

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

Running Title: *Merghani et al.; Coronary Disease in Master Endurance Athletes*

Ahmed Merghani, MRCP¹; Viviana Maestrini, PhD^{2,3}; Stefania Rosmini, MRCP⁴;
Andrew T. Cox, MRCP¹; Harshil Dhutia, MRCP¹; Rachel Bastiaenan, PhD¹;
Sarojini David, MRCP⁴; Tee Joo Yeo, MD⁵; Rajay Narain, MRCP¹; Aneil Malhotra, MRCP¹;
Michael Papadakis, MD¹; Mathew G. Wilson, PhD⁶; Maite Tome, MD¹; Khaled AlFakih, MD³;
James C. Moon, MD²; Sanjay Sharma, MD¹

¹Department of Cardiovascular Sciences, St. George's, University of London, London, United Kingdom; ²The Barts Heart Centre, University College London, London, United Kingdom;

³Department of Cardiovascular, Respiratory, Geriatric, Anesthesiologic and Nephrologic Sciences, Sapienza University of Rome, Rome, Italy; ⁴University Hospital Lewisham, London, United Kingdom; ⁵National University Heart Centre, Singapore;

⁶Orthopaedic and Sports Medicine Hospital, Aspetar, Qatar

Address for Correspondence:

Sanjay Sharma, MD
Cardiology Clinical and Academic Group
St. George's, University of London
St. George's University Hospital
NHS Foundation Trust
Cranmer Terrace
London SW17 0RE, United Kingdom
Tel +44 208 7255939
Fax +442082979100
Email sasharma@sgul.ac.uk

Abstract

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

Methods—We assessed 152 masters athletes aged 54.4 ± 8.5 years (70% male) and 92 controls of similar age, sex and low Framingham 10 year CAD risk scores with an echocardiogram, exercise stress test, CT coronary angiogram, and cardiovascular magnetic resonance imaging (CMRI) with late gadolinium enhancement (LGE) 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% vs 22.2%; $p=0.009$) compared with sedentary males and only male athletes showed a $CAC \geq 300$ Agatston units (AU) (11.3%), and a luminal stenosis $\geq 50\%$ (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 $CAC > 70^{\text{th}}$ percentile for age and/or luminal stenosis $\geq 50\%$ in male athletes: OR 1.08 (95% CI 1.01-1.15); $p=0.016$. 15 (14%) male athletes but none of the controls revealed LGE on CMRI. Of these, 7 had a pattern consistent with previous myocardial infarction including 3 (42%) with a luminal stenosis $\geq 50\%$ 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 AU 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. Whereas coronary plaques are more abundant in athletes, their stable nature could mitigate the risk of plaque rupture and acute myocardial infarction.

Key Words: atherosclerosis; myocardial fibrosis; arrhythmia; Masters Athletes, Endurance exercise, coronary calcification

Clinical Perspective

What is new?

- Although overall CAC prevalence was similar between masters athletes and health sedentary controls, male athletes were more likely to have very high CAC 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.
- While 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^{3,4,5,6}. In contrast, some athletes engage in several hours of intensive training per day, exceeding the daily recommendations by 10-15 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 aged and older (masters) athletes who have exercised intensely since youth and who constitute an increasing proportion of participants in endurance events⁷. While ostensibly fit and healthy, several studies have reported high coronary artery calcium (CAC) scores^{8,9,10} 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 master athletes^{12,13,14,15,16}. However, existing studies are limited by small sample sizes, focus on men only,^{8,9,10,11,12} and inclusion of athletes with risk factors for atherosclerosis^{8,9,10,11,12}. Only one of these major studies has demonstrated increased atherosclerosis in the athletes after adjusting for their lower Framingham risk scores⁸, therefore further studies are essential to address the controversy¹⁷. 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 UK through an advertisement placed in a popular athletic magazine¹⁸. 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 90mmHg), hypercholesterolemia ($>$ 5.18mmol/l), and active or former smokers.

Master athletes were defined as aged $>$ 40 years, who ran \geq 10 miles or cycled \geq 30 miles per week and have continued to do so for at least 10 years and had competed in a minimum of 10 endurance events including marathons (26.2miles; 42.2km), half marathons (13.1miles; 21.1km), 10km races, or endurance cycling races ranging from 41.1 miles to 161.5miles; 66 to 260km) over a 10 year period. Participants who responded to the advertisements by email or telephone were sent a copy of the participant information leaflet and invited to attend for preliminary screening tests prior to recruitment.

Healthy controls were recruited through advertisements placed in email staff bulletins at three 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; 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 electrocardiogram (EKG) and biochemical tests including a fasting blood glucose level and serum lipid profile.

Health questionnaires inquired about demographics, cardiac symptoms, medical, smoking, family history of cardiac disease and exercise history. The exercise history included the 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.

82 (35%) athletes and 110 (54.4%) controls were excluded due to the presence of established risk factors for CAD (Supplementary figure 1). The final cohort consisted of 152 athletes and 92 relatively sedentary healthy controls and all underwent echocardiography, cardiopulmonary exercise stress test, 24-hour Holter, CT coronary angiogram, and cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE).

Transthoracic echocardiography

Two dimensional echocardiography was performed using a Philips iE33 echocardiographic machine (Amsterdam, The Netherlands). Standard views were obtained to measure wall thickness and cavity size. Doppler measurements were performed in accordance with published recommendations²⁰.

Computerized tomographic (CT) coronary angiography (CTCA)

Computerised tomographic calcium scoring and CTCA were performed using a 64 slice LightSpeed VCT XTe GE scanner (GE Healthcare, Milwaukee. US). SmartScore commercial software (GE Healthcare, Milwaukee. US) was used for calcium scoring. For CTCA,

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

Coronary artery calcium(CAC) scores were plotted against published percentiles for age and sex matched cohorts²¹. Plaque morphology, and degree of coronary luminal stenosis were assessed visually as per established guidelines^{22,23} and independently verified by a cardiologist (KF) and radiologist (SD) 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%, 30-49%, 50-69% and > 70%. Significant coronary atherosclerosis was defined as a CAC >70th percentile and/or the presence of a plaque associated with \geq 50% luminal stenosis in a single coronary segment.

Cardiovascular Magnetic Resonance Scan

Cardiovascular magnetic resonance scans were performed using a 1.5T magnet (Avanto, Siemens Medical Solutions). Left and right ventricular function, chamber dimensions and volumes and myocardial mass were assessed by cine steady-state free precession sequences. Late gadolinium enhancement (LGE) images were obtained after the intravenous bolus injection of 0.1mmol/Kg gadoterate meglumine (Dotarem; Guerbet, Paris, France) to identify regional fibrosis. Inversion times were adjusted to null normal myocardium and LGE images were phase swapped to exclude artefact 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 non-specific and less reliable to interpret. Reporting required the agreement of 3 cardiologists with expertise in CMR (VM or SR, and JM) blinded to the status of the participant.

Cardiopulmonary exercise test

Cardio-pulmonary exercise testing was performed using an upright position with a COSMED E100w cycle ergometer (Rome, Italy) with an incremental ramp protocol of 20-25 Watts/minute. Subjects were encouraged to exercise to exhaustion. Continuous 12-lead EKG was performed in all subjects. Myocardial ischaemia 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 (Rome, Italy) as described previously²⁴.

Twenty-Four Hour Holter Monitoring

Twenty-four hour ambulatory EKG monitoring was performed using Lifecard CF Holters (Spacelabs Healthcare, USA). Non-sustained ventricular tachycardia was defined as ≥ 3

consecutive broad complexes faster >120bpm and supraventricular tachycardia as ≥ 5 consecutive regular narrow complexes >130 bpm.²⁵ Sinus pauses were defined as > 2.5 seconds²⁶.

Statistical Analysis

Data are expressed as mean \pm standard deviation (SD), or n (%) as appropriate and analysed using SPSS, version 22, (IBM, Chicago, IL). 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 chi 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 analysed 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 fifth to seventh decade, total serum cholesterol, serum HDL, 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 aged 54.4 \pm 8.5 years; range 40-82 years (men=55.1 \pm 9.1 and women=53.1 \pm 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-7th decades but controls had a higher body surface area compared to athletes (Table 1).

Athletes had participated in endurance exercise for an average of 31 ± 12.6 years. There was a broad range of athletic ability 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 10k 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 h 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 more than 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 left ventricular (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 to controls (43.3 ± 7.2 ml/min/kg v

29.9 ± 6.6 ml/min/kg; $p < 0.0001$) which translated to a predicted peak oxygen consumption of $138 \pm 20.4\%$ v $96.5 \pm 17.6\%$ for age and size ($p < 0.0001$).

Coronary calcium score

The majority of athletes (52% male and 78% female) and controls (59% male and 68% female) had a normal coronary artery calcium score (CAC=0 Agatston units) and only 25 (16%) athletes and 18 (19.5%) controls had a CAC > 70th percentile. Overall there were no significant differences between athletes and controls with respect to the proportion with CAC = 0 or CAC > 70th percentile (Table 3). The median CAC score for both athletes and controls was zero.

When CAC scores were analysed 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 vs 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 v 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%) v 12(22%); $p=0.009$]. Male athletes were also more likely to have multiple plaques compared with sedentary males (Figure 2 a, Table 3) and multi-vessel plaques 21.7% v 3.7% ($p=0.0024$). Coronary plaques (calcified or non-calcified) 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 to 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% v 42%), $CAC > 100$ Agatston units (17% v 25%), $CAC > 70^{\text{th}}$ percentile (16% v 13%) or a luminal stenosis $\geq 50\%$ (8.5% v 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, there were 125 plaques 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 non-calcified. Purely calcified plaques were more common in male athletes compared with sedentary males [72(72.7%) vs 8(30.8%); $p=0.0002$] whereas sedentary males had a higher prevalence of mixed morphology plaques [16(61.5%) vs 23(23.2%); $p=0.0006$].

There were no differences in plaque morphology between athletic and sedentary females (Figure 3).

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 $CAC >70^{\text{th}}$ percentile in 4 arbitrary groups: (i) sedentary males; (ii) males who ran < 25 miles per week or cycled $\leq 100\text{km}$ (62 miles) per week, (iii) males who ran 25-35 miles per week or cycled between 100-150 km per week (67-93 miles per week) and (iv) males who ran > 35 miles per week or cycled $>150\text{km}$ (93 miles) per week and failed to find a significant relationship between exercise dose and $CAC > 70^{\text{th}}$ percentile ($p =0.26$).

Determinants of significant coronary artery disease

Risk factors for significant CAD among male athletes in univariable analyses included age [OR 1.058 (IC 95% 1.058-1.116); $p=0.039$] and years of training [1.063 (IC95% 1.017-1.110); $p=0.006$]. Multivariable analysis revealed that years of training was the only independent variable for significant CAD in the athletic men [OR 1.080 (IC95% 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 ($\geq 50\%$ luminal stenosis) in the left anterior descending artery with corresponding myocardial infarction in the anterior wall. However, 4 had normal coronary arteries. There was no relationship between myocardial fibrosis and exercise intensity, years of training or number of competitions. Only one female athlete had CMR LGE compared to none of the female controls which, was subendocardial distribution in the presence of normal coronary arteries.

Ten (9.4%) male athletes showed a single burst of non-sustained ventricular tachycardia ranging from 5-11 beats compared to 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. Non sustained VT was detected in just one female athlete who had a normal CAC, no evidence of luminal stenosis on CT coronary angiography or 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 to sedentary individuals²⁹. In contrast, three previous studies have shown a higher burden of atherosclerosis in endurance athletes compared to controls^{8,9,10} 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 exclude the possibility that many of them had adopted an active life style in middle age and had higher risk factors during most of their lives. Our study in life-long 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, there were no significant differences 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 profile)⁸ and slightly higher than a Dutch study of 318 asymptomatic athletic men with a generally low risk profile where 37% were former or current smokers¹⁰. The percentage of male athletes with a CAC > 100 Agatston units was also lower in our study compared with the others 8.9% v 36.1%⁸ and 16.4%¹⁰ respectively. These observations suggest that the higher coronary calcium scores in previous studies likely reflected 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 (≥ 300

AU) CAC scores (11.3% v 0%) a greater number of atherosclerotic plaques (44.3% v 22.2%) including multivessel plaques and a greater proportion showed coronary luminal narrowing \geq 50% (7.5% v 0%).

Possible mechanisms for increased coronary plaque burden in master athletes

The precise mechanisms for these observations in masters athletes are unknown. Endothelial damage from increased shear stress forces during exercise due to a hyper dynamic coronary circulation, mechanical bending of the coronary arteries during vigorous cardiac contraction, exercise induced spasm of the coronary arteries producing non-laminar flow, exercise associated hypertension, generation of oxidative free radicals³⁰ 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 master athletes³². 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 oestrogens 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 to males.²⁸

Differences in plaque composition between master men athletes and controls

Although male athletes had a higher burden of coronary plaques compared with male controls, the morphology 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 non calcified plaques among runners compared with nonrunners, however over 50% of the runners had at least one risk factor for atherosclerosis⁹. 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 fissuring 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 runners³⁸.

Whereas it is plausible that calcific plaques in masters athletes protect from acute myocardial infarction due to plaque rupture, the same stable calcified plaques may cause sufficient coronary stenosis and demand ischaemia 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 non-sustained 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 non-sustained VT showed normal coronary arteries suggesting that non-atherosclerotic mechanisms such as coronary spasm, increased thrombogenicity,^{39,40} coronary embolic or myocarditis may also contribute to myocardial scarring and/or ventricular arrhythmias in male athletes engaged in lifelong endurance sports.

Relationship between exercise dose and coronary calcification

The dose-response relationship between exercise and cardiovascular health has generated scientific and lay interest since 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 to sedentary non-joggers, whereas strenuous joggers who exercised approximately four times greater than the current recommendations for healthy physical activity exhibited mortality rates similar to sedentary individuals.⁵ This study had very 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 over one million British women showed that women engaging in daily strenuous physical activity had a higher risk of CAD compared to women performing strenuous physical activity 2-3 times per week. However, just over a quarter of strenuously exercising women were smokers compared to 14-16% of women performing less exercise which may provide a partial explanation for these findings⁴¹. In contrast, the data from the Henry Ford exercise testing project (The Fit study) showed that middle aged individuals capable of exercising to very 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 benefit⁴². Similarly, a meta-analysis of population studies comprising over 650,000 men and women with a median age of 62 years (range 21-92 years) revealed that exercising up to 10 times above the recommended physical activity levels were not associated with increased mortality compared with individuals exercising in accordance to consistent with current recommendations⁴³. 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 in excess of a 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, there are several inherent limitations that warrant mention. This study was not entirely homogenous with respect to sex and included only 30% females that 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 non-specific 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. Most importantly the cross sectional in design of the study 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 master athletes and 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 aged lifelong masters endurance athletes with a low atherosclerotic risk profile had no coronary artery calcium. A proportion of male athletes without pre-existing 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 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.

Acknowledgments

We would like to acknowledge the support of the British Heart foundation for this project.

Sources of Funding

Dr Merghani received by a junior research fellowship from the British Heart Foundation, United Kingdom. Sanjay Sharma has been a recipient of grants from the British Heart Foundation and Cardiac Risk in Young.

Disclosures

None

References

1. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet*. 1953;265:1111–1120.
2. Tanasescu M, Leitzmann MF, Rimm EB, Willett W, Stampfer MJ, Hu FB. Exercise Type and Intensity in Relation to Coronary Heart Disease in Men. *JAMA*. 2002;288:1994–2000.
3. Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin B a, Macera C a, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093.
4. O'Donovan G, Blazeovich AJ, Boreham C, Cooper AR, Crank H, Ekelund U, Fox KR, Gately P, Giles-Corti B, Gill JMR, Hamer M, McDermott I, Murphy M, Mutrie N, Reilly JJ, Saxton JM, Stamatakis E. The ABC of Physical Activity for Health: a consensus statement from the British Association of Sport and Exercise Sciences. *J Sports Sci*. 2010;28:573–591.
5. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of Jogging and Long-Term Mortality. *J Am Coll Cardiol*. 2015;65:411–419.
6. Lee D, Lavie CJ, Vedanthan R. Optimal Dose of Running for Longevity. *J Am Coll Cardiol*. 2015;65:420–422.
7. Lepers R, Cattagni T. Do older athletes reach limits in their performance during marathon running? *Age (Dordr)*. 2012;34:773–781.
8. Möhlenkamp S, Lehmann N, Breuckmann F, Bröcker-Preuss M, Nassenstein K, Halle M, Budde T, Mann K, Barkhausen J, Heusch G, Jöckel K-H, Erbel R. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J*. 2008;29:1903–1910.
9. Schwartz RS, Kraus SM, Schwartz JG, Wickstrom KK, Peichel G, Garberich RF, Lesser JR, Oesterle SN, Knickelbine T, Harris KM, Duval S, Roberts WO, O'Keefe JH. Increased Coronary Artery Plaque Volume Among Male Marathon Runners. *Mo Med*. 2014;111:85.
10. Braber TL, Mosterd A, Prakken NH, Rienks R, Nathoe HM, Mali WP, Doevendans P a, Backx FJ, Bots ML, Grobbee DE, Velthuis BK. Occult coronary artery disease in middle-aged sportsmen with a low cardiovascular risk score: The Measuring Athlete's Risk of Cardiovascular Events (MARC) study. *Eur J Prev Cardiol*. 2016;23:1677–1684.
11. Wilson M, O'Hanlon R, Prasad S, Deighan A, Macmillan P, Oxborough D, Godfrey R, Smith G, Maceira A, Sharma S, George K, Whyte G. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol*. 2011;110:1622–1626.
12. Breuckmann F, Lehmann N, Ladd S, Schmermund A, Schlosser T, Jo K, Erbel R. Myocardial Late Gadolinium Enhancement: Prevalence, Pattern, and Prognostic Relevance in Marathon Runners. *Radiology*. 2009;251:50–57.
13. Chugh SS, Weiss JB. Sudden Cardiac Death in the Older Athlete. *J Am Coll Cardiol*. 2015;65:493–502.
14. Tunstall-Pedoe DS. Marathon cardiac deaths : the london experience. *Sport Med*. 2007;37:448–450.
15. Roberts WO, Roberts DM, Lunos S. Marathon related cardiac arrest risk differences in men and women. *Br J Sports Med*. 2012;10:1–4.
16. Webner D, Duprey KM, Drezner J a, Cronholm P, Roberts WO. Sudden cardiac arrest and

- death in United States marathons. *Med Sci Sports Exerc.* 2012;44:1843–1845.
17. O’Keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel R a, McCullough P a. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clin Proc.* 2012;87:587–595.
 18. Athletics weekly [Internet]. :www.athleticsweekly.com. Available from: <http://www.athleticsweekly.com/>
 19. US department of health and social services. Physical Activity Guidelines for Americans [Internet]. 2008 [cited 2015 Aug 19];Available from: www.health.gov/paguidelines
 20. Oxborough D, Zaidi A, Gati S, Papadakis M, Sheikh N, Sharma S. A Guideline for the Practice of Echocardiography in the Cardiovascular Screening of Sports Participants: A Joint Policy Statement of the British Society of Echocardiography and Cardiac Risk in the Young. *ECHO – J Br Soc Echocardiogr.* 2013;1:1–8.
 21. McClelland RL, Chung H, Detrano R, Post W, Kronmal R a. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113:30–37.
 22. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr.* 2014;8:342–358.
 23. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JAC, Rader DJ, Rubin GD, Shaw LJ, Wiegers SE. Assessment of Coronary Artery Disease by Cardiac Computed Tomography: A Scientific Statement From the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on C. *Circulation.* 2006;114:1761–1791.
 24. Sharma S, Elliott PM, Whyte G, Mahon N, Virdee MS, Mist B, McKenna WJ. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol.* 2000;36:864–870.
 25. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, Dorian P, Huikuri H, Kim Y-H, Knight B, Marchlinski F, Ross D, Sacher F, Sapp J, Shivkumar K, Soejima K, Tada H, Alexander ME, Triedman JK, Yamada T, Kirchhof P, Lip GYH, Kuck KH, Mont L, Haines D, Indik J, Dimarco J, Exner D, Iesaka Y, Savelieva I. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Heart Rhythm.* 2014;11:e166-196.
 26. Ector H, Verlinden M, Eynde EV, Bourgois J, Hermans L, Fagard R, Geest HD. Bradycardia, Ventricular Pauses, Syncope, and Sports. *Heart Rhythm.* 2015;324:591–594.
 27. Roberts WO, Schwartz RS, Kraus SM, Schwartz JG, Peichel G, Garberich RF, Lesser JR, Oesterle SN, Wickstrom KK, Knickelbine T, Harris KM. Long-Term Marathon Running Is Associated with Low Coronary Plaque Formation in Women. *Med Sci Sport Exerc.* 2016;Ahead of Print. DOI: 10.1249/MSS.0000000000001154.
 28. Barrett-Connor E. Sex Differences in Coronary Heart Disease. *Circulation.* 1997;95:252–264.
 29. Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. *Circulation.* 1993;87:1076–1082.
 30. Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? *Cardiovasc Res.* 2005;67:187–197.

31. Suzuki K, Nakaji S, Yamada M, Liu Q, Kurakake S, Okamura N, Kumae T, Umeda T, Sugawara K. Impact of a competitive marathon race on systemic cytokine and neutrophil responses. *Med Sci Sport Exerc.* 2003;35:348–355.
32. Barry D, Kohrt W. Acute effects of 2 hours of moderate-intensity cycling on serum parathyroid hormone and calcium. *Calcif Tissue Int.* 2007;80:359–365.
33. Riedel M, Mugge A. Oestrogen and protection against myocardial ischaemia. *Lancet.* 1993;2:872.
34. Barrett-Connor E, TL B. Estrogen and coronary heart disease in women. *JAMA.* 1991;265:1861–1867.
35. Ahmadi N, Nabavi V, Hajsadeghi F, Flores F, French WJ, Mao SS, Shavelle D, Ebrahimi R, Budoff M. Mortality incidence of patients with non-obstructive coronary artery disease diagnosed by computed tomography angiography. *Am J Cardiol.* 2011;107:10–16.
36. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, Carr JJ, Budoff MJ, Allison MA. Calcium Density of Coronary Artery Plaque and Risk of Incident Cardiovascular Events. *JAMA.* 2014;607:271–278.
37. LaMonte MJ, FitzGerald SJ, Levine BD, Church TS, Kampert JB, Nichaman MZ, Gibbons LW, Blair SN. Coronary artery calcium, exercise tolerance, and CHD events in asymptomatic men. *Atherosclerosis.* 2016;189:157–162.
38. James J, Merghani A, Sharma S. Sudden Death in Marathon Runners. *Card Electrophysiol Clin.* 2013;5:43–51.
39. Siegel AJ, Stec JJ, Lipinska I, Van Cott EM, Lewandrowski KB, Ridker PM, Tofler GH. Effect of marathon running on inflammatory and hemostatic markers. *Am J Cardiol.* 2015;88:918–920.
40. Lee KW, Lip GYH. Acute versus habitual exercise, thrombogenesis and exercise intensity. *Thromb Haemost.* 2004;91:416–419.
41. Armstrong MEG, Green J, Reeves GK, Beral V, Cairns BJ. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation.* 2015;131:721–729.
42. Feldman DI, Al-Mallah MH, Keteyian SJ, Brawner C a, Feldman T, Blumenthal RS, Blaha MJ. No evidence of an upper threshold for mortality benefit at high levels of cardiorespiratory fitness. *J Am Coll Cardiol.* 2015;65:629–630.
43. Arem H, SC M, Patel A, Al E. Leisure time physical activity and mortality: A detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175:959–967.

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

DEMOGRAPHICS	Males			Females		
	Controls (±SD, range)	Athletes (±SD, range)	P	Controls (±SD, range)	Athletes (±SD, range)	P
	54	106		38	46	
Age (years)	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 (centimetres)	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 (Kilograms)	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 ethnicity 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	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	1
Family History of CAD (age>40)	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)	
V02 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
V02 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 HOUR EKG	Males			Females		
	Controls	Athletes	P	Controls	Athletes	P
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
NSVT	0 (0%)	10 (9.4%)	0.02	0 (0%)	1 (2.2%)	1
Sinus Pauses (≥2.5 seconds)	0 (0%)	11 (10.4%)	0.02	0 (0%)	0 (0%)	1

CAD=coronary artery disease, LDL=Low density lipoprotein, NSVT=Non-sustained ventricular tachycardia

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

ECHOCARDIOGRAPHY	Males			Females		
	Controls	Athletes	P	Controls	Athletes	P
	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
RV outflow tract (mm)	33.0 (±3.3)	36.1 (±5.2)	<0.0001	30.2 (±3.1)	31.9 (±4.1)	0.05
RV basal diameter (mm)	40.1 (±6.5)	47.1 (±6.4)	<0.0001	35.1 (±7.7)	42.6 (±8.5)	<0.0001
LV 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
PAP (mm Hg)	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	Males			Females		
	Controls	Athletes	P	Controls	Athletes	P
LV 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
LV 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
RV 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)	0 (0%)	15 (14.2%)	0.004	0 (0%)	1 (2.2%)	1

EDV= End diastolic volume, IVSd=interventricular septal thickness in diastole, LGE = Late Gadolinium Enhancement, LV = left ventricular, LVIDd = Left ventricular internal diameter end diastole, MRI = magnetic resonance imaging, PAP = pulmonary artery pressure, RV = right ventricular

Table 3. Coronary artery calcium score and CT coronary angiography results in masters athletes and controls

Parameter	Males			Females		
	Controls	Athletes	P	Controls	Athletes	P
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

CAC = coronary artery calcium

Circulation

Figure Legends

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

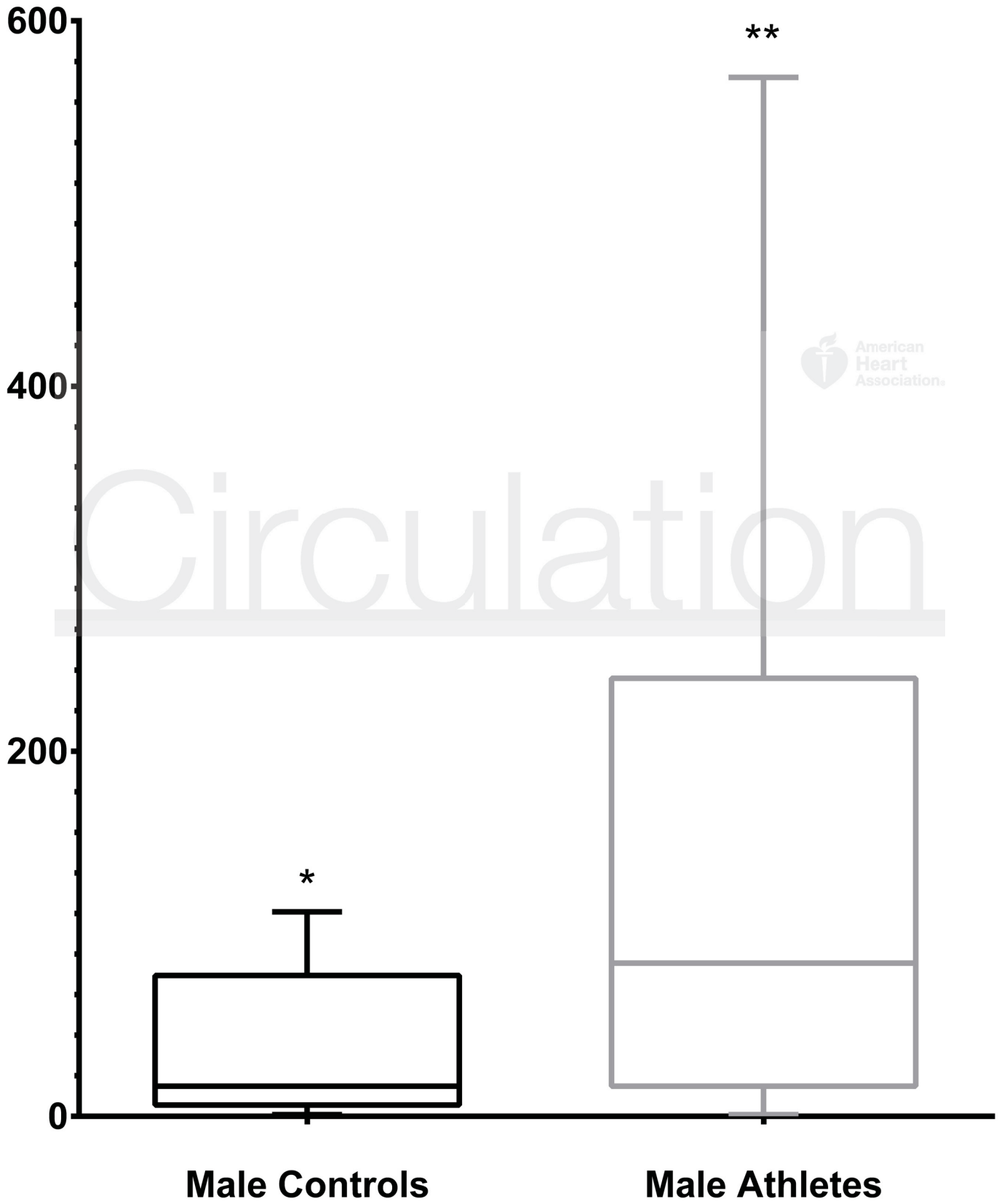
Figure 2. Coronary plaques and luminal stenoses artery in male athletes and relatively sedentary healthy males a) Number of atherosclerotic plaques observed on CT angiography in male athletes and relatively sedentary males, b) Distribution of coronary plaques in athletic men (99 coronary plaques) and relatively sedentary males (26 coronary plaques), c) Luminal stenoses in male athletes and sedentary males.

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

Figure 4. Myocardial fibrosis in athletes demonstrated by late gadolinium enhancement on CMR. a) Distribution of fibrosis, b) Sub epicardial 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=Males, F=Females

Coronary calcium score in agatston units

Downloaded from <http://circ.ahajournals.org/> by guest on July 6, 2017

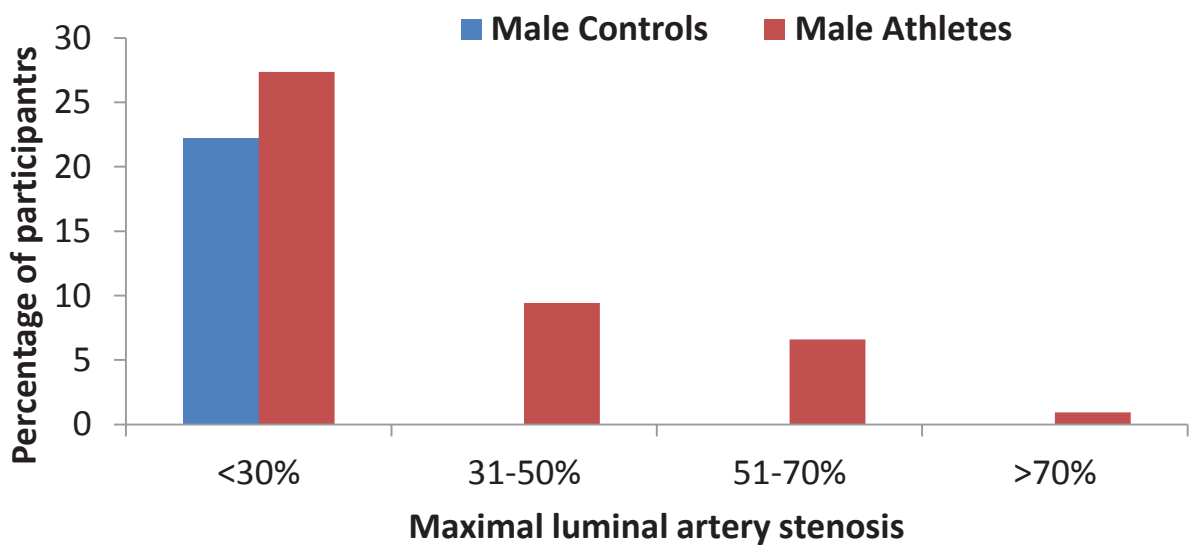
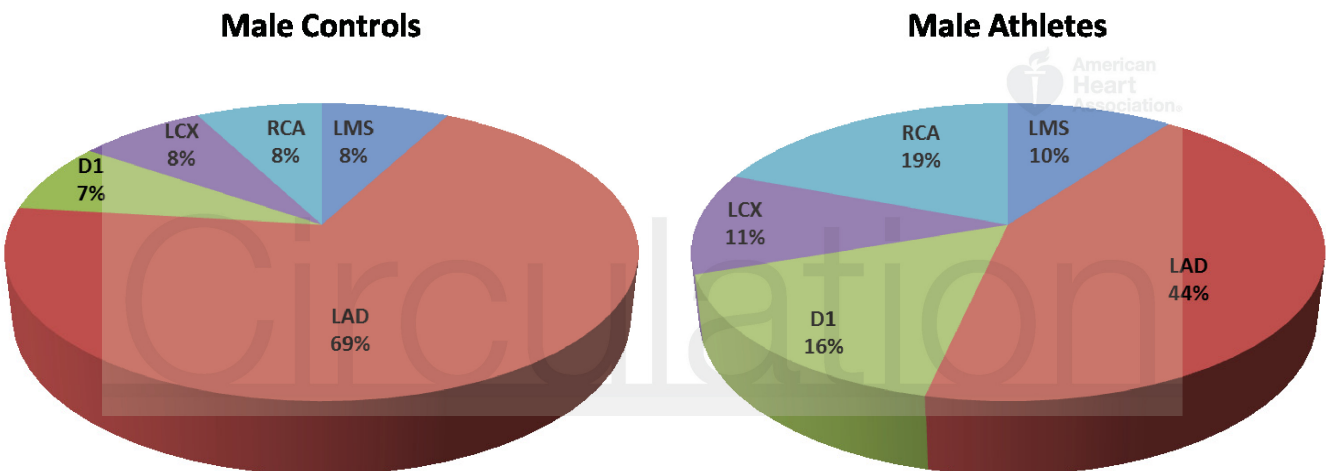
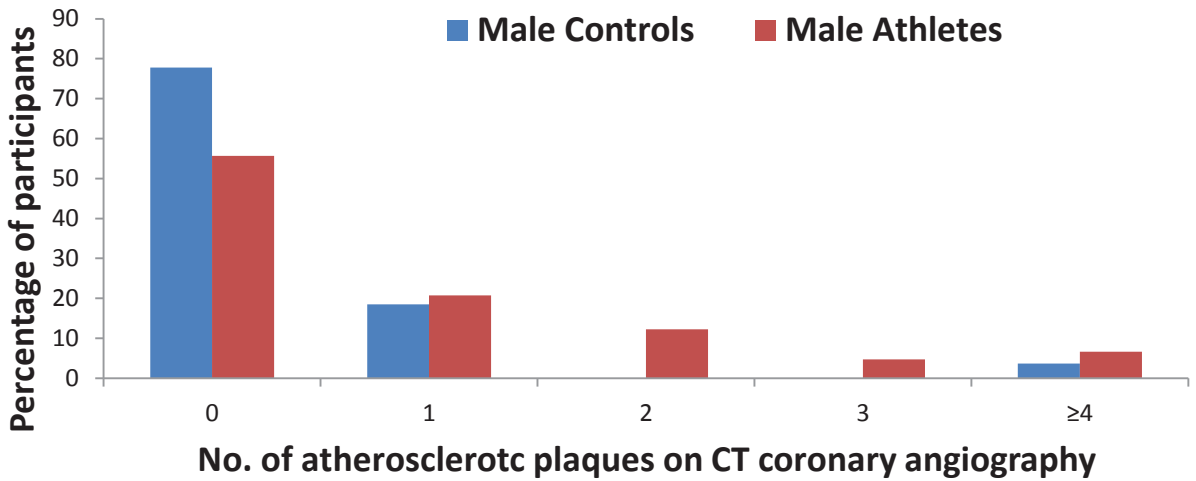


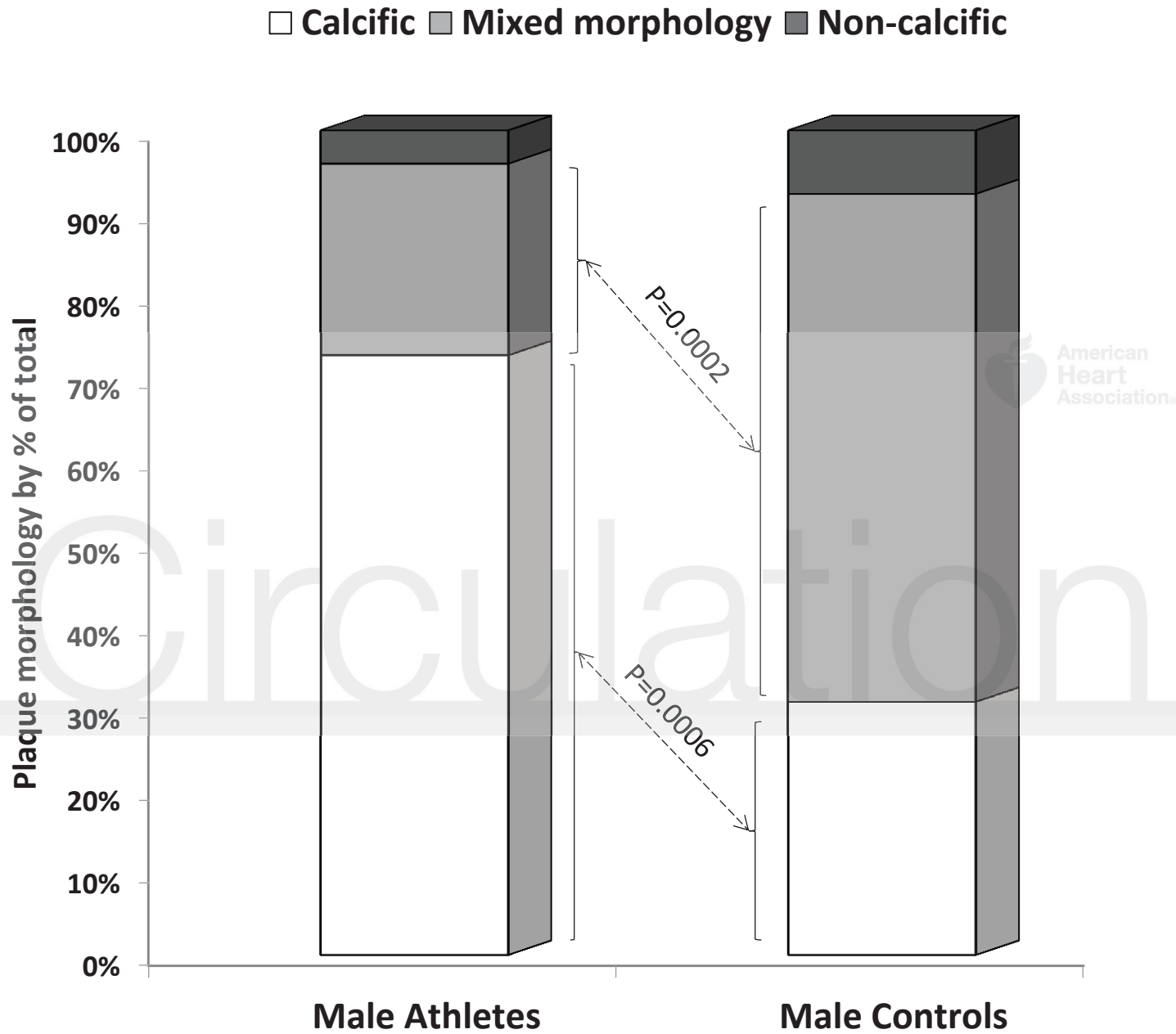
Circulation

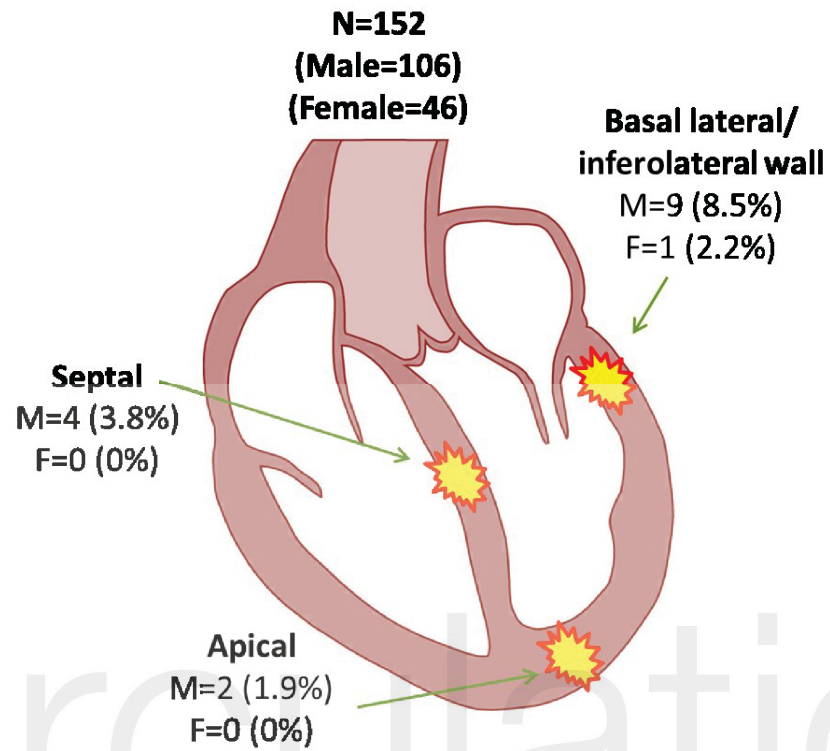
Male Controls

Male Athletes

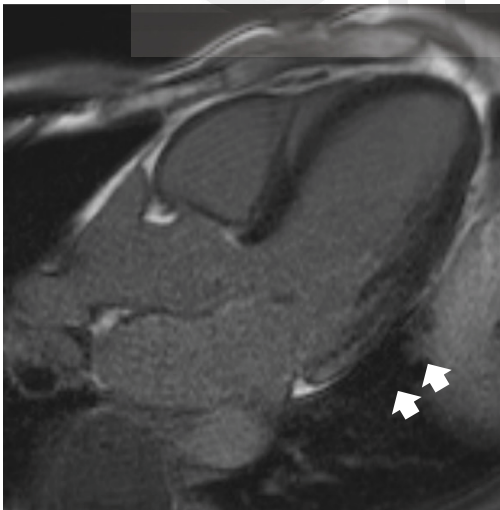
a.



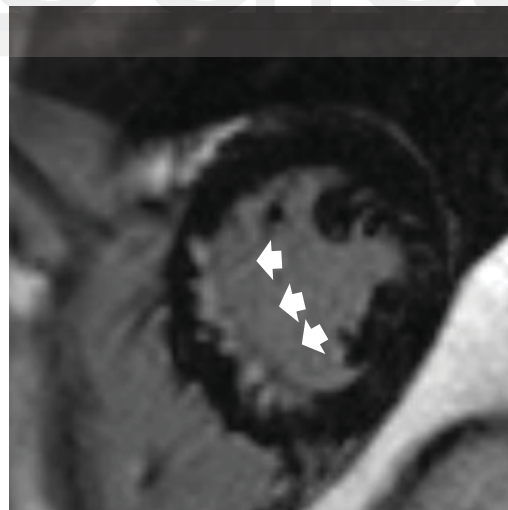




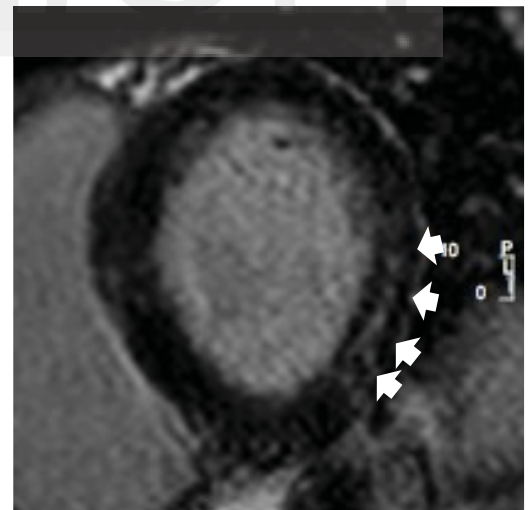
b.



c.



d.



Circulation

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

Ahmed Merghani, Viviana Maestrini, Stefania Rosmini, Andrew T. Cox, Harshil Dhutia, Rachel Bastiaenen, Sarojini David, Tee Joo Yeo, Rajay Narain, Aneil Malhotra, Michael Papadakis, Mathew G. Wilson, Maite Tome, Khaled AlFakih, James C. Moon and Sanjay Sharma

Circulation. published online May 2, 2017;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2017 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/early/2017/05/02/CIRCULATIONAHA.116.026964>

Data Supplement (unedited) at:

<http://circ.ahajournals.org/content/suppl/2017/05/02/CIRCULATIONAHA.116.026964.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>

Supplemental Publication Material

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

