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ORIGINAL ARTICLE

Association between physical activity and coronary artery calcification estimated by computed tomography: A systematic review

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KEYWORDS
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Abstract
Background: The relationship between physical activity and coronary artery calcification (CAC) was evaluated in different studies during the last years, although the results were conflicting.
Objective: The main objective of the present systematic review was to assess the association between different levels of physical activity and CAC score estimated by computed tomography (CT).
Methods: This systematic review was performed according to PRISMA guidelines. A literature search was performed to detect studies that evaluated the association between physical activity and CAC score. The levels of physical activity evaluated were those reported by the original publications. The CAC score was estimated by CT and was reported in Agatston units.
Results: Twenty six studies including 89,405 subjects were considered eligible for this research. The studies developed in the general population showed different results regarding the association between physical activity and CAC score: no association (7 studies), a positive association (4 studies), an inverse relationship (6 studies), a U-shaped relationship (2 studies), or different results depending on the subgroup evaluated (2 studies). In the largest studies, a positive association was observed. When we analyzed the studies that evaluated athletes, four studies showed a positive association between exercise intensity and CAC.
Conclusion: This systematic review showed disparate results regarding the association between physical activity and CAC score. The largest studies and most studies developed in athletes suggest that intense physical activity could be associated with high CAC score, although this hypothesis should be confirmed in future research.

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PALABRAS CLAVE
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Tomografía computarizada;
Atletas

Asociación entre la actividad física y el calcio arterial coronario estimado por tomografía computarizada: una revisión sistemática

Resumen

Antecedentes: La relación entre la actividad física y el calcio arterial coronario (CAC) fue evaluada en diferentes estudios durante los últimos años, aunque los resultados fueron contradictorios.

Objetivo: El principal objetivo fue evaluar la asociación entre diferentes niveles de actividad física y la puntuación de CAC estimada por tomografía computarizada (TC).

Métodos: Esta revisión sistemática se realizó de acuerdo con las guías PRISMA. Se realizó una búsqueda bibliográfica para detectar estudios que evaluaran la asociación entre la actividad física y la puntuación de CAC. Los niveles de actividad física evaluados fueron los informados por las publicaciones originales. La puntuación de CAC se estimó por TC y se informó en unidades Agatston.

Resultados: Veintiséis estudios que incluyeron 89.405 sujetos se consideraron elegibles para esta investigación. Los estudios desarrollados en población general mostraron diferentes resultados en cuanto a la asociación entre la actividad física y la puntuación de CAC: ninguna asociación (7 estudios), una asociación positiva (4 estudios), una relación inversa (6 estudios), una relación en forma de «U» (2 estudios), o resultados diferentes según el subgrupo evaluado (2 estudios). Los estudios más grandes y 4 de los estudios que evaluaron atletas reportaron una asociación positiva.

Conclusión: Esta revisión sistemática mostró resultados dispares en cuanto a la asociación entre la actividad física y la puntuación de CAC. Los estudios más grandes y la mayoría de los estudios desarrollados en atletas sugieren que la actividad física intensa podría asociarse con una mayor puntuación de CAC, aunque esta hipótesis debería confirmarse en futuras investigaciones.

Introduction

Physical activity is important for maintaining cardiovascular health and higher levels of exercise are associated with a lower risk of cardiovascular events.[1] For this reason, the current guidelines have emphasized limiting sedentary behaviour and promoting physical activity to improve cardiorespiratory fitness and reduce cardiovascular outcomes.[2]

There are emerging data that suggest a U-shaped relationship between exercise intensity and adverse cardiovascular events.[3] Moderate to vigorous physical activity is beneficial for reducing adverse outcomes, but the shape of the association would depend on cardiovascular health status.[4] A linear association between physical activity and mortality reductions was observed in patients with a history of cardiovascular disease. However, a curvilinear association was found in healthy individuals or in subjects with cardiovascular risk factors between physical activity and mortality. The mechanisms underlying these findings are uncertain, but some evidence suggests that extreme exercise can cause myocardial fibrosis and coronary atherosclerosis.[5,6] Shearing forces within coronary arteries during high heart rates, circulating interleukins, and the production of free radicals were implicated as possible factors.[3]

Coronary artery calcification (CAC) has emerged as an independent predictor of coronary heart disease in subjects free of cardiovascular disease and provides predictive information beyond standard cardiovascular risk factors.[7] Several studies have evaluated the relationship between physical activity and CAC in the general population, although the results were conflicting.[8–27] Some studies reported an inverse association, although others showed a positive relationship, a U-shaped relationship, or no relationship between physical activity and CAC.[28] In addition, inconsistent results were also reported in studies that evaluated athletes.[29–34]

Therefore, the main objective of the present systematic review was to assess the association between different levels of physical activity and CAC score estimated by computed tomography.

Material and methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[35] This systematic review was registered in PROSPERO (CRD42022331302).

A literature search was performed to detect studies that have evaluated the association between physical activity and CAC estimated by computed tomography. Two independent reviewers searched the electronic PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane Controlled Trials databases using ''physical activity'' or ''exercise'' terms combined with the following terms: ''coronary artery calcification'', ''coronary atherosclerosis'', ''coronary artery calcium score'' and ''computed tomography''. The final article search ended on 15 April 2022.

The following inclusion criteria were used to select eligible studies: (1) Observational studies that have evaluated two or more levels of physical activity. The levels of physical activity evaluated were those reported by the original publications; (2) Observational studies that have quantified the CAC score using computed tomography. In all cases, the CAC score was reported in Agatston units. There were no idiomatic, geographical or publication restrictions. Excluded studies included expert opinions, reviews or case-series studies.

When the data was available, the effect sizes and 95% confidence intervals (CI) were reported as relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs) according to the reports of the original publications.

The risk of bias was assessed using the Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-1) tool.[36] It evaluates 7 domains related to bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. The categories for risk of bias judgements are ''Low risk'', ''Moderate risk'', ''Serious risk'' and ''Critical risk'' of bias. The ''No information'' category should be used only when insufficient data are reported to permit a judgement. Any discrepancy between the two reviewers was resolved through discussion and by involving a third reviewer.

The studies were summarized in four groups by the association between physical activity and CAC: (1) no association, (2) positive association, (3) inverse association and, (4) an U shape association.

Meta-analysis was not possible due to heterogeneity of the populations included, the different strata of physical activity evaluated and the different effect measurements reported.

Results

The search included 736 potentially relevant articles after title screening, and 640 studies were excluded after title/abstract screening, as these were duplicate studies or did not assess the purpose of this study. After careful reading of the articles, 70 studies were removed, because these studies did not report the exposure/event of interest. A flow diagram of the study's screening process has been shown in Fig. 1.

Twenty six studies including 89,405 subjects were identified and considered eligible for this systematic review. In total, eleven studies had a cross-section design, ten studies were prospective/retrospective cohorts, and five studies were a cross-sectional analysis on a prospective/retrospective cohort. Two studies reporting the same data were analyzed together (Kwasniewska et al., 2014/2016). Twenty studies included general populations and six studies evaluated athletes. The characteristics of the studies included in this review are shown in Tables 1 and 2.

In all studies we assessed the level of bias. In total, 5 studies were assessed as being at serious risk of bias, while the rest of the studies were assessed as being at moderate risk of bias (Fig. 2).

Studies showing no association

Taylor et al.[8] showed that army personnel men without coronary heart disease (CHD) in the upper quartile of sports activity had a similar prevalence of CAC compared with men in the lower quartile (21.2% vs. 20.4%; p = 0.88). CAC was uncommon in women and was also unrelated to physical activity score. Similarly, another prospective study (follow-up 10 years) found no association between CAC score and physical activity (p = 0.35) when evaluating adults without coronary disease.[9] Bertoni et al. showed that after adjustment for confounding variables, increasing moderate/vigorous physical activity was not associated with CAC in adults without prior clinical cardiovascular disease (CVD).[11] The adjusted RR (95% CI) for CAC score > 0 for women and men with > 140 MET-hour/week physical activity (reference 0–34 MET-hour/week) were 0.97 (0.87–1.10) and 1.03 (0.96–1.11), respectively. Likewise, a small cross-sectional study did not show an association between pedometer steps and CAC score when evaluating young post-menopausal women.[12] Another cross-sectional study reported that there was no association between physical activity counts/minute (adjusted OR [95% CI] for high tertile vs. low tertile: 1.19 [0.68–2.10]), moderate to vigorous physical activity (adjusted OR [95% CI] for $\geq$ 30 min/day vs. <30 min/day: 1.09 [95% CI 0.52-2.29]), or sedentary time (adjusted OR [95% CI] for high tertile vs. low tertile: 0.93 [0.54–1.59]), and risk of detectable CAC.[13] Similar findings were reported in another prospective cohort that analyzed 1850 participants with baseline CAC = 0 who underwent a follow-up CAC scan at visit 5 (median 9.6 years after baseline).[18] In this case, there was no significant association between regular physical activity and persistent CAC = 0 (HR 0.95, 95% CI 0.83–1.09). In addition, Feuchtner et al. analyzed the association between different groups of physical activity (inactive, low endurance exercises and moderate or high endurance exercises) and CAC score in patients referred to coronary computed tomographic angiography.[24] The authors showed that CAC scores did not differ between groups. Another cross-sectional analysis on a prospective cohort reported no association between the quintiles of recreational physical activity and the CAC score (p = 0.65) in subjects free of CVD and CAC score > 0.[25] However, quintile 5 of non-recreational physical activity showed a trend towards lower CAC score (p = 0.05).

On the other hand, two studies conducted specifically on athletes also found no association between physical activity and CAC. A small study reported that the prevalence of CAC score > 100 or CAC score > 75th percentile was higher in veteran male recreational athletes who performed less physical activity (<50 MET/hour/week) compared to those who exercised more (>100 MET/hour/week), although the difference was not statistically significant (p > 0.05).[33] Additionally, Kleiven et al. showed that there was no association between high volumes of high-intensity endurance exercise training and progression of CAC ($\geq$ 10 Agatston units increase in CAC) in a longitudinal study (follow-up 5 years) of middle-aged recreational athletes (adjusted OR 0.97, 95% CI 0.62-1.50).[34]

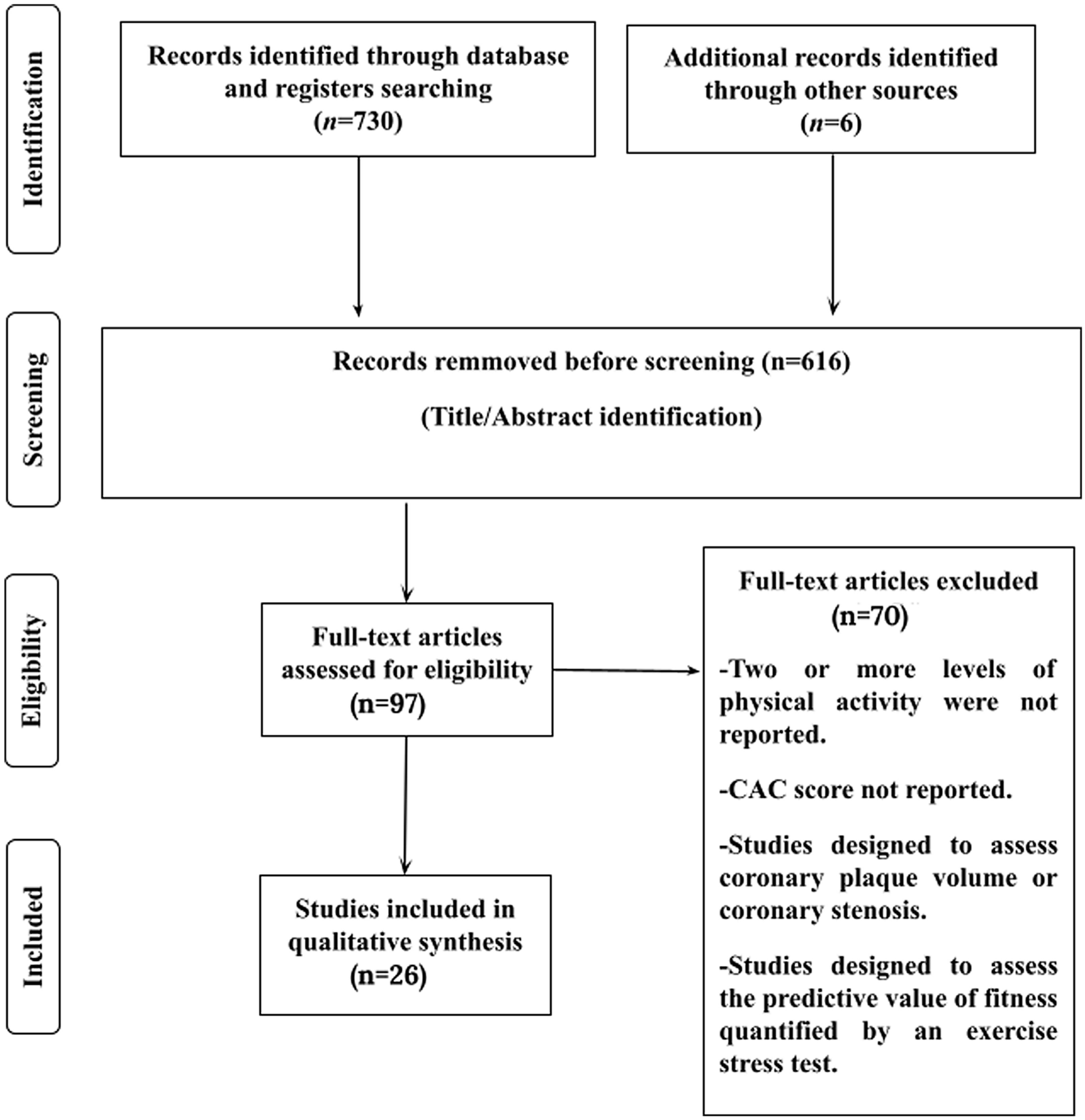

Figure 1 Flow diagram of the study screening process. CAC: coronary arterial calcification.

Studies showing a positive association

Laddu et al. showed that the proportion of subjects with a CAC score > 0 was higher in the participants who exercised more (below physical activity guidelines: 29%; meeting physical activity guidelines: 33.2%, three times physical activity guidelines: 41.8%, $p < 0.001$), in a large cohort (follow-up 25 years) of young people.[21] The group of three times physical activity guidelines had higher adjusted OR of CAC > 0 (OR 1.27, 95% CI: 0.95–1.70) compared to below physical activity guidelines group, although the difference was not statistically significant. Weinberg et al. analyzed post-menopausal women without CHD undergoing outpatient CAC scanning.[14] In hormone therapy users, increased physical activity was associated with an increased mean CAC score. Women in the top quartile of physical activity had a 22% increased prevalence of CAC ($p = 0.03$). In addition, DeFina et al. showed that men with at least 3000 MET-min/week were more likely to have prevalent CAC $\geq$ 100 (adjusted RR 1.11, 95% CI 1.03–1.20) compared with those accumulating lesser amounts of physical activity.[23] Similar findings were reported in a large prospective cohort with 5-year follow-up.[26] Compared with inactive subjects, the estimated adjusted 5-year average increases in CAC in moderately active and health-enhancing physically active participants were 3.20 (0.72–5.69) and 8.16 (4.80–11.53), respectively. Among participants with CAC = 0 at baseline, compared with sedentary participants, the adjusted HR (95% CI) for developing CAC > 0 in participants who were moderately active and health-enhancing physically active were

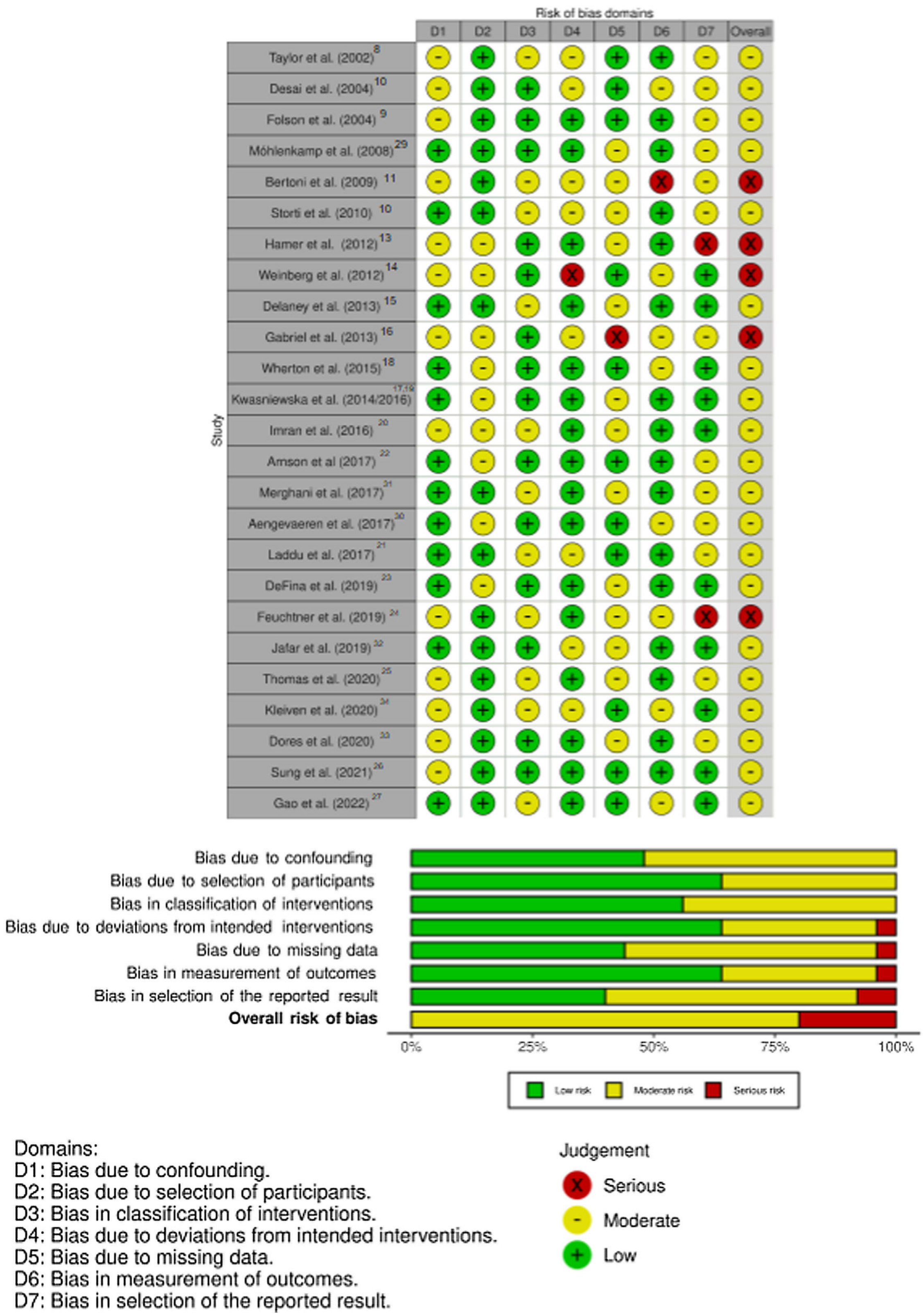

Figure 2 Bias assessment of included studies.

1.04 (0.94–1.15) and 1.21 (1.05–1.38; p for trend = 0.01), respectively. Finally, another prospective cohort (follow-up 8.9 years) showed that participants in the three times physical activity guidelines group had a higher risk of CAC progression than those in the below physical activity guideline group (adjusted HR 1.51; 95% CI 1.18-1.94).[27]

When we analyzed the studies that included only athletes, most of them found a positive association between

Table 1 Characteristics of the populations included and the operational definitions of the studies carried out on the general population.

Study (year)	*n*	Population	CAC measurement	Physical activity strata
Cross-sectional studies or cross-sectional analysis on prospective/retrospective cohorts				
Taylor et al. (2002)[8]	630	Army personnel without CHD, aged 39–45 years. Mean age 25.4 ± 0.5 years, 82% men.	EBCT scanner. CAC score > 0 were considered to be positive for CAC.	Physical activity was quantified using the Baecke physical activity questionnaire. The quartiles of this variable were analyzed.
Desai et al. (2004)[10]	779	Asymptomatic patients with multiple metabolic risk factors without prior CVD or diabetes (66.8% men).	EBCT scanner.	Sedentary (no physical activity), moderate physical activity (30 min 1-2 times/ week), and long-duration physical activity (30 min 3 times/week).
Bertoni et al. (2009)[11]	6482	Adults aged 45-84 years without prior clinical CVD. Mean age 62.4 ± 10.3 years, 52.3% women.	Cardiac-gated EBCT scanner or a multidetector system.	The MESA Typical Week Physical Activity Survey was performed. The summary measures were reported in total MET-hours/week for 3 intensity levels (light, moderate, vigorous).
Storti et al. (2010)[12]	173[a] 121[b]	Younger post-menopausal women (mean age 56.8 ± 2.9 years) from the WOMAN study and older post-menopausal women (mean age 73.9 ± 3.8 years) from the WWF study.	EBCT scanner.	Physical activity was measured using a pedometer over a 7-day period. The quartiles of this variable were analyzed.
Hamer et al. (2012)[13]	443	Healthy men and women aged 56-79 years without history of CHD. Mean age 66 ± 6 years.	EBCT scanner.	Accelerometer (7 consecutive days) and self-reported questionnaire. Moderate to vigorous physical activity (<10 min/day, 10 to 30 min/day and ≥30 min/day), and tertiles of physical activity counts/min and sedentary time were analyzed.
Weinberg et al. (2012)[14]	544	Post-menopausal women without prior clinical CHD undergoing outpatient CAC scanning. Mean age 60.1 ± 7 years	EBCT scanner.	Self-administered Baecke questionnaire.
Imran et al. (2016)[20]	2971	Men and women without CHD. Mean age 55 years, 60% women.	Cardiac CT scanner.	Standardized questionnaire was used to ascertain the number of blocks walked daily to compute the walking metabolic equivalent hours per week
Arnson et al. (2017)[22]	10,690	Asymptomatic patients who underwent CAC scanning. Mean age 55.7 ± 11 years, 66% men.	EBCT or a multislice CT scanner.	A self-reported exercise scale was used. Score of 0–1: no exercise; score of 2–5: low exercise; score 6–8: moderately active; score of 9–10: highly active.
DeFina et al. (2019)[23]	21,758	Men ≥ 40 years free of CVD. Maan age 51.7 ± 8.4 years.	EBCT scanner.	A self-reported physical activity questionnaire was performed. Physical activity levels were categorized into the following 3 groups: at least 3000 or more, 1500 to 2999, and less than 1500 MET-min/week.

Table 1 (*Continued*)

Study (year)	*n*	Population	CAC measurement	Physical activity strata
Feuchtner et al. (2019)[24]	252	Patients referred to CCTA with suspected CHD without history of CVD. Median age: 55 years, 39.7% women.	Cardiac -gated 64-slice CT scanner.	Inactive (no physical activity), low endurance exercises (1-2 times per week or < 30 minutes per episode), and moderate or high endurance exercises (regular exercise for>1 year for≥3 times per week of at least 1 h per episode).
Thomas et al. (2020)[25]	3393	Men and women aged 45–84 years and free of clinical CVD with CAC score > 0. Mean age 66.3 ± 9.5 years, 57.8% men.	EBCT or a multislice CT scanner.	Quintiles of recreational (walking exercise, dance, team sports, dual sports, individual exercise activities) and non-recreational physical activity (household chores, yard work, care of others, walking for transportation, and occupational activities).
Prospective or retrospective cohorts				
Folson et al. (2004)[9]	360	Adults without CHD, aged 45–64 years.	A single-slice helical or a 4-slice CT system.	Sport index (0, low to 5, high).
Delaney et al. (2013)[15]	5656	Adults aged 45-84 years without prior clinical CVD. Mean age 61 years, 53% women.	Cardiac-gated EBCT scanner or a multidetector system. Incident CAC was defined as a CAC score > 0 upon follow up with a baseline score of 0.	The MESA Typical Week Physical Activity Survey was performed. The summary measures were reported in total MET-hours/week for 3 intensity levels (light, moderate, vigorous).
Gabriel et al. (2013)[16]	146	Post-menopausal women. Mean age at baseline 61.9 ± 1.7 years.	EBCT scanner	Paffenbarger Physical Activity Questionnaire, Modifiable Activity Questionnaire and accelerometers were performed. Moderate- to vigorous- intensity activities are defined as those requiring ≥ 3 METS.
Kwasniewska et al. (2014/2016)[17,19]	62	Asymptomatic male volunteers with stable physical activity levels and without chronic diseases or pharmacotherapy. Mean age 59.9 ± 8.6 years.	64-Slice computed tomography scanner.	Low-to moderate level: < 2050 kcal/week. High level: 2050–3840 kcal/week. Very high level: > 3840 kcal/week.
Wherton et al. (2015)[18]	1850	Adults free of CVD with baseline CAC score = 0. Mean age 57.1 ± 8.6 years, 37% men.	EBCT scanner or a multidetector CT.	Regular physical activity: > 150 min per week of moderate intensity physical activity or > 75 min per week of vigorous intensity physical activity.
Laddu et al. (2017)[21]	3175	Men and women aged 18–30 years. Mean age 25.4 ± 0.5 years, 56.6% women.	Cardiac-gated multi-detector CT scanner.	A self-reported physical activity questionnaire was performed. Groups: Below physical activity guidelines[c], meeting physical activity guidelines and three times physical activity guidelines.
Sung et al. (2021)[26]	25,485	Men and women ≥ 30 years free of overt CVD. Mean age 42 ± 6.1 years, 89.2% men.	64-Slice CT scanner.	IPAQ-SF was performed. Three groups (inactive, moderately active and health-enhancing physically active) were defined.

Table 1 (*Continued*)

Study (year)	*n*	Population	CAC measurement	Physical activity strata
Gao et al. (2022)[27]	2497	Men and women aged 18–30 years. Mean age 40.4 ± 3.6 years, 44.9% men.	Cardiac-gated multi-detector CT scanner. CAC progression: (1) CAC > 0 at follow-up among participants with baseline CAC = 0; (2) an annualized change of ≥ 10 at follow-up among those with baseline CAC > 0.	Below physical activity guidelines[c], meeting physical activity guidelines, three times physical activity guidelines

CAC: coronary arterial calcification; CCTA: coronary computed tomographic angiography; CHD: coronary heart disease; CT: computed tomography; CVD: cardiovascular disease; EBTC: Electron beam computed tomography; IPAQ-SF: International Physical Activity Questionnaire Short Form; MESA: The Multi-Ethnic Study of Atherosclerosis; MET: metabolic equivalent.
[a] WOMEN study.
[b] WWF study.
[c] 150 min of moderate intensity activity per week.

exercise level and CAC. Aengevaeren et al. evaluated asymptomatic men who engaged in competitive or recreational leisure sports.[30] Sport men with at least 2000 MET-min/week were more likely to have prevalent CAC > 0 (adjusted OR 3.20, 95% CI 1.56-6.57) compared with those accumulating < 1000 MET-min/week (p = 0.001). Likewise, the participants with less physical activity showed less frequently a CAC score = 0 compared to the subjects who did less exercise (<1000 MET-min/week: 57% vs > 2000 MET-min/week: 32%; $p < 0.05$). Similar results were reported by Merghani et al. after evaluating a group of master athletes compared to a control group.[31] In this case, 12 (11.3%) male athletes had a CAC score ≥ 300 versus none of the sedentary males (p = 0.009). The median CAC score in male athletes with a CAC ≥ 1 was higher than in sedentary males with a CAC ≥ 1 (86 versus 3; p = 0.02). However, no differences in CAC scores were seen between athletic and sedentary females. Conflicting results were reported in another study published by Möhlenkamp et al.[29] A CAC score = 0 was more frequent in marathon runners than in age-matched controls, but was similar when compared with Framingham risk score-matched controls. Also, the rates of CAC score>100 were similar in marathon runners and age-matched controls (36.1% vs 36.3%, p = 0.96) but higher rates in marathon runners were observed when compared with Framingham risk score-matched controls (36.1% vs 21.8%, $p < 0.01$). Finally, Jafar et al. reported that among runners participating in extreme distance running (marathon runners. and ultramarathon runners) showed more frequently a CAC > 0 compared to the non-marathon runners (73.3% versus 23.1%, $p < .0002$).[32] When controlling for age, sex, and number of years running, marathon and ultramarathon runners were 8.8 times more likely than non-marathon runners to have a positive CAC scores.

Studies showing an inverse association

A cross-sectional study that evaluated asymptomatic patients with multiple metabolic risk factors showed that the CAC score was lower in participants who did more physical activity.[10] The 75th percentile CAC scores were 248, 118 and 75 in the sedentary, moderate or long duration physical activity groups, respectively ($p < 0.05$). Additionally, sedentary patients showed a CAC score > 400 more frequently than the patients in the long duration physical activity group (45% vs 17%, $p < 0.05$). In the previously discussed study by Weinberg et al.,[14] the results were different when analyzing hormone therapy non-users. In this case, a significant inverse relationship between increasing physical activity and CAC score was observed. Women in the top quartile of physical activity had a 56% reduced prevalence of CAC ($p < 0.01$). Similarly, another study showed that there was a significant inverse association between pedometer steps and CAC score (p = 0.002) in a sub-analysis of WWF study.[12] Older post-menopausal women in the bottom quartile of the pedometer steps showed an adjusted OR of 1.4 (95% CI, 1.09–1.81) compared to women in the top quartile.

Delaney et al. reported that vigorous physical activity was associated with a reduction in the risk of incident CAC (RR = 0.97, 95% CI 0.94-1.00, p = 0.048) when analyzing adults in primary prevention.[15] In this study, incident CAC was defined as a CAC score > 0 upon follow up (4 years) with a baseline score of 0. In addition, Gabriel et al. investigated the association between CAC and physical activity in a cohort of post-menopausal women (follow-up 12 years).[16] CT scanners were collected at two follow-up visits and participants were classified into one of three groups: (1) no detectable CAC (0 CAC at both visits); (2) incident CAC (0 CAC at the first- and >0 CAC at the last-visit); or (3) prevalent CAC

Table 2 Characteristics of the populations included and the operational definitions of the studies carried out on athletes.

Study (year)	*n*	Population	CAC measurement	Physical activity strata
Cross-sectional studies				
Móhlenkamp et al. (2008)[29]	1188[a]	Apparently healthy male marathon runners aged 50 years. Controls matched for age and risk factors (2:1) and age-matched controls (8:1).	EBCT scanner.	Athletes vs. sedentary controls.
Aengevaeren et al. (2017)[30]	284	Asymptomatic men ≥ 45 years without CVD, who engaged in competitive or recreational leisure sports and had undergone a normal sports medical examination. Mean age 55 ± 7 years.	Cardiac-gated 256-slice CT scanner.	Exercise volume groups: <1000, 1000-2000, or >2000 METs-min/week.
Merghani et al. (2017)[31]	244[b]	Masters athletes without CVD and controls of similar age, sex, and low Framingham score. Mean age 54.4 ± 8.5 years, 70% male. Athletes ran ≥ 10 miles or cycled ≥ 30 miles per week and have continued to do so for ≥ 10 years, and competed in ≥ 10 endurance events, including marathons, half marathons, 10 km races, or endurance cycling races over a 10-year period.	64-Slice CT scanner.	Athletes vs. sedentary controls.
Jafar et al. (2019)[32]	56	Runners who had run competitively for 10 or more years without cardiovascular risk factors or history of CVD.	160-Slice CT scanner	Exercise questionnaire. Group A: ultramarathons runners; Group B: marathon runners; Group C: non marathon runners.
Dores et al. (2020)[33]	105	Asymptomatic male athletes aged ≥ 40 years with low to intermediate risk, who exercised > 4 hours/week for > 5 years. Mean age 48 ± 6 years.	64-Slice CT scanner.	Exercise volume was assessed by the MET score (METs/hour/week). Exercise volume was classified by tertile.
Prospective or retrospective cohorts				
Kleiven et al. (2020)[34]	61	Athletes > 16 years who participate in the 91-km-long recreational mountain bike race. Subjects were excluded if they had known CVD, or if they had a resting ECG suggestive of underlying pathology at screening. Mean age 45.9 ± 9.6 years, 74% men.	CT scanner.	Training volume was defined as the self-reported number of hours per week of high-intensity exercise (>6 MET).

CAC: coronary arterial calcification; CT: computed tomography; CVD: cardiovascular disease; ECG: electrocardiogram; EBTC: electron beam computed tomography; MET: metabolic equivalent.
[a] 108 athletes, 216 controls matched for age and risk factors and 864 age-matched controls.
[b] 152 athletes and 92 controls.

(>0 CAC at both visits). Accelerometer-derived moderate-vigorous physical activity were significantly higher in the no detectable CAC group when compared to the prevalent CAC group ($p < 0.05$). However, physical activity levels were not significantly different between the incident and no detectable CAC groups, and there were no differences between the groups when evaluating exercise by self-report. Another cross-sectional study reported that healthy participants with a level of physical activity > 15-22.5 MET-hours/week had a 46% lower prevalence of CAC score = 100 (adjusted prevalence ratio 0.54, 95% CI 0.36−0.81) as compared to the reference group (= 3.75 MET-hours/week).[20] Arnson et al. reported that the sedentary patients showed a CAC score > 400 more frequently (11.2% vs 10.5%) than the patients in the highly active group ($p < 0.05$) when analyzed asymptomatic patients who underwent CAC scanning.[22] The OR for having a CAC score > 400 was 1.25 (95% CI 1.04−1.50; $p = 0.02$) for the no-exercise group compared with the highly active group. However, the adjusted OR became non-significant.

Studies showing a U-shaped relationship

Kwaśniewska et al. reported a U-shaped relationship when analyzing a group of healthy male volunteers in a prospective study (follow-up 24.7 years).[17,19] Mean CAC values (SD) were 286.1 (361.9), 10.7 (28.9), and 106.1 (278.3), in the groups with low-to-moderate, high, and very high physical activity level, respectively ($p < 0.001$ low-to-moderate vs high; and $p < 0.05$ low-to-moderate vs very high). Moreover, the proportion of subjects with CAC = 0 were 3.8%, 47.6%, and 40%, in the groups with low-to-moderate, high, and very high physical activity level, respectively ($p < 0.01$).

Discussion

This systematic review included the full body of evidence that examined the relationship between different levels of physical activity and CAC score estimated by computed tomography. The findings were conflicting, and considering the quality of the studies evaluated, inconclusive.

Regular physical activity is considered protective against coronary artery plaque development based on its favourable effects on many cardiovascular risk factors.[37] However, the dose-response relationship between exercise and health remains incompletely understood. Several mechanisms that could link physical training with CAC and plaque development have been proposed. The exercise-induced increase in cardiac output may increase mechanical stress on the coronary vessel wall, leading to endothelial dysfunction.[28] Likewise, haemodynamic stress-induced exercise can promote vascular inflammation.[38] In this sense, Michaelides et al. showed that shorter exercise duration was associated with favourable antioxidant and vascular effects, while longer exercise blunted these beneficial effects and was accompanied by adverse effects on vascular function, mainly in older coronary patients.[39] Other less explored mechanisms such as the effect of exercise on vitamins and minerals or the use of performance enhancing drugs could be related to the vascular process observed in athletes.[28,40,41] Although, a ''protective effect'' of exercise favouring calcification of non-calcified plaques previously present in the arteries cannot be ruled out.

In this systematic review, when analyzing the association between physical activity and CAC score in the studies carried out in the general population, we have found contradictory results. In total, 7 studies did not show an association, 4 studies showed a positive association, 6 studies reported an inverse relationship, 2 studies reported a U-shaped relationship, while two studies reported different results depending on the subgroup evaluated. However, when we analyzed the largest cross-sectional study[23] and the two largest prospective cohorts,[26,27] a positive association between exercise level and CAC score was observed. Likewise, when we analyzed the studies that evaluated athletes, four studies showed a positive association between the level of physical activity and the CAC score,[29−32] while other two studies analyzed did not find a relationship between exercise and the prevalence or progression of coronary calcification, respectively.[33,34]

Interestingly, an increase in CAC score related to physical activity may not necessarily reflect an increase in cardiovascular risk. Physical activity could attenuate the risk associated with coronary calcification. Arnson et al. demonstrated that among individuals with similar CAC scores, those in the highest physical activity category had a lower risk of all-cause mortality compared with those in the lowest physical activity category.[22] Similar results were reported by DeFina et al. when evaluating individuals with CAC score < 100.[23] In addition, German et al. showed that high physical activity was not associated with an increased risk of mortality, even among individuals at high-risk of CVD (CAC $\geq$ 100).[42] Furthermore, Möhlenkamp et al. found that the rate of cardiovascular events was higher in runners with higher CAC scores, although these findings were similar to the rates of events observed in the control group.[29]

Different types of cardiovascular calcification were described.[43] Atherosclerotic calcification occurs at sites of atherosclerotic plaques, where there is a combination of cellular necrosis, inflammation, and cholesterol deposition. In contrast, medial artery calcification proceeds through a different process and is associated with vessel wall stiffening. Thus, some authors have proposed that exercise-associated calcification is more related to medial artery calcification.[28] Consequently, the observed cardiovascular risk could be lower. This phenomenon could be similar to that observed with the use of statins: statins were associated with increased plaque calcification but it unequivocally reduced cardiovascular risk.[44] Unfortunately, the differentiation between both types of calcification cannot be performed reliably using computed tomography.

To find out if the physical activity performed by the subjects is enough to achieve a healthy state or not, studies commonly analyze the type, duration, frequency and intensity of exercise. Of all the components included in the exercise recommendation, intensity is generally considered to be the most critical for aerobic fitness and the one with the most favourable impact on cardiovascular risk factors.[45] However, the studies that evaluated the association between exercise and coronary calcification did not use homogeneous definitions of physical activity. In fact, many of them analyzed different exercise characteristics in a combined way. Consequently, we cannot discriminate which characteristics of physical activity could have a greater influence on coronary artery calcification.

This systematic review has some limitations. Firstly, quantitative analysis (meta-analysis) was not possible due to heterogeneity of the populations included and because the reported measures of exposure and effect were different. Secondly, the studies included in our analysis were all observational. Consequently, the presence of biases and confounders was highly expected. In this review, no study was classified as low risk of bias. However, ''low risk'' corresponds to the risk of bias in a high quality randomized trial. Only exceptionally will an non-randomized study be assessed as at low risk of bias due to confounding. Finally, the difficulty of capturing physical activity exposure via questionnaire has many limitations, such as inaccurate participant recall, duration of the assessment period, arbitrary cut-points for categorization, and potentially differential activities by gender or age.

Conclusion

This systematic review showed disparate results regarding the association between physical activity and CAC score. The largest studies and most studies developed in athletes suggest that intense physical activity could be associated with high CAC score, although it does not necessarily imply a higher cardiovascular risk. New studies should be developed to clarify this phenomenon.

Authors' contributions

WM and LB participated in the conception and design of the research. WM, LB and MF participated in the data collection. The interpretation of the data and the statistical analysis was done by WM and LB. WM, LB, MF and DPA drafted the manuscript. All authors performed a critical review of the final document. All authors have read and agreed to the published version of the manuscript.

Ethical approval

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Availability of data and material

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Conflict of interest

None.

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