density, au	3.0 [1.9-3.5]	2.6 [1.6-3.2]	3.0 [2.0-3.4]	.25
Regions of interest, n	5 [2-16]	3 [1-7]	4 [2-10]	.20
Location of CAC, n (%)				
Left anterior descending	34 (90%)	53 (87%)	43 (84%)	.78
Ramus circumflexus	13 (34%)	23 (38%)	20 (39%)	.89
Right coronary artery	17 (45%)	22 (36%)	21 (41%)	.68
Proximal segments*	32 (84%)	49 (80%)	39 (77%)	.66

Au, arbitrary units; CAC, coronary artery calcification; Data is presented as median [interquartile range] or n (%). \* = proximal segments defined as segments 1,5,6 and 11<sup>1</sup>.

**Supplemental Table 4.** A comparison of plaque characteristics across exercise volume groups in participants with computed tomography coronary angiography evidence of atherosclerotic plaques.

	Lifelong exercise volume (MET-min/week)			P-value
	<1000 (n=49)	1000-2000 (n=75)	>2000 (n=58)	
<b><i>Presence of plaques</i></b>				
Calcified, n (%)	31 (63%)	44 (59%)	41 (71%)	.36
Non-Calcified, n (%)	18 (37%)	25 (33%)	16 (28%)	.59
Mixed (both), n (%)	34 (69%)	53 (71%)	28 (48%)	.017*
Mixed < 130 HU, n (%)	21 (43%)	25 (33%)	12 (21%)	.046*
Mixed >130 HU, n (%)	20 (41%)	37 (49%)	23 (40%)	.47
<b><i>Dominant plaque types</i></b>				
ONLY Calcified, n (%)	8 (16%)	10 (13%)	22 (38%)	.002*
ONLY Non-Calcified, n (%)	3 (6%)	6 (8%)	4 (7%)	.92
ONLY Mixed (both), n (%)	9 (18%)	22 (29%)	10 (17%)	.18
ONLY Mixed >130 HU, n (%)	3 (6%)	10 (13%)	5 (9%)	.39
ONLY Mixed <130 HU, n (%)	5 (10%)	7 (9%)	3 (5%)	.58
<b><i>Location of plaques</i></b>				
Left anterior descending, n (%)	47 (96%)	67 (89%)	49 (85%)	.16
Ramus circumflexus, n (%)	18 (37%)	26 (35%)	24 (41%)	.73

Right coronary artery, n (%)	24 (49%)	29 (39%)	27 (47%)	.47
Proximal segments <sup>†</sup> , n (%)	43 (88%)	64 (85%)	45 (78%)	.32

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HU = Hounsfield Units; \* = P-value < .05. <sup>†</sup> = proximal segments defined as segments 1,5,6 and 11<sup>1</sup>.