Association of Epicardial Adipose Tissue and High-Risk Plaque Characteristics: A Systematic Review and Meta-Analysis

Nitesh Nerlekar, MBBS, MPH; Adam J. Brown, MD, PhD; Rahul G. Muthalaly, MBBS; Andrew Talman, BBiomedSc, MD; Thushan Hettige, MBBS; James D. Cameron, MD, MEngSc; Dennis T. L. Wong, MBBS, PhD

Background—Epicardial adipose tissue (EAT) is hypothesized to alter atherosclerotic plaque composition, with potential development of high-risk plaque (HRP). EAT can be measured by volumetric assessment (EAT-v) or linear thickness (EAT-t). We performed a systematic review and random-effects meta-analysis to assess the association of EAT with HRP and whether this association is dependent on the measurement method used.

Methods and Results—Electronic databases were systematically searched up to October 2016. Studies reporting HRP by computed tomography or intracoronary imaging and studies measuring EAT-v or EAT-t were included. Odds ratios were extracted from multivariable models reporting the association of EAT with HRP and described as pooled estimates with 95% confidence intervals (CIs). Analysis was stratified by EAT measurement method. Nine studies (n=3772 patients) were included with 7 measuring EAT-v and 2 measuring EAT-t. Increasing EAT was significantly associated with the presence of HRP (odds ratio: 1.26 [95% CI, 1.11–1.43]; *P*<0.001). Patients with HRP had higher EAT-v than those without (weighted mean difference: 28.3 mL [95% CI, 18.8–37.8 mL]; *P*<0.001). EAT-v was associated with HRP (odds ratio: 1.19 [95% CI, 1.06–1.33]; *P*<0.001); however, EAT-t was not (odds ratio: 3.09 [95% CI, 0.56–17]; *P*=0.2). Estimates remained significant when adjusted for small-study effect bias (odds ratio: 1.13 [95% CI, 1.03–1.28]; *P*=0.04).

Conclusions—Increasing EAT is associated with the presence of HRP, and patients with HRP have higher quantified EAT-v. The association of EAT-v with HRP is significant compared with EAT-t; however, a larger scale study is still required, and further evaluation is needed to assess whether EAT may be a potential therapeutic target for novel pharmaceutical agents.

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Key Words: epicardial fat • high-risk plaque • meta-analysis • vulnerable plaque

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Epicardial adipose tissue (EAT) is a metabolically active fat depot, abundant in proinflammatory cytokines, and has been correlated with the extent and severity of coronary artery disease (CAD).[1] EAT shares the same embryologic origin of omental and mesenteric fat[2,3] and encases the coronary arteries with no fascial barrier.[4] Consequently, it has been postulated that EAT may display vasocrine or paracrine effects on the adjacent arterial wall to influence atherosclerotic plaque composition, resulting in the development of high-risk plaque (HRP).[5–9] The presence of HRP has shown association with future adverse prognosis,[10,11] but the management of these patients remains uncertain. HRP may be visualized invasively by several methods including intravascular ultrasound and optical coherence tomography and noninvasively by computed tomography (CT) coronary angiography with good diagnostic agreement between techniques.[12–14] EAT may be measured either volumetrically by CT coronary angiography or noncontrast CT (EAT-v) or by a linear thickness measurement on echocardiography (EAT-t). Both thickness and volume measures have been associated with incident CAD[1]; however, linear thickness may underrepresent the totality of EAT.

The objective of this systematic review and meta-analysis was to explore the association between EAT and the presence of HRP. The secondary aims were to evaluate whether increasing EAT volume is associated with HRP presence and

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Clinical Perspective

What Is New?

- Increasing epicardial adipose tissue (EAT) volume is associated with the presence of high-risk coronary artery plaque characteristics.
- Patients with high-risk coronary plaque features have quantitatively higher EAT volumes.
- EAT should ideally be measured by complete volumetric analysis rather than by linear thickness measurements.

What Are the Clinical Implications?

- Incorporation of EAT measurement with routinely performed cardiac computed tomography may assist in improved risk stratification for patients.
- EAT may represent an important cardiovascular therapeutic target.

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the strength of association with presence of HRP by EAT measurement method.

Materials and Methods

Data Sources and Search Strategy

The search was conducted using the Medline, Embase, and PubMed databases with no start date up to October 2016. Keywords using Medical Subject Headings included *epicardial adipose tissue, epicardial fat, pericardial adipose tissue, pericardial fat, vulnerable plaque, high-risk plaque, low-attenuation plaque, napkin ring, positive remodeling, spotty calcification, coronary artery disease, plaque characteristics, plaque composition, plaque vulnerability, thin-cap fibroatheroma, intravascular ultrasound, optical coherence tomography*, and *angioscopy*. The reference lists of eligible articles were hand-searched for additional articles. Searches were restricted to human studies. We conducted this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, and the trial was registered with PROSPERO (registration no. CRD42017055473). A flow chart describing the study search is presented in Figure 1, and an example of the search term strategy is shown in Table S1.

Study Selection

The following inclusion criteria were used for the study: patients undergoing either intracoronary imaging or CT coronary angiography evaluation with reported HRP features, noninvasive measurement of EAT by either CT-derived volume (on contrast or noncontrast CT) or linear thickness (by CT or echocardiography), and reports fully published in peer-reviewed journals. For intracoronary imaging studies, HRP was defined as the presence of thin-cap fibroatheroma. For CT studies, HRP included plaques with ≥1 of the following features: low-attenuation plaque, positive remodeling, spotty calcification, and the napkin ring sign. Study specific definitions of HRP are reported in Table S2.

Data Extraction

Odds ratios (ORs) and their respective 95% confidence intervals (95% CIs) for association of EAT with HRP were extracted. If possible, ORs from multivariable models that adjusted for other CAD risk factors were used, and covariates within the model were recorded. Mean and standard deviation of EAT volume between groups with and without HRP were entered. Studies reporting medians with interquartile ranges were converted to means, as recommended previously.[15]

End Points

The primary end point was the pooled association of EAT with the presence of HRP. Secondary end points included the pooled quantitative difference of EAT-v in patients with and without HRP and the association of EAT with HRP stratified by EAT measurement method (EAT-v or EAT-t).

Statistical Analysis

Statistical analysis was performed using StataMP 14.0 (StataCorp). ORs were examined on the log scale and transformed for graphical presentation with 95% CI reported. If multiple outcomes were reported (ie, by individual plaque feature or by grouped features), the analyzed estimate was the association of EAT with any HRP if specified. Random-effects modeling was used with the method of DerSimonian and Laird.[16] The weighted mean difference for EAT between groups with and without HRP was calculated. Statistical heterogeneity was evaluated by the I^2 statistic and quantified as low (<25%), moderate (25–75%), or high (>75%).[17] Sensitivity analysis was performed by EAT measurement method (EAT-v or EAT-t, by pooled estimates of similarly defined EAT covariate parameters; ie, when EAT was included as a continuous variable or assessed in 10-mL increments and for individual plaque features, if possible). Additional sensitivity analysis using random effects with the Hartung–Knapp–Sidik–Jonkman (HKSJ) approach was used to explore effect sizes when 2 studies were grouped.[18,19] Exploratory metaregression was performed to assess the influence of independent variables (mean study ages, mean EAT volume, mean study body mass index, and proportion of HRP). Publication bias was assessed by the Egger and Begg test. In addition, the Duval and Tweedie trim-and-fill method was used to investigate publication bias,
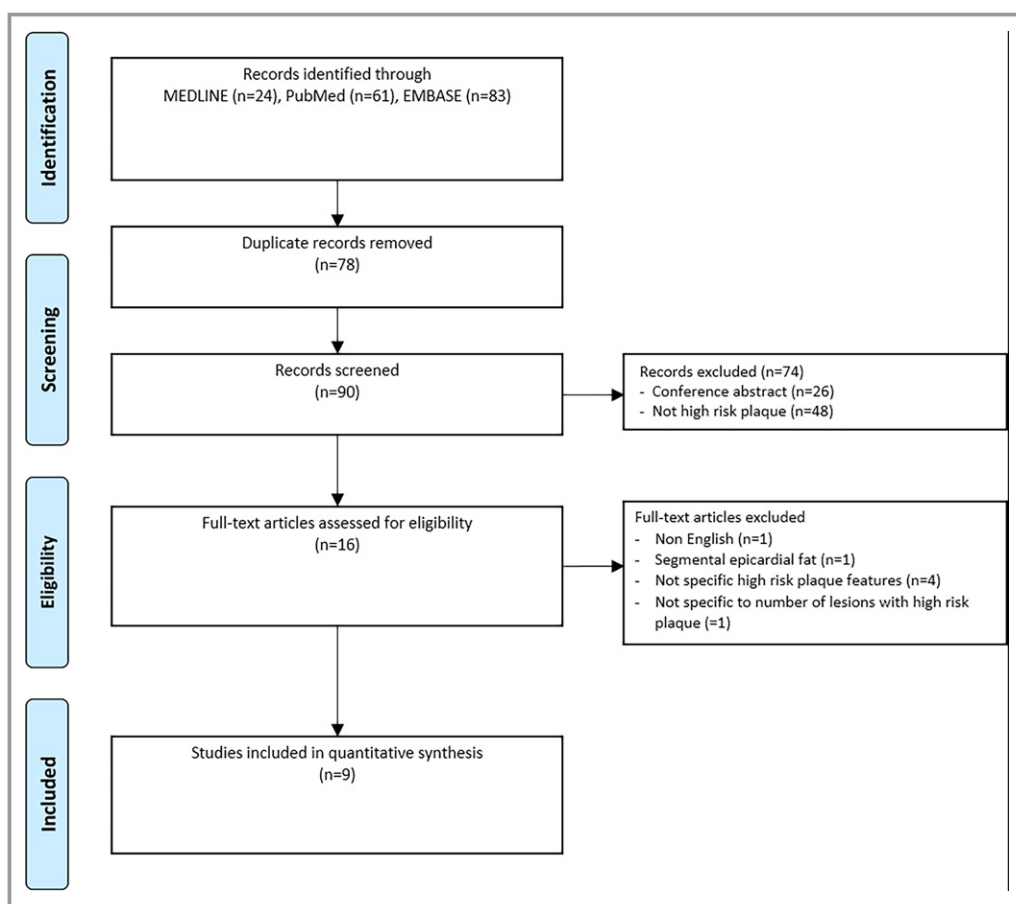
Figure 1. Search strategy.

and systematic exclusion of individual studies was used to assess changes in the pooled estimate. A 2-sided *P* value of <0.05 was considered significant.

Results

A total of 90 publications were reviewed with 9 studies included for final analysis (3772 participants; Figure 1). One study was excluded because it presented the association of EAT with plaque lipid percentage rather than specified numbers of patients with HRP.[20] Seven studies reported CT assessment of HRP[21–27] (n=3573) and 2 studies reported invasive assessment of HRP[29,30] (n=199). Seven studies measured EAT-v[21–26,29,30] (n=3284), and 2 studies measured EAT-t[27,28] (n=488). All study designs were cross-sectional. All patients were from cohorts with suspected CAD, with 2 studies evaluating patients with suspected acute coronary syndrome.[21,22] Study characteristics are presented in Tables 1 and 2, and regression modeling outcomes and model covariates are presented in Table 3. Individual-study EAT measurement characteristics and HRP definitions are presented in Table S2.

The prevalence of HRP ranged widely, from 4% to 59% at a per-patient level (Table 1). The primary end point demonstrated a significant association of increasing EAT with the presence of HRP (pooled OR: 1.26 [95% CI, 1.11–1.43]; *P*<0.001, I^2=81%; Figure 2).

Analysis to assess quantitative differences in EAT between patients with and without HRP demonstrated a weighted mean difference of +28.3 mL in those patients with HRP (95% CI, 18.8–37.8 mL]; *P*<0.001; I^2: 58%) based on 4 studies (Figure 3).

When stratified by EAT measurement method, in the 7 studies measuring EAT-v, the pooled OR was significantly associated with HRP presence (OR: 1.19 [95% CI, 1.06–1.33]; *P*<0.001, I^2: 78%). However, no significant association was observed with the 2 EAT-t studies and presence of HRP (OR: 3.09 [95% CI, 0.56–17]; *P*=0.20; I^2: 90%; Figure 4). This remained statistically nonsignificant on sensitivity analysis with the HKSJ method (Table 4).

Sensitivity analysis was performed to assess pooled estimates of studies using EAT as a similarly measured covariate. Two studies analyzed EAT-v in 10-mL increments and demonstrated a pooled OR of 1.18 (95% CI, 1.12–1.24;

Table 1. Demographic, EAT, and HRP Parameters of Included Studies

Study	EAT Method	Population	N	EAT Value	HRP Proportions
Lu et al[21]	EAT-v (CACS)	Suspected ACS	467	Median EAT: 108.5 cm³ (IQR: 76.4–140.6 cm³) With HRP: 123 cm³ (IQR: 93–156 cm³) Without HRP: 98 cm³ (IQR: 68–127 cm³)	HRP in 167 (36%) patients; NRS in 15%; PR in 32.3%; LAP in 23.4%; SpC: in 91%
Schlett et al[22]	EAT-v (CTCA)	Suspected ACS	358	Median EAT: 95.2 cm³ (IQR: 66–130.1) With HRP: 151.9 cm³ (IQR: 109.0–179.4) Without HRP: 110 cm³ (IQR: 81.5–137.4)	Any HRP in 13 (4%) patients
Rajani et al[24]	EAT-v (CACS)	Suspected CAD	402	Mean EAT: 103±51 cm³ With any HRP: 116±53 cm³ Without HRP: 99±57 cm³	Any HRP in 113 (59%) patients; LAP in 67 (35%); PR in 93 (48%)
Oka et al[23]	EAT-v (CACS)	Suspected CAD	357	Mean EAT: 125±44 mL; EAT analysis threshold of 100 mL	87 (24%) with all 3 HRPs LAP: EAT <100 mL: 52%; EAT ≥100 mL: 27% PR: EAT <100 mL: 58%; EAT ≥100 mL: 37% LAP with or without PR: EAT <100 mL: 46%; EAT ≥100 mL: 25%
Ito et al[25]	EAT-v (CACS)	Suspected CAD (symptomatic) with CACS 0	1308	Mean EAT: 98.1±41.3 cm³ With HRP: 133±40.2 cm³ Without HRP: 95.1±40.3 cm³	Any HRP in 63 (5%) patients
Nakanishi et al[26]	EAT-v (CTCA)	Suspected CAD in patients with CKD	275	Mean EAT: CKD: 111±41 mL (n=110) No CKD: 81±29 mL (n=165)	Any HRP in 44 (16%) patients
Ito et al[29]	EAT-v (CTCA)	Scheduled for PCI and underwent CT in addition to OCT	117 (244 plaques)	EAT-v Tertiles: T1: <104.1 cm³ (n=39) T2: 104.1 to 130.7 cm³ (n=39) T3: >130.7 cm³ (n=39)	Total TCFA: 51 (21%) plaques T1: Single TCFA n=6 (15%); Multiple TCFA n=1 (3%) T2: Single TCFA n=7 (18%); Multiple TCFA n=3 (8%) T3: Single TCFA n=12 (31%); Multiple TCFA n=8 (21%) Minimum fibrous cap thickness: T1: 102.7±69.2 μm; T2: 102.5±56.5 μm; T3: 78.2±43.9 μm Maximal lipid arc: T1: >2 quadrants, 13 (33%); T2: >2 quadrants, 14 (36%); T3: >2 quadrants, 25 (64%) CT characteristics: T1: LAP, 4 (10%); PR, 8 (21%) T2: LAP, 14 (36%); PR, 13 (33%) T3: LAP, 16 (41%); PR, 21 (54%)
Park et al[28]	EAT-t (Echo)	Angiographically significant CAD undergoing PCI with or without IVUS	82	Mean EAT-t: 3.4±2.2 mm EAT-t 3.5 mm threshold: EAT <3.5 mm (n=21); EAT ≥3.5 mm (n=39)	TCFA (n): EAT <3.5 mm: 3.3±2.2; EAT ≥3.5 mm: 2.1±1.6 Mean volume index necrotic core (mm³/mm): EAT <3.5 mm: 0.3±0.2; EAT ≥3.5 mm: 0.6±0.4 Plaque volume (mm³): EAT <3.5 mm: 1360.1±492.1; EAT ≥3.5 mm: 1048.5±398.2

Table 1. Continued

Study	EAT Method	Population	N	EAT Value	HRP Proportions
Tachibana et al[27]	EAT-t (Echo)	Suspected CAD	406	EAT-t 5.8 mm threshold: EAT ≥5.8 mm (n=238); EAT <5.8 mm (n=168)	HRP in 45 (11%) patients LAP: EAT <5.8 mm: 4%; EAT ≥5.8 mm: 24% PR: EAT <5.8 mm: 39%; EAT ≥5.8 mm: 60% LAP+PR: EAT <5.8 mm: 3%; EAT ≥5.8 mm: 17%

ACS indicates acute coronary syndrome; CACS, coronary artery calcium score (noncontrast computed tomography); CAD, coronary artery disease; CKD, chronic kidney disease; CT, computed tomography; CTCA, computed tomography coronary angiography; EAT, epicardial adipose tissue; EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume; HRP, high-risk plaque; IQR, interquartile range; IVUS, intravascular ultrasound; LAP, low-attenuation plaque; NRS, napkin ring sign; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PR, positive remodeling; SpC, spotty calcification; T, tertile; TCFA, thin-cap fibroatheroma.

$P<0.001$; I^2: 0%) that became nonsignificant when analyzed with the HKSJ method (OR: 1.18 [95% CI, 0.84–1.64]; $P=0.10$). In the 2 studies that analyzed EAT-v as a continuous variable, the pooled OR was 1.18 (95% CI, 0.77–1.81; $P=0.44$; I^2: 52%), which remained nonsignificant after analysis with HKSJ (Table 4). EAT measured in the remaining studies were modeled as per standard deviation or by a dichotomous threshold level and not formally pooled.

Further sensitivity analysis was performed to assess the association between specific HRP subtypes with information obtainable from 2 studies. An association was demonstrated between increasing EAT and low-attenuation plaque (OR: 2.79 [95% CI, 1.71–4.53]; $P<0.001$; I^2: 0%), positive remodeling, (OR: 1.93 [95% CI, 1.25–2.99]; $P=0.003$; I^2: 0%), and the presence of both features (OR: 2.58 [95% CI, 1.55–4.28]; $P=0.001$; I^2: 0%). The results for both low-attenuation plaque and positive remodeling became statistically nonsignificant after application of the HKSJ method, but the presence of both features remained significantly associated with increasing EAT (Table 4).

Exploratory metaregression demonstrated no significant influence of varying study-level predictors on the overall effect size; these included mean BMI (OR: 0.95 [95% CI, 0.79–1.14];

$P=0.55$), mean age (OR: 1.03 [95% CI, 0.96–1.10]; $P=0.38$), population proportion of HRP (OR: 0.99 [95% CI, 0.98–1.00]; $P=0.42$), and mean EAT volume (OR: 1.00 [95% CI, 0.97–1.03]; $P=0.99$).

There was evidence of publication bias by calculation of the Egger test for small-study effects ($P=0.005$). Using the trim-and-fill method, the overall estimate remained significant for the association of EAT and HRP (pooled estimate OR: 1.13 [95% CI, 1.03–1.28]; $P=0.04$; I^2: 81%; Figure S1). Analysis to assess the influence of single studies on the effect estimate demonstrated a persistent significant association of increasing EAT with HRP. The lowest pooled estimate OR of 1.16 (95% CI, 1.06–1.27; $P=0.001$; I^2: 74%) occurred with the exclusion of Tachibana et al, and the highest pooled estimate OR of 1.27 (95% CI, 1.12–1.45; $P<0.001$; I^2: 70%) occurred with the exclusion of Lu et al (Table S3).

Discussion

The results from this meta-analysis of 9 observational studies demonstrate 3 important findings. First, increasing EAT is

Table 2. Study Demographic Data

Study	Diabetes Mellitus(%)	Hypertension (%)	Hyperlipidemia (%)	BMI	Ethnicity	Age, y	Sex (%)
Lu et al[21]	17	53	45	29±5	Not specified	54±8	53
Schlett et al[22]	10	39	37	28 (25–32)	Not specified	51 (45–59)	62
Rajani et al[24]	14	54	63	27±4	Not specified	66 (23–92)	56
Oka et al[23]	31	68	50	24±5	Japanese institution	66±11	63
Ito et al[25]	8	33	26	23±4	Japanese institution	59±12	46
Nakanishi et al[26]	38	65	59	24±4	Japanese institution	65±10	66
Park et al[28]	29	61	20	25±3	Korean Institution	59±11	54
Ito et al[29]	24	61	44	24±3	Japanese institution	66±9	82
Tachibana et al[27]	27	58	31	23±4	Japanese institution	68±13	57

Values are expressed as total study cohort proportions (%), mean±SD, or median (interquartile range). BMI indicates body mass index.

Table 3. EAT Modeling Outcomes and Model Covariates

Study	EAT Modeling	Regression Outcomes	Covariates in Multivariable Model	Threshold/ROC AUC Values
Lu et al[21]	Indexed and absolute EAT	Any HRP with indexed EAT-v: OR: 1.04 (95% CI, 1–1.08; P=0.04) Any HRP with absolute EAT-v: OR: 1.02 (95% CI, 1–1.03; P=0.046)	Age, sex, number of cardiovascular risk factors, log CACS, >50% stenosis	Optimal threshold 62.3 cm^3/m^2 with sensitivity 48.5%, specificity 72.7%; no ROC AUC specified
Schlett et al[22]	EAT per SD (49.8 mL)	Presence of HRP: OR: 1.79 (95% CI, 1.13–2.76; P=0.008)	Not specified	Not reported
Rajani et al[24]	Log EAT-v	Any HRP: OR: 1.7 (95% CI, 0.9–3.4; P=0.038) LAP: OR: 2.4 (95% CI, 1.1–5.1; P=0.02) PR: OR: 1.8 (95% CI, 1.0–3.4; P=0.07) Both HRP features: OR: 2.6 (95% CI, 1.1–6.2; P=0.03)	Age, BMI, diabetes mellitus, hypercholesterolemia, smoking, family history, hypertension	ROC AUC of 0.756 for any HRP presence with sensitivity 62%, specificity 84%; optimal threshold of EAT <74.07 cm^3 excluded any HRP
Oka et al[23]	High vs low-EAT-v (100 mL threshold)	LAP: OR: 3.08 (95% CI, 1.66–5.83; P<0.001) PR: OR: 2.08 (95% CI, 1.12–3.88; P=0.02) SpC: OR: 1.11 (95% CI, 0.61–2.04; P=0.73) LAP+PR: OR: 2.56 (95% CI, 1.38–4.85; P=0.003) All 3 features: OR: 1.65 (95% CI 0.81–3.44; P=0.17)	Age, sex, hypertension, diabetes mellitus, smoking, BMI, VAT area, CACS	Using a threshold of 100 mL, sensitivity for LAP+PR was 80%, specificity was 41%
Ito et al[25]	EAT-v per 10 cm^3	Any HRP: OR: 1.19 (95% CI, 1.12–1.27; P<0.01)	Male, diabetes mellitus, hypertension, BMI	ROC AUC of 0.75 for any HRP presence at optimal threshold 127.1 cm^3 with sensitivity 64%, specificity 81%
Nakanishi et al[26]	EAT-v per 10 mL	Presence of HRP: OR: 1.15 (95% CI, 1.05–1.26; P=0.003)	Age per 10 y, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, BMI	. . .
Ito et al[29]	Highest tertile of EAT	Presence of TCFA: OR: 2.92 (95% CI, 1.13–7.55; P=0.027) Correlation of EAT with fibrous cap thickness: r=−0.400, P<0.01	ACS, BMI	ROC AUC of 0.721 for detection of TCFA with optimal threshold 126.7 cm3, sensitivity 69% specificity 71%
Park et al[28]	High vs low-EAT-t (3.5 mm threshold)	Total TCFAs in symptom-related vessel: β=0.106 (95% CI, 0.004–0.208; P=0.043)	BMI, diabetes mellitus, dyslipidemia, metabolic syndrome	Not specified
Tachibana et al[27]	High vs low-EAT-t (5.8 mm threshold)	Presence of HRP: OR: 7.98 (95% CI, 2.77–22.98; P<0.01)	Age, sex, BMI, VAT, hypertension, dyslipidemia, diabetes mellitus, smoker, CACS >100, stenotic vessel number, renal insufficiency, statins	ROC AUC of 0.77 for HRP (combination of LAP+PR) at threshold of 5.8 mm with sensitivity 83%, specificity 64%

ACS indicates acute coronary syndrome; BMI, body mass index; CACS, coronary artery calcium score (noncontrast computed tomography); CI, confidence interval; EAT, epicardial adipose tissue; EAT-t, EAT thickness; EAT-v, volumetric EAT; HRP, high-risk plaque; LAP, low-attenuation plaque; OR, odds ratio; PR, positive remodeling; ROC AUC, receiver operating characteristic area under the curve; SpC, spotty calcification; TCFA, thin-cap fibroatheroma; VAT, visceral adipose tissue.

significantly associated with the presence of HRP features. Second, patients with HRP have a significantly increased volume of EAT compared with those without HRP. Third, EAT is associated with HRP presence ideally when measured by complete volumetric analysis rather than EAT linear thickness measurements.

EAT is a visceral adipose tissue depot rich in proinflammatory and proatherogenic cytokines including monocyte
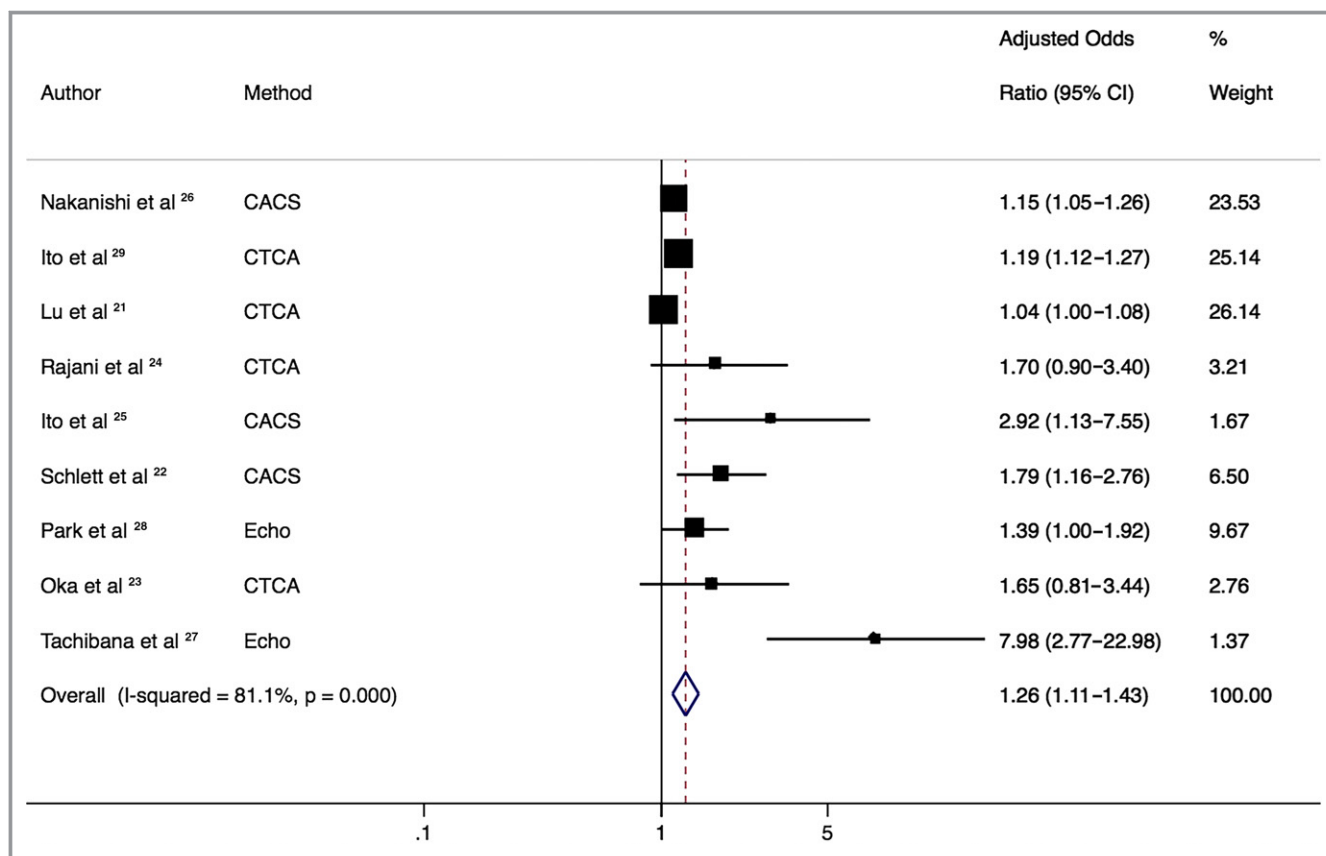
Figure 2. Association of epicardial adipose tissue (EAT) with presence of high-risk plaque (HRP). Forest plot displays summary odds ratios and 95% confidence intervals (CIs) for the increasing association of EAT with HRP. Method represents the radiologic method of calculating EAT. This demonstrates a significant association of increasing EAT with HRP. CACS indicates coronary artery calcium score (noncontrast computed tomography); CTCA, computed tomography coronary angiography; Echo, echocardiography.

chemoattractant protein 1, IL-6 (interleukin 6). IL-1β, IL-6sR, and tumor necrosis factor α.[31] Because of EAT's anatomic proximity to the adjacent myocardium and lack of fascial barrier with the epicardial coronary arteries, there may be paracrine or vasocrine signaling of cytokines between the surrounding fat and the underlying arterial wall.[2] This suggested pathophysiology is analogous to the visceral intra-abdominal adipose tissue surrounding the portal circulation that is purported to influence the development of hepatic steatosis.[32] It has been demonstrated that increased EAT volume is related to both the extent and the lesion severity of coronary stenosis[33] and that EAT contains a greater amount of inflammatory cytokines than serum circulating levels and subcutaneous adipose stores.[34] The apposition of EAT with the arterial adventitia suggests the "outside-in" hypothesis of atherosclerosis, whereby the inflammatory milieu of EAT leads to vascular inflammation of the adventitia progressing inward to the intima, leading to plaque formation. Consequently, it is possible that cellular cross-talk may lead to the development of plaque characteristics considered to be "high risk" given their association with major adverse cardiovascular events. It has also been reported that high EAT levels are associated with mortality, although it remains unclear whether these levels are specifically related to preceding cardiovascular events.[35] Our results indicate a uniform association of increasing EAT with HRP, but further study is needed to establish the influence and interaction of these parameters with prognosis. Importantly, we aimed to use risk estimates from multivariable models, which suggests an incremental effect of EAT with HRP presence beyond traditional cardiovascular risk factors.

Because there is no guideline-advocated technique for EAT quantification, individual studies are subject to authors' discretion and experience. The interobserver variability for EAT-t has shown mixed results,[36] and a measure of linear thickness by 2-dimensional assessment may under- or overrepresent total EAT volume due to changes in probe angulation. It has been suggested that a threshold of 7 mm confers elevated EAT-t; this is a significantly higher threshold than our included studies and may also influence interpretation. Only 1 previous study evaluated EAT-t versus EAT-v, in 71 patients, and reported a modest correlation (r=0.595).[37]
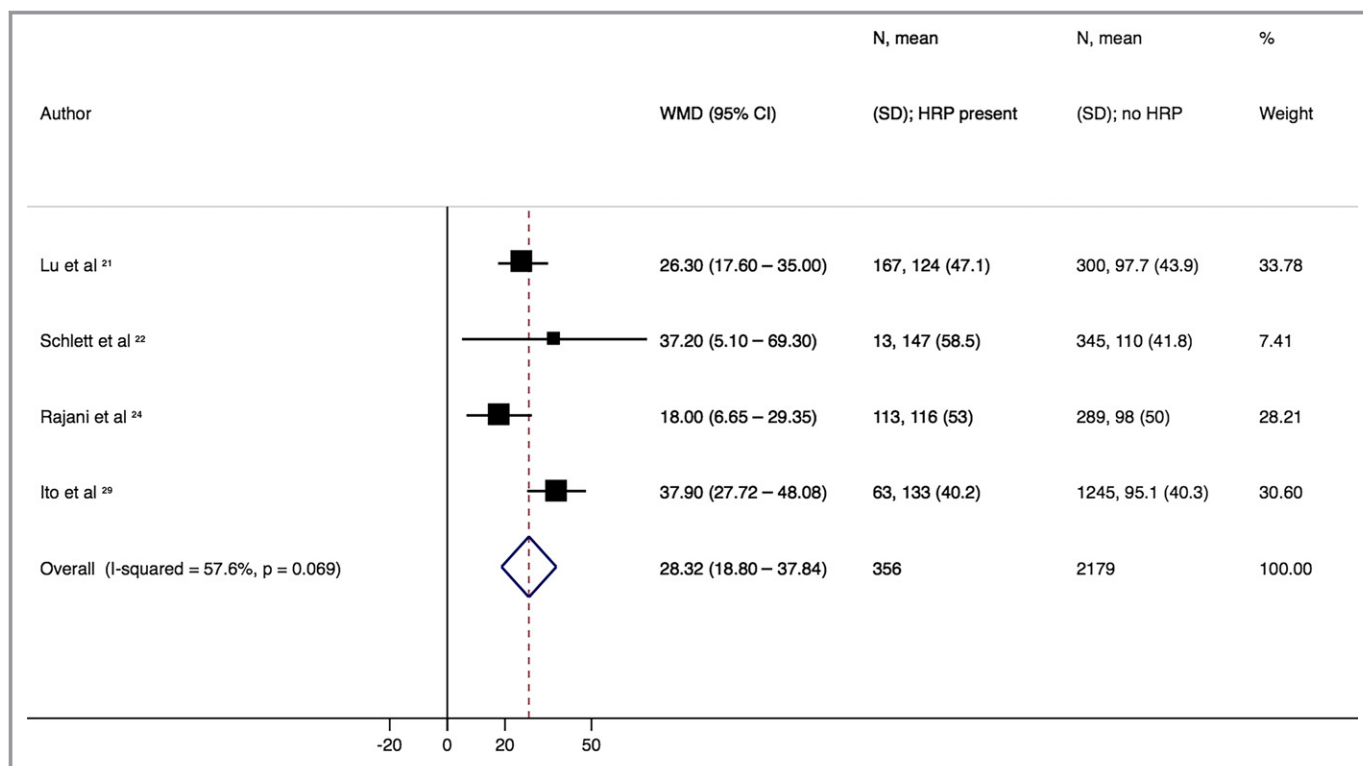
Figure 3. Difference in quantitative epicardial adipose tissue (EAT). Forest plot displays weighted mean differences (WMDs) and 95% confidence intervals (CIs) for differences between patients with and without high-risk plaque (HRP). This indicates that patients with HRP have a significantly higher volume of EAT (WMD: 28.3 mL [95% CI, 18.8–37.8 mL]) compared with those patients without HRP.

EAT-v, however, also has limitations, with differing values measurable with the use of contrast media[38] and possible differences related to vendor-specific software algorithms. In our analysis of EAT-v versus EAT-t, we demonstrated that EAT-t had a decidedly wide CI for the association with HRP and failed to reach statistical significance, although this is based on only 2 studies with a total of 488 patients. On the contrary, EAT-v displayed a significant association with HRP with more precise confidence limits. We attempted to explore the association further by analyzing the modeling method of EAT, which demonstrated uncertainty in estimates for differing techniques and highlighted the need for a standardized and consistent approach when incorporating EAT into models to assess disease outcomes.

In our subgroup analysis of EAT association with HRP subtype, we noted a strong association individually with low-attenuation plaque and positive remodeling as well as with the presence of both features after adjustment for conventional cardiovascular risk factors. Association with individual plaque feature types diminished due to imprecision in 95% CIs but remained for the presence of both high-risk features. The largest study to date, of 3158 patients by Motoyama et al, reported that these HRP characteristics, defined as the presence of either feature or both, are strongly associated with future acute coronary syndrome development (adjusted

hazard ratio: 8.24 [95% CI, 5.26–12.96]; *P*<0.001).[10] EAT was not measured in this study, and its contribution to prognosis remains unclear.

It is notable that some observational studies have demonstrated a lack of relationship between EAT and significant CAD[39,40]—similar to our included studies, all of which are observational and prone to significant bias. Biases include selection and ascertainment bias and variable use of predictors in regression modeling that may alter reported estimates and contribute to between-study heterogeneity. To assess study quality, we evaluated the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification[41–43] (Tables S4 and S5), which apportions an overall study-quality assessment. Because none of the trials are, by definition, of high quality, given that they are not randomized controlled trials, the overall information quality is regarded as low and should be interpreted as such without drawing firm conclusions that may alter clinical decision making. Despite the inconsistency of CAD association, given the association of HRP with cardiac prognosis, it remains plausible that EAT may influence plaque composition that may not be diagnosed as functionally or anatomically significant. Rigorous prospective study to assess the role of EAT in atherogenesis is still warranted.

The management of HRP features is uncertain. EAT is currently measured only for research purposes; however, the
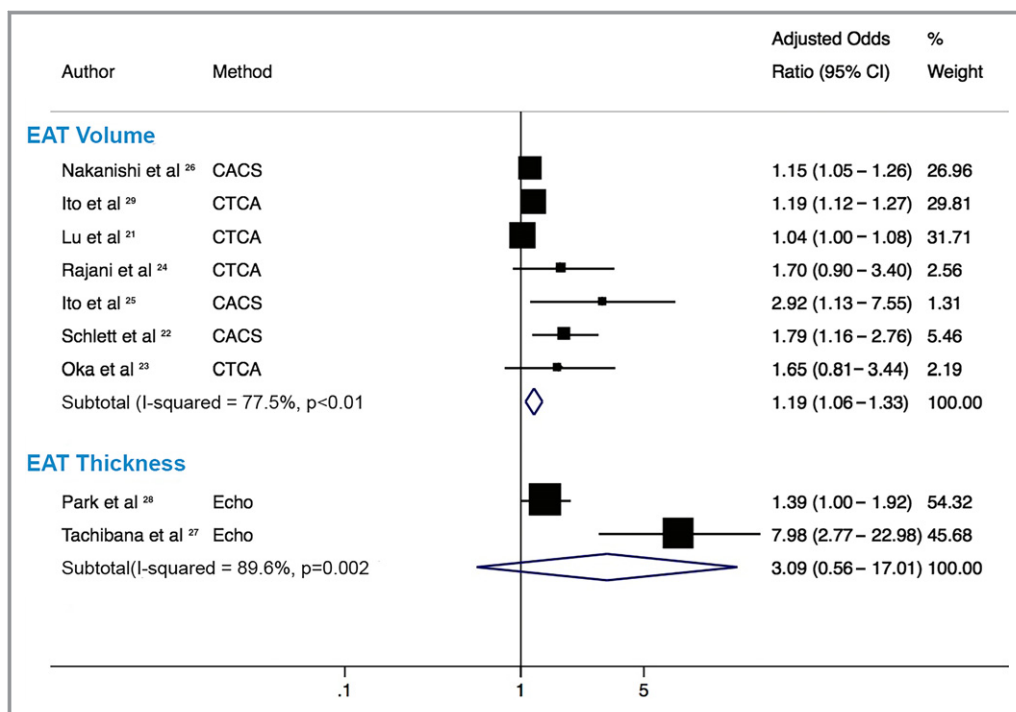
Figure 4. Pooled estimates by epicardial adipose tissue (EAT) measurement method. Forest plot displays odds ratios and 95% confidence intervals (CIs) for the association of increasing EAT with high-risk plaque (HRP) stratified by measurement method of EAT measurement, either by volume or thickness. This demonstrates that increasing EAT volume has a significant association with HRP; however, increasing EAT thickness is not significantly associated with HRP and has a markedly wide CI crossing the line of unity. CACS indicates coronary artery calcium score (noncontrast computed tomography); CTCA, computed tomography coronary angiography; Echo, echocardiography.

importance of assessing EAT and its association with HRP relates to a potential target for therapeutic intervention. EAT has demonstrated temporal changes in plaque and cardiovascular risk. In a study of nonobese patients undergoing serial CT over 4 years, an increase in EAT volume was associated with HRP as well as future acute coronary syndrome despite optimal management of cardiovascular risk factors.[44] Calorie restriction and bariatric surgery rather than exercise have shown promise as methods for EAT reduction, as explored recently in a meta-analysis by Rabkin and Campbell,[45] and animal data have demonstrated that selective surgical excision of EAT slows the progression of atherosclerosis.[46] It remains to be seen whether targeted EAT reduction may improve dynamic atherosclerosis in human participants, and randomized controlled trial data are lacking.

Study Limitations

Our analysis is limited by the observational nature of included studies and by a lack of access to patient-level data to allow adjustment for other covariates that may influence EAT including sex differences and stratification and assessment by other population features such as traditional cardiovascular

risk factors of hypertension, hyperlipidemia and diabetes mellitus. We attempted to account for this by using model estimates that adjusted for several of these variables. The majority of studies were also performed in Japanese centers, which may limit the generalizability of our findings to other ethnic populations. Another important limitation is the inclusion of only 2 studies evaluating EAT thickness and other subgroup parameters. The interpretation of results is limited by this methodology because of the potential lack of power and the inability to draw firm conclusions. Importantly, we noted that when more robust statistical methods were applied when few studies were pooled, statistical significance was reversed, highlighting the need for more data in these areas. We noted a significant degree of heterogeneity, a limitation that has been demonstrated in other published EAT meta-analyses that report I^2 values >90%.[1,47] This is probably in part representative of variable EAT quantification methods and differing measures of EAT as a covariate in regression analyses. We attempted to adjust for this heterogeneity by systematic exclusion of studies that did not significantly attenuate the summary estimates from statistical significance and by sensitivity analysis by subgroup analysis and exploratory metaregression.

Table 4. Sensitivity Analysis of Random-Effects Meta-Analysis With Alternative Methods When Pooled Estimates Were From Combination of 2 Studies

Variable	Random-Effects Method	Pooled OR	95% CI	P Value
EAT measurement method				
EAT thickness[27,28]	DL	3.09	0.56–17.01	0.20
	HKSJ	3.09	0–19	0.49
Covariate modeling method				
EAT continuous[21,24]	DL	1.18	0.77–1.81	0.44
	HKSJ	1.18	0.08–18.5	0.58
EAT per 10 mL[25,26]	DL	1.18	1.12–1.24	<0.01
	HKSJ	1.18	0.96–1.45	0.06*
HRP subtype				
LAP[23,24]	DL	2.79	1.71–4.53	<0.01
	HKSJ	2.79	0.59–13.2	0.08*
PR[23,24]	DL	1.93	1.25–2.99	0.003
	HKSJ	1.93	0.77–4.84	0.07*
Both LAP and PR[23,24]	DL	2.58	1.55–4.28	<0.01
	HKSJ	2.58	2.34–2.83	0.005

References indicate studies that were pooled. ORs are presented using DL and HKSJ methods. CI indicates confidence interval; DL, DerSimonian and Laird; EAT, epicardial adipose tissue; HKSJ, Hartung–Knapp–Sidik–Jonkman; HRP, high-risk plaque; LAP, low attenuation plaque; OR, odds ratio; PR, positive remodeling.
*Signifies when there was a change in P value resulting in statistical nonsignificance ($P>0.05$) after applying the HKSJ method.

Conclusion

Increasing EAT is associated with the presence of HRP, ideally, when measured by complete volumetric analysis. Further investigation is still required to establish the role of EAT-t in evaluating HRP and consistent methods for modeling EAT as a variable for disease outcomes and the effect of EAT on individual HRP features. Incorporating the measurement of EAT into clinically performed CT coronary angiography has the potential to improve patient risk stratification. Further prospective studies are needed to confirm this finding, which holds potential as a novel therapeutic target for atherosclerotic treatment.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Example search strategy (Embase)

#	Searches	Results
1	Epicardial adipose tissue.mp.	1249
2	Epicardial fat.mp.	1481
3	Pericardial adipose tissue.mp	161
4	Pericardial fat.mp	550
5	Vulnerable plaque.mp	2196
6	High risk plaque.mp	288
7	Low attenuation plaque.mp	101
8	Napkin ring.mp	94
9	Positive remodelling	125
10	Spotty calcification	170
11	Plaque characteristics	1228
12	Plaque composition	1734
13	Plaque vulnerability	1745
14	Thin cap fibroatheroma	773
15	Necrotic core	2091
16	Exp intravascular ultrasound/	12695
17	Exp optical coherence tomography/	36156
18	Exp computer assisted tomography/	778928
19	Computed tomography coronary angiography.mp	1140
20	Cardiac computed tomography.mp	2526
21	Exp coronary artery calcium score	3230
22	Exp coronary angiography/	2916
23	1 or 2 or 3 or 4	2877
24	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	7800
25	16 or 17 or 22	51500
26	18 or 19 or 20 or 21	779979
27	23 and 24 and 25	26
28	23 and 24 and 26	57

Table S2. Study EAT measurement parameters and HRP definitions

Author	EAT measure method	Definition of HRP features
Lu et al.[1]	EAT definition: fat within pericardial sac. Method: Semi-automated. Software: Volume Viewer, Siemens Medical Solutions, Germany Interval: 1cm Superior border: mid-level RPA Inferior border: diaphragm HU range: -195 to -45 HU	PR: RI of >1.1 maximal outer vessel diameter at plaque divided by average of the proximal and distal normal vessels LAP: <30 HU SpC: <3mm CP extending <1.5mm long-axis vessel diameter & two-thirds vessel circumference NRS: ring of peripheral high attenuation surrounded by core of low attenuation in a non-calcified plaque
Schlett et al.[2]	EAT definition: fat within pericardial sac. Method: Manual Software: Leonardo, Siemens Medical Solutions Interval: 1cm Superior border: mid-level RPA. Inferior border: not specified. HU range: -190 to -30 HU	PR: >1.05 remodelling index LAP: <30 HU SC: <3mm diameter CP HRP defined as at least 2 characteristics in lesions>50% luminal narrowing
Rajani et al.[3]	EAT definition: fat within pericardial sac. Method: Semi-automated Software: QFAT, Cedars-Sinai Medical Centre Interval: 3mm (total 20-40 slices per pt) Superior border: RPA take-off Inferior border: First slice where PDA visualised HU range: -190 to -30 HU	LAP: <30 HU PR: >1.05 (maximal outer arterial wall diameter along plaque exceeding proximal reference by 5%
Oka et al.[4]	EAT definition: adipose tissue between epicardial surface of myocardium and pericardium Method: Manual Software: Not specified. VAT measured with Virtual Place, AZE Inc., Japan Interval: 1cm Superior border: 1cm above left main coronary artery (atrial appendage) Inferior border: cardiac apex HU range: -250 to -30 HU	CT-low density plaque: < 39 HU PR: remodelling index >1.05 SpC: calcium burden length <3/2 vessel diameter and width <2/3 vessel diameter
Ito et al.[5]	EAT definition: adipose tissue within the visceral epicardium Method: Manual Software: Not specified Interval: Not specified. 8-12 slices per patient Superior border: Mid left atrium Inferior border: left ventricular apex HU range: -190 to -30 HU	LAP: <30 HU PR: RI >1.1 (ratio of outer vessel area of lesion to outer vessel area of proximal reference site
Nakanishi et al.[6]	EAT definition: adipose tissue within the pericardial sac Method: Semi-automated Software: Synapse Vincent, Japan Interval: not specified. 7-10 planes Superior border: bifurcation pulmonary artery Inferior border: last slice containing any portion of the heart HU range: -250 to -30 HU	LAP: <30 HU PR: RI >1.1
Ito et al.[7]	EAT definition: adipose tissue within the visceral epicardium Method: Manual Software: Not specified. CT with Aquarius NetStation, USA Interval: not specified. Superior border: not specified Inferior border: not specified HU range: -250 to -40 HU	**CT:** LAP: <30 HU PR: RI >1.1 (ratio of outer vessel area of lesion to outer area of proximal reference site) **OCT:** Necrotic lipid pools quantified as number of quadrants Cap thickness measured at thinnest section of distance from lumen to inner border of lipid pool. TCFA = plaque with necrotic lipid pool in ≥2 quadrants within a plaque and fibrous cap <=65µm

Park et al.[8]	Method: 2D parasternal long-axis view; point on the free wall of RV to assess anterior echo-lucent space between linear echo-dense parietal pericardium and RV epicardium Cardiac cycle timing: End-diastole. Thickest point of EAT in each of 3 cycles measured and average value used	Plaque components: Fibrous – areas of dense collagen Fibrofatty – fibrous tissue with interspersed lipid in collagen Dense calcium – calcium with no adjacent necrosis Necrotic core – necrotic regions containing cholesterol clefts, foam cells, microcalcification TCFA: necrotic core ≥10% plaque area without overlying fibrous tissue and having >40% plaque burden in 3 consecutive frames
Tachibana et al.[9]	Method: 2D parasternal long-axis view; point on the free wall of RV along midline of ultrasound beam perpendicular to aortic annulus Cardiac cycle timing: End-systole. Average of three cardiac cycles used	PR: RI >1.05 (cross sectional lesion vessel area divided by proximal reference vessel area) LAP: <30 HU

CT – computed tomography, CP – calcified plaque, EAT – epicardial adipose tissue, HRP – high risk plaque, HU – Hounsfield units, LAP – low attenuation plaque, NRS – napkin ring sign, OCT – optical coherence tomogprahy, PDA – posterior descending artery, PR – positive remodelling, RPA – right pulmonary artery, SpC – spotty calcification, TCFA – thin-cap fibroatheroma. VAT – visceral adipose tissue

Table S3. Sensitivity analysis displaying pooled odds ratios and 95% confidence intervals with systematic exclusion of individual studies.

Excluded study	Pooled OR	Lower 95% CI	Upper 95% CI	I^2	p-value
Lu et al[1]	1.27	1.12	1.45	70%	<0.001
Schlett et al.[2]	1.17	1.06	1.30	80%	0.003
Rajani et al.[3]	1.19	1.07	1.33	82%	0.001
Oka et al.[4]	1.20	1.07	1.33	82%	0.001
Ito et al.[5]	1.24	1.08	1.43	78%	0.003
Nakanishi et al.[6]	1.24	1.09	1.42	82%	0.002
Park et al.[8]	1.25	1.09	1.43	83%	0.001
Ito et al.[7]	1.19	1.07	1.32	81%	0.001
Tachibana et al.[9]	1.16	1.06	1.27	74%	0.001

Table S4. Newcastle-Ottawa Scale (NOS) Evaluation of Study Quality

| STUDY	SELECTION	COMPARABILITY	OUTCOME
Lu et al.[1]	****	**	***
Schlett et al. [2]	****	**	***
Rajani et al. [3]	*****	**	***
Oka et al.[4]	****	**	***
Ito et al.[5]	****	**	***
Nakanishi et al.[6]	***	**	***
Park et al.[8]	****	**	***
Ito et al.[7]	***	**	***
Tachibana et al [9]	****	**	**

The Newcastle-Ottawa Scale (NOS) evaluates the included studies based on selection, comparability and outcome. The maximum score for each criteria is 5, 2 and 3, respectively, with the maximum total score equalling 10

Table S5. GRADE quality assessment

STUDY	INITIAL GRADE	BIAS ASSESSMENT	FINAL GRADE
Lu et al.[1]	Low	**Bias**: Low; **Applicability**: Low; **Imprecision**: Low	Low
Schlett et al.[2]	Low	**Bias**: Low; **Applicability**: Low; **Imprecision**: High	Low
Rajani et al.[3]	Low	**Bias**: Low; **Applicability**: Low; **Imprecision**: Low	Low
Oka et al. [4]	Low	**Bias**: Unclear; **Applicability**: Low; **Imprecision**: High	Low
Ito et al. [5]	Low	**Bias**: Unclear; **Applicability**: Low; **Imprecision**: Low	Low
Nakanishi et al[6]	Low	**Bias**: Unclear; **Applicability**: High; **Imprecision**: Low	Low
Park et al.	Low	**Bias**: Unclear; **Applicability**: Unclear; **Imprecision**: Unclear	Low
Ito (2012) et al.	Low	**Bias**: Unclear; **Applicability**: Low; **Imprecision**: Unclear	Low
Tachibana et al	Low	**Bias**: High; **Applicability**: Unclear; **Imprecision**: High	Very Low

GRADE classification adapted from the GRADE Handbook [10-12] to evaluate quality of evidence in observational studies. All studies are observational and therefore considered of low quality. Assessment based on bias (factors including eligibility criteria, control of confounding), applicability (assessment of intervention) and imprecision (assessment of modelling methods and outcomes). Assessment is graded as either a low risk of bias, high risk of bias or unclear risk of bias.

Figure S1. Funnel plot

Figure S1. Funnel plot with pseudo 95% confidence limits
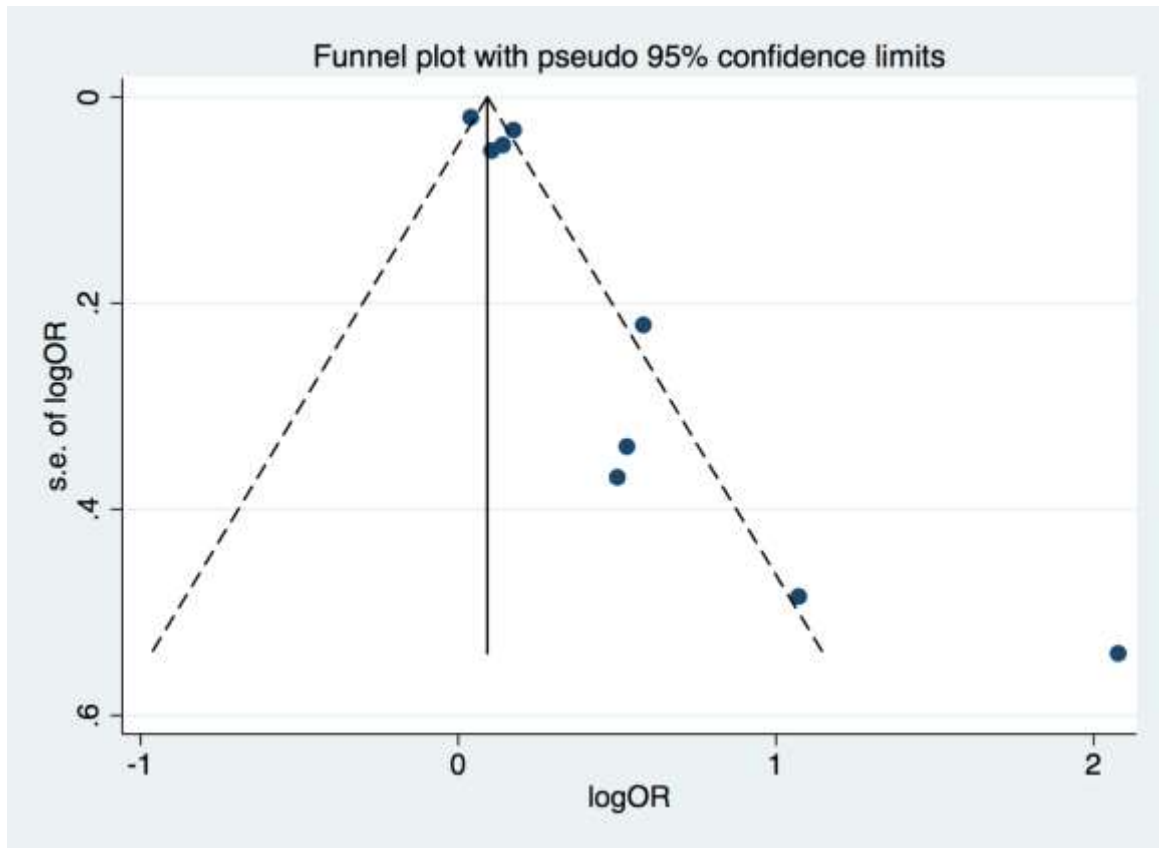
Egger's test for small study effects: p = 0.005

Overall summary estimate using trim and fill method: 1.13 (95% CI 1.03-1.28, p=0.04, I^2=81%)

Supplemental References:

1. Lu MT, Park J, Ghemigian K, Mayrhofer T, Puchner SB, Liu T, Fleg JL, Udelson JE, Truong QA, Ferencik M, Hoffmann U. Epicardial and paracardial adipose tissue volume and attenuation - association with high-risk coronary plaque on computed tomographic angiography in the romicat ii trial. *Atherosclerosis*. 2016;251:47-54.

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