



Prevalence of Subclinical Coronary Artery Disease in Masters Endurance Athletes With a Low Atherosclerotic Risk Profile

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BACKGROUND: Studies in middle-age and older (masters) athletes with atherosclerotic risk factors for coronary artery disease report higher coronary artery calcium (CAC) scores compared with sedentary individuals. Few studies have assessed the prevalence of coronary artery disease in masters athletes with a low atherosclerotic risk profile.

METHODS: We assessed 152 masters athletes 54.4±8.5 years of age (70% male) and 92 controls of similar age, sex, and low Framingham 10-year coronary artery disease risk scores with an echocardiogram, exercise stress test, computerized tomographic coronary angiogram, and cardiovascular magnetic resonance imaging with late gadolinium enhancement and a 24-hour Holter. Athletes had participated in endurance exercise for an average of 31±12.6 years. The majority (77%) were runners, with a median of 13 marathon runs per athlete.

RESULTS: Most athletes (60%) and controls (63%) had a normal CAC score. Male athletes had a higher prevalence of atherosclerotic plaques of any luminal irregularity (44.3% versus 22.2%; $P=0.009$) compared with sedentary males, and only male athletes showed a CAC ≥300 Agatston units (11.3%) and a luminal stenosis ≥50% (7.5%). Male athletes demonstrated predominantly calcific plaques (72.7%), whereas sedentary males showed predominantly mixed morphology plaques (61.5%). The number of years of training was the only independent variable associated with increased risk of CAC >70th percentile for age or luminal stenosis ≥50% in male athletes (odds ratio, 1.08; 95% confidence interval, 1.01–1.15; $P=0.016$); 15 (14%) male athletes but none of the controls revealed late gadolinium enhancement on cardiovascular magnetic resonance imaging. Of these athletes, 7 had a pattern consistent with previous myocardial infarction, including 3(42%) with a luminal stenosis ≥50% in the corresponding artery.

CONCLUSIONS: Most lifelong masters endurance athletes with a low atherosclerotic risk profile have normal CAC scores. Male athletes are more likely to have a CAC score >300 Agatston units or coronary plaques compared with sedentary males with a similar risk profile. The significance of these observations is uncertain, but the predominantly calcific morphology of the plaques in athletes indicates potentially different pathophysiological mechanisms for plaque formation in athletic versus sedentary men. Coronary plaques are more abundant in athletes, whereas their stable nature could mitigate the risk of plaque rupture and acute myocardial infarction.

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Clinical Perspective

What Is New?

- Although overall coronary artery calcium prevalence was similar between masters athletes and health sedentary controls, male athletes were more likely to have high coronary artery calcium scores and coronary plaques.
- Among male athletes, coronary plaques were predominantly calcified, whereas plaques in sedentary men were predominantly of mixed morphology, indicating that different pathophysiological mechanisms may be responsible for plaque formation in athletic and sedentary individuals.
- A small proportion of athletic men showed scarring consistent with myocardial infarction on cardiac magnetic resonance imaging compared with none of the sedentary males.

What Are the Clinical Implications?

- Longstanding endurance exercise may modestly increase the likelihood of developing calcified coronary plaques.
- Although this observation could be interpreted as a deleterious consequence of exercise, it is also possible that the calcified and stable nature of the plaques may mitigate the risk of plaque disruption and acute myocardial infarction.

Regular exercise confers a low risk profile for atherosclerosis and is associated with a 50% reduction in adverse events from coronary artery disease (CAD).^{1,2} The amount of physical activity required to achieve these benefits is 150 minutes of moderate exercise per week.³⁻⁶ In contrast, some athletes engage in several hours of intensive training per day, exceeding the daily recommendations by 10- to 15-fold, and many regularly participate in endurance events such as marathon running.

The past 2 decades have observed an exponential rise in the number of middle-age and older (masters) athletes who have exercised intensely since youth and who constitute an increasing proportion of participants in endurance events.⁷ Although ostensibly fit and healthy, several studies have reported high coronary artery calcium (CAC) scores⁸⁻¹⁰ and myocardial fibrosis^{11,12} in such athletes. These studies generate controversy because, although exercise is associated with a reduction in adverse events from CAD, coronary atherosclerosis is also the most common cause of exercise-related sudden death in masters athletes.¹²⁻¹⁶ However, existing studies are limited by small sample sizes, focus on men only,⁸⁻¹² and inclusion of athletes with risk factors for atherosclerosis.⁸⁻¹² Only 1 of these major studies has demonstrated increased atherosclerosis in the athletes

after adjusting for their lower Framingham risk scores.⁸ Therefore, further studies are essential to address the controversy.¹⁷ The present study investigated the coronary arteries of a large cohort of masters athletic men and women without established conventional risk factors for CAD who had engaged in several decades of endurance exercise.

METHODS

Subjects

Masters athletes were recruited from elite running and cycling clubs in the United Kingdom through an advertisement placed in a popular athletic magazine.¹⁸ *Athletics Weekly* is published in print form and online and is the world's only weekly athletics magazine, with a broad readership covering all aspects of athletics and affiliated endurance sports. Exclusion criteria included a history of CAD, family history of premature (<40 years) CAD, diabetes mellitus, hypertension (BP $\geq 140/\geq 90$ mmHg), hypercholesterolemia (>5.18 mmol/L), and active or former smokers. Masters athletes were >40 years of age, ran ≥ 10 miles or cycled ≥ 30 miles per week and have continued to do so for ≥ 10 years, and competed in ≥ 10 endurance events, including marathons (26.2 miles, 42.2 km), half marathons (13.1 miles, 21.1 km), 10 km races, or endurance cycling races ranging from 41.1 to 161.5 miles, 66 to 260 km) over a 10-year period. Participants who responded to the advertisements by e-mail or telephone were sent a copy of the participant information leaflet and invited to attend for preliminary screening tests before recruitment.

Healthy controls were recruited through advertisements placed in e-mail staff bulletins at 3 large London hospitals and had age, sex, and Framingham 10-year CAD risk profiles similar to the athletes. Controls engaged in exercise (mainly walking, jogging, or swimming) in accordance with the physical activity recommendations for health^{4,19} and were subject to identical exclusion criteria. Written consent was obtained from all participants, and ethical approval was granted by the National Research Ethics Service and the South West-Central Bristol committee.

Preliminary Screening Tests

Between September 2013 and June 2016, 234 athletes and 202 controls completed a health questionnaire and underwent a physical examination, 12-lead EKG, and biochemical tests, including a fasting blood glucose level and serum lipid profile.

Health questionnaires inquired about demographics, cardiac symptoms, medical history, smoking history, family history of cardiac disease, and exercise history. The exercise history included years of competitive exercise, number of competitive endurance events, weekly average running/cycling distances, and personal best times for marathons. Physical examination included measurement of height, weight, peripheral pulse, and blood pressure and auscultation of the heart.

Eighty-two (35%) athletes and 110 (54.4%) controls were excluded because of the presence of established risk factors for CAD (Figure 1 in the online-only Data Supplement). The final cohort consisted of 152 athletes and 92 relatively sedentary healthy controls, and all underwent echocardiography, a

cardiopulmonary exercise stress test, 24-hour Holter, a computerized tomographic (CT) coronary angiogram (CTCA), and cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE).

Transthoracic Echocardiography

Two-dimensional echocardiography was performed using a Philips iE33 echocardiographic machine. Standard views were obtained to measure wall thickness and cavity size. Doppler measurements were performed in accordance with published recommendations.²⁰

CTCA

CT calcium scoring and CTCA were performed using a 64-slice LightSpeed VCT XTe GE scanner. SmartScore commercial software was used for calcium scoring. For CTCA, prospective gating was used with a commercially available protocol (SnapShot Pulse, GE Healthcare) and the following scanning parameters: slice acquisition 64 x 0.625 mm, smallest x-ray window, Z-coverage value of 20 mm with an increment of 20 mm, gantry rotation time of 350 ms, and a field of view of 25 cm. Subjects with a resting heart rate >60 beats per minute were given intravenous metoprolol 5 to 20 mg to achieve a heart rate of <60 beats per minute. In addition, all subjects received 2 doses of sublingual Glycerol trinitrate 400 µg. The coronary circulation was visualized using 90 mL of Ioversol (Optiray 350 mg I/mL, Covidien UK) contrast (flow rate of 6 mL/second), followed by 100 mL of 0.9% saline. A scout scan was performed, followed by a prospectively gated calcium score scan (gantry rotation time of 350 ms, 120 kV, and 150 mA) from the tracheal bifurcation to the diaphragm, choosing 5 to 7 scan blocks (field of view, 25 cm) and a prospectively gated CT coronary angiogram with tube voltage 80 to 100 kV adapted to body size and a tube current ranging from 500 to 600 mA. The CTCA images were reconstructed with slice thickness of 0.625 mm using a medium-soft tissue convolution kernel. All images were transferred to an external workstation (ADW 4.5, GE Healthcare) for analysis.

CAC scores were plotted against published percentiles for age- and sex-matched cohorts.²¹ Plaque morphology and degree of coronary luminal stenosis were assessed visually per established guidelines^{22,23} and independently verified by a cardiologist (K.F.) and radiologist (S.D.) with expertise in CTCA who were blinded to the subject's exercise history. An atherosclerotic plaque was defined as an irregularity causing any degree of luminal stenosis. Luminal stenoses were graded as <30%, 30% to 49%, 50% to 69%, and >70%. Significant coronary atherosclerosis was defined as a CAC >70th percentile or presence of a plaque associated with ≥50% luminal stenosis in a single coronary segment.

CMR Scan

CMR scans were performed using a 1.5T magnet (Avanto, Siemens Medical Solutions). Left ventricular (LV) and right ventricular function, chamber dimensions and volumes, and myocardial mass were assessed by cine steady-state free precession sequences. LGE images were obtained after the intravenous bolus injection of 0.1 mmol/Kg gadoterate meglumine (Dotarem) to identify regional fibrosis. Inversion times were adjusted to null normal myocardium, and LGE images were

phase swapped to exclude artifact where required. LGE was considered to represent focal myocardial fibrosis. Significant LGE was reported if it was in the compacted myocardium of the LV, excluding right ventricular insertion point LGE, right ventricular free wall LGE, and trabeculae or papillary muscle LGE because these are considered nonspecific and less reliable to interpret. Reporting required the agreement of 3 cardiologists with expertise in CMR (V.M. or S.R., and J.M.) blinded to the status of the participant.

Cardiopulmonary Exercise Test

Cardiopulmonary exercise testing was performed using an upright position with a COSMED E100w cycle ergometer with an incremental ramp protocol of 20 to 25 watts/minute. Subjects were encouraged to exercise to exhaustion. Continuous 12-lead EKG was performed in all subjects. Myocardial ischemia was defined as ≥−0.2 mV or horizontal or down sloping ST segment depression. Breath-by-breath gas exchange analysis was performed using a dedicated COSMED Quark CPEX metabolic cart as described previously.²⁴

Twenty-Four-Hour Holter Monitoring

Twenty-four-hour ambulatory EKG monitoring was performed using Lifecard CF Holters (Spacelabs Healthcare). Nonsustained ventricular tachycardia was defined as ≥3 consecutive broad complexes faster >120 beats per minute and supraventricular tachycardia as ≥5 consecutive regular narrow complexes >130 beats per minute.²⁵ Sinus pauses were defined as >2.5 seconds.²⁶

Statistical Analysis

Data are expressed as mean±standard deviation or n (%) as appropriate and analyzed using SPSS, version 22 (IBM). Continuous variables were tested for normality using a Shapiro-Wilk test. Group differences were tested with an independent sample *t* test or Mann-Whitney *U* test for normally and non-normally distributed variables, respectively. The Fishers exact test and the χ -squared test were used to assess categorical data. Given prior reports of sex differences in the cardiac implications of exercise,^{15,27,28} the cardiac CT, echocardiographic, and CMR data were analyzed in a sex-specific manner.

Among masters athletes, univariable analyses were performed to identify variables associated with significant CAD (defined as a CAC score >70th percentile or a coronary luminal stenosis >50%), including age, family history of coronary artery disease in the 5th to 7th decades, total serum cholesterol, serum high-density lipoprotein, systolic blood pressure stratified by sex, and years of exercise. A multivariable logistic regression model was constructed retaining all variables associated with CAD in the univariable analyses, including an interaction variable (compound of age and years of training).

RESULTS

Demographics and Exercise History

Athletes were 54.4±8.5 years of age; range 40 to 82 years (men=55.1±9.1 and women=53.1±7.1 years,

respectively); 70% were men and 92% were white. None of the participants reported a prior history of cigarette smoking. There were no significant differences between athletes and controls with respect to age, ethnicity, blood pressure, serum cholesterol, and Framingham 10-year CAD risk scores or a family history of CAD in the 5th to 7th decades, but controls had a higher body surface area compared with athletes (Table 1).

Athletes had participated in endurance exercise for an average of 31 ± 12.6 years. A broad range of athletic ability was apparent, ranging from recreational sports participants to previous national champions ($n=16$), world champions ($n=5$), and world record holders ($n=2$). The majority of athletes were runners who engaged in a combination of 10 k events, half marathons, and full marathons (77%), with a median of 13 marathon runs per athlete. Ten athletes had run >100 marathons. Cyclists comprised the remainder of the athlete group and competed in a median of 85 races each. Mean weekly training hours among athletes was 7.7 ± 3.5 hours, with a median of 7 hours. Controls exercised for 1.9 ± 0.5 hours per week, with a median of 1.5 hours. None of the controls had participated in prior endurance events, and none had exercised for >2.5 hours of moderate exercise per week.

Cardiac Structure and Function

Consistent with previous studies, athletes exhibited larger cardiac dimensions compared with controls. The mean end-diastolic LV volume on CMR was 14.6% and 14.1% higher in male and female athletes, respectively, compared with controls ($P<0.0001$). Both male and female athletes showed a 9.9% increase in maximal LV wall thickness compared with respective controls ($P<0.0001$). There were no differences in LV ejection fraction between athletes and controls, but athletes had a larger LV stroke volume, higher right ventricular ejection fraction, and superior indices of LV diastolic function (Table 2). Athletes also demonstrated significantly higher peak oxygen consumption compared with controls (43.3 ± 7.2 mL/minute/kg versus 29.9 ± 6.6 mL/minute/kg; $P<0.0001$), which translated to a predicted peak oxygen consumption of $138 \pm 20.4\%$ versus $96.5 \pm 17.6\%$ for age and size ($P<0.0001$).

CAC Score

The majority of athletes (52% male and 78% female) and controls (59% male and 68% female) had a normal CAC score (0 Agatston units), and only 25 (16%) athletes and 18 (19.5%) controls had a CAC >70 th percentile. Overall, there were no significant differences between athletes and controls with respect to

the proportion with CAC=0 or CAC >70 th percentile (Table 3). The median CAC score for both athletes and controls was zero.

When CAC scores were analyzed with respect to absolute values, male athletes revealed a higher prevalence of moderate to severely elevated coronary CAC scores ≥ 300 ; 12 (11.3%) male athletes had a CAC score ≥ 300 Agatston units versus none of the sedentary males ($P=0.009$). The median CAC score in male athletes with a CAC ≥ 1 was higher than in sedentary males with a CAC ≥ 1 (86 versus 3; $P=0.02$) (Figure 1). No differences in CAC scores were seen between athletic and sedentary females (Table 3).

Coronary Plaques and Luminal Irregularities or Stenoses

Male athletes had a higher prevalence of coronary plaques compared with sedentary males (47 [44%] versus 12 [22%]; $P=0.009$). Male athletes were also more likely to have multiple plaques compared with sedentary males (Figure 2a, Table 3) and multivessel plaques 21.7% versus 3.7% ($P=0.0024$). Coronary plaques (calcified or noncalcified) were equally prevalent in the main left coronary arteries among male athletes and sedentary men, but athletes showed a more diffuse distribution of irregularities throughout the coronary tree that were more common in the right coronary artery and first diagonal branch (Figure 2b). Sedentary men with plaques had relatively minor luminal narrowing ($<30\%$); however, 8 (7.5%) male athletes had a luminal stenosis $\geq 50\%$ compared with none of the male controls ($P=0.05$) (Figure 2c). Male runners ($n=82$) and cyclists ($n=24$) did not differ with respect to CAC >0 (50% versus 42%), CAC >100 Agatston units (17% versus 25%), CAC >70 th percentile (16% versus 13%), or a luminal stenosis $\geq 50\%$ (8.5% versus 4.2%).

There were no differences in CAC or the number of plaques between female athletes and their relatively sedentary counterparts (Table 3).

Coronary Plaque Morphology

Overall, 125 plaques were observed in the 106 male athletes and 54 male controls. The majority of plaques were calcific (80 [64%]), 39 (31.2%) were of mixed morphology, and 6 (4.8%) were noncalcified. Purely calcified plaques were more common in male athletes compared with sedentary males (72 [72.7%] versus 8 [30.8%]; $P=0.0002$), whereas sedentary males had a higher prevalence of mixed morphology plaques (16 [61.5%] versus 23 [23.2%]; $P=0.0006$). No differences in plaque morphology were discovered between athletic and sedentary females (Figure 3).

Table 1. Demographics and Arrhythmia Profile in Controls and Masters Athletes

Demographics	Men			Women		
	Controls	Athletes	P Value	Controls	Athletes	P Value
N	54	106		38	46	
Age, y	52.5 (8.4, 41–71)	55.1 (9.1, 40–82)	0.08	54.2 (9.6, 40–77)	53.1 (7.1, 40–71)	0.54
Height, cm	178.6 (6.5, 163.5–192)	177.4 (7.1, 151–194)	0.35	163.2 (7.1, 145–179)	164.9 (5.4, 154–179)	0.21
Weight, kg	83.7 (13.0, 57.9–109)	72.9 (8.4, 54–97)	<0.0001	65.1 (12.2, 44–99)	58.4 (9.7, 47–103)	0.004
Body surface area, m ²	2.02 (0.17, 1.8–2.1)	1.9 (0.12, 1.8–2)	<0.0001	1.71 (0.18, 1.5–2)	1.62 (0.12, 1.4–1.8)	0.005
White, n (%)	49 (91)	99 (93)	0.54	31 (82)	44 (96)	0.07
CAD Framingham Risk Score, %	4.29 (2.96, 0.04–13.7)	4.33 (3.3, 0.6–19)	0.9	1.74 (1.27, 0.4–5.1)	1.32 (0.79, 0.09–3.6)	0.08
Systolic blood pressure, mmHg	124.2 (7.3, 112–138)	126.8 (9.4, 103–139)	0.1	122.7 (10.3, 98–139)	123.0 (11.7, 94–139)	0.9
Diastolic blood pressure, mmHg	78.8 (6.0, 63–94)	79.4 (7.1, 61–99)	0.56	77.3 (8.0, 52–91)	75.9 (8.3, 57–89)	0.45
Total cholesterol, mmol/L	4.49 (0.3, 4–5)	4.57 (0.42, 4–5)	0.29	4.37 (0.43, 4–5)	4.47 (0.41, 4–5)	0.3
LDL cholesterol, mmol/L	2.9 (0.3, 1.7–3.2)	2.9 (0.4, 1.6–3.1)	0.92	2.9 (0.3, 2.2–3.2)	2.8 (0.3, 2.1–3.1)	0.23
Active or former smokers, n (%)	0 (0)	0 (0)	1	0 (0)	0 (0)	1
Family history of CAD (>40 years of age)	13 (24.1%)	16 (15.1%)	0.19	11 (28.9%)	10 (21.7%)	0.46
Hours exercise per week	1.9 (0.3, 1.6–2.5)	7.5 (3.8, 4–20)	<0.0001	1.9 (0.4, 1.5–2.5)	7.7 (2.9, 4–15)	<0.0001
Years of endurance exercise	—	33.4 (12.9, 10–47)			26.1 (10.9, 10–30)	
VO ₂ max, ml/min/kg	30.9 (6.14, 22.7–42.9)	44.4 (7.0, 26.6–64.2)	<0.0001	24.5 (5.4, 12.3–37)	40.4 (7.3, 27.9–55.6)	<0.0001
VO ₂ max, % predicted	95.5 (17.0, 69–129)	132.9 (16.2, 106–188)	<0.0001	97.5 (19.4, 51–133)	150.7 (25.0, 106–208)	<0.0001
24-hg EKG, n (%)						
Atrial fibrillation	0 (0)	7 (6.6)	0.1	0 (0)	0 (0)	1
Supraventricular tachycardia	2 (3.7)	12 (11.3)	0.14	2 (5.3)	5 (10.9)	0.45
Nonsustained ventricular tachycardia	0 (0)	10 (9.4)	0.02	0 (0)	1 (2.2)	1
Sinus pauses (≥2.5 s)	0 (0%)	11 (10.4%)	0.02	0 (0%)	0 (0%)	1

Values in parentheses indicate SD and range. CAD indicates coronary artery disease; and LDL, low-density lipoprotein.

Relationship Between Exercise Volume and Significant Atherosclerosis

We investigated the relationship between exercise dose and significant coronary calcification in males by comparing the number of males with a CAC >70th percentile in 4 arbitrary groups: (1) sedentary males, (2) males who ran <25 miles per week or cycled ≤100 km (62 miles) per week, (3) males who ran 25 to 35 miles per week or cycled 100 to 150 km per week (67–93 miles per week), and (4) males who ran >35 miles per week or cycled >150 km (93 miles) per week and failed to find a significant relationship between exercise dose and CAC >70th percentile ($P=0.26$).

Determinants of Significant CAD

Risk factors for significant CAD among male athletes in univariable analyses included age (odds ratio, 1.058; 95% confidence interval, 1.058–1.116; $P=0.039$) and years of training (odds ratio, 1.063; 95% confidence interval, 1.017–1.110; $P=0.006$). Multivariable analysis revealed that years of training was the only indepen-

dent variable for significant CAD in the athletic men (odds ratio, 1.080; 95% confidence interval, 1.014–1.149; $P=0.016$).

Myocardial Fibrosis

Significant CMR LGE was observed in 15 (14.2%) male athletes compared with none of the male controls ($P=0.004$). The distribution of fibrosis is shown in Figure 4. Seven (6.6%) male athletes showed subendocardial LGE (consistent with myocardial infarction), 5 (4.7%) had a midmyocardial distribution, and 3 (2.8%) had an epicardial distribution. Of the 7 athletic males with evident myocardial infarction, 3 (42.8%) showed significant CAD (≥50% luminal stenosis) in the left anterior descending artery with corresponding myocardial infarction in the anterior wall. However, 4 had normal coronary arteries. No relationship was found between myocardial fibrosis and exercise intensity, years of training, or number of competitions. Only 1 female athlete had CMR LGE compared with none of the female controls, which was subendocardial distribution in the presence of normal coronary arteries.

Table 2. Cardiac Structure and Function in Controls and Masters Athletes

	Men			Women		
	Controls	Athletes	P Value	Controls	Athletes	P Value
Echocardiography						
N	54	106		38	46	
Aortic sinus, mm	33.7 (4.4)	33.2 (3.6)	0.4	29.0 (8.2)	29.6 (3.2)	0.37
Left atrial diameter, mm	36.0 (4.4)	38.2 (5.3)	0.002	32.9 (4.8)	33.8 (4.2)	0.31
LVIDd, mm	48.4 (5.0)	50.0 (5.1)	0.047	45.1 (4.2)	45.4 (4.1)	0.73
IVSd, mm	9.5 (1.3)	10.4 (1.4)	<0.0001	8.2 (1.2)	9.1 (1.3)	0.001
Right ventricular outflow tract, mm	33.0 (3.3)	36.1 (5.2)	<0.0001	30.2 (3.1)	31.9 (4.1)	0.05
Right ventricular basal diameter, mm	40.1 (6.5)	47.1 (6.4)	<0.0001	35.1 (7.7)	42.6 (8.5)	<0.0001
Left ventricular ejection fraction, %	62.3 (6.1)	62.0 (7.7)	0.85	61.3 (6.5)	65.5 (7.5)	0.023
E/E' average	6.6 (1.7)	6.5 (1.6)	0.71	7.8 (2.0)	6.2 (1.2)	0.002
Pulmonary artery pressure, mmHg	18.8 (4.2)	20.8 (7.9)	0.35	16.5 (4.4)	19.9 (6.4)	0.02
TAPSE, mm	22.3 (3.6)	26.2 (5.0)	<0.0001	22.9 (3.5)	26.0 (4.7)	0.001
Cardiovascular MRI						
Left ventricular end diastolic volume, ml	145.7 (28.6)	166.9 (30.2)	<0.0001	115.2 (14.6)	131.4 (19.2)	<0.0001
Stroke volume, ml	97.5 (20.3)	110.1 (20.3)	0.001	79.0 (9.0)	92.3 (3.2)	<0.0001
Left ventricular ejection fraction, %	67.5 (5.4)	66.4 (5.7)	0.31	68.6 (4.2)	70.6 (4.9)	0.06
Cardiac mass, g	133 (27.6)	161.7 (27.2)	<0.0001	100.5 (20.4)	110.02 (18.5)	0.034
Right ventricular ejection fraction, %	65.3 (1.7)	72.4 (6.5)	0.029	63 (3.5)	75.9 (5.6)	<0.0001
Left atrial area, cm ²	22.2 (4.7)	26.9 (4.4)	<0.0001	19.4 (4.3)	24.7 (3.5)	<0.0001
Right atrial area, cm ²	23.8 (5.7)	29.5 (5.7)	<0.0001	19.0 (3.7)	23.8 (4.9)	<0.0001
Fibrosis (LGE), n (%)	0 (0)	15 (14.2)	0.004	0 (0)	1 (2.2)	1

Values in parentheses indicate standard deviation. EDV indicates end diastolic volume; IVSd, interventricular septal thickness in diastole; LGE, late gadolinium enhancement; LV, left ventricular; LVIDd, left ventricular internal diameter end diastole; and MRI, magnetic resonance imaging.

Ten (9.4%) male athletes showed a single burst of nonsustained ventricular tachycardia ranging from 5 to 11 beats compared with none of the sedentary males. Of these, 3 had a subendocardial (myocardial infarction) pattern of LGE affecting the anterior wall, and all 3 revealed $\geq 50\%$ stenosis in the left anterior descending artery. Nonsustained ventricular tachycardia was detected in just 1 female athlete who had a normal CAC, no evidence of luminal stenosis on CT coronary angiography, and no evidence of LGE on CMR.

DISCUSSION

Habitual moderate physical activity is associated with fewer cardiac events. It is assumed that the lower risk of CAD in physically active individuals is through the control of acquired risk factors for atherosclerosis. Ultra-endurance athletes have also been reported to have a greater vasodilatory capacity compared with sedentary individuals.²⁹ In contrast, 3 previous studies have shown a higher burden of atherosclerosis in endurance athletes compared with controls,^{8–10} raising concerns that prodigious amounts of exercise may actually accelerate the coronary atherosclerotic process. These studies included athletes with established risk factors for CAD or could not ex-

clude the possibility that many of them had adopted an active lifestyle in middle age and had higher risk factors during most of their lives. Our study of lifelong masters athletes without conventional risk factors for CAD and a mean Framingham risk score of 3.4% demonstrated that most (61%) athletes showed no evidence of CAD. Also no significant differences were discovered between the athletes and controls with respect to the number of individuals with completely normal calcium scores. The number of male athletes with a CAC=0 in this study was significantly higher than in a previous study from Germany of 108 middle-age marathon runners of similar age but higher risk profile⁸ and slightly higher than a Dutch study of 318 asymptomatic athletic men with a generally low risk profile where 37% were former or current smokers.¹⁰ The percentage of male athletes with a CAC >100 Agatston units was also lower in our study compared with the German marathon runners (18.9% versus 36.1%).⁸ These observations suggest that the higher coronary calcium scores in previous studies likely reflected a higher atherosclerotic risk profile rather than a potentially deleterious exercise effect.

However, compared with sedentary men of similar age and a similarly low atherosclerotic risk profile, athletic males in this study had a higher prevalence of high

Table 3. Coronary Artery Calcium Score and Computerized Tomographic Coronary Angiography Results in Masters Athletes and Controls

Parameter	Men			Women		
	Controls	Athletes	P Value	Controls	Athletes	P Value
N	54	106		38	46	
Overall median CAC score	0	0	1	0	0	1
Median CAC score in individuals with coronary calcium	3	86	0.02	7	7	0.67
>50th percentile	12 (22.2)	29 (27.4)	0.57	12 (31.6)	10 (21.7)	0.53
>70th percentile	8 (14.8)	16 (15.1)	0.5	10 (26.4)	9 (19.6)	0.79
CAC >0 Agatston units	22 (40.7)	51 (48.1)	0.4	12 (31.6)	10 (21.7)	0.33
CAC >10 Agatston units	10 (18.5)	44 (41.5)	0.0045	8 (21)	5 (10.9)	0.24
CAC ≥100 Agatston units	4 (7.4)	20 (18.9)	0.06	4 (10.5)	3 (6.5)	0.62
CAC ≥300 Agatston units	0 (0)	12 (11.3)	0.009	2 (5.2)	2 (4.3)	1
CAC ≥400 Agatston units	0 (0)	8 (7.5)	0.05	1 (2.6)	1 (2.2)	1
≥1 plaque	12 (22.2)	47 (44.3)	0.009	8 (21.1)	7 (15.2)	0.57
≥2 plaques	2 (3.7)	25 (23.6)	0.0014	2 (5.3)	3 (6.5)	1
≥2 vessels with plaques	2 (3.7)	23 (21.7)	0.0024	2 (5.3)	2 (4.3)	1
>50% luminal stenosis	0 (0)	8 (7.5)	0.05	0 (0)	0 (0)	1
Vessel wall calcification without luminal stenosis	10 (19.2)	4 (3.8)	0.005	4 (10.5)	3 (6.5)	0.7

Values are n (%). CAC indicates coronary artery calcium.

(≥300 Agatston units) CAC scores (11.3% versus 0%), a greater number of atherosclerotic plaques (44.3% versus 22.2%), including multivessel plaques, and a greater proportion showed coronary luminal narrowing ≥50% (7.5% versus 0%).

Possible Mechanisms for Increased Coronary Plaque Burden in Masters Athletes

The precise mechanisms for these observations in masters athletes are unknown. Endothelial damage from increased shear stress forces during exercise because of a hyperdynamic coronary circulation, mechanical bending of the coronary arteries during vigorous cardiac contraction, exercise-induced spasm of the coronary arteries producing nonlaminar flow, exercise-associated hypertension, generation of oxidative free radicals,³⁰ and a systemic inflammatory response from repeated bouts of intensive exercise³¹ have been suggested as possible factors. It is also conceivable that acutely high parathyroid hormone concentrations produced by exercise may accelerate coronary calcification in masters athletes.³² The absence of increased CAD in female athletes has also been reported in a recent smaller study²⁷ and may be attributable to the protective effect of estrogens or the fact that atherosclerosis in general appears in females older than the female athletes assessed in this study.^{33,34} Female athletes were 2 years younger than male athletes, whereas CAD generally occurs 10 years later in females compared with males.²⁸

Differences in Plaque Composition Between Male Masters Athletes and Controls

Although male athletes had a higher burden of coronary plaques compared with male controls, the morphology

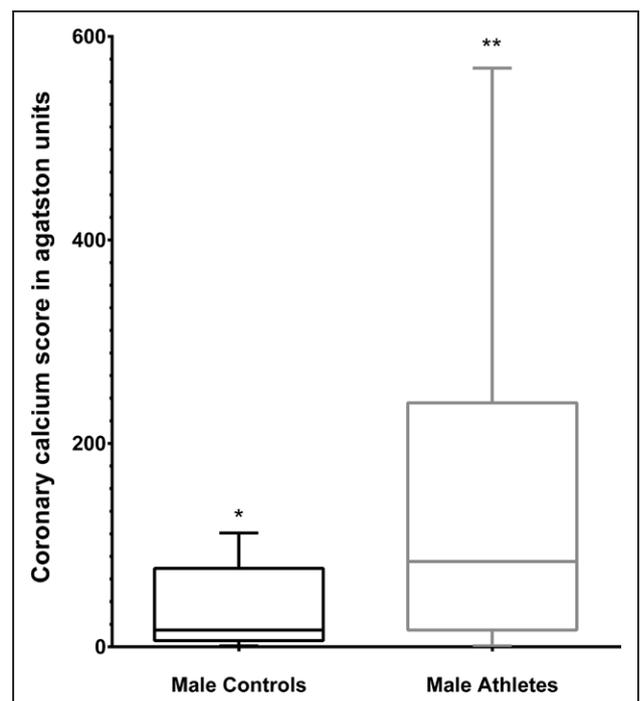


Figure 1. Tukey Box-and-whisker plot of coronary artery calcium (CAC) scores in male athletes and relatively sedentary healthy males with CAC ≥1 Agatston units. *Control outliers 226 to 570. **Athlete outliers 723 to 3422.

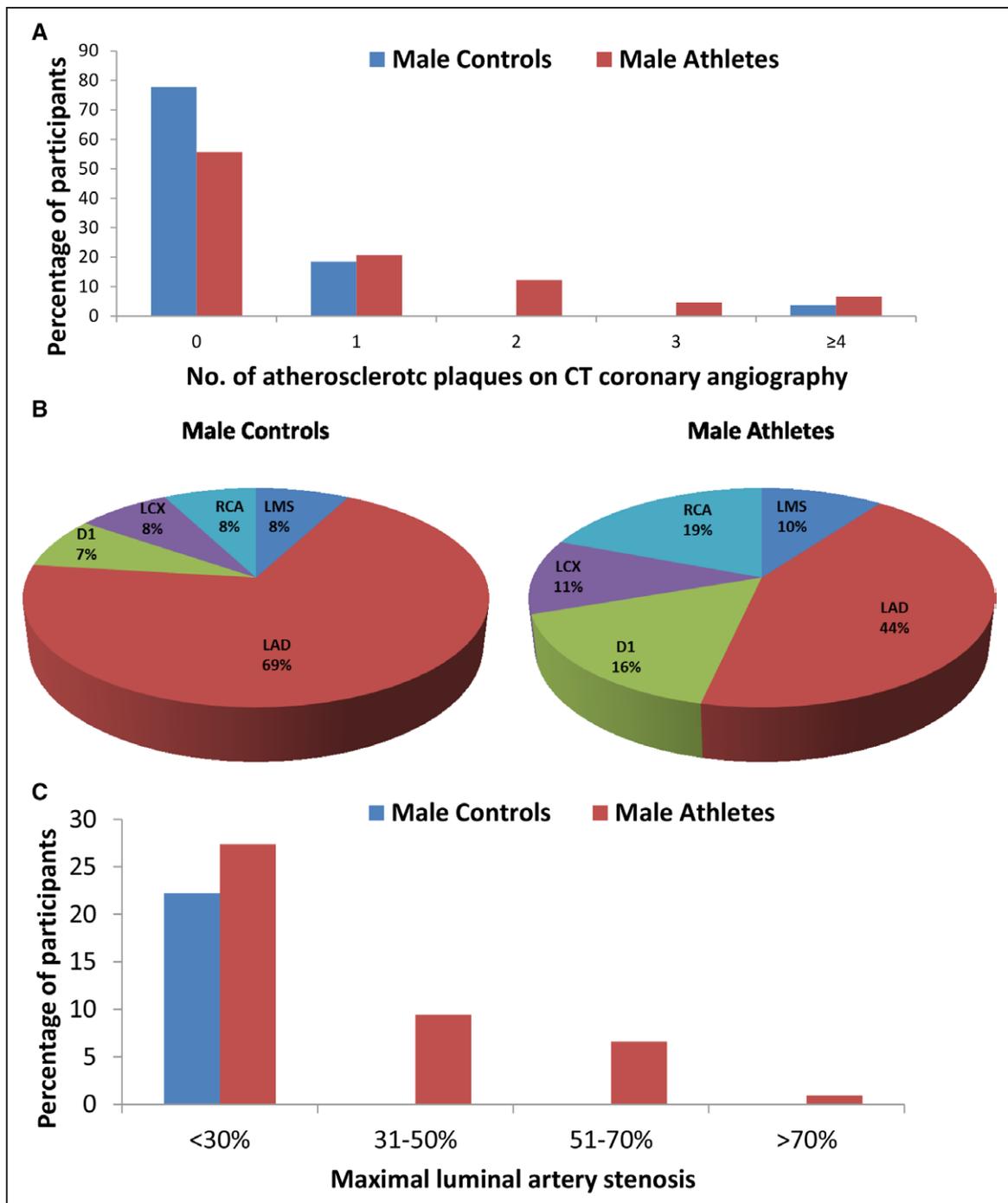


Figure 2. Coronary plaques and luminal stenoses artery in male athletes and relatively sedentary healthy males.

A, Number of atherosclerotic plaques observed on computerized tomographic (CT) angiography in male athletes and relatively sedentary males. **B**, Distribution of coronary plaques in athletic men (99 coronary plaques) and relatively sedentary males (26 coronary plaques). **C**, Luminal stenoses in male athletes and sedentary males.

of these plaques was predominantly calcific. The only other study to examine coronary plaque morphology in marathon runners showed a high prevalence of both calcified and noncalcified plaques among runners compared with nonrunners; however, >50% of the runners had ≥ 1 risk factor for atherosclerosis.⁹ Calcified plaques

are considered stable, less prone to rupture, and associated with a lower risk of adverse coronary events, including mortality.^{35,36} In contrast, mixed morphology plaques, which were more common in sedentary men and a previous study of runners with risk factors for CAD, are lipid rich and more vulnerable to fissur-

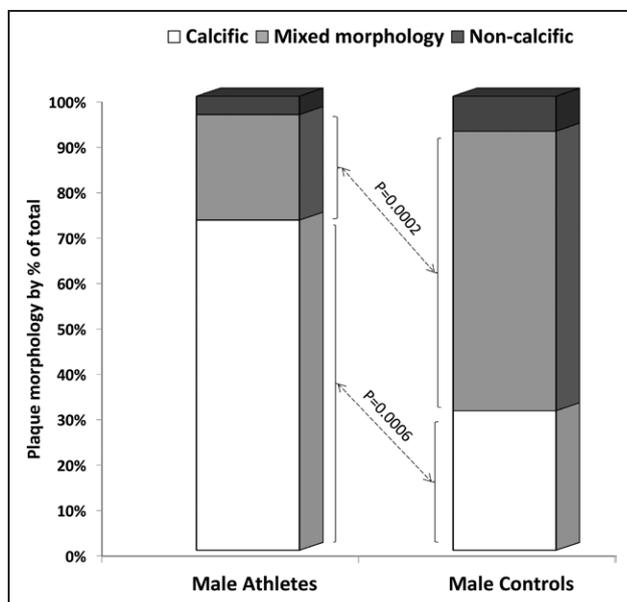


Figure 3. Plaque morphology in male athletes (99 coronary plaques) and relatively sedentary males (26 coronary plaques).

ing and subsequent thrombosis. These differences in plaque morphology suggest that the pathophysiology of arteriosclerosis in athletes may differ from relatively

sedentary individuals. It has previously been shown that among individuals with subclinical CAD (CAC >100 Agatston units), a high degree of fitness reduces the risk of adverse cardiac events by 75%,³⁷ and it is possible that the higher coronary plaque burden in lifelong endurance athletes may be partly mitigated by the stable nature of their more calcified plaques and could explain the overall low risk of myocardial infarction in established marathon runners.³⁸

Although it is plausible that calcific plaques in masters athletes protect from acute myocardial infarction because of plaque rupture, the same stable calcified plaques may cause sufficient coronary stenosis and demand ischemia to produce myocardial scarring and fatal arrhythmias in some athletes. Consistent with this possibility is the observation of myocardial fibrosis compatible with a CAD pattern and nonsustained ventricular tachycardia in 3 of 8 (37.5%) male masters athletes with a luminal stenosis $\geq 50\%$. However, 4 (60%) male athletes with a CAD pattern of fibrosis and 7 (70%) with nonsustained ventricular tachycardia showed normal coronary arteries, suggesting that nonatherosclerotic mechanisms such as coronary spasm, increased thrombogenicity,^{39,40} coronary embolic or myocarditis may also contribute to myocardial scarring or ventricular arrhythmias in male athletes engaged in lifelong endurance sports.

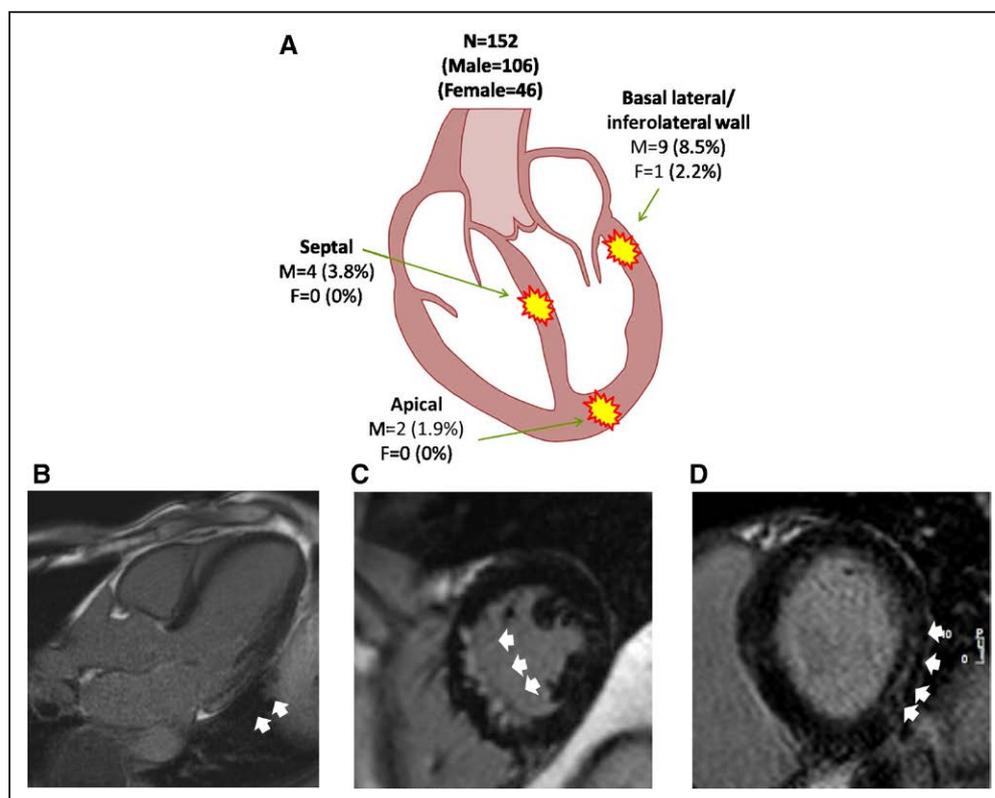


Figure 4. Myocardial fibrosis in athletes demonstrated by late gadolinium enhancement on cardiovascular magnetic resonance.

A, Distribution of fibrosis. **B**, Subepicardial scar in a 61-year-old male athlete. **C**, Subendocardial scar in a 73-year-old runner. **D**, Basolateral mid-wall fibrosis in a 52-year-old male athlete. M indicates males; and F, females.

Relationship Between Exercise Dose and Coronary Calcification

The dose-response relationship between exercise and cardiovascular health has generated scientific and lay interest because increasing numbers of individuals have trained for and engaged in multiple endurance events. The Copenhagen study reported a U-shaped relationship between running dose and all-cause mortality. Light and moderate joggers had lower all-cause mortality compared with sedentary nonjoggers, whereas strenuous joggers who exercised ≈ 4 times more than the current recommendations for healthy physical activity exhibited mortality rates similar to sedentary individuals.⁵ This study had few mortal events ($n=2$) among the most active participants and did not provide the precise cause of death. A 9-year prospective study of >1 million British women showed that women engaging in daily strenuous physical activity had a higher risk of CAD compared with women performing strenuous physical activity 2 to 3 times per week. However, 25% of strenuously exercising women were smokers compared with 14% to 16% of women performing less exercise, which may provide a partial explanation for these findings.⁴¹ In contrast, the data from the Henry Ford exercise testing project (The Fit study) showed that middle-age individuals capable of exercising to strenuous workloads ≥ 14 METS ($n=1900$) showed a 60% reduction in all-cause mortality compared with the reference group exercising at a workload (10–11 METS) conventionally considered to be associated with maximal benefit.⁴² Similarly, a meta-analysis of population studies comprising $>650\,000$ men and women with a median age of 62 years (range 21–92) revealed that exercising ≤ 10 times above the recommended physical activity levels was not associated with increased mortality compared with individuals exercising in accordance with current recommendations.⁴³ Although our study was not designed to measure outcomes, we could not demonstrate a relationship between the dose of exercise and coronary atherosclerosis even among males who cumulatively managed mileage >1 marathon per week. We were also unable to show any relationship between exercise duration and intensity and myocardial fibrosis.

Limitations

As far as the authors are aware, this is the first large study to investigate subclinical CAD in a large cohort of athletes of both sexes with an otherwise low risk profile for atherosclerosis. However, several inherent limitations warrant mention. This study was not entirely homogenous with respect to sex and included only 30% females, which may have reduced the power of detecting any significant differences between female athletes

and respective controls. The age range of our women also suggests that probably many were not menopausal and may have been protected from atherosclerosis. We cannot exclude the possibility that presumably healthy runners were attracted to this study because they had sensed some nonspecific alteration in exercise level or that some athletes did not fully disclose prior historical risk factors for CAD, such as an unhealthy diet or an unfavourable family history, which might have resulted in engagement in high-endurance exercise. Diet is a potential confounder but does not feature in current conventional risk stratification models such as the Framingham CAD score. Although all our athletes denied the use of illicit performance-enhancing drugs capable of accelerating atherosclerosis, we did not perform any laboratory investigations to exclude this possibility.

Multiple parameters were tested, and we did not adjust for multiple testing; thus, our significant findings should be considered exploratory. It is important to note that the study's cross-sectional design does not allow for any definitive causation effect between exercise and CAD or the potential downstream effects of CAD, such as myocardial fibrosis and arrhythmias. Long-term studies reporting cardiac events are not yet available in masters athletes. Although our study revealed a higher coronary plaque burden and subclinical myocardial infarction in men engaged in lifelong endurance athletes, our findings cannot necessarily be considered to reflect increased event rates in this cohort in the future.

CONCLUSION

The majority (60%) of middle-age lifelong masters endurance athletes with a low atherosclerotic risk profile had no CAC. A proportion of male athletes without preexisting risk factors for CAD revealed higher CAC scores and a greater number of atherosclerotic coronary plaques compared with healthy but relatively sedentary counterparts. The precise significance of these observations is uncertain, but differences in plaque morphology between male athletes and sedentary men indicate different pathophysiological mechanisms for arteriosclerosis. Whereas higher CAC scores and greater coronary plaques in athletic men may be interpreted as a deleterious effect of exercise on the coronary arteries, the calcific and stable nature of the plaques among athletic men may also be considered as protective against plaque rupture and acute myocardial infarction. Additional studies are required in larger cohorts to clarify the mechanisms and clinical relevance of our findings.

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DISCLOSURES

None.

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FOOTNOTES

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Prevalence of Subclinical Coronary Artery Disease in Masters Endurance Athletes With a Low Atherosclerotic Risk Profile

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Supplementary figure 1: Schematic flow diagram illustrating the recruitment of master athletes and controls.

