Title: Exercise and Coronary Atherosclerosis: Observations, Explanations, Relevance and Clinical Management

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Author(s): Thijs Eijsvogels, Radboud university medical center
Vincent Aengevaeren, Radboud university medical center
Arend Mosterd, Meander Medical Centre
Sanjay Sharma, St George's University of London
Niek Prakken, University Medical Center Groningen
Stefan Möhlenkamp, Krankenhaus Bethanien, Department of Cardiology
Paul Thompson, Hartford Hospital
Birgitta Velthuis, University Medical Center Utrecht

Exercise and Coronary Atherosclerosis:

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Aengevaeren, Exercise and Coronary Atherosclerosis

Vincent L. Aengevaeren, MD[a,b]

Arend Mosterd, MD, PhD[c]

Sanjay Sharma, MD[d]

Niek H.J. Prakken, MD, PhD[e]

Stefan Möhlenkamp, MD[f]

Paul D. Thompson, MD[g]

Birgitta K. Velthuis, MD, PhD[h]

Thijs M.H. Eijsvogels, PhD[a]

Radboud Institute for Health Sciences, Departments of Physiology[a] and Cardiology[b],

Radboud University Medical Center, Nijmegen, The Netherlands

[c]Department of Cardiology, Meander Medical Center, Amersfoort, The Netherlands

[d]Cardiology Clinical and Academic Group, St George's University of London, United Kingdom

[e]Department of Radiology, University Medical Center Groningen, The Netherlands

[f]Clinic of Cardiology and Intensive Care Medicine, Bethanien Hospital Moers, Moers, Germany

[g]Division of Cardiology, Hartford Hospital, Hartford, CT, USA

[h]Department of Radiology, University Medical Center Utrecht, The Netherlands

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Addresses for correspondence:

Dr. Vincent Aengevaeren, Department of Physiology (392), Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands, Tel +31 24 36 13 650, Fax +31 24 36 16413,

E-mail: Vincent.Aengevaeren@radboudumc.nl

Dr. Thijs Eijsvogels, Department of Physiology (392), Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands, Tel +31 24 36 13 674, Fax +31 24 36 16413,

E-mail: Thijs.Eijsvogels@radboudumc.nl

Abstract

Physical activity and exercise training are effective strategies for reducing the risk of cardiovascular events, but multiple studies have reported an increased prevalence of coronary atherosclerosis, usually measured as coronary artery calcification (CAC), among middle-aged and older athletes. Our review of the medical literature demonstrates that the prevalence of CAC and atherosclerotic plaques, which are strong predictors for future cardiovascular morbidity and mortality, was higher in athletes compared with controls, and was higher in the most active athletes compared with less active athletes. However, analysis of plaque morphology revealed fewer mixed plaques and more often only calcified plaques among athletes, suggesting a more benign composition of atherosclerotic plaques. This review describes the effects of physical activity and exercise training on coronary atherosclerosis in middle-aged and older athletes and aims to contribute to the understanding of the potential adverse effects of the highest doses of exercise training on the coronary arteries. For this purpose, we will review the association between exercise and coronary atherosclerosis measured using computed tomography, discuss the potential underlying mechanisms for exercise-induced coronary atherosclerosis, determine the clinical relevance of coronary atherosclerosis in middle-aged athletes and describe strategies for the clinical management of athletes with coronary atherosclerosis to guide physicians in clinical decision making and treatment of athletes with elevated CAC scores.

Introduction

Cardiovascular diseases (CVD) are the dominant cause of death worldwide, accounting for approximately 18 million deaths per year (31% of total mortality)[1]. Atherosclerotic coronary heart disease is the leading cause of deaths attributable to CVD and accounts for almost 45% of all cases. There is clear evidence that chronic physical activity and exercise training significantly reduce the risk for cardiovascular events[2]. However, several recent studies have suggested that high-volume high-intensity exercise training may actually increase the prevalence and severity of coronary atherosclerosis[3-5]. Interestingly, analysis of plaque morphology has shown fewer mixed plaques and more often only calcified plaques in the athletes, suggesting a more stable atherosclerotic pattern. The mechanisms leading to increased coronary atherosclerosis in athletes are largely unknown. Furthermore, the clinical relevance of these findings and how to manage athletes with coronary atherosclerosis are unclear. In this review we describe the short-term and long-term effects of exercise training on coronary atherosclerosis in middle-aged and older athletes. This review will summarize the association between exercise and coronary atherosclerosis measured using computed tomography (CT), discuss the potential underlying mechanisms, determine the clinical relevance of atherosclerosis in middle-aged athletes and describe strategies for managing athletes with coronary atherosclerosis.

Methods to assess coronary atherosclerosis characteristics

Two different CT-scan protocols can be used for the assessment of coronary atherosclerosis. A non-contrast CT-scan demonstrates the amount of coronary artery calcification (CAC), which is expressed as a CAC score (CACS) in Agatston units[6]. The CACS is predictive of future CVD events[7, 8]. The CACS is the product of CAC volume and CAC density, and although CAC volume has a positive association with cardiovascular events, CAC density is inversely associated with cardiovascular events[9], suggesting that not all CACS have the same risk. Coronary CT angiography (CCTA) uses contrast to assess luminal

stenoses, plaque characteristics and plaque volume. Luminal stenoses are visually graded and significant stenoses (>50%) are strongly associated with cardiovascular events[10]. The number of segments affected can also be summed to produce a segment involvement score, which is a strong predictor of events[11]. Both CACS and CCTA derived scores predict events, but the addition of the number, location and severity of stenoses from CCTA does not appear to improve event prediction more than standard risk factors and CACS alone in asymptomatic patients[12], suggesting that CACS is as good a predictor of cardiovascular events in such patients.

Plaques can be characterized as calcified, non-calcified or mixed (containing both calcified and non-calcified material) plaques, with a distinct difference in prognosis. Mixed plaques are associated with the worst prognosis, whereas calcified plaques are associated with the best event-free survival and non-calcified plaques have an associated risk in between[13]. CCTA also allows the identification of potentially high-risk plaque features such as the napkin ring sign (a ring of high attenuation around a low-attenuation plaque suggesting atheroma with a thin fibrous cap), vessel expansion or "positive remodeling", low (<30) Hounsfield unit plaque suggesting lipid enrichment, and spotty calcification[14]. CCTA plaque characteristics and high-risk plaque features are good predictors of CVD risk[13, 15], although the spatial resolution of CT-scans is too low to reliably identify the most vulnerable (thin-cap) plaques[16]. New software allows quantification of plaque volume which will likely improve understanding and risk prediction of coronary atherosclerosis[17].

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Findings in the general population

Physical activity is defined as any bodily movement that results in energy expenditure beyond resting levels[18], and is often quantified as Metabolic Equivalent of Task (MET) minutes or hours per week. Physical activity can include activities at work, during commuting or during recreation.

Regular physical activity and exercise improves cardiovascular risk factors including blood

pressure, serum lipid profile, glucose control and cardiovascular function, but studies examining the relationship between physical activity and CAC have reported an inverse relationship (n=8 studies[19-26]), positive relationship (n=2 studies[24, 27]), U/J-shaped relationship (n=3 studies[23, 25, 26]) or no relationship (n=7 studies[19, 20, 28-32], **Supplemental Table 1**). Population cohorts have demonstrated a wide prevalence of CAC (CACS>0) ranging from 29%[27] to 93%[20]. This variation in CAC prevalence is partly attributable to differences in age, sex and cardiovascular risk factors. For example, women aged 74±4 years had a prevalence of CAC of 74%[20], whereas women aged 62±4 years had a CAC prevalence of 40%[20]. CAC prevalence differs among physical activity categories (**Figure 1A**), but not after adjustment for potential confounders (**Figure 1B**). No clear sex differences were observed in the association between physical activity and CAC.

The variability in outcomes in studies of the relationship between physical activity and CAC may also be due to the methods used to measure physical activity. For example, a study showed that physical activity measured by accelerometer was inversely associated with CACS, but there was no association when levels of physical activity were determined with subjective questionnaires[19]. The quality of questionnaires, whether past or current activity is measured, and if total activity or only intentional exercise is measured could also impact findings. The spectrum of physical activity levels in the study population may also affect results since an inverse relationship was found at low levels of physical activity[22] and a positive relationship was found at the highest physical activity levels[27], suggesting a difference in the relationship between physical activity and CAC at different activity levels. Finally, differences in age of the participants may also contribute to the conflicting findings, as an inverse association was found between physical activity and CACS among older (74±4 years) post-menopausal women where there was no significant association in younger (57±3 years) post-menopausal women[20]. This may be due to the age- and sex-dependence of CAC with a low prevalence in middle-aged women[33].

Similar associations were observed between CAC and cardiorespiratory fitness. Cardiorespiratory fitness comprises a set of attributes that individuals inherit or achieve through exercise training that is measured by their ability to perform physical activity[18]. Several Korean studies found an inverse association between cardiorespiratory fitness and CAC among mainly middle-aged men[34-36]. Similar results were found in middle-aged women from the Cooper Clinic[37], however the observed modest inverse relationship between fitness and CAC was no longer significant after adjustment for traditional risk factors. In contrast, the CARDIA study found a positive association between cardiorespiratory fitness and CAC[38] in young adults followed for 27 years, which disappeared after multivariate adjustment. Kermott *et al.*[39] found a reverse J-shaped association between fitness and CAC prevalence in middle-aged men, with an increased CAC prevalence in the fittest group. This effect remained significant after adjustment for some variables (age, body mass index and family history), but did not include a full adjustment for potential confounders. Adjustment for confounding factors plays an important role in the association between physical activity, cardiorespiratory fitness and CAC. Therefore, adequate and clearly described adjustment of confounding factors is important when presenting and interpreting the results. Taken together, studies assessing the relationship between physical activity, cardiorespiratory fitness and CAC have shown mixed results, potentially due to differences in study population and methods, with no clear net effect towards either a positive or inverse association.

Endurance exercise training

Exercise is a subset of physical activity that is planned, structured, repetitive, and intended to improve or maintain physical fitness[18]. Endurance exercise training refers to repetitively performing aerobic physical activity, such as running or cycling, to obtain a training adaptation.

Lin *et al* studied the acute effects of endurance exercise on coronary atherosclerosis characteristics in eight participants of the Race Across the USA (a 140-day foot race)[40]. Four runners had

at least 1 cardiovascular risk factor and coronary atherosclerosis at baseline and showed increases in primarily non-calcified plaque volume after the race[40]. Runners with no baseline coronary atherosclerosis remained free of coronary atherosclerosis post-race. Although the numbers are small, these data raise the possibility that high-volume endurance exercise may accelerate coronary atherosclerosis in vulnerable individuals.

Most studies have assessed the long-term effect of endurance exercise training on coronary atherosclerosis (**Supplemental Table 2**). **Figure 2** summarizes findings of studies that compared the prevalence of CAC between athletes and less active individuals. CAC is present in 34 to 71% of athletic cohorts (**Figure 2A**) and 11% to 36% have CACS≥100, a value often used to signify increased risk (**Figure 2B**). Differences in age and cardiovascular risk factors contribute to this variability. For example, CAC was present in 71% of 108 male marathon runners (57±6 years old) of whom 12% had a history of hypertension and 57% was a current (4.6%) or former (52%) smoker[3], whereas CAC was present in only 48% of 106 male athletes (54±9 years old) without cardiovascular risk factors[5].

Only 1 of 3 studies found a higher prevalence of CAC among the most active athletes (**Figure 2A**). Aengevaeren *et al.* divided 284 male athletes into 3 groups based on their lifelong exercise volume[4]. CAC prevalence was higher in the most active athletes (>2000 MET-min/week, $OR_{adjusted}$=3.2; 95% confidence interval [CI], 1.6–6.6) compared with the least active athletes (<1000 MET-min/week), but there was no difference in CAC area, density and number of lesions among exercise volume groups in those with CAC[4]. Möhlenkamp *et al.* compared 108 male marathon runners with 864 age-matched controls and 216 age and risk factors matched controls[3]. CAC prevalence was lower in the marathon runners *versus* age-matched controls, but did not differ when matched for age and cardiovascular risk factors. Merghani *et al.* found no difference in the prevalence of CAC between 106 male athletes (≥10 miles of running or ≥30 miles of cycling per week for ≥10 years) and 54 male controls (median of 1.5 hours of exercise/week), all without cardiovascular risk factors[5]. In contrast to Aengevaeren *et al.*, Möhlenkamp *et al.* and Merghani

et al. did report higher CACS in athletes with CAC compared to controls with CAC (**Figure 2C**).

Three of 4 studies revealed a greater prevalence of CACS≥100 in more active subjects and the 4th study showed a trend approaching significance (p=0.06, **Figure 2B**). For example, among 21,758 men divided into 3 groups based on their physical activity volumes (<1,500 MET-min/week, 1,500-2,999 MET-min/week and ≥3,000 MET-min/week)[41], the most active individuals had an 11% greater risk for CACS ≥100 compared with those accumulating <3,000 MET-min/week (relative risk of 1.11, 95%CI, 1.03-1.20). Interestingly, despite the higher risk for CACS ≥100 for the most active individuals, CAC volume, density and number of lesions did not differ between physical activity groups within each category of CAC (CACS ≥100 and <100).

Using CCTA, an American study compared 50 marathon runners with 23 sedentary controls who underwent CCTA for clinical indications and found significantly higher plaque volume, both calcified (83.8±67.7 mm^3 *vs.* 44.0±36.8mm^3, p<.0001) and non-calcified (116.1±95.7 mm^3 *vs.* 81.5 ± 58.1 mm^3, p=.04), in the runners[42], but the runners were older (59±7 *vs.* 55±10 years, p=0.051) than the controls. The British study found an increased prevalence of atherosclerotic plaques in male athletes (44%) *versus* controls (22%, p=0.01)[5], but found no differences among female study participants. The Dutch study found an increased plaque prevalence in the most active (77%, $OR_{adjusted}$=3.3; 95% CI, 1.6–7.1) *versus* the least active (56%) male middle-aged athletes[4]. Interestingly, in both the British and Dutch studies, the most active individuals had a more benign atherosclerotic plaque composition, with less mixed plaques and more often only calcified plaques[4, 5] (**Figure 3**). Exercise intensity and sporting discipline may also affect the results. Only very vigorous exercise (>9 MET) was associated with atherosclerotic plaque (OR=1.56, 95% CI: 1.17–2.08 per hour/week) and CAC prevalence (OR=1.47, 95% CI: 1.14–1.91 per hour/week) in the Dutch study[4]. Moreover, cyclists appeared to have a lower risk of atherosclerotic plaque (OR= 0.41; 95%CI, 0.19-0.87) and CAC (OR=0.55; 95%CI, 0.26-1.16) compared with runners and individuals performing other sports (e.g. soccer, hockey, water polo, etc.)[43].

Future longitudinal studies are required to investigate whether CAC progression is accelerated in athletes. Although the studies in endurance athletes are relatively small and include mostly men, the results suggest more coronary atherosclerosis in (the most active) athletes whereas plaque morphology appears possibly more benign.

Influence of sex and race

Limited data is available in female athletes, but small studies (n=46[5] and n=26[44]) do not suggest increased coronary atherosclerosis[5] and possibly a lower prevalence of coronary atherosclerosis[44] in female athletes compared with controls. Supplemental data from DeFina *et al*. showed no association between physical activity and CACS ≥100 in 9,501 women (p=.91)[41]. The lower prevalence of coronary atherosclerosis in some studies of female marathon runners may be due to selection of control subjects, who in one study[44] were referred for CCTA to evaluate coronary artery disease and had significantly higher body mass index, hypertension, hyperlipidemia, smoking history and family history for coronary artery disease. There is insufficient data on the association between exercise volumes and coronary atherosclerosis characteristics among female athletes and studies in male athletes cannot be extrapolated to females. Therefore, the influence of female sex is not specifically addressed in the following sections.

Race is known to impact CAC[45]. However, most studies have evaluated only white individuals. Laddu *et al.* performed race-specific analyses and found different associations between physical activity and CAC in black and white non-athletic subjects[27], suggesting that race may affect this association. Consequently, we have not addressed the influence of race in the following sections.

Strength training

Strength training aims to increase skeletal muscle strength and size by repetitively performing anaerobic physical activity such as weightlifting. No differences were found in the prevalence of CAC and distribution of CACS categories between retired American football players (n=150, 51±10 years old) and age-matched community controls (n=150, 51±10 years old)[46]. Linemen, typically the largest players who are often classified as overweight or obese, had similar CAC prevalence compared to non-linemen[46]. However, another study comparing linemen with non-linemen among 931 retired professional American football players (≈54 years old) found that the linemen had a higher prevalence of CAC and severity of CACS compared to non-linemen[47]. CACS>100 (OR=1.59; 95%CI, 1.01-2.49) remained greater in the linemen after full adjustment for cardiovascular risk factors and ethnicity[47].

The use of performance enhancing drugs may accelerate coronary atherosclerosis. Anabolic-androgenic steroid use is prevalent among strength-trained athletes, with an estimated ≈3 million users in the United States[48]. Steroids are mainly used to increase muscle mass, performance and personal appearance[48], however, they are also popular among endurance athletes to aid in recovery and strength[49]. A pilot study found higher CACS than expected, based on reference values from the Cooper Clinic, in 14 professional body builders with a long history of steroid use[50]. Seven of 14 (50%) had CAC compared to an expected value of 3 (21%). Of those with CAC, 6 of 7 had CACS >90th percentile. Baggish *et al*[51] compared coronary atherosclerosis between anabolic steroid using and non-using weightlifters, and non-weightlifting controls. Anabolic steroid use was associated with increased coronary plaque volume (users: 3 [0–174] mm^3 *versus* non-users: 0 [0–69] mm^3, p=.012) as was cumulative lifetime duration of use[51]. Widespread use of anabolic steroids did not appear until the 1980's and 1990's, so the long-term atherosclerotic effects are likely to become more apparent in the near future, when (ex-)users reach middle age and beyond[48, 51].

Potential explanations for increased coronary atherosclerosis in athletes

The mechanisms underlying increased coronary atherosclerosis in athletes are largely unknown, but there are several potential, although speculative, pathways that may link exercise training to CAC and plaque development (**Figure 4**).

Catecholamines increase heart rate and cardiac contractility during exercise. The exercise-induced increase in cardiac output may increase mechanical stress on the coronary vessel wall and disrupt laminar blood flow patterns, leading to vessel wall injury and accelerated atherosclerosis[52]. High blood pressure may accelerate coronary atherosclerosis[53] and since systolic blood pressure increases during exercise, this may contribute to accelerated atherosclerosis. The finding that very vigorous exercise was associated with atherosclerotic plaque and CAC prevalence[4] fits with this hypothesis since the most intense exercise is associated with the greatest increases in both heart rate and systolic blood pressure.

The effects of exercise on vitamins, minerals and hormones, may also influence the association between exercise and coronary atherosclerosis. Serum vitamin D concentrations are inversely related to CAC[54, 55] and could accelerate atherosclerosis in athletes who are often deficient in vitamin D[56]. Similarly, magnesium can prevent vascular calcification via multiple mechanisms[57], and serum magnesium concentrations are inversely associated with CAC[58], whereas athletes may have low magnesium concentrations[59]. Parathyroid hormone increases during exercise[60]. The increase in parathyroid hormone likely follows a decrease in ionized calcium concentration during exercise. The reason and fate of the reduced serum concentration of calcium are unknown[61]. However, higher levels of parathyroid hormone are associated with greater atherosclerotic disease burden[62]. Repeated exposure to higher levels of parathyroid levels post-exercise in athletes may therefore accelerate coronary atherosclerosis.

Running induces a large pressure concussion wave during foot strike, which alters coronary hemodynamics and could accelerate coronary atherosclerosis[63, 64]. This effect is also dependent on the timing of steps during running with reference to the cardiac cycle[63, 64].

Inflammation has a major role in the development of coronary atherosclerosis[65] and exercise modulates inflammation. Chronic exercise lowers inflammation[66], but acutely exercise can increase inflammation[67]. Although there is far more evidence supporting a suppression of inflammation in athletes, high-intensity, frequent and prolonged exercise could potentially produce an inflammatory effect, thereby accelerating coronary atherosclerosis.

Other potential explanations for increased coronary atherosclerosis that have not been sufficiently adjusted for in previous studies include dietary intake, psychological stress and genetics. It is also possible that performance enhancing drugs or immune-modulating medication could contribute to the higher prevalence of CAC and plaque among athletes[68].

Clinical relevance

Prevalence and severity of CAC and atherosclerotic plaques are strongly associated with 5- and 10-year risk of cardiovascular events in the general and patient populations[7, 8, 10, 13], yet there is strong evidence that elite and amateur athletes live longer than the general population[69, 70]. Exercise training increases longevity by approximately 3 to 6 years with the most benefit for athletes performing endurance sports[70, 71]. The increase in cardiorespiratory fitness following aerobic exercise training is also positively associated with increased longevity[72].

Möhlenkamp *et al.* were the first to examine the prognosis of higher CACS in athletes. They followed 108 marathon runners for 6±1 years and found a higher event rate in higher CAC categories (1 of 69 [1%] in CAC<100; 3 of 25 [12%] in CAC 100 to 399; and 3 of 14 [21%] in CAC ≥400; P=0.002), similar to the observed event rates in their control cohort[73]. However, this study was limited by the small sample size (n=108) and few events (n=7). A more recent study showed that the amount of self-reported exercise impacts the relationship between CACS and mortality among asymptomatic patients[74]. Among individuals with similar CACS, performing "no exercise" had a hazard ratio of 2.35 (95%CI, 1.49–3.70) for

all-cause mortality, whereas "low exercise" had a hazard ratio of 1.56 (95%CI, 1.06–2.30) and "moderate exercise" had a hazard ratio of 1.29 (95%CI, 0.86–1.95) compared to highly active patients (reference group). Similarly, higher cardiorespiratory fitness significantly reduces the risk of cardiovascular events. Lamonte *et al.* showed that individuals with a fitness ≥10 METs had a 73% reduction in cardiovascular events compared to those with a fitness <10 METs when adjusting for CACS[75]. More recent data from the Cooper Clinic Longitudinal study revealed a reduction of 11% for each additional MET of fitness (hazard ratio, 0.89; 95% CI, 0.84–0.94) when adjusting for CACS categories (scores of 0, 1–99, 100–399, and ≥400)[76]. In a subsequent publication, DeFina *et al.* demonstrated that among individuals with CACS<100, those in the highest physical activity category (≥3,000 MET-min/week) had a lower risk of all-cause mortality compared to those in the lowest physical activity category (<1,500 MET-min/week)[41]. The beneficial association between physical activity and all-cause mortality was attenuated for individuals with CACS ≥100 (hazard ratio 0.77; 95% CI, 0.52-1.15 for the highest *versus* the lowest physical activity category), whereas CACS≥100 was more prevalent among the most active individuals compared to the less active individuals (relative risk: 1.11; 95%CI, 1.03-1.20).

Increases in exercise and cardiorespiratory fitness thus seem to lower the cardiovascular risk of CAC. This risk reduction may follow from a large coronary flow reserve due to a combination of increases in epicardial coronary artery diameter, coronary vasodilatory capacity, capillary density and vasomotor reactivity produced by exercise training[77-79]. Similarly, high-volume athletes also have a biological age of their large blood vessels that is ~ 30 years younger than their chronological age[80, 81], with substantially improved ventriculo-arterial coupling[82].

Coronary atherosclerotic plaques associated with increasing exercise volume may also be more stable and less likely to rupture. We found that the most active athletes had fewer mixed plaques and more often only calcified plaques[4, 5], which are associated with a lower risk of cardiovascular events[13, 15]. Similarly, high-intensity statin therapy increases CAC, but decreases coronary atheroma volume and

cardiovascular risk[83]. Thus, an increase in CACS may not necessarily reflect an increase in cardiovascular risk. Exercise may increase calcification similar to the increase observed with statin therapy, without an associated increase in cardiovascular risk.

Intimal and medial vascular calcification differ based on their causal pathways and risk for cardiovascular diseases[84, 85]. Calcification in an atherosclerotic plaque occurs primarily in the intimal layer of the vessel wall[84] and is associated with luminal stenosis and potential plaque rupture. Medial calcification is associated with vessel wall stiffening, specifically with aging, chronic kidney disease and metabolic diseases such as disorders of calcium and phosphate metabolism[85, 86]. Athletes may be more prone to developing medial rather than intimal calcification through smooth muscle damage in the vascular wall or exercise-induced metabolic changes. However, the differentiation between intimal and medial calcification cannot be performed reliably using CT and ex-vivo histological analysis is the standard[86].

Overall, current evidence suggests that higher CACS in athletes are similarly associated with an increased CV risk as in a non-athletic cohort, however the absolute risk of CAC is likely lower in athletes due to several beneficial adaptations (**Figure 5**). The relevance of increased CAC in athletes deserves careful attention and additional longitudinal studies are required to study the influence of exercise on coronary atherosclerosis.

Clinical management

Based on our findings and until the significance of coronary calcification in athletes is better defined, we do not recommend the routine assessment of CACS in athletes based purely on their training history. CAC scoring could be considered in asymptomatic individuals aged 40-75 years with a 10-year atherosclerotic CVD risk of 5-20% and should be considered only in selected individuals with risk below 5%[87]. Our general guidance is not to repeat CAC scoring, particularly in athletes treated with statins,

because CACS may increase with statin therapy and continued exercise training, and CAC does not reverse with aggressive lipid therapy[88]. Repeated CACS after approximately 5 to 10 years may provide additional information for risk prediction of major cardiovascular events, with the most recent CACS providing the best risk estimate[89], however this strategy appears only reasonable for those in whom follow-up results may influence treatment[87, 90].

Treatment should be individualized depending on the athlete's overall risk for cardiovascular disease. All athletes should be questioned about symptoms of myocardial ischemia, family history of atherosclerotic coronary artery disease, current and prior risk factors. It is important to note that well-trained individuals may present with atypical symptoms of coronary artery disease such as a decline in exercise performance, shortness of breath or fatigue. Symptomatic athletes should be investigated and managed in the same fashion as the general population. Asymptomatic athletes, including those with high CACS, should be informed that the significance of CAC in middle-aged and older athletes is currently unclear.

In athletes with LDL cholesterol levels ≥70 mg/dL or ≥1.8 mmol/L and CACS ≥100 or ≥75th percentile compared to their age and sex matched, non-athletic peers, statin therapy should be considered following atherosclerotic CVD risk calculation and clinician-patient risk discussion[90, 91]. Risk enhancers such as extensive (non-calcified) atherosclerotic plaque on CCTA or a strong family history for premature CVD support initiating statin therapy. The American guidelines for lipid management favor statin therapy when CACS>0 if the 10-year atherosclerotic CVD risk is ≥7.5%[90]. However, this cut point is very sensitive to the scoring system used. Given that the CACS is known in these individuals, the ASTRO-CHARM risk calculator can be used[92], which incorporates CACS and calculates 10-year risk of fatal or non-fatal myocardial infarction or stroke. Athletes with CACS ≥400 should be advised to commence (high-intensity) statin therapy and other atherosclerotic risk factors should be strictly managed. Aspirin may be considered for individuals not at increased bleeding risk[93]. Episodic use of aspirin (e.g. pre-race) has been

suggested to prevent exercise-related sudden cardiac arrests[94], however evidence for this approach is lacking.

Since CAC scoring is not routinely recommended, the current guidelines do not clearly indicate how to proceed with additional testing in asymptomatic athletes with high CACS[95, 96]. The following options can be considered when evaluating an asymptomatic athlete. Management strategies differ per region in the world (e.g. United States *versus* Europe), country and even per physician. Additional testing strongly depends on hospital logistics, costs and availability of tests. CCTA may be considered in athletes with CAC to assess the number and nature of coronary plaques and to quantify the degree of luminal narrowing. In some hospitals, all individuals with a CACS>0 proceed to CCTA. Exercise or pharmacological stress testing may also be considered to check for inducible myocardial ischemia. In individuals with CACS ≥400 and/or luminal stenoses >50% an exercise stress test or stress imaging tests should be considered to detect evidence of ischemia. Evidence of ischemia could prompt coronary intervention or provide guidance for setting exercise heart rate limits, suggest modification of training, and prompt consideration of additional preventive therapy such as beta blockers. Some physicians may proceed to invasive coronary angiography with fractional flow reserve measurements. In the future, CCTA-based fractional flow reserve measurements may lower the need for invasive coronary angiography. At present, there are insufficient data to provide definitive recommendations for additional testing in asymptomatic athletes with CAC.

American[97] and European[98] guidelines are available for exercise recommendations in athletes with subclinical coronary artery disease and many of such athletes are detected by coronary artery calcification scoring. These recommendations generally allow participation in all sports, even in athletes with high CACS, if the athlete is asymptomatic, has no evidence of ischemia or electrical instability, and has a normal ejection fraction. As such, athletes can continue their exercise training despite a high CACS. Although the most active individuals with CACS≥100 did not have a higher risk for (cardiovascular)

mortality compared to less active individuals with similar CACS[41], presence of CAC is strongly associated with clinical outcomes, also in athletes. Since exercise does appear to increase CAC, future longitudinal studies are required to confirm this recommendation.

Future research

Future longitudinal studies are necessary to further investigate the association between exercise training and the development and progression of coronary atherosclerosis among athletes and its clinical relevance. Also, more insight is needed into the mechanisms responsible for increased coronary atherosclerosis in athletes. In this regard, the emerging ability of CT to identify coronary inflammation through measuring the perivascular fat attenuation index may provide additional information regarding the link between exercise and coronary atherosclerosis[99]. Most studies included primarily male white runners so little is known on how exercise affects coronary atherosclerosis in females, different ethnicities and across sporting disciplines. Future ultra-low dose CT-scanning will make assessment of CACS more feasible by lowering the radiation exposure in healthy subjects[100]. Furthermore, the current CAC scoring using the Agatston score may be refined in the future since it has previously been shown that the volume and density component have a different association with cardiovascular events. Other potentially meaningful characteristics of calcifications such as number of lesions or location/distribution may be added in such a new CAC scoring method[6].

Conclusion

Studies investigating the relationship between physical activity/exercise and coronary atherosclerosis in the general population have revealed mixed results that show no clear net effect, whereas studies in athletes demonstrated a higher prevalence of coronary atherosclerosis compared to less active controls. Increased coronary atherosclerosis in athletes may be mediated via several mechanisms. The clinical

relevance of increased coronary atherosclerosis in athletes is unclear, but no CAC or plaque is better than any atherosclerosis. Higher CACS amongst athletes may not necessarily reflect an increased risk for cardiovascular events similar to the general population since exercise promotes beneficial coronary adaptations and increased calcification may be associated with plaque stabilization, which likely explains some of the significant reduction in cardiovascular events due to exercise training. Statin therapy and (intensive) risk factor management are recommended for athletes with CAC, depending on their CACS and estimated 10-year atherosclerotic cardiovascular disease risk to stabilize plaques and prevent coronary events. Future longitudinal studies are anticipated to further investigate the role of exercise in coronary atherosclerosis.

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Affiliations

From Departments of Physiology (V.L.A., T.M.H.E.) and Cardiology (V.L.A.), Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands; Department of Cardiology, Meander Medical Center, Amersfoort, the Netherlands (A.M.); Cardiology Clinical and Academic Group, St George's University of London, United Kingdom (S.S.); Department of Radiology, University Medical Center Groningen, The Netherlands (N.H.J.P.); Clinic of Cardiology and Intensive Care Medicine,

1 Bethanien Hospital Moers, Moers, Germany (S.M.); Division of Cardiology, Hartford Hospital, CT (P.D.T.)

2 and Department of Radiology, University Medical Center Utrecht, The Netherlands (B.K.V.).

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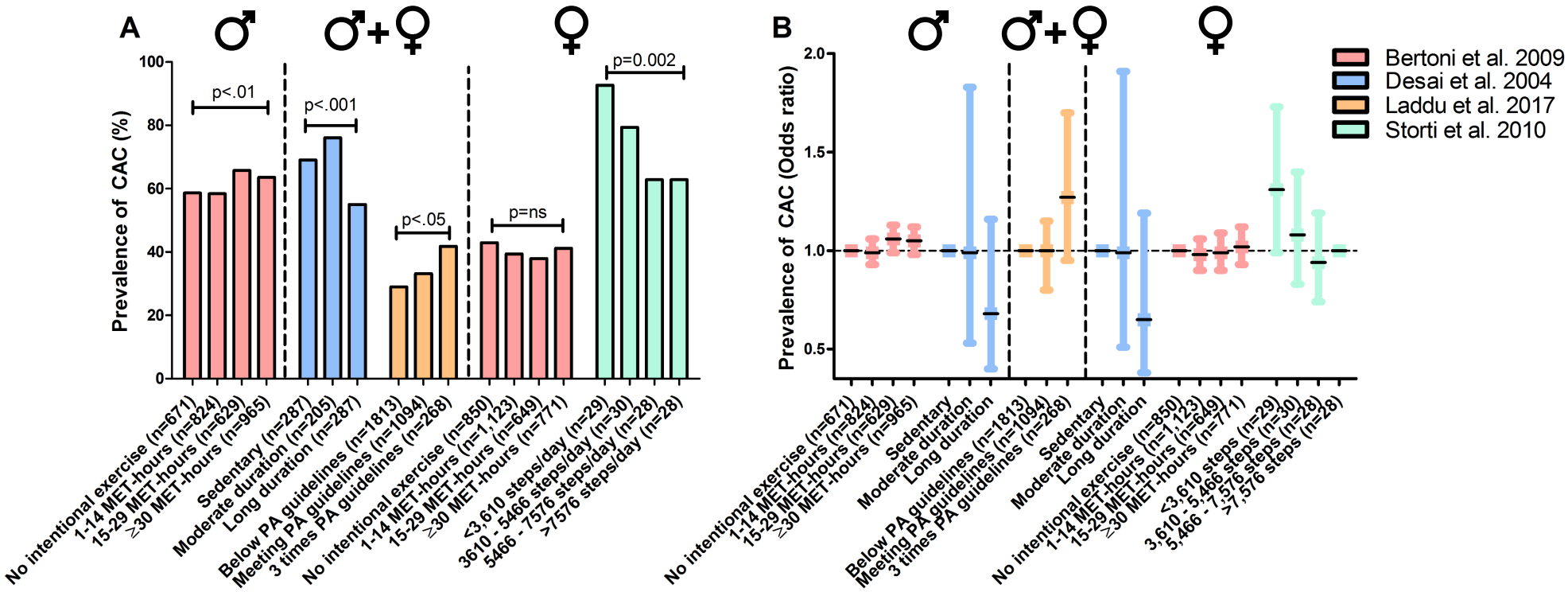
Figure 1 Prevalence of coronary artery calcification in the general population. Studies reporting CAC prevalence and adjusted odds ratios for the association between physical activity and CAC are shown. Panel A illustrates percentage of CAC prevalence (CACS>0) across physical activity/exercise groups; Panel B illustrates adjusted odds ratios for CAC prevalence across physical activity/exercise groups. In Panel B, Desai et al. (blue color) included 520 men and 259 women, but the sample size per physical activity categories was not reported. In summary, there is no clear net effect towards either a positive or inverse association between physical activity volumes and CAC prevalence in general population studies. CAC, coronary artery calcification. CACS, CAC score.

Figure 2 Prevalence of coronary artery calcification and coronary artery calcification scores in studies comparing male athletes with controls. Panel A illustrates the prevalence of CACS >0 within athletic and control subjects, Panel B illustrates the prevalence of CACS >100 and Panel C illustrates the CACS within those individuals with prevalent CAC. These data illustrate increased coronary artery calcification in (the most active) athletes. CAC, coronary artery calcification; CACS, CAC score. RF, risk factors. AU, arbitrary units.

Figure 3 Coronary plaque morphology in athletes. Panel A illustrates the percentages of different coronary plaque morphologies of the 99 plaques in athletes and 26 plaques in the control subjects (total equals 100%). Panel B illustrates the percentages of different coronary plaque morphologies in athletes with plaques, divided by lifelong exercise volume, whereas Panel C illustrates the percentage of athletes with plaques who had only calcified, only non-calcified or only mixed plaque morphology. Adapted and reprinted with permission from Merghani et al.[5] (Panel A) and Aengevaeren et al[4] (Panel B and C).

Figure 4 Potential explanations for increased coronary atherosclerosis in athletes. Icons from flaticon.com.

Figure 5 The benefits and risks of long-term exercise training on coronary function, morphology and atherosclerosis.


A
♂
♂+♀
♀
Prevalence of CAC (%)
100
80
60
40
20
0
p<.01
p<.001
p<.05
p=ns
p=0.002
No intentional exercise (n=671)
1-14 MET-hours (n=824)
15-29 MET-hours (n=629)
≥30 MET-hours (n=965)
Sedentary (n=287)
Moderate duration (n=205)
Long duration (n=287)
Below PA guidelines (n=1813)
Meeting PA guidelines (n=1094)
3 times PA guidelines (n=268)
No intentional exercise (n=850)
1-14 MET-hours (n=1,123)
15-29 MET-hours (n=649)
≥30 MET-hours (n=771)
<3,610 steps/day (n=29)
3610 - 5466 steps/day (n=30)
5466 - 7576 steps/day (n=28)
>7576 steps/day (n=28)
B
♂
♂+♀
♀
Prevalence of CAC (Odds ratio)
2.0
1.5
1.0
0.5
Bertoni et al. 2009
Desai et al. 2004
Laddu et al. 2017
Storti et al. 2010
No intentional exercise (n=671)
1-14 MET-hours (n=824)
15-29 MET-hours (n=629)
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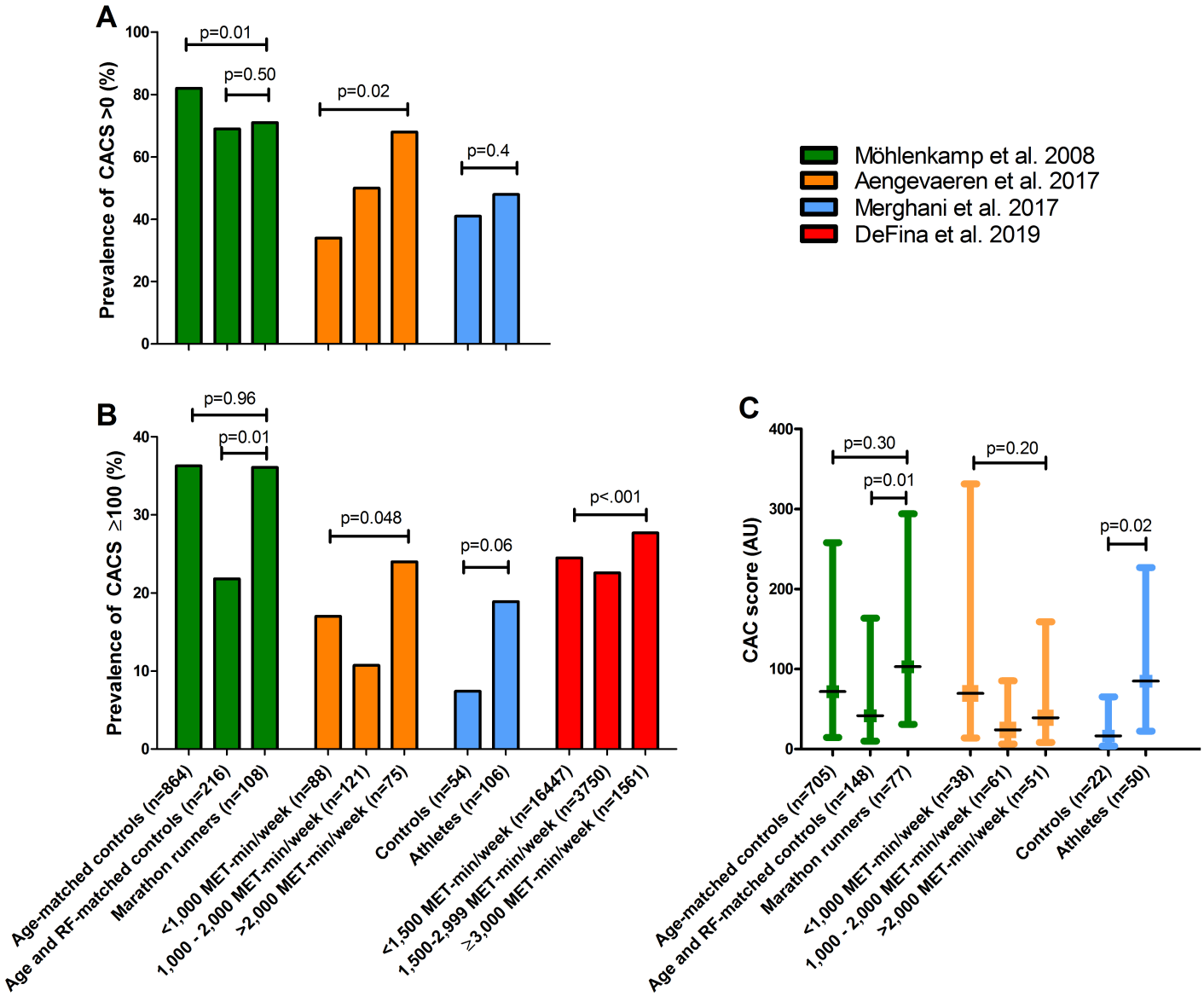
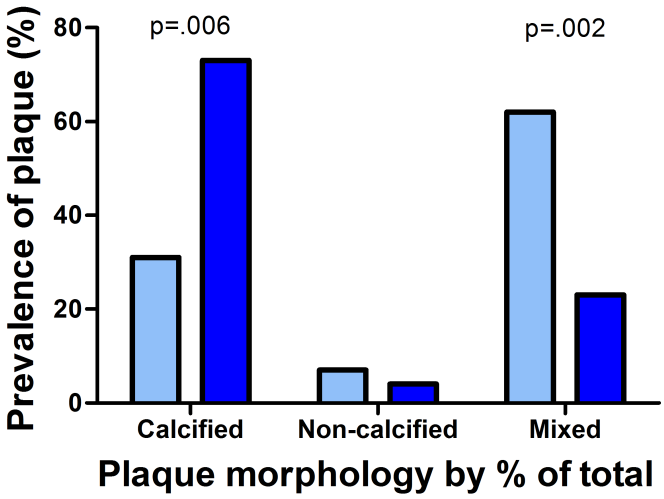
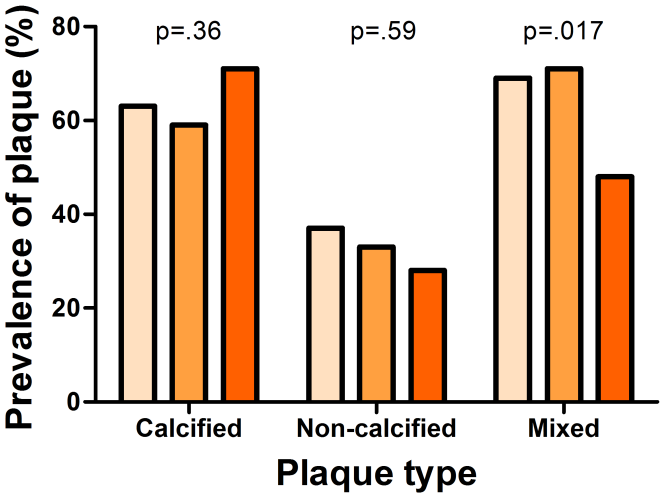
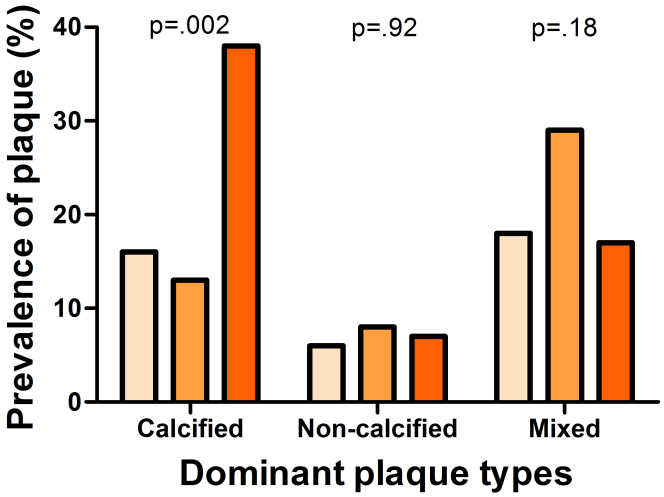
<3,610 steps (n=29)
3,610 - 5,466 steps (n=30)
5,466 - 7,576 steps (n=28)
>7,576 steps (n=28)


A
Prevalence of CACS >0 (%)
100
80
60
40
20
0
p=0.01
p=0.50
p=0.02
p=0.4
Möhlenkamp et al. 2008
Aengevaeren et al. 2017
Merghani et al. 2017
DeFina et al. 2019
B
Prevalence of CACS ≥100 (%)
40
30
20
10
0
p=0.96
p=0.01
p=0.048
p=0.06
p<.001
Age-matched controls (n=864)
Age and RF-matched controls (n=216)
Marathon runners (n=108)
<1,000 MET-min/week (n=88)
1,000 - 2,000 MET-min/week (n=121)
>2,000 MET-min/week (n=75)
Controls (n=54)
Athletes (n=106)
<1,500 MET-min/week (n=16447)
1,500-2,999 MET-min/week (n=3750)
≥3,000 MET-min/week (n=1561)
C
CAC score (AU)
400
300
200
100
0
p=0.30
p=0.01
p=0.20
p=0.02
Age-matched controls (n=705)
Age and RF-matched controls (n=148)
Marathon runners (n=77)
<1,000 MET-min/week (n=38)
1,000 - 2,000 MET-min/week (n=61)
>2,000 MET-min/week (n=51)
Controls (n=22)
Athletes (n=50)


p=.006
p=.002
Prevalence of plaque (%)
80
60
40
20
0
Calcified
Non-calcified
Mixed
Plaque morphology by % of total


Merghani et al.
Controls
Athletes
Aengevaeren et al.
<1000 MET-min/week
1000 - 2000 MET-min/week
>2000 MET-min/week

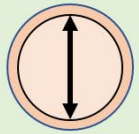

p=.36
p=.59
p=.017
Prevalence of plaque (%)
80
60
40
20
0
Calcified
Non-calcified
Mixed
Plaque type


p=.002
p=.92
p=.18
Prevalence of plaque (%)
40
30
20
10
0
Calcified
Non-calcified
Mixed
Dominant plaque types

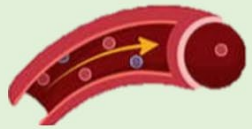

Potential explanations for increased coronary atherosclerosis in athletes
Altered coronary hemodynamics[63,64]
↑ Parathyroid hormone[60-62]
↓ Magnesium[57-59]
↓ Vitamin D[54-56]
Disrupted laminar flow[52]
↑ Mechanical stress[52]
↑ Systolic blood pressure[53]
↑ Inflammation[65,67]
Imbalanced diet
Psychological stress
Genetics
Performance enhancing drugs[51]
Immune-modulating medication
Mg
MAGNESIUM
12
VITAMIN
D

Exercise-induced adaptations of coronary arteries

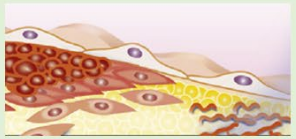
↑ Epicardial coronary diameter & capillary density



Improved coronary function



More benign plaque composition



↑ Coronary atherosclerosis

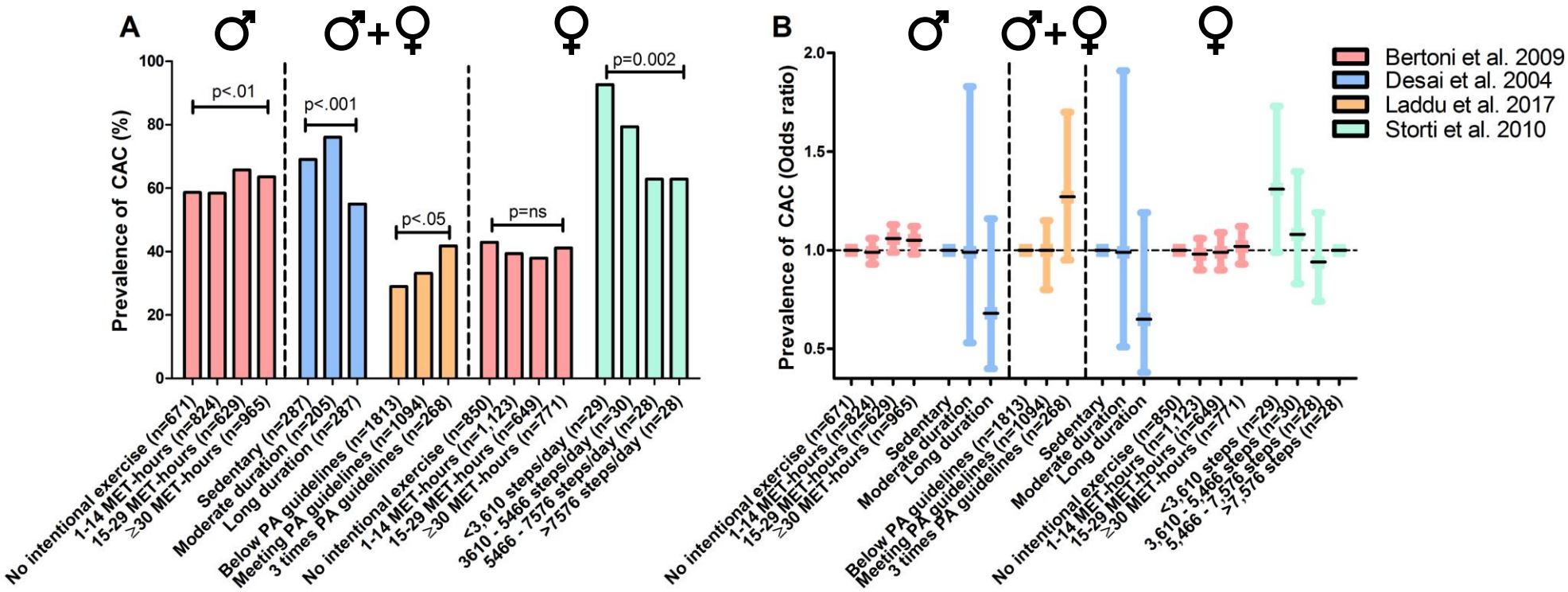
Clinical consequences

Higher life expectancy

Lower risk of plaque rupture

Less consequences of stenoses?

↑ Coronary atherosclerosis = ↑ risk


A
♂
♂+♀
♀
Prevalence of CAC (%)
100
80
60
40
20
0
p<.01
p<.001
p<.05
p=ns
p=0.002
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♂
♂+♀
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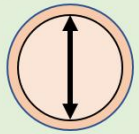
5,466 - 7,576 steps (n=28)
>7,576 steps (n=28)

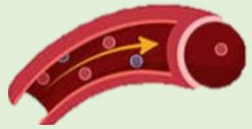

Potential explanations for increased coronary atherosclerosis in athletes
Altered coronary hemodynamics[63,64]
↑ Inflammation[65,67]
Imbalanced diet
Psychological stress
Genetics
Performance enhancing drugs[51]
Immune-modulating medication
↑ Parathyroid hormone[60-62]
↓ Magnesium[57-59]
Mg
MAGNESIUM
12
↓ Vitamin D[54-56]
VITAMIN
D
Disrupted laminar flow[52]
↑ Mechanical stress[52]
↑ Systolic blood pressure[53]

Exercise-induced adaptations of coronary arteries

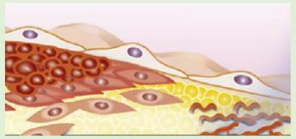
↑ Epicardial coronary diameter & capillary density



Improved coronary function



More benign plaque composition



↑ Coronary atherosclerosis

Clinical consequences

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