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REVIEW

Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis

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To conduct a systematic review and meta-analysis on the crude and adjusted associations between epicardial adipose tissue (EAT) volume determined by computed tomography (CT) and coronary artery disease (CAD). MEDLINE, Scopus, and Web of Science databases were screened for all observational studies assessing the association between EAT volume and CAD. We calculated pooled odds ratio (OR) or hazard ratio (HR) and 95% confidence intervals (CI) for the association per 10 cm^3 variation of EAT by five different definitions of CAD: obstructive or significant coronary stenosis (luminal narrowing ≥50% and ≥70%, respectively), presence of coronary artery calcification (CAC), myocardial ischaemia, and major adverse cardiovascular events (MACE) using DerSimonian and Laird random-effects models. Seventy studies were identified comprising 41 534 subjects, mainly derived from community-based or hospital-based low-to-intermediate pretest probability of CAD populations. Participants with any outcome of CAD had a higher mean volume of EAT than those without. Accordingly, the analysis of crude associations showed that EAT volume was associated with obstructive stenosis, significant stenosis, any CAC, and MACE. Based on the analysis of adjusted associations, although attenuated, EAT volume remained associated with obstructive stenosis (OR 1.055, 95% CI 1.033–1.078; $I^2 = 63.5\%$), significant stenosis (OR 1.514, 95% CI 1.262–1.815; $I^2 = 51.8\%$), myocardial ischaemia (OR 1.062, 95% CI 1.006–1.122; $I^2 = 86.9\%$), and MACE (HR 1.040, 95% CI 1.024–1.056; $I^2 = 64.7\%$) but was only borderline significant with CAC (OR 1.007, 95% CI 1.000–1.011; $I^2 = 75.8\%$). In low-to-intermediate cardiovascular risk subjects, EAT volume was independently associated with coronary artery stenosis, myocardial ischaemia, and MACE.

Keywords epicardial fat • epicardial adipose tissue volume • coronary artery disease • coronary artery calcification • myocardial ischaemia • major cardiovascular events • computed tomography

Introduction

Over the last decade, several studies have reported a significant association between epicardial adipose tissue (EAT) and coronary artery stenosis,[1–36] coronary artery calcification (CAC),[18,27,33,37–52] myocardial ischaemia,[1,15,19,22,44,53–58] and major adverse cardiovascular events (MACE).[10,45,59–70] However, it remains controversial whether EAT *per se* is associated with coronary artery disease (CAD) or whether these associations result from shared cardiovascular risk factors.

The EAT is the visceral fat of the heart located between the visceral pericardium and the myocardium that under physiological conditions exerts cardioprotective functions, but, in dysmetabolic states, it has been associated with arterial hypertension, diabetes mellitus, dyslipidaemia, and global and visceral obesities.[18,34,49,71,72] Despite these strong correlations, some clinical studies showed that EAT remains independently associated with CAD.[50,59,73] However, other studies revealed that this association was no longer significant after adjustment for established cardiovascular risk factors.[1,12,14]

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The interest in EAT relies on not only its key localization and peculiar metabolic properties but also its clinical measurability. EAT volume can be calculated in the same non-contrasted computed tomography (CT) scanning of CAC score and, although currently unclear, EAT volume might complement the prognostic information provided from the calcium scoring and might increase the predictive value of non-contrasted cardiac CT without additional radiation exposure or contrast administration.[45,61,65]

In this systematic review and meta-analysis, we aimed to compute the crude and cardiovascular risk factors-adjusted association between EAT volume, determined by CT, with obstructive stenosis, significant stenosis, presence of CAC, evidence of myocardial ischaemia and MACE. As a secondary aim, we performed a subgroup analysis by obesity, ethnicity and method of EAT volume quantification.

Methods

Search strategy

This study followed the protocols specified in the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.[74] A comprehensive MEDLINE, Scopus, and Web of Science search of the literature assessing the association between EAT and CAD was performed. To identify and retrieve all potentially relevant articles regarding this topic, the search was performed utilizing the following expression: [('epicardial adipose tissue' OR 'epicardial fat' OR 'subepicardial adipose tissue' OR 'subepicardial fat' OR 'cardiac adipose tissue' OR 'cardiac fat') AND ('coronary artery disease' OR 'coronary artery calcification' OR 'coronary artery calcium score' OR 'coronary stenosis' OR 'coronary atherosclerosis' OR 'myocardial ischemia' OR 'myocardial perfusion defects' OR 'acute coronary syndrome' OR 'major adverse cardiovascular events')]. An additional manual search was performed by analysing the reference list of original publications and review articles. The search was restricted to articles that were published until 23 January 2016.

Eligibility criteria

Only full-size articles of English language published in peer-reviewed journals were considered for this meta-analysis. Observational cross-sectional studies, case–control studies, or cohort studies were eligible for this meta-analysis if the following requirements were met:

(1) Inclusion of adult (>18 years old) participants;
(2) Quantification of EAT volume using cardiac CT;
(3) Description of the crude and adjusted association measures between the EAT volume and CAD outcomes.

Studies were excluded if they were conducted in special patient populations: immune-mediated diseases, human immunodeficiency virus infection, on dialysis chronic kidney disease, diabetic and pregnant women. If multiple articles were published from the same cohort, we included data from the study with the most detailed report of and/or the largest sample size.

Data quality assessment

Potentially relevant articles were evaluated by two independent reviewers (J.M. and D.A.) using a standardized form and any disagreement was subsequently resolved by all authors. Methodological quality of all studies was assessed using the revised and validated version of the Methodological Index for Non-Randomized Studies (MINORS).[75]

Statistical analysis

We computed summary measures for the association of EAT with five different definitions of CAD: (i) presence of obstructive stenosis defined by the presence of at least one coronary artery stenosis higher than 50% on the CT or invasive angiography; (ii) presence of significant stenosis defined by the presence of least one coronary artery stenosis higher than 70% on the CT or invasive angiography; (iii) presence of CAC defined as Agatston calcium score >0 Hounsfield Units (HU); (iv) myocardial ischaemia defined by the presence of myocardial perfusion defects on at least two segments, or coronary fractional flow reserve lower than 80% in at least one coronary lesion, or by the presence of a coronary artery stenosis higher than 90%; and (v) MACE including non-fatal myocardial infarction, unstable angina, unplanned myocardial revascularization, cardiovascular death, and all-cause death that has been studied as a time-to-event variable. We recorded the EAT volume mean and its standard deviation (SD) or the median with 25th and 75th percentiles values for each subgroup of CAD. Then, the EAT volume mean differences, along with their 95% confidence intervals (CIs) were calculated. The random-effect model[76,77] was used to compute the effect, per 10 cm^3 variation, of EAT on the outcome measures of CAD. The association measures included odds ratio (OR) and its respective 95% CI for obstructive stenosis, significant stenosis, CAC presence, and myocardial ischaemia and hazard ratio (HR) along with the respective 95% CIs for MACE. In a secondary analysis, we compared the association of EAT volume with CAD between studies according to the study populations' BMI, ethnicity and by the method of EAT quantification, and a meta-regression analysis was performed to determine their impact on the adjusted association of EAT with CAD. Heterogeneity between individual studies estimates was assessed using the Q statistic and I^2 statistic.[78] A forest plot was constructed showing the individual studies with the pooled estimates. Publication bias was assessed using the Egger test and the funnel plot analysis, and the trim-and-fill method of Duval and Tweedie.[77,79] All statistical analyses were performed using STATA software (version 13.1, StataCorp LP, College Station, TX, USA).

Results

Characteristics of the included studies

From a total of 1283 studies initially identified, 77 matched our eligibility criteria, and 4 additional studies were included after checking the reference list of the articles. Eleven studies were then excluded because: (i) represented reports based on the same original study database ($n = 2$),[80,81] (ii) included only diabetic patients ($n = 1$),[49] or (iii) comprised insufficient or incongruent data ($n = 8$).[82–90] This yielded a total of 70 studies included in qualitative analysis and 33 of those included in quantitative analysis (meta-analysis) (*Figure 1*). These studies were assessed as high-quality publications (median MINORS score of 18; 25th and 75th percentile of 16 and 19, respectively). Accordingly, this systematic review and meta-analysis comprised data from 41 534 subjects, mainly derived from community-based or hospital-based low-to intermediate-pretest probability of CAD populations. The association of EAT volume with the presence of coronary stenosis was reported in 36 cross-sectional studies (see Supplementary data online, *Table S1*).[1–36] The cross-sectional association of EAT volume with CAC was provided by 18 studies,[1,18,27,33,37–42,45–47,51,52,90] and 4 cohort studies provided data on the longitudinal association between EAT volume and CAC progression.[43,44,48,50] (see Supplementary data online, *Table S2*). Ten

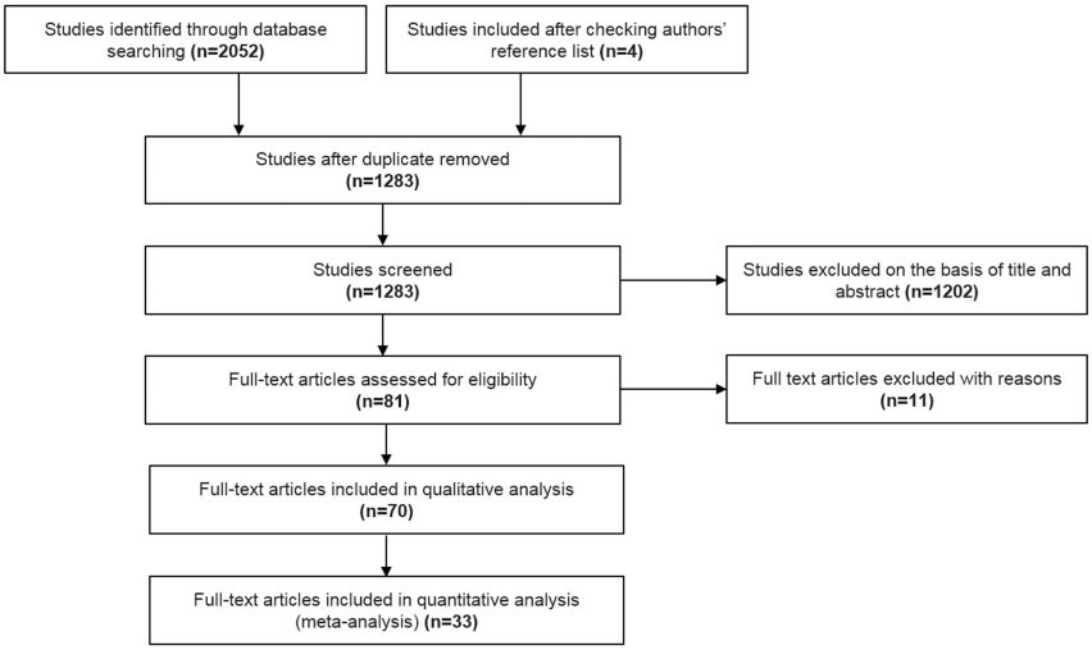

Figure 1 Study flowchart.

cross-sectional studies reported the association with myocardial ischaemia (see Supplementary data online, *Table S3*).[1,15,19,22,53–58] Fourteen cohort studies investigated the link between EAT and MACE (see Supplementary data online, *Table S4*).[10,45,59–70] Nine studies provided detailed data addressing the association of EAT volume with specific plaque components (calcified vs. non-calcified vs. mixed[5,13,14,16,23,31] or fibrous vs. lipid vs. fibrocalcific[91]) and with plaque eccentricity.[36] In two separate studies, Nakanishi *et al.*[44,70] determined the longitudinal association of changes in EAT volume with CAC progression and MACE incidence.

Crude association between EAT volume and CAD

The volume of EAT was significantly higher in subjects who presented with coronary stenosis, coronary calcification, and myocardial ischaemia or who suffered MACE in comparison with those without any evidence of CAD (*Figure 2*). Based on the analysis of studies providing the unadjusted association, we found that EAT volume was strongly associated with obstructive CAD, significant CAD, CAC presence, and MACE (*Figure 3*).

Adjusted association between EAT volume and CAD

Forty-four studies comprising a total of 36 429 participants reported the association of EAT volume with CAD after adjustment for measures of obesity, including BMI,[1,9,10,12-14,17,18,22,23,27,29,32,33,36,38,42-46,50,52,62-65,68] waist circumference[23,36,51,67] or visceral abdominal fat,[14,18,26,37,42,46,52] and traditional cardiovascular risk factors[1,3,6,9,10,12,14–18,22,27,29,31–33,36,37,42,44,45,51–55,57,61,62,66,68,69,90], with some studies additionally for the effect of conventional cardiovascular drugs[26,27,46,50,51,68]; few studies normalized the EAT volume for body size[2,30,39,43,66] and other included markers of systemic inflammation[29,36,52,62,68] in their models (see Supplementary data online, *Table S5*). *Figure 4* illustrates the forest plot of studies addressing the adjusted association of EAT volume with CAD. The analysis of data provided from the most complete multivariable model showed that, although attenuated, EAT volume remained associated with the presence of obstructive and significant stenosis, myocardial ischaemia and MACE but was only borderline significant for the presence of CAC. Due to different statistical methods, two studies[45,69] addressing the association between the EAT volume and MACE, namely the large Heinz Nixdorf Recall cohort study, could not be included in the computation of summary estimate measure. Both of these studies showed a significant association between EAT volume and MACE beyond the cardiovascular risk factors and, therefore, their absence would not affect the direction of the association of EAT with MACE, and its magnitude above the unit can, possibly, be higher than that reported in this meta-analysis.

Secondary analyses

A subgroup analysis of studies focusing on non-obese populations showed a stronger independent association between EAT volume and CAD with a pooled association measure of 1.155 (95% CI 1.086–1.228; $I^2 = 68.5\%$) vs. 1.012 (95% CI 1.010–1.023) in the other studies (see Supplementary data online, *Figure S1*).[6,9,23,63] Similarly, the independent association of EAT with CAD was significantly higher among the Asian studies compared with non-Asian studies (adjusted estimate of 1.084, 95% CI 1.061–1.108; $I^2 = 50.4\%$).[6,9,14,23,29,38,63,64] (see Supplementary data online, *Figure S2*). The EAT volume mean differences between subjects with and

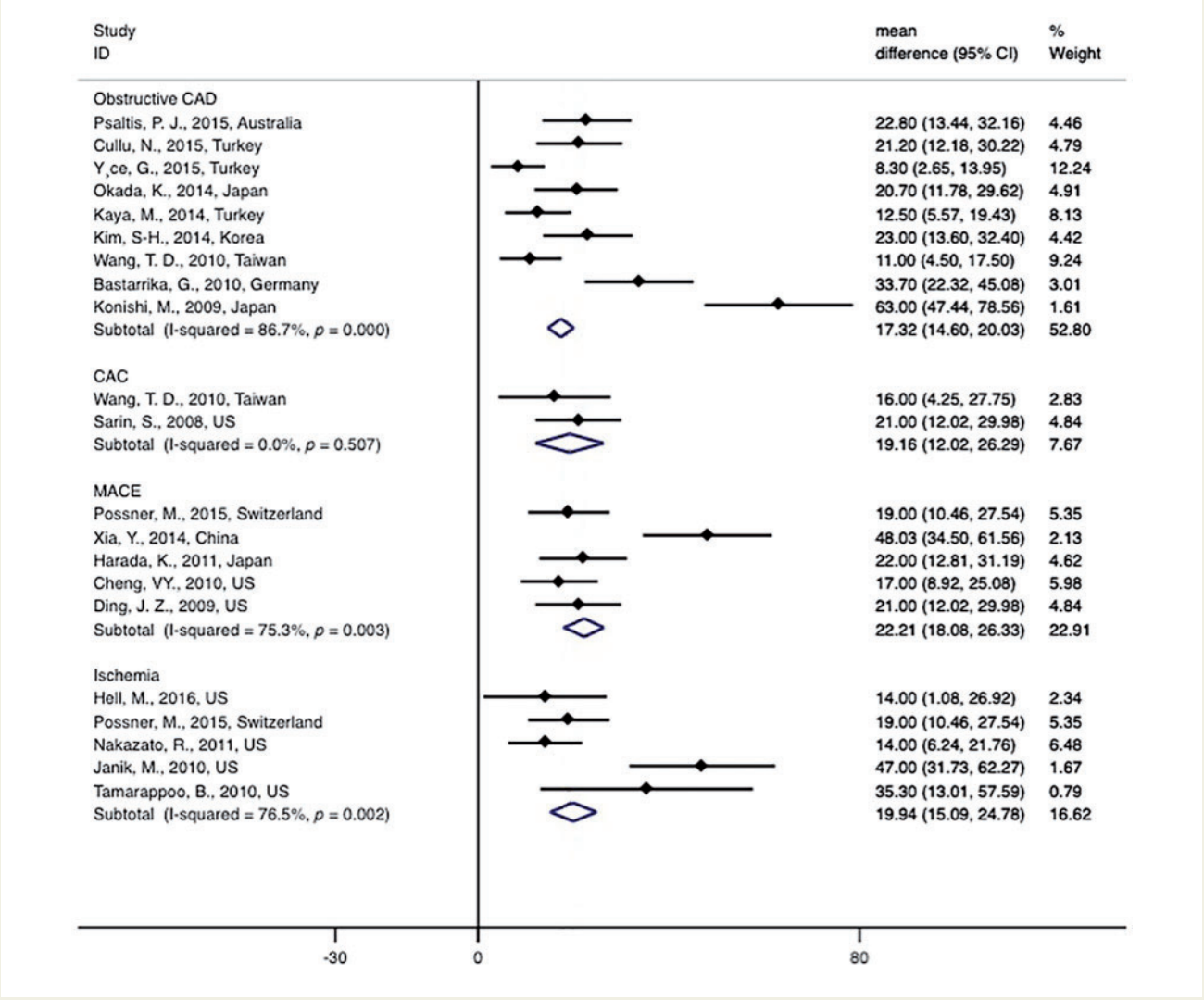

Figure 2 EAT volume mean differences between subjects with and without CAD by outcome subgroups. EAT volume is given in cubic centimetre. CAC, coronary artery calcification; CAD, coronary artery disease; EAT, epicardial adipose tissue; MACE, major adverse cardiovascular events.

without CAD did not differ according to the image data set (non-contrast vs. contrast CT) used to quantify EAT volume (see Supplementary data online, *Figure S3*). Supplementary data online, *Table S6* shows the meta-regression coefficients for the effect of study populations' BMI and ethnicity and the method of EAT quantification on the association of EAT with CAD.

Heterogeneity and publication bias

There were significant differences in EAT volume mean values between individual studies indicated by the statistical test for heterogeneity ($Q = 79.8$, $I^2 = 78.7\%$, $P < 0.001$). Similarly, we found significant differences in the unadjusted effect and adjusted effect of EAT on CAD between individual studies (for crude analysis, $Q = 99.4$, $I^2 = 72.9\%$, $P < 0.001$, and for adjusted analysis, $Q = 139.8$, $I^2 = 80\%$, $P < 0.001$). *Figure 5* illustrates the asymmetry of funnel plots of publications that reported the crude (*Figure 5A*) and adjusted (*Figure 5B*) associations of EAT volume with CAD (*P*-value for crude analysis of 0.031 and for adjusted analysis of <0.001 from Egger test for funnel plot symmetry). Corresponding to the Duval and Tweedie's trim-and-fill input method and after correction for potential unpublished studies, there was no evidence that publication bias would affect the adjusted association of EAT with the presence of coronary stenosis (estimated pooled OR 1.068, 95% CI 1.011–1.128; $P = 0.018$), CAC (estimated pooled OR 1.021, 95% CI 0.976–1.069; $P = 0.363$), MACE (estimated pooled HR 1.030, 95% CI 1.011–1.063; $P = 0.023$), or myocardial ischaemia (estimated pooled OR 1.009, 95% CI 1.001–1.169; $P = 0.042$).

Discussion

Main findings

The present systematic review and meta-analysis on the association of EAT volume determined by CT and CAD was based on 70 published

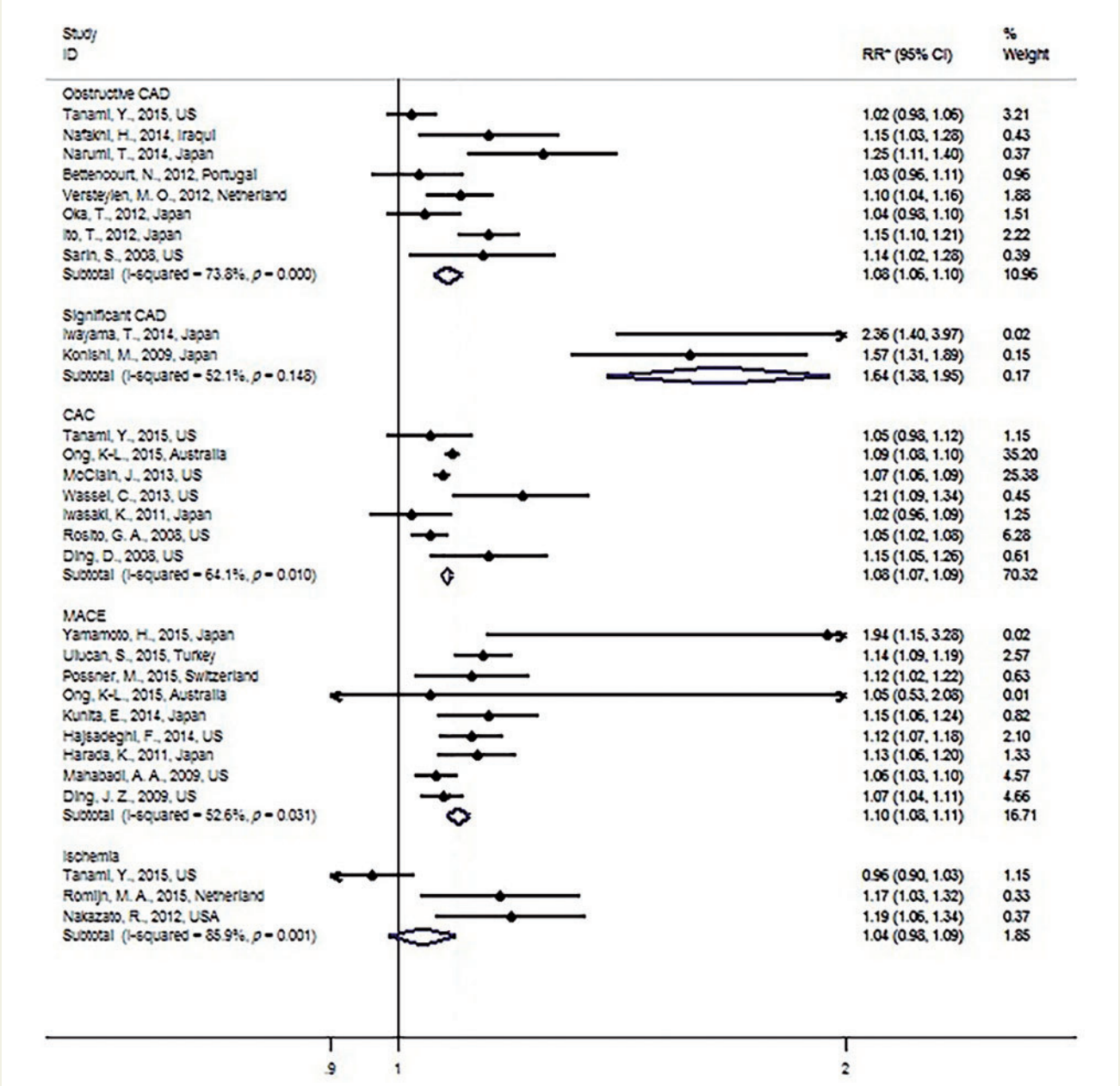

Figure 3 Forest plot of studies describing the crude association of EAT volume with CAD by outcome subgroups. RR* relates to 10 cm^3 of EAT volume. RR* describes the measure of association including the odds ratio with ≥1 coronary stenosis ≥50%, CAC >0, and myocardial ischaemia and the hazard ratio with MACE. CAC, coronary artery calcification; CAD, coronary artery disease; EAT, epicardial adipose tissue; MACE, major adverse cardiovascular events.

studies comprising 41 534 subjects. To improve the validity and usefulness of our conclusions, we performed a stratified analysis according to five different definitions of CAD: obstructive and significant stenosis, CAC, myocardial ischaemia and MACE. Our results demonstrated that (i) the volume of EAT was higher in subjects who presented with coronary stenosis, CAC, myocardial ischaemia, and MACE; (ii) in adjusted analysis these associations remained significant for the presence of obstructive and significant stenosis, myocardial ischaemia, and MACE but not for the presence of coronary calcification.

Causes of heterogeneity

In spite of our analysis by subgroups of CAD, significant heterogeneity remained between studies (I^2 often higher than 75%). Therefore, other sources of heterogeneity had to be considered.

Study population

The association between EAT and CAD may depend on study populations' clinical features such as their pretest probability of CAD

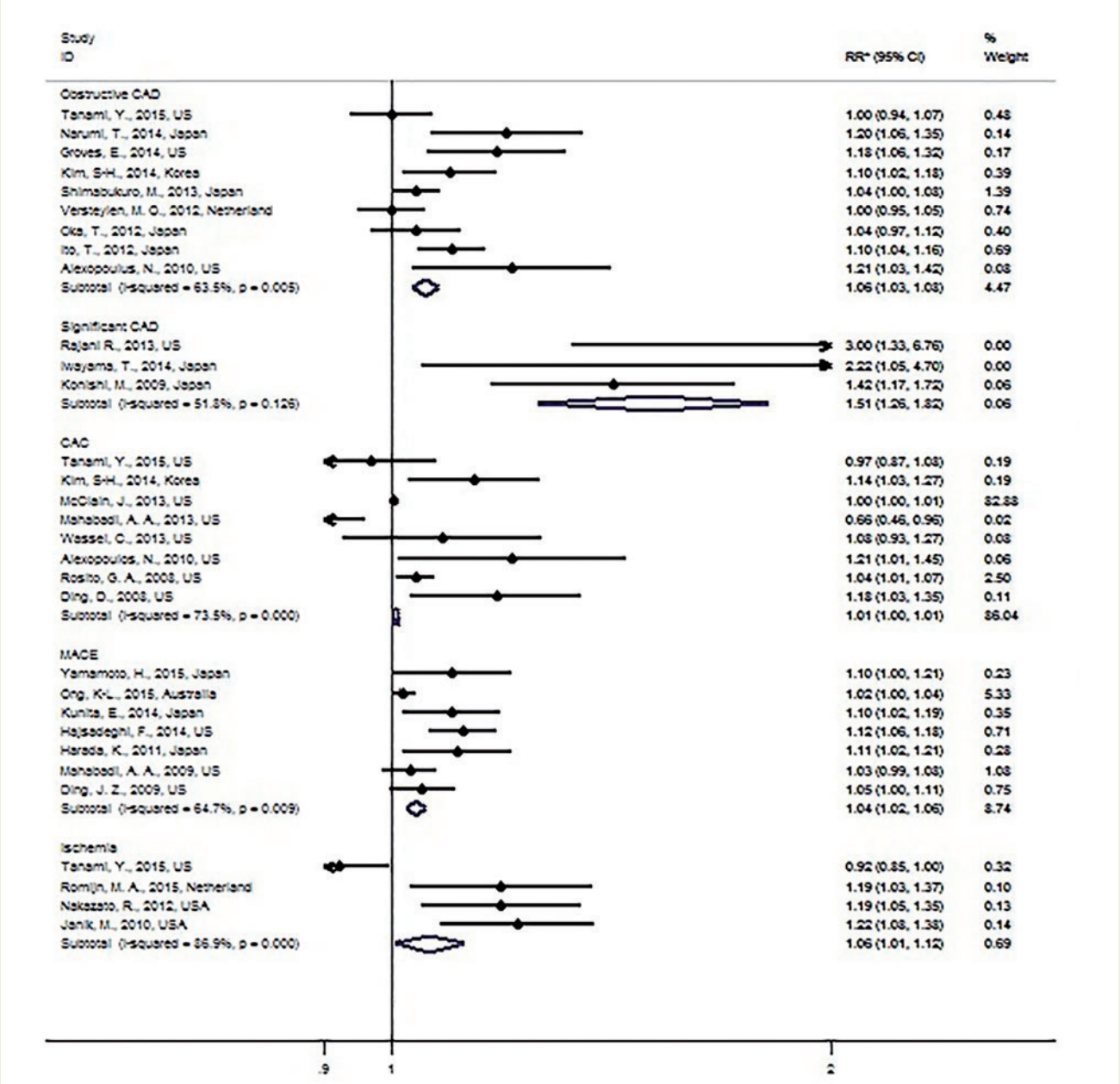

Figure 4 Forest plot of publications describing the adjusted association of EAT volume with CAD by outcome subgroups. RR* relates to 10 cm^3 of EAT volume. RR* describes the measure of association including the odds ratio with ≥1 coronary stenosis ≥50%, CAC >0, and myocardial ischaemia and the hazard ratio with MACE. CAC, coronary artery calcification; CAD, coronary artery disease; EAT, epicardial adipose tissue; MACE, major adverse cardiovascular events.

(community-based vs. hospital-based study populations or symptomatic low-to-intermediate vs. high-risk patients), body fat distribution, ethnicity, or gender. Five community-based prospective cohorts contributed to the pooled results accounting for approximately 20 000 subjects: Framingham Heart Study,[46,67] MESA (Multi-Ethnic Study of Atherosclerosis),[36,39,47,52,68] Heinz Nixdorf Recall Study,[45,50,68] EISNER (Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research) Study,[41,44,53,55,57,69] and Rotterdam Study.[51] This could bias lower the association between EAT and CAC, given the low prevalence of CAC (e.g. CAC >0) expected in these very low-risk subjects. Additionally, as a consequence of CT high sensitivity and negative predictive value for CAD detection, most of the participants recruited from hospital registries had low-to-intermediate cardiovascular risk and were referred to CT for exclusion of the disease; few studies included both low-to-intermediate (the majority) and high-risk or with previously known CAD[1,4,6,8,14,22,32,61] patients and only two studies were conducted in the setting of acute coronary syndrome.[64,66] As we did not have

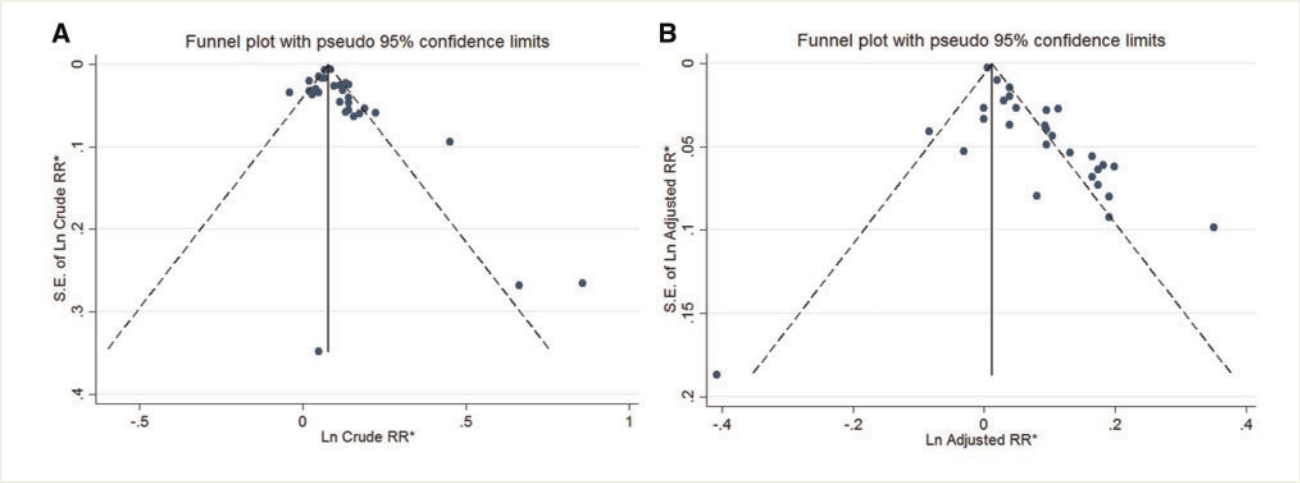

Figure 5 Funnel plot of studies reporting crude (*A*) and adjusted (*B*) associations of EAT volume with CAD. RR* describes the measure of association including the odds ratio with ≥1 coronary stenosis ≥50%, CAC >0, and myocardial ischaemia and the hazard ratio with MACE.

access to individual patient data from all studies reviewed and we based on published information only, we were not able to model the impact of patients' cardiovascular risk on the association of EAT with CAD, and consequently, our conclusions might not be able to be extrapolated to high pretest probability of CAD populations.

Body fat distribution differences might also have contributed to the overall heterogeneity in the sense that some studies suggest a statistically significant interaction between EAT and BMI.[18,29,59,63] Consistently, our subgroup analysis evidenced a stronger association of EAT with CAD in non-obese patients.

Furthermore, even though Tanami *et al.*[1] and McClain *et al.*[39] did not find differences in the association of EAT and CAC score across race/ethnic groups, we showed a higher association between EAT and CAD in Asian subjects ($n = 4990$ subjects) compared with the non-Asians. Fat distribution, in general, and EAT, in specific, varies among the ethnic group with Blacks having a lower average of EAT than Whites and Asians[1,39] and Asians, generally, having a higher percentage of body fat than White people of the same age and gender.[92]

It remains uncertain but there is evidence suggesting that EAT may have a different role in the pathophysiology of CAD according to gender. Some studies showed that EAT was highly associated with CAC in men than in women.[18,36,51] By contrast, McClain *et al.*[39] in the MESA study, as well as Rosito *et al.*[46] in the Framingham Heart Study found no sex interaction in the association of EAT with CAC.

Method of EAT volume quantification

Another aspect contributing to heterogeneity might be related to the methodology applied to measure the EAT volume. We found differences regarding the attenuation thresholds for fat detection (the most commonly used was -190 to -30 HU, but the lower limit ranged from -600 to -190 HU and the upper limit ranged from -50 to -20 HU), the CT protocol (non-contrast vs. contrasted-CT imaging), and the CT scanner features. The volumetric assessment of EAT in CT was initially validated for non-contrast calcium scoring, but the more recent articless have used contrast CT scans. In this systematic review and meta-analysis, the EAT volume was quantified using contrasted-CT in 22 studies.[6–10,13,17,22,23,25,26,29,30,32,33,38,70] A recent paired comparison of the volume of EAT measured in non-contrast and contrast CT showed that calcium score scanning and coronary angiography CT image data sets are both feasible for EAT assessment but its volume can be underestimated in contrast CT acquisition even after post-contrast attenuation adjustment.[93] However, in this review, the EAT volumes mean differences between subjects with and without disease did not differ according to the images set used both in subgroup and in meta-regression analyses.

Statistical methods

Finally, heterogeneity may also result from differences in the statistical methods. A great variety of strategies and models were found; here, we presented the results per variation of 10 cm^3 of EAT to help direct comparisons among studies; the variables for which each study adjusted the association between EAT and CAD can be found in Supplementary data online, *Table S5*.

EAT volume was independently associated with coronary stenosis, MACE, and myocardial ischaemia but not with coronary calcification

The results of this systematic review and meta-analysis on low-to-intermediate cardiovascular risk subjects suggest that EAT is linked to coronary stenosis, coronary events and myocardial ischaemia, irrespective of its association with cardiovascular risk factors. Therefore, the association of EAT with CAD is not totally explained by shared cardiovascular risk factors, but EAT, itself, may contribute to limiting-flow plaque growth, plaque instability, and coronary events. These findings are supported by two case-control studies including diabetic and non-diabetic patients who showed a significant association of EAT with the presence of any coronary plaque in both diabetic and non-diabetic patients.[12,27] Additionally, in a large cohort of non-obese without metabolic syndrome subjects, Narumi *et al.*,[6] clearly demonstrated that EAT was associated with the presence of

obstructive stenosis even after controlling for age, sex, and systolic blood pressure. In contrast, even though EAT volume and CAC were correlated in univariate analysis, this association depended on the atherosclerotic risk factors. As previously discussed, this association can, possibly, be underestimated considering the prevalence of CAC in this review population. Nevertheless, in the CORE320 multicentre study, which included 67% of intermediate-high and 31% of high pretest probability of CAD participants, EAT was associated with CAC in the crude analysis, but it did not hold significant after controlling for cardiovascular risk factors as well.[1] These findings, together with the reported independent association of EAT with coronary stenosis and coronary events, indicate that EAT may be linked with coronary atherosclerosis by different signalling pathways from that of CAC such as the development of non-calcified,[16,29,33] and potentially unstable[13,31,91] coronary plaques in low-to-intermediate risk subjects. Alexopoulos *et al.*[33] showed that EAT volume was significantly higher in patients with mixed or non-calcified plaques compared with patients with calcified plaques or with no plaques. Similarly, Tsushima *et al.*[29] demonstrated, in a cohort of 352 subjects with CAC score of zero (very low cardiovascular risk) that patients with higher EAT volume were associated with non-calcified plaques independently of visceral abdominal fat and cardiovascular risk factors. These associations were anatomically clarified in the study of Ito *et al.*[91] who demonstrated, by optimal coherence tomography, that EAT volume was associated with low-attenuation plaques and extension of the necrotic lipid pool, correlated inversely with fibrous cap thickness and predicted independently acute coronary syndromes.

Clinical implications

Irrespective of the potential causal mechanistic pathways that underlie the above mentioned associations, our findings might indicate that EAT and CAC can be both imaging biomarkers of CAD, and consequently, they are associated with each other in crude analysis but probably refer to different and complementary aspects of the disease. In the Heinz Nixdorf Recall Study, EAT volume predicted the incidence of MACE even when the CAC score was considered in the model,[45] indicating that EAT can, possibly, add a statistically significant different and complementary information of that given by CAC score. Although these data are supported by Groves *et al.*[27] and Kunita *et al.*,[63] Possner *et al.*[61] found no improved risk stratification by EAT volume when the CAC score or myocardial perfusion were known. In contrast, the only study investigating subgroups with the largest relative advantage of EAT above the CAC score showed that EAT volume was able to complete the prognostic value of CAC score but only in patients with marked coronary calcification (CAC score > 400).[65] Furthermore, beyond its diagnostic interest, EAT measurement may also help as an imaging biomarker of disease progression and response to treatment. In contrary to CAC score, which represents an irreversible pathological process, EAT seems to be a dynamic fat depot that may be affected by lifestyle modifications and therapies. A significant reduction in the EAT accumulation was shown after very low-calorie diet,[94] bariatric surgery,[95] aerobic exercise,[96] and statins therapy.[97] However, limited studies have explored the longitudinal association of changes in EAT volume with the incidence or progression of CAD over time.[44,70]

Conclusions

The present systematic review and meta-analysis indicates that EAT is an independent predictor of non-calcified flow-limiting or vulnerable plaques in low-to-intermediate-risk patients. Further investigation is required to study whether and in what degree the EAT is associated with each plaques' components and high-risk plaque features and, importantly, to confirm its incremental predictive value as an adjunct of CAC score or coronary angiography. How to EAT quantity and quality are related to CAD in high-risk patients have not been specifically addressed.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

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Conflict of interest: None declared.

Reference

The entire list of references is available as Supplementary data online.