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CLINICAL RESEARCH

Running: the risk of coronary events†

Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners

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Aims To quantify the prevalence of coronary artery calcification (CAC) in relation to cardiovascular risk factors in marathon runners, and to study its role for myocardial damage and coronary events.

Methods and results In 108 apparently healthy male marathon runners aged ≥50 years, with ≥5 marathon competitions during the previous three years, the running history, Framingham risk score (FRS), CAC, and presence of myocardial late gadolinium enhancement (LGE) were measured. Control groups were matched by age (8:1) and FRS (2:1) from the Heinz Nixdorf Recall Study. The FRS in marathon runners was lower than in age-matched controls (7 vs. 11%, $P < 0.0001$). However, the CAC distribution was similar in marathon runners and age-matched controls (median CAC: 36 vs. 38, $P = 0.36$) and higher in marathon runners than in FRS-matched controls (median CAC: 36 vs. 12, $P = 0.02$). CAC percentile values and number of marathons independently predicted the presence of LGE (prevalence = 12%) ($P = 0.02$ for both). During follow-up after 21.3 ± 2.8 months, four runners with CAC ≥ 100 experienced coronary events. Event-free survival was inversely related to CAC burden ($P = 0.018$).

Conclusion Conventional cardiovascular risk stratification underestimates the CAC burden in presumably healthy marathon runners. As CAC burden and frequent marathon running seem to correlate with subclinical myocardial damage, an increased awareness of a potentially higher than anticipated coronary risk is warranted.

Keywords Marathon running • Cardiovascular risk stratification • Coronary artery calcium • Late gadolinium enhancement

Introduction

Regular physical exercise improves the cardiovascular risk profile and reduces cardiovascular disease (CVD) morbidity and mortality.[1,2] Vigorous exercise, on the other hand, increases the short-term risk of coronary events.[3] Coronary atherosclerosis is the main underlying cause of exercise-related coronary events not only among elderly persons unaccustomed to exercise,[4] but also in adult athletes including marathon runners.[5,6]

Over the past decades, the number of recreational marathon runners, including those at older age, is constantly rising. This trend may have implications for pre-participation cardiovascular

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risk stratification. Identification of marathon runners at risk is difficult and the need for cardiovascular medical examinations remains controversial.[7,8] The risk of sudden cardiac death associated with marathon running has been suggested to be too low to recommend routine screening for coronary artery disease (CAD).[9] In master athletes, pre-participation medical evaluations are nonetheless advised as a prudent measure before entering master sports training programmes.[8,10] Standard clinical exercise tests can, however, be normal, even in the presence of rupture-prone coronary plaques.[5,11,12]

Based on prospective studies in various cohorts,[13] it is speculated that advanced coronary artery calcification (CAC) in endurance athletes may be associated with an increased risk of cardiac events.[5] Yet, the role of subclinical coronary atherosclerosis in cardiovascular risk assessment has not been studied in marathon runners. In patients with CAD, the presence of cardiac magnetic resonance imaging (cMRI)-based myocardial late gadolinium enhancement (LGE) may reflect prior myocardial damage and is associated with an impaired prognosis,[14] but its association with subclinical CAC burden in healthy marathon runners is unknown.

This study was designed to quantify the prevalence of CAC in relation to cardiovascular risk factors in marathon runners, and to study its role for myocardial damage and coronary events.

Methods

Details on the Marathon study design have been reported previously.[15] Participants were recruited in three ways: 1) an advertisement in a German marathon journal ('Runners World'), 2) a press conference during inauguration of the study, and 3) inclusion of colleagues and friends of participants, if inclusion criteria were met. Matched control groups were selected from the Heinz Nixdorf Recall Study (HNRS).[16] Both studies were approved by the local ethics committee and by the National Institute of Radiation Protection (Bundesamt für Strahlenschutz, Munich, Germany). All participants gave written informed consent prior to participation in both studies including informed consent for clinical follow-up and evaluation of hospital records.

Inclusion and exclusion criteria

Males $\geq$50 years were eligible, if they had completed at least five full-distance marathons (42.195 km) during the preceding three years. Exclusion criteria comprised history of established heart disease, diabetes mellitus, angina pectoris, and renal failure, musculo-skeletal disease at inclusion preventing future regular marathon running, psychiatric disease, and unwillingness to give informed consent.[15] Two males were excluded from the study because of prior unreported myocardial infarction in one and severe renal failure because of untreated prostate disease in another.

Cardiovascular risk factors

Details on cardiovascular risk factor quantification and laboratory measurements have been described elsewhere.[15,16] Blood pressure was measured with an automated oscillometric blood pressure device (Omron 705-CP, Omron, Germany). Current smoking was defined as a history of cigarette smoking during the past year. Participants were defined diabetic if they either reported a physician's diagnosis of diabetes, if they were taking anti-diabetic medication, or if their fasting glucose level was >126 mg/dL. All questionnaires, including those to quantify weekly exercise,[17] interviews, and test protocols were identically used in both studies. The Framingham risk score (FRS) was computed as previously described.[16]

Electron-beam computed tomography

Non-enhanced electron-beam computed tomography (EBCT) scans were performed on C-150 scanners (GE Imatron, South San Francisco, USA). EBCT scans for the studies were obtained at three sites with identical scanning protocols as previously described.[18] The Agatston CAC score was quantified and percentile CAC values were calculated based on data from the HNRS.[18] The CAC score was not given to participants or to general practitioners in both studies.

Cardiac magnetic resonance imaging

cMRI scans were performed in the marathon study but not in the HNRS. All examinations were performed on a 1.5 T MR scanner equipped with high-performance gradients (Magnetom Avanto, Siemens, Erlangen, Germany). An inversion recovery fast low angle shot sequence (IR-turboFLASH: TR 8.0 ms, TE 4.0 ms, TI 180–240 ms, FA 20°) was acquired in short- and long-axis views 10–15 min after injection of 0.2 mmol/kg body weight of gadolinium-diethylene triamine pentaacetic acid (DTPA) (Magnevist, Schering AG, Berlin, Germany) to identify LGE. Pattern and extent of LGE were assessed using short- and long-axis views[19] and were defined as present only if detectable in two orthogonal planes. A repeat cMRI study was performed when LGE was detected.

Follow-up and definition of coronary events

Follow-up information was obtained from annual questionnaires and personal communication. Events were confirmed from hospital records. Coronary events were defined as sudden coronary death, myocardial infarction, and coronary revascularization.

Statistical analysis

For comparison with the general population, two groups matching the marathon runners (group I) were drawn from the HNRS cohort, restricted to males without CAD, aged $\geq$50 ($n = 1842$). These were group II: 1:8 matching in four-year age classes, group III: 1:2 matching within $\pm$3 years of age, within $\pm 3\ kg/m^2$ body mass index (BMI), within $\pm$4% Framingham risk per 10 years, and by smoking status (present/former/never smokers). Furthermore, the matched cohort group III was restricted to HNRS participants without a history of stroke or diabetes ($n = 1597$). Matching was performed using PROC SURVEYSELECT of SAS (SAS Institute Inc., Cary, NC, USA) to generate group II and the algorithm described in Schröder *et al.*[20] to generate group III.

Data were presented as mean $\pm$ SD, median—25th and 75th percentiles (Q1 and Q3), or proportions, where appropriate. Correlations involving CAC score were calculated according to Spearman, associations with physical activity parameters were also analysed with linear regression analyses for log-transformed (CAC + 1). To compare matching factors between groups, the Mann–Whitney *U* test, χ^2 test, or Fisher's exact test were employed. To evaluate group effects controlling for matching factors, general linear or logistic models (PROC GLM or PROC LOGISTIC of SAS) were used. Because of the strongly skew CAC distribution, models for CAC were based on ranks. Predictive models for CAC were also calculated using general linear models, with the Agatston score transformed as $\log_2(\text{CAC} + 1)$. All linear regression models were inspected by analysis of residuals and checked for nonlinear dependencies. Except models for $\log_2(\text{CAC} + 1)$ there were no abnormalities.

Presence of LGE was modelled by logistic regression in one and two variables. Because of the low number of LGE, *P*-values from a two-variable model, comprising number of marathons (logarithmized), and CAC percentile values, were recalculated with exact logistic regression using LogXact (Cytel Software Corporation, Cambridge, MA, USA).

Event-free survival rates were estimated following the Kaplan–Meier method and overall group differences were evaluated by log-rank statistics. In addition, a Cox regression model with log-transformed CAC—$\log_2(\text{CAC} + 1)$—as independent variable was calculated.

Results

One hundred and eight male runners aged 50–72 years were included in the study. They had completed 20 marathons (median value, Q1–Q3: 14–42), had started marathon running nine years ago (Q1–Q3: 7–16), and trained 55 km (approximately 35 miles) (Q1–Q3: 45–65) on five days per week throughout the year.

Matching

Our attempt to match two males out of 1597 eligible males from the HNRS with each marathon runner by age, BMI, and FRS did not result in an equal FRS but in a lower FRS in marathon runners than in group-III controls (7.0 ± 3.6 vs. 7.7 ± 3.4%, $P = 0.03$) (*Table 1*).

Risk factor distribution

Compared with age-matched controls, marathon runners had a 42% higher high-density lipoprotein cholesterol, an 18% lower low-density lipoprotein-cholesterol, a 19% lower rate of ever smoking, a 12% lower systolic blood pressure, and a 15% lower BMI (*Table 1*), resulting in a 51% lower mean 10 year FRS (7.0 ± 3.6 vs. 14.3 ± 8.2%, $P < 0.0001$).

Physical activity

Marathon runners had higher weekly metabolic equivalents (METs) and lower heart rates than both control groups (*Table 1*). We found no age-adjusted Spearman correlation between weekly METs and CAC in marathon runners ($R^2 = 0.02$, $P = 0.13$) or in age-matched controls ($R^2 = 0.001$, $P = 0.36$). In marathon runners, CAC was also not associated with years of running ($R^2 = 0.024$, $P = 0.12$), with the number of marathon races completed ($R^2 = 0.007$, $P = 0.39$), or with training mileage ($R^2 = 0.014$, $P = 0.23$). Regression analyses revealed no hints for

Table 1 Demographic variables and risk factors

	Participants of the Heinz Nixdorf Recall Study			*P*-value group I vs. group II	*P*-value group I vs. group III
	Marathon runners (group I)	Age-matched controls (8:1) (group II)	Controls matched for age and risk factors (2:1) (group III)		
n	108	864	216	n.a.	n.a.
Age (years)	57.2 ± 5.7	57.2 ± 5.9	57.1 ± 5.6	0.96	0.93
BMI	24.0 ± 2.3	28.1 ± 4.0	24.9 ± 2.1	<0.0001	0.0004
Systolic blood pressure (mmHg)	121 ± 14	137 ± 18	127 ± 14	<0.0001	0.02
History of hypertension (%)	12.0	40.8	28.4	<0.0001	0.005
Total cholesterol (mg/dL)	227 ± 42	228 ± 38	215 ± 32	0.91	0.0004
LDL cholesterol (mg/dL)	121 ± 29	147 ± 36	131 ± 31	<0.0001	0.05
HDL cholesterol (mg/dL)	73.8 ± 17.3	51.9 ± 14.7	60.6 ± 14.7	<0.0001	<0.0001
Smoking status					
Current (%)	4.6	28.4	4.6	<0.0001	n.a.
Former (%)	51.9	42.1	51.9	0.41	n.a.
Diabetes (%)	0	8.6	0	0.002	n.a.
10-year Framingham risk score	7 (4–9)	11 (9–18)	7 (6–9)	<0.0001	0.03
History of stroke (%)	0	2.2	0	0.12	n.a.
Weekly exercise (MET/week)	4686 ± 2285	1389 ± 1876	1748 ± 2200	<0.0001	<0.0001
Resting heart rate (b.p.m.)	65 ± 10	76 ± 12	74 ± 11	<0.0001	<0.0001

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; b.p.m., beats per minute; MET, metabolic equivalent; n.a., not available. All subjects were free of overt coronary artery disease, i.e. history of myocardial infarction or coronary revascularization. Data are presented as mean ± SD, proportions (%), or median values. The numbers in brackets indicate Q1–Q3, i.e. 25th and 75th percentile. All group I/group II comparisons adjusted for age, all group I/group III comparisons (excepting matching factors) adjusted for age, BMI, Framingham risk, smoking status.

Table 2 Distribution of coronary artery calcification (CAC) measures in the three groups

	Participants of the Heinz Nixdorf Recall Study			*P*-value group I vs. group II	*P*-value group I vs. group III
	Marathon runners (group I)	Age-matched controls (8:1) (group II)	Controls matched for age and risk factors (2:1) (group III)		
$\log_2$(CAC + 1) (mean ± SD)	4.1 ± 3.6	4.9 ± 3.3	3.8 ± 3.4	0.28	0.02
CAC (Q1/median/Q3)	0/36/217	3/38/187	0/12/78	0.36	0.02
zero CAC (%)	28.7	18.4	31.5	0.01	0.50
CAC >75th percentile (%)	25.0	24.2	14.8	0.85	0.01
CAC 0 to <10	40.74	34.61	48.61		
CAC 10 to <100	23.15	29.05	29.63	0.52	0.02
CAC 100 to <400	23.15	22.80	13.43		
CAC ≥400	12.96	13.54	8.33		

Comparisons in continuous or binary measures adjusted for matching factors (age for group I/group II, age, body mass index, Framingham risk, smoking status for group I/group III).

curve-linearity in any of these relations, and the respective 95% confidence intervals (CIs) of estimated slopes all included zero.

Prevalence and extent of coronary artery calcification

A zero CAC score was more frequent in marathon runners than in age-matched controls, but was similar when compared with FRS-matched controls (*Table 2*). The overall CAC score distribution was similar in marathon runners and age-matched controls (*Table 2*) with similar rates of CAC ≥ 100 in these groups (36.1 vs. 36.3%, $P = 0.96$) but higher rates in marathon runners when compared with FRS-matched controls (36.1 vs. 21.8%, $P = 0.01$) (*Table 2*).

Prevalence and predictors of myocardial late gadolinium enhancement

cMRI studies were performed in 102 subjects. Reasons for non-participation were a cochlear metal implant ($n = 1$), metal splinter in a rib ($n = 1$), claustrophobia ($n = 1$), refusal of contrast administration ($n = 2$), and poor image quality ($n = 1$). LGE was observed in 12 persons (12%) with $n = 5$ (42%) showing a subendocardial scar pattern typical of ischaemia and $n = 7$ (58%) with a mid-myocardial patchy pattern suggesting non-ischaemic origin. Runners with LGE had a higher CAC score vs. those without LGE [median CAC (Q1–Q3): 192 (129–603) vs. 26 (0–159), $P = 0.0046$]. In univariate analysis, the CAC score, CAC percentile values, and the number of marathons but not the FRS were associated with LGE (*Table 3*). In multivariable analysis, CAC percentile distribution and the number of marathons remained independently associated with the presence of LGE (*Table 3*). These associations were confirmed by exact logistic regression.

Table 3 Univariate and multivariate analysis for predictors of myocardial late gadolinium enhancement (LGE)

	Increase of units	OR	95% CI	*P*-value
Univariate analysis				
Absolute CAC score [$\log_2$(CAC + 1)]	Two-fold	1.36	1.08–1.71	0.009
CAC percentile value	5 units	1.17	1.03–1.34	0.02
Number of marathons completed (log-transformed)	Two-fold	1.62	1.07–2.46	0.02
Framingham risk score	5%	1.55	0.79–3.01	0.2
Multivariate analysis				
CAC percentile value	5 units	1.19	1.03–1.38	0.02
Number of marathons completed (log-transformed)	Two-fold	1.65	1.08–2.52	0.02

OR, odds ratio; CI, confidence interval. CAC percentile values were chosen for the multivariable model, because CAC percentile values incorporate the age-adjusted extent of CAC.

Follow-up and events

No marathon runner died during 21.0 months [interquartile range (IQR) 18.6–24.0 months) of follow-up. Coronary events occurred in four runners (*Table 4*). Two of these were sudden (hard) coronary events and two others were revascularizations. The first runner with an event (CAC = 874, *Table 4*) was successfully resuscitated after 7 km during a 10 km race. Coronary angiography revealed significant stenoses (>80% lumen reduction) in all three vessels. The second runner with an event (CAC = 472, *Table 4*) underwent uneventful coronary artery bypass graft (CABG) surgery because of left main disease and significant angiographic two-vessel disease, which was identified during additional testing, as previously published in detail.[11] Revascularization in the third event (CAC = 171, *Table 4*) was triggered by an electrocardiogram (EKG)

Table 4 Risk factors and test results of participants with events during follow-up

Risk factors/test results at baseline	Subjects with an event during follow-up				Normal range[a]
	1	2	3	4	
Age (years)	66	64	55	62	
BMI (kg/m^2)	22.5	24.6	22.0	22.0	<25
Systolic blood pressure (mmHg)	110/61	105/67[b]	153/96	138/82	<120/80
History of hypertension	No	Yes	No	Yes	No
Total cholesterol (mg/dL)	344	201	233	240	<240
LDL cholesterol (mg/dL)	170	116	98	131	<160
HDL cholesterol (mg/dL)	109	60	100	65	>40
Smoking status	Former	Never	Former	Former	Never
10-year Framingham risk score (%)	8	7	6	10	The lower the better
CAC score (Agatston units)	874	472	171	128	zero CAC
CAC percentile rank	86	81	73	60	zero CAC
Myocardial LGE	Yes	No	Yes	Yes	No
Resting heart rate (b.p.m.)	48	58	63	42	50–100
Weekly MET	4241	4806	8296	5054	
Marathons completed (no.)	14	22	65	140	
Findings on invasive angiography	Three-VD	Two-VD	Myocardial bridge/ One-VD	Three-VD	
Type of event	VT during exercise, stent	Stent/ CABG	Stent	VT during exercise, CABG	

Note that details on subject 2 have previously been reported.[11]
LGE, late gadolinium enhancement; VD, vessel disease; b.p.m., beats per minute; VT, ventricular tachycardia; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CAC, coronary artery calcium; MET, metabolic equivalent; no., number.
[a]For asymptomatic males without known CAD.
[b]On 5 mg Ramipril (Sanofi Aventis, Frankfurt, Germany) once daily.

performed after a marathon competition demonstrating ST-elevation. A subsequent echocardiogram showed septal wall motion abnormality, which was followed by invasive angiography, demonstrating significant left anterior descending stenosis and myocardial bridging of a septal branch. The fourth event (CAC = 128, *Table 4*) occurred just after moderate physical exercise. The participant was successfully resuscitated. Coronary angiography demonstrated significant three-vessel disease followed by CABG surgery. At present, all these runners are fit and well.

Distribution of CAC in runners with events was as follows—CAC <100: 0 of 69 (0%); CAC 100 to <400: two of 25 (8%), and CAC ≥400: two of 14 (14.3%). The difference in event rates among CAC groups reached statistical significance using log-rank analysis but just failed to reach statistical significance using Cox regression analysis (*Figure 1*).

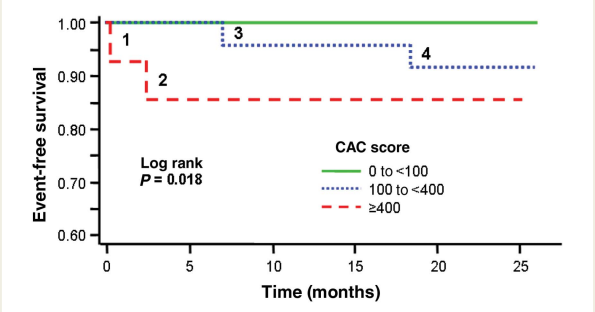

Figure 1 Kaplan–Meier estimates of event-free survival by extent of coronary artery calcification (CAC). No marathon runners with CAC <100 experienced a coronary event, while 8% and 14.3% of those with CAC 100 to <400 and ≥400, respectively, required revascularization during follow-up. Using Cox regression analysis, hazard ratios for a two-fold increase in $\log_2$(CAC+1) were: hazard ratio = 1.51, 95% confidence interval = 0.97–2.36, $P = 0.07$. The numbers pertain to the subjects with events in *Table 3*.

Discussion

The present study was designed to examine the prevalence of subclinical atherosclerosis in relation to cardiovascular risk factors and their role for myocardial damage and outcome in accomplished recreational marathon runners. To our surprise, given the substantial evidence that physical activity reduces CAD event rates,[1,2,21] a CAC score ≥100 was present in 36% of runners, which was not different from age-matched controls, even though the FRS was much lower. Further, the CAC score exceeded that in controls matched for age and FRS. The CAC score was predictive of

myocardial damage, which was evidenced by LGE in 12% of runners. Our outcome data suggest that higher CAC scores may be associated with higher rates of events. There are several possible explanations for these findings.

With respect to the mismatch between FRS and the extent of CAC in marathon runners, many of the runners have commenced marathon running in middle-age. Consequently, their cardiovascular risk factors could have been reduced by exercise training and may not reflect their life-long risk exposure. In fact, more than half of our runners were previous smokers and 5% of runners reported active smoking. This would also explain the comparatively low CAC scores in controls matched for age and FRS, which may have had life-long protection from the atherogenic effect of cardiovascular risk factor exposure. The clinical implication of this possibility is that standard risk factor estimates may lead runners and their physicians to underestimate the athletes' true risk. Risk stratification in marathon runners is further rendered difficult by improved microvascular function in marathon runners, which can compensate for severe epicardial plaque burden and thereby concealing the true extent of coronary atherosclerosis.[11] This may in part explain why all runners in our study were asymptomatic at rest and during running despite considerable atherosclerosis in so many.

In our study, CAC scores were not related to any measure of physical activity in any of the groups. Given the expected population-wide annual increase in CAC of 15–20%,[18] regular marathon running seems not to protect runners from CAC progression once CAC is present. In fact, we even cannot exclude the possibility that exercise to this degree has deleterious effects on coronary arteries. This seems unlikely given the substantial experimental[22] and clinical[1,2,23,24] evidence for the benefits of regular physical activity, but no epidemiological studies have so far examined individuals engaged in such prodigious amounts of exercise as our marathon runners. Several mechanisms may be involved: regular exhaustive exercise during marathon and its required training may induce a rise in vascular oxidative stress because of a high-flow, high-pressure condition, to a point at which it challenges anti-oxidative capacity.[22] Bursts of inflammatory cytokines, which almost invariably occur during marathon running,[25] may also accelerate the atherosclerotic disease process and impair intramyocardial microvascular integrity, whereas no ischaemia is detected during a short-term diagnostic exercise protocol.

The possibility that marathon running and the required training aggravates pre-existing non-calcified atherosclerosis and has a role in LGE development is clearly speculative based on our cross-sectional data. However, it is interesting given recent reports of myocardial injury during marathon running and the observation of prevalent myocardial damage in our runners. Others have demonstrated increases in myocardial troponin levels in recreational marathon runners and other endurance athletes.[26–29] The cause of such possible myocardial damage is unclear, but unlikely owing to epicardial coronary artery obstruction. Evidence of myocardial damage was found in 12% of our 108 runners. A pattern highly suggestive of myocardial ischaemia was seen in 42% of these, whereas the others demonstrated more patchy defects. We have previously shown that infusion of small particles of 10–100 μm in diameter into porcine coronary arteries leads to haemorrhagic and patchy patterns of myocardial damage, depending on particle size.[30] Embolization of microthrombi or atherosclerotic plaque material into the microvasculature is also conceivable during marathon running, because excessive mechanical forces may put strain on plaques and thereby cause plaque erosion or fissuring with subsequent epicardial thrombus formation[8] and microembolization.[31] An increased exercise-induced thrombogenicity from increased catecholamine-induced platelet aggregation, or an imbalance in fibrinolytic/prothrombotic factors[32,33] may also have a role in such thrombus formation. It is therefore possible that both the myocardial injury reported after marathon running[26–29] and the myocardial damage in our marathon runners are in part due to small thrombotic or even atherosclerotic emboli.

The presence of myocardial LGE has recently been shown to predict cardiac events in patients with CAD.[14] In marathon runners, such damaged myocardium may be a substrate for an increased susceptibility to arrhythmias in response to increased exercise-related catecholamine levels,[8] and hence may contribute to cardiac events. In our study, CAC scores were higher in those runners with LGE, supporting a pathophysiological link between epicardial subclinical plaque burden and intramyocardial microvascular damage, as indicated above. Even though CAC is not a measure of plaque vulnerability at that site,[34] the increasing rate of coronary events in parallel with increasing CAC scores may indicate increased plaque vulnerability or susceptibility for plaque rupture or fissuring somewhere else in the coronary tree. The precise mechanism by which elevated epicardial plaque burden may increase the likelihood of myocardial damage and vulnerability, remains to be shown.

Limitations

Our data do not apply to women and may not be representative for all marathon runners, as we cannot exclude recruitment bias. Participants may have had previous risk factors, a recent reduction in exercise capacity or recently discovered CVD in a relative. However, we have excluded all subjects with known CVD, diabetes, or any symptoms of CVD, and participants have been running regularly for nine years. The risk factor profile in our cohort is therefore typical for many marathon runners and is expected to be worse in many others. This pertains in particular to diabetic athletes, who have been excluded from this study.

Because of different recruitment strategies and inclusion criteria between the two studies, our findings are subject to selection bias: marathon runners were self-referred because they could not be randomly selected as the participants in the HNRS. They also had to be fit and healthy beyond age 50 to be included, while this was not the case in the HNRS.

Our cohort of marathon runners is heterogeneous with regard to duration of regular physical exercise and marathon running, as evidenced by the interquartile ranges of years of active running, number of marathons completed, and the weekly training mileage. Participants may also differ in their engagement in sports other than marathon running. We believe, though, that our findings reflect the typical spectrum of risk factor and atherosclerosis burden in males >50 years participating in marathons.

It is conceivable that the ratio of calcified and non-calcified atherosclerotic plaque differs among persons who are regularly

exposed to exhaustive exercise and those who are not, because repetitive increases in shear stress and mechanical forces may predominantly impact on the calcified plaque component. Currently, there are no data to support this hypothesis, which can only be assessed non-invasively by additional administration of contrast agent and high-resolution computed tomographic techniques.

We have discussed oxidative stress, microembolization, bursts of inflammation or increased thrombogenicity as potential mechanisms for the pathogenesis of LGE. Yet, other mechanisms, such as subclinical myocarditis, vasculitis, or cardiomyopathy[19] as well as coronary vasospasm or anomalies including myocardial bridging[5] may also have been involved in its development in some athletes, even though marathon runners with any known current or previous CVD were excluded from this study. Further, the HNRS cohort did not undergo CMR scanning at baseline investigation, which precludes a comparison of the prevalence of LGE among these cohorts.

Two events were revascularizations and were in part subject to surveillance bias. The significant stenoses in runners free of symptoms may have been missed outside this prospective study. Even though statistically significant, our event data should therefore be interpreted with caution and longer follow-up in larger cohorts is required. Ideally, event rates in marathon runners should be compared with those in the control groups. However, outcome data from the HNRS will only be available in 2009. Our findings are in a similar magnitude, though, as previously reported from other asymptomatic low-risk cohorts and are in line with existing evidence on the prognostic value of CAC.[13]

Conclusions

Regular marathon running has a beneficial effect on the cardiovascular risk factor profile but the extent of calcified coronary plaque is underestimated from that risk factor profile, with 36% of marathon runners aged $\geq$50 having a CAC score $\geq$100 and 9% of these requiring coronary revascularization during two years of follow-up. Advanced CAC scores seem to contribute to increased myocardial damage and appear to impair outcome. Frequent marathon running may not protect these athletes from the risk of coronary events.

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References

1. Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity and Metabolism (Subcommittee on Physical Activity). *Circulation* 2003;**107**:3109–3116.
2. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events. Potential mediating mechanisms. *Circulation* 2007;**116**:2110–2118.
3. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. Triggering of sudden death by vigorous exercise. *N Engl J Med* 2000;**343**:1355–1361.
4. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion: protection against triggering by regular exertion. *N Engl J Med* 1993;**329**:1677–1683.
5. Thompson PD, Balady GJ, Chaitman BR, Clark LT, Levine BD, Myerburg RJ. Task force 6: coronary artery disease. *J Am Coll Cardiol* 2005;**45**:1348–1353.
6. Noakes TD, Opie LH, Rose AG, Kleynhans PH, Schepers NJ, Dowdeswell R. Autopsy-proved coronary atherosclerosis in marathon runners. *N Engl J Med* 1979;**301**:86–89.
7. Maron BJ, Douglas PS, Graham TP, Nishimura RA, Thompson PD. Task Force 1: preparticipation screening and diagnosis of cardiovascular disease in athletes. *J Am Coll Cardiol* 2005;**45**:1322–1326.
8. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes M, Fulton JE, Gordon NF, Haskell WL, Link MS, Maron BJ, Mittleman MA, Pelliccia A, Wenger NK, Willich SN, Costa F. Exercise and acute cardiovascular events. Placing the risks into perspective. A scientific statement from the AHA council on nutrition, physical activity, and metabolism and the council on clinical cardiology. In collaboration with the American College of Sports Medicine. *Circulation* 2007;**115**:2358–2368.
9. Maron BJ, Poliac LC, Roberts WO. Risk for sudden cardiac death associated with marathon running. *J Am Coll Cardiol* 1996;**28**:428–431.
10. Maron BJ, Araújo CG, Thompson PD, Fletcher GF, de Luna AB, Fleg JL, Pelliccia A, Balady GJ, Furlanello F, Van Camp SP, Elosua R, Chaitman BR, Bazzarre TL. Recommendations for preparticipation screening and the assessment of cardiovascular disease in masters athletes. An advisory for healthcare professionals from the working groups of the World Heart Federation, the International Federation of Sports Medicine, and the AHA Committee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation* 2001;**103**:327–334.
11. Möhlenkamp S, Böse D, Mahabadi AA, Heusch G, Erbel R. On the paradox of exercise: coronary atherosclerosis in an apparently healthy marathon runner. *Nat Clin Pract Cardiovasc Med* 2007;**4**:396–401.
12. Tunstall Pedoe DS. Marathon cardiac deaths: the London experience. *Sports Med* 2007;**37**:448–450.
13. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, Lauer MS, Post WS, Raggi P, Redberg RF, Rodgers RP, Shaw LJ, Taylor AJ, Weintraub WS, Harrington RA, Abrams J, Anderson JL, Bates ER, Eisenberg MJ, Grines CL, Hlatky MA, Lichtenberg RC, Lindner JR, Pohost GM, Schofield RS, Shubrooks SJ, Stein JH, Tracy CM, Vogel RA,

Wesley DJ. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the ACC Foundation Clinical Expert Consensus Task Force developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007;**49**:378–402.

14. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, Davis RB. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006;**113**:2733–2743.
15. Möhlenkamp S, Schmermund A, Kröger K, Kerkhoff G, Bröcker-Preuss M, Adams V, Hensel M, Kiefer D, Lehmann N, Moebus S, Leineweber K, Elsenbruch S, Barkhausen J, Halle M, Hambrecht R, Siegrist J, Mann K, Budde T, Jöckel KH, Erbel R. Coronary atherosclerosis and cardiovascular risk in master male marathon runners. Rationale and design of the Marathon Study. *Herz* 2006;**31**:575–585.
16. Erbel R, Möhlenkamp S, Lehmann N, Schmermund A, Moebus S, Stang A, Grönemeyer D, Seibel R, Mann K, Volbracht L, Dragano N, Siegrist J, Jöckel KH, on behalf of the Heinz Nixdorf Recall Study Investigative Group. Sex related cardiovascular risk stratification based on quantification of atherosclerosis and inflammation. *Atherosclerosis* 2008;**197**:662–672.
17. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;**32**(Suppl. 9):S498–S504.
18. Schmermund A, Möhlenkamp S, Berenbein S, Pump H, Moebus S, Roggenbuck U, Stang A, Seibel R, Grönemeyer D, Jöckel KH, Erbel R, on behalf of the Heinz Nixdorf Recall Study Investigative Group. Population-based assessment of subclinical coronary atherosclerosis using electron beam CT. *Atherosclerosis* 2006;**185**:177–182.
19. Hunold P, Schlosser T, Vogt FM, Eggebrecht H, Schmermund A, Bruder O, Schuler WO, Barkhausen J. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. *Am J Roentgenol* 2005;**184**:1420–1426.
20. Schröder M, Hüsing J, Jöckel KH. An implementation of automated individual matching for observational studies. *Methods Inf Med* 2004;**43**:516–520.
21. Pedersen JO, Lilienthal Heitmann B, Schnohr P, Grønbæk M. The combined influence of leisure-time physical activity and weekly alcohol intake on fatal ischaemic heart disease and all-cause mortality. *Eur Heart J* 2008;**29**:1–9.
22. Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? *Cardiovasc Res* 2005;**67**:187–197.
23. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. *Circulation* 2000;**102**:1358–1363.
24. Yu S, Yarnell JWG, Sweetnam PM, Murray L. What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart* 2003;**89**:502–506.
25. 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 Sports Exerc* 2003;**35**:348–355.
26. Neilan TG, Januzzi JL, Lee-Lewandrowski E, Ton-Nu TT, Yoerger DM, Jassal DS, Lewandrowski KB, Siegel AJ, Marshall JE, Douglas PS, Lawlor D, Picard MH, Wood MJ. Myocardial injury and ventricular dysfunction related to training levels among non-elite participants in the Boston Marathon. *Circulation* 2006;**114**:2325–2333.
27. Fortescue EB, Shin AY, Greenes DS, Mannix RC, Agarwal S, Feldman BJ, Shah MI, Rifai N, Landzberg MJ, Newburger JW, Almond CS. Cardiac troponin increases among runners in the Boston Marathon. *Ann Emerg Med* 2007;**49**:137–143.
28. Rifai N, Douglas PS, O'Toole M, Rimm E, Ginsburg GS. Cardiac troponin T and I, electrocardiographic wall motion analyses, and ejection fractions in athletes participating in the Hawaii ironman triathlon. *Am J Cardiol* 1999;**83**:1085–1089.
29. Scharhag J, Herrmann M, Urhausen A, Haschke M, Herrmann W, Kindermann W. Independent elevations of N-terminal pro-BNP and cardiac troponins in endurance athletes after prolonged strenuous exercise. *Am Heart J* 2005;**150**:1128–1134.
30. Möhlenkamp S, Beighley PE, Pfeifer EA, Behrenbeck TR, Sheedy PF II, Ritman EL. Intramyocardial blood volume, perfusion and transit time in response to embolization of different sized microvessels. *Cardiovasc Res* 2003;**57**:843–852.
31. Heusch G, Schulz R, Baumgart D, Haude M, Erbel R. Coronary microembolization. *Prog Cardiovasc Dis* 2001;**44**:217–230.
32. Bärtsch P. Platelet activation with exercise and risk of cardiac events. *Lancet* 1999;**354**:1747–1748.
33. 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* 2001;**88**:918–920.
34. Schmermund A, Erbel R. Unstable coronary plaque and its relation to coronary calcium. *Circulation* 2001;**104**:1682–1687.