Meta-Analysis of Relation of Epicardial Adipose Tissue Volume to Left Atrial Dilation and to Left Ventricular Hypertrophy and Functions

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Many studies have explored the hypothesis that epicardial adipose tissue (EAT) accumulation adversely affects cardiac remodeling. We assessed, through a systematic review and meta-analysis, whether EAT is linked to left atrial (LA) and left ventricular (LV) structure and function, irrespective of global or abdominal visceral adiposity. We searched MEDLINE, Scopus, and Web of Science for studies evaluating the association of EAT volume quantified by computed tomography with cardiac morphology and function. We used DerSimonian and Laird random-effects models to summarize the adjusted-effect of 10 ml variation of EAT on LA size, LV mass, LV diastolic and systolic functions parameters, and presence of diastolic dysfunction. We quantified heterogeneity using I^2 statistic. We included 19 studies. Quantitative analysis by cardiac parameters, including LA dimension (n = 2,719), LV mass (n = 2,519), diastolic function (n = 3,741), and systolic function (n = 2,037) showed that EAT was associated with LA dilation (pooled B-coefficient: 0.12 mm; 95% confidence interval [CI] 0.08 to 0.17; I^2: 97%), LV hypertrophy (pooled B-coefficient: 1.21 g; 95% CI 0.63 to 1.79; I^2: 77%), diastolic dysfunction (odds ratio: 1.35; 95% CI 1.16 to 1.57; I^2: 0%), higher E/E′ ratio (pooled B-coefficient: 0.28 cm/s; 95% CI 0.08 to 0.49; I^2: 67%), lower E′ velocity (pooled B-coefficient: −0.16 cm/s; 95% CI −0.22 to −0.09; I^2: 43%), and E/A ratio (pooled B-coefficient: −0.01; 95% CI −0.02 to −0.001; I^2: 70%), independently of body mass index. There was no association between EAT and LV systolic function. In conclusion, EAT volume measured by computed tomography was independently associated with LA dilation, LV hypertrophy, and diastolic dysfunction.
 (Am J Cardiol 2019;123:523−531)

Over the past years, epicardial adipose tissue (EAT) has been studied as a determinant of the anatomical substrate of atrial fibrillation[1] and heart failure.[2] The mechanisms by which EAT may alter cardiac structure and function include fibro-fatty infiltrations of the subepicardium,[3] increased intramyocardial lipid content,[4] and the secretion of proinflammatory, pro-oxidant, and profibrotic adipocytokines.[5] Moreover, because EAT is independently associated with coronary artery disease (CAD), it may also indirectly affect myocardial structure and function inducing myocardial ischemia.[6] Several lines of evidence suggest a strong relation between EAT accumulation and the degree of systemic inflammation associated with obesity.[7] In some studies, however, the associations of EAT with LA dilation and LV diastolic dysfunction were independent of body mass index (BMI) or visceral abdominal fat.[8] Nevertheless, in other studies, these associations lost statistical significance after adjustment for BMI and other cardiovascular risk factors.[9,10] Regarding these existing discrepancies in the literature, we aimed to compute the pooled adjusted association of EAT with LA and LV morphology and function parameters, through a systematic review and meta-analysis of observational studies reporting association measures of total EAT volume assessed by computed tomography (CT) with LA diameter, LV mass, and LV diastolic and systolic functions.

Methods

We conducted the present study according to the protocols specified in the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. The study

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Funding: Mancio J is supported by the Fundação Portuguesa para a Ciência e Tecnologia (SFRH/BD/104369/2014) and by the Sociedade Portuguesa de Cardiologia ("Bolsa de investigação João Porto"). This report is a result of the project DOCnet (NORTE-01-0145-FEDER-000003) supported by the Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF).

PROSPERO Registration: This study protocol was registered with PROSPERO (ID: CRD42017080849) Porto (Portugal).

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See page 530 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2018.10.020

protocol was registered in PROSPERO (ID: CRD42017080849). We searched MEDLINE, Scopus, and Web of Science for publications reporting association measures between EAT and parameters of cardiac structure and function using the following expression: (["Epicardial adipose tissue" OR "Epicardial fat" OR "Pericardial adipose tissue" OR "Pericardial fat" OR "Cardiac adipose tissue" OR "Cardiac fat" OR "Subepicardial adipose tissue" OR "Subepicardial fat" OR "Heart fat" OR "Heart adipose tissue"] AND ["Left atrium" OR "Left atrial" OR "Left ventricular" OR "Left ventricle"]). We also searched the references list of original publications and review reports. Observational studies, including cross-sectional, case-control studies, or cohort designs were eligible, if the following requirements were met: inclusion of adults (≥18 years old), quantification of total and/or periatrial EAT volumes using CT, and description of obesity-adjusted measures of association for the relation between EAT and/or periatrial adipose tissue, with different parameters that characterize the morphology and/or function of the LA and/or LV.

In this study, we considered EAT as the adipose tissue located inside the pericardial cavity; studies combining both intrapericardial and extrapericardial fat into a single measure were excluded. We also excluded studies conducted in special study populations, namely immune-mediated diseases, human immunodeficiency virus infection, on dialysis chronic kidney disease and pregnant women, because in these populations, EAT dysfunction is explained by mechanisms different than general population (i.e., increased inflammatory burden), and therefore, the magnitude of the effect size is expected to vary accordingly. If multiple publications from the same or overlapping populations were available, the most recent or comprehensive information was included in this meta-analysis. Only full-size reports of English language published in peer-reviewed journals were considered. Potentially relevant reports were evaluated by 2 independent reviewers (JM and DA) and any disagreement was individually discussed and resolved by all authors. Methodologic quality of all studies was assessed using the revised and validated version of the Methodological Index for Non-Randomized Studies (MINORS). For each study, the following information was collected: first author surname, publication year, country where the study was conducted, study design, source of participants, method of EAT volume quantification, method of cardiac structure and function assessment, measures of association with the respective 95% confidence intervals (CI), and covariates included in the multiple regression models; for studies reporting several multiple-adjusted effect size estimates, we selected those accounting for the largest number of potential confounders; when stratified results by gender were provided, association measures in male and female were recorded. To compute the pooled adjusted-effect size estimates, we used DerSimonian and Laird random-effect method. Dependent variables included LA size (dimension, area, volume, volume index), LA function (LA conduction, reservoir, and booster pump functions), LV mass, presence of LV diastolic function (as a dichotomous variable), diastolic function parameters, including E/E′ ratio, septal and lateral E′ velocities, and E/A ratio, and LV systolic function (LV ejection fraction, septal S′ velocity and 3D-strain). Before pooling B-coefficients, we assured that all values described a variation in the dependent variable per 10 ml of EAT. Briefly, when B-coefficients were provided per unit variation of the independent variable, we multiplied the given coefficient by the

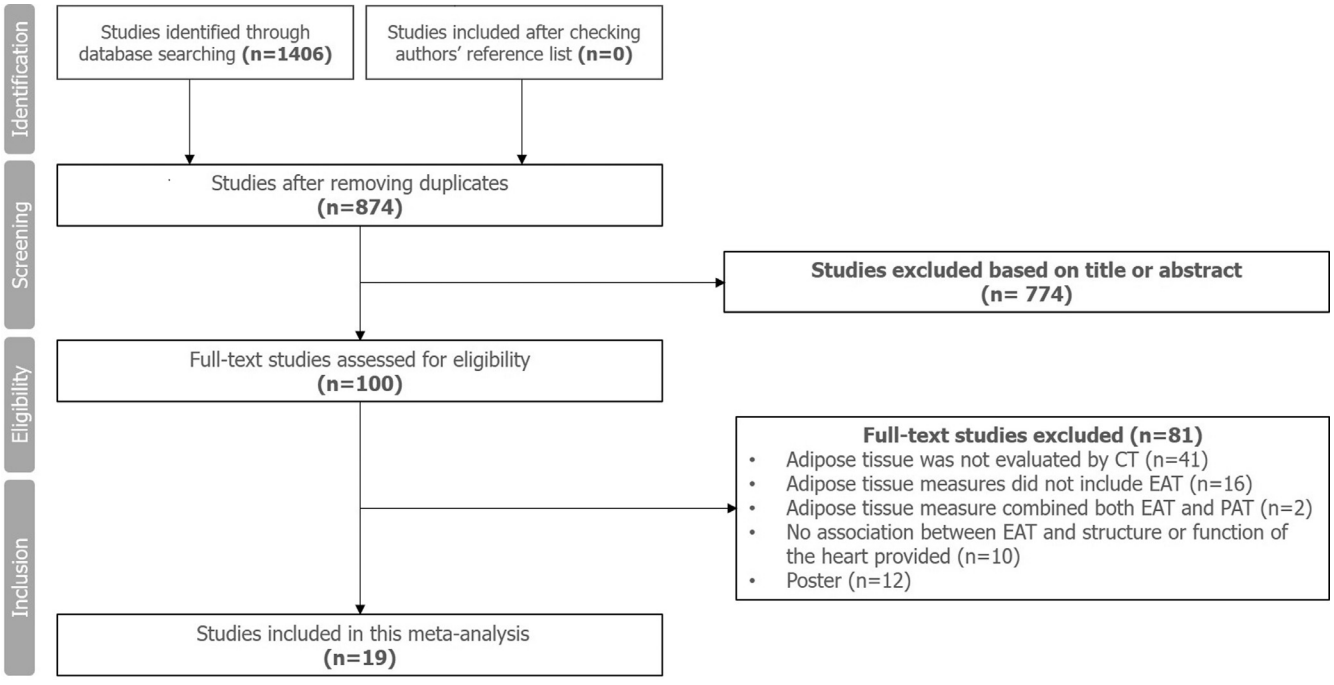

Figure 1. Systematic review flowchart.
CT = computed tomography; EAT = epicardial adipose tissue; LA = left atrial; LV = left ventricular.

number of 10; when the B-coefficients were provided by variation of 1 standard variation of the independent variable, we first divided the B-coefficient value by the SD to obtain the B-coefficient per unit change, and finally, this value was multiplied by 10. Heterogeneity between estimates from individual studies was assessed using the I^2 statistic. Publication bias was assessed using the Egger test and the funnel plot analysis, and the trim and fill method of Duval and Tweedie. All statistical analyses were performed using STATA software (version 13.1, StataCorp LP, Texas).

Results

Systematic review flowchart is depicted in Figure 1. A total of 19 reports matched our search criteria.[9,11–23] In them, 17 studies reported the association with total EAT volume[9–21,24–26] and 6 studies investigated the association with periatrial EAT.[9,13,20–23] The former studies included 8,838 subjects, in which cardiac morphology and function were assessed by transthoracic echocardiography (n = 12),[9,11–13,15–18,24,25,27] CT (n = 6),[19–21,25–27] or magnetic resonance imaging (n = 1)[10] to report the association with LA dimensions/function (n = 12),[9–11,13,14,18–21,27] and/or LV parameters (n = 10).[10–12,14–18,24–27] Studies reporting the association with periatrial EAT included 1,734 subjects and all reported the effect of periatrial EAT on LA parameters. Overall, these studies were assessed as high-quality publications (median MINORS score of 18; 25th and 75th percentile of 17 and 18, respectively). Supplementary Table 1 summarizes the characteristics and main findings of studies reporting the association between total EAT volume and cardiac structure and function. Supplementary Table 2 describes the studies reporting the associations with periatrial EAT. Supplementary Table 3 provides additional information regarding to technical details of EAT and cardiac evaluations.

Total EAT volume was independently associated with higher LA dimension; in studies adjusting for BMI, per 10 ml increase of EAT, LA dimension increased 0.12 mm (95% CI 0.08 to 0.17; I^2: 96%). However, in studies additionally adjusting for abdominal visceral fat, EAT did not remain associated with LA dimension (pooled B-coefficient of 0.03 mm, 95% CI −0.003 to 0.06; I^2: 85%; Figure 2).[10,14,18]

There was an independent association between total EAT volume and higher LV mass; LV mass increased 1.21 g (95% CI 0.63 to 1.79; I^2: 77%) per 10 ml increase of

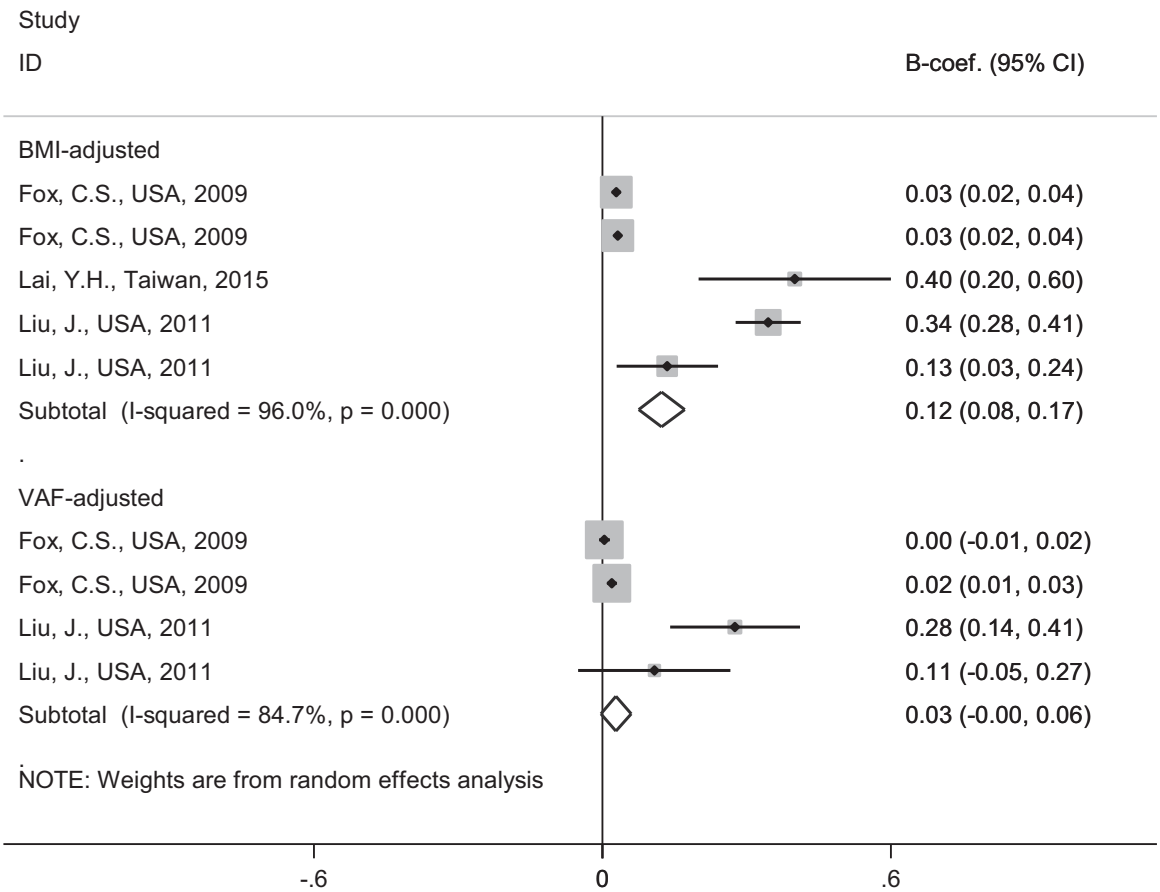

Figure 2. Forest plot of studies describing the association between EAT volume and LA dimension adjusted for BMI, and additionally for VAF.[10,14,18]
BMI = body mass index; EAT = epicardial adipose tissue; LA = left atrial; VAF = visceral abdominal fat.

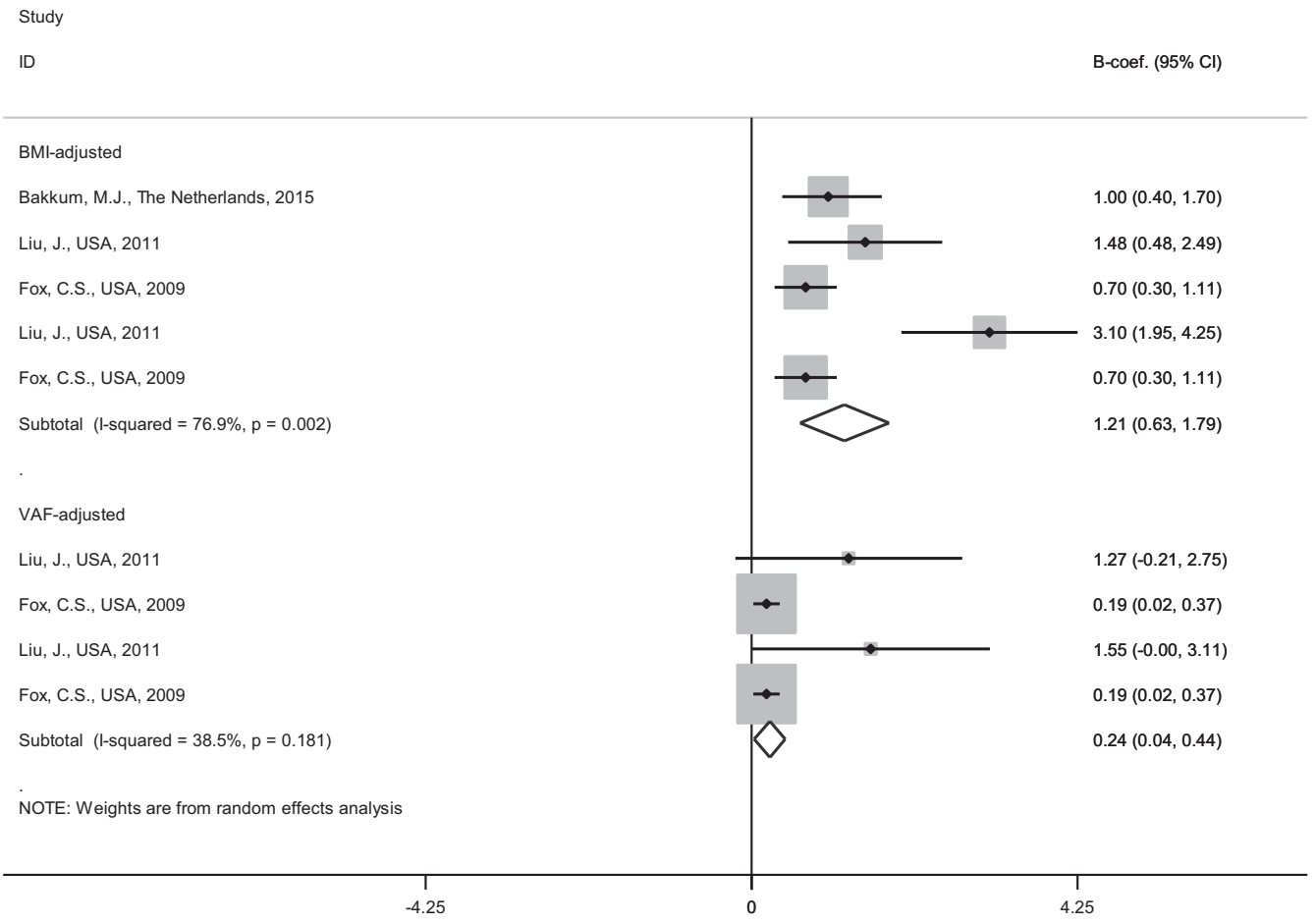

Figure 3. Forest plot of studies describing the association between EAT volume and LV mass for BMI, and additionally for VAF.[10,18,26]
BMI = body mass index; EAT = epicardial adipose tissue; LV = left ventricular; VAF = visceral abdominal fat.

EAT, independently of BMI. The association of EAT with LV mass remained significant in studies adjusting for abdominal visceral fat. (pooled B-coefficient: 0.24 g, 95% CI 0.04 to 0.44; I^2: 38%) although (Figure 3).[10,18,26]

EAT volume was associated with the presence of diastolic dysfunction (odds ratio: 1.35, 95% CI 1.16 to 1.57; I^2: 0%). Increased EAT volume correlated with lower septal E′ velocity (pooled B-coefficient: −0.16 cm/s, 95% CI −0.22 to −0.09; I^2: 43%), lower lateral E′ velocity (pooled B-coefficient: −0.11 cm/s, 95% CI −0.19 to −0.03) and increased E/E′ ratio (pooled B-coefficient: 0.28, 95% CI 0.15 to 0.45; I^2: 67%). Accordingly, there was a BMI-independent association between EAT volume and lower EA ratio (pooled B-coefficient: −0.01, 95% CI −0.02 to −0.001; I^2: 70%), but not after further adjustment for abdominal visceral fat (pooled B-coefficient: −0.00, 95% CI −0.01 to 0.01; I^2: 0%; Figure 4).[14–18]

We did not find a significant association between EAT volume and LV ejection fraction (pooled B-coefficient: −0.08, 95% CI −0.28 to 0.12; I^2 = 51%; Figure 5).[14,18] Similarly, Lai et al did not report an association between EAT volume and medial S′ velocity (B-coefficient: 0.01, 95% CI −0.01 to 0.05).[14] However, Ng et al found EAT volume associated with LV systolic dysfunction assessed by 3D-speckle tracking echocardiography.[12]

Figure 6 depicts the funnel plot for studies reporting the association of EAT volume with LA dimension and LV mass (A), and medial E′ velocity and LV ejection fraction (B). The visual inspection of these funnel plots suggests no publication bias for LA dimension (Egger's test, p = 0.09), septal E′ velocity (Egger's test, p = 0.13), and LV ejection fraction (Egger's test, p = 0.54), but the effect of EAT on LV mass might have been overestimated (Egger's test, p = 0.04). Corresponding to the Duval and Tweedie's trim and fill input method, the expected summary B-coefficient for EAT and LV mass would be −0.24 (95% CI −1.34 to 0.86).

Discussion

In this review, we pooled adjusted association measures of the volume of EAT by CT and cardiac structure and function. We observed a small, but BMI-independent, effect of EAT on LA dilation, LV hypertrophy, and LV diastolic dysfunction; no associations were found between EAT and systolic function.

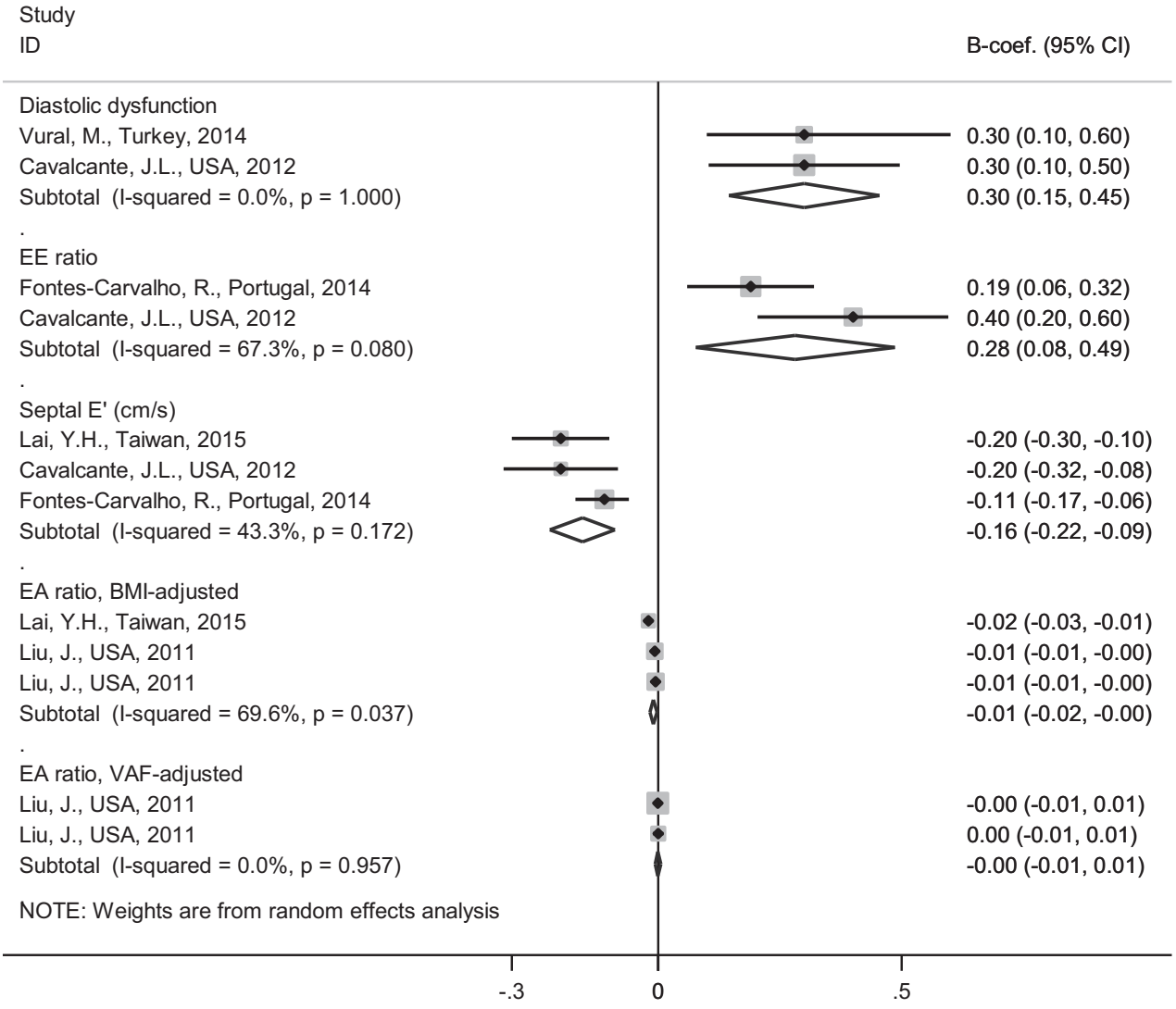

Figure 4. Forest plot of studies describing the association between EAT volume and LV diastolic dysfunction.[14–18]
BMI = body mass index; EAT = epicardial adipose tissue; LV = left ventricular; VAF = visceral abdominal fat.

Obesity may worsen myocardial remodeling by several mechanisms namely, activation of the renin-angiotensin system and autonomic nervous system, which altogether increase peripheral arterial resistance and, consequently, lead to LV hypertrophy and diastolic impaired function.[28] Excessive body fat also imposes augmented preload by determining hyperdynamic circulation and chronic volume overload. Moreover, altered glucose and free fatty acid supply and utilization by cardiac myocytes can be involved in the pathogenesis of obesity-related cardiomyopathy. Finally, adipose tissue contributes to the pool of systemic adipokines that mediate systemic inflammation, by increased secretion of leptin, resistin and visfatin, and downregulation of adiponectin, which were associated with myocardial dysfunction and heart failure.[29,30]

As an ectopic fat depot, EAT is increased and dysregulated in obesity. EAT may act as a local mediator of obesity-related systemic inflammation; however, in this study, we also showed that EAT, per se, is associated with increased LA dilation, LV mass, and diastolic function impairment, independently of BMI or abdominal visceral obesity (except, LA dimension). Hence, it is likely that even in nonobese subjects, defined using BMI, EAT may adversely affect the remodeling of the heart. Figure 7 illustrates the hemodynamic and metabolic factors through which obesity influence myocardial remodeling.

Different from remote visceral fat depots, EAT is in direct contact with the myocardium, which creates favorable anatomical conditions for a reciprocal communication between EAT and the myocardium.[30] In comparison to subcutaneous adipose tissue, EAT is characterized by higher expression of proinflammatory (tumor necrosis-α (TNF-α), interleukin-6 (IL-6), MCP-1, interleukin 1- β (IL1-β)), pro-oxidant (NADPH-oxidase, superoxide dismutase-2, catalase, glutathione S-transferase P, protein disulfide isomerase), profibrotic (activin A[31] and metalloproteinases (MMP)[32]and angiogenic (vascular endothelial growth factor receptor 1, endothelin 1, angiotensin II receptor 1)-regulatory genes as

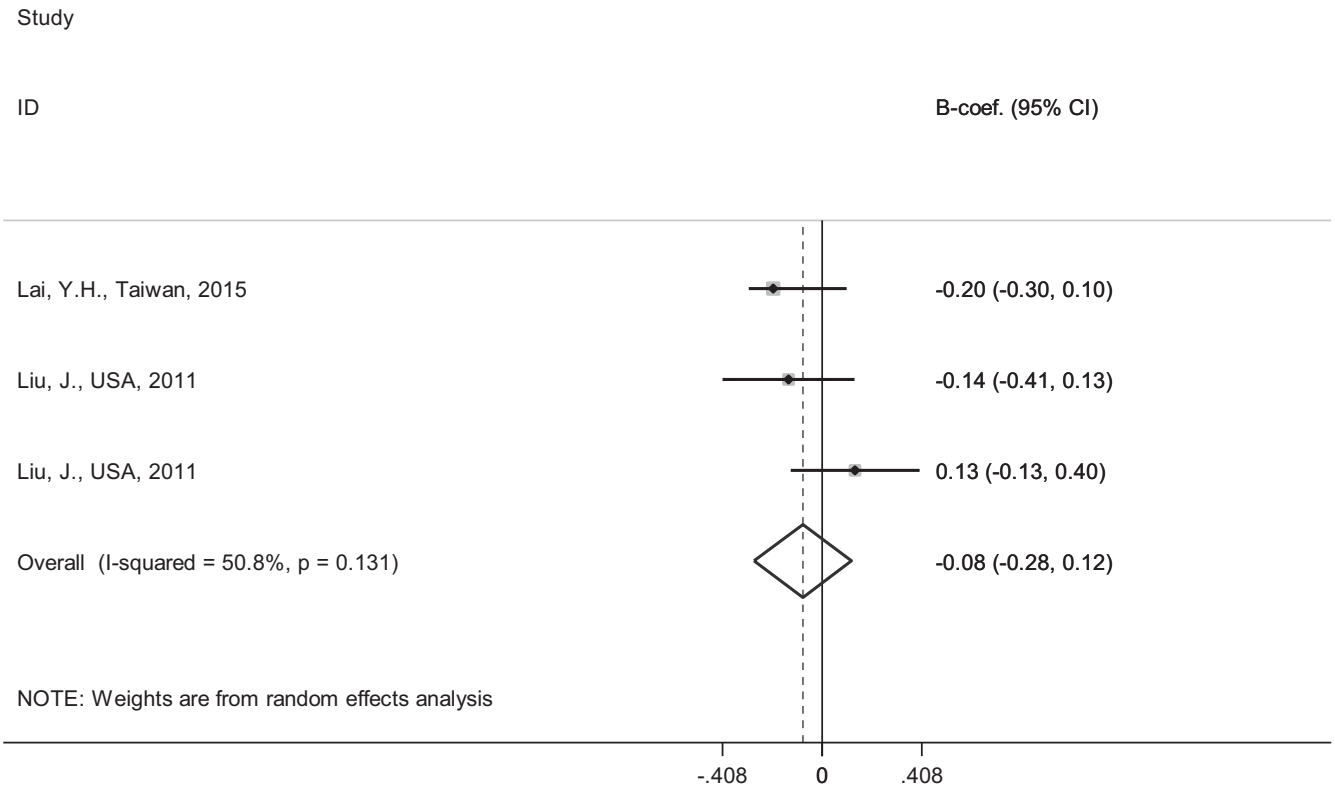

Figure 5. Forest plot of studies describing the association between EAT volume and LV ejection fraction.[14,18]
EAT = epicardial adipose tissue; LV = left ventricular.

well as greater infiltration by immune cells, particularly M1 proinflammatory macrophages.[30,33] These local proinflammatory, pro-oxidant, and profibrotic conditions result in impaired myocardial relaxation, reduced diastolic compliance, and elevated LV filling pressures. Increased myocardial lipid content, which is concurrent with increased EAT volume, causes myocardial disarray, inflammation, and alteration in the extracellular matrix composition.[3] Moreover, abnormal accumulation of EAT increases ventricular workload, leading to LV hypertrophy, poorer myocardial

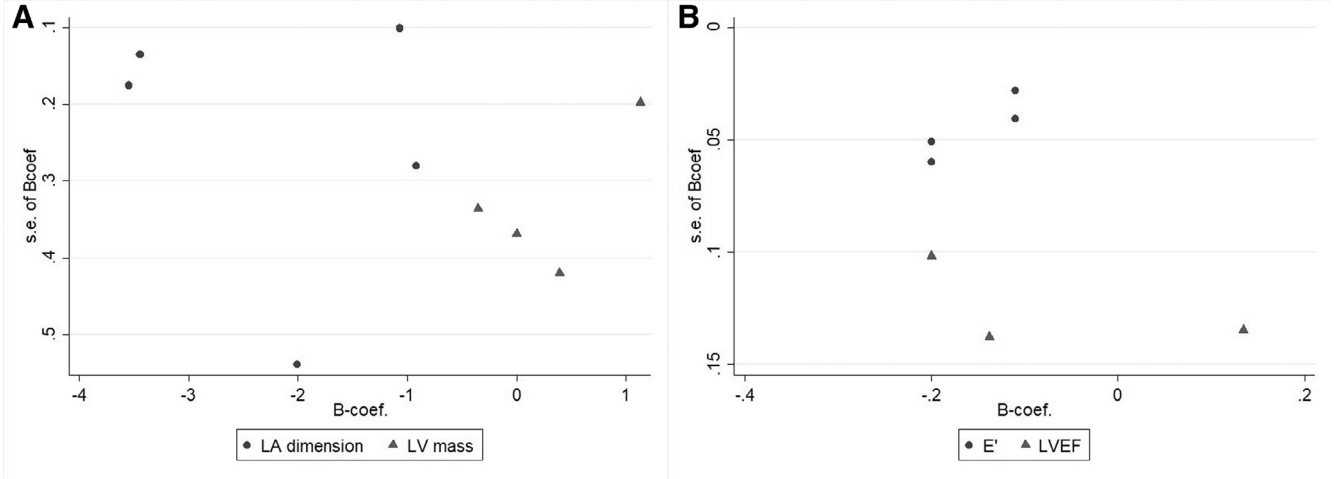

Figure 6. Funnel of studies describing the association of EAT volume with LA dimension and LV mass (A) and septal E′ velocity and LVEF (B).
LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction.

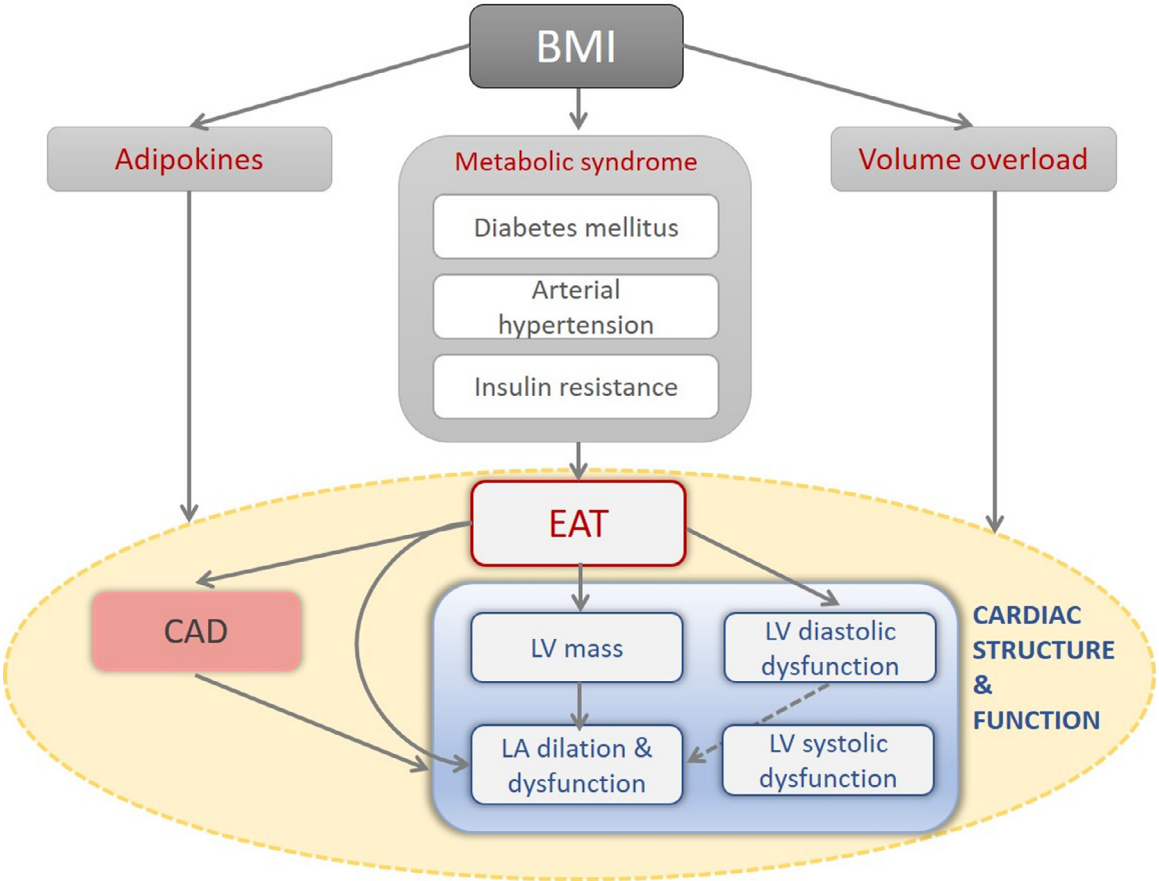

Figure 7. Indirect and direct mechanisms by which epicardial adipose tissue may affect cardiac remodeling. Epicardial adipose tissue (EAT) accumulation and dysfunction is strongly associated with obesity, and therefore, with the systemic hemodynamic and metabolic disorders linked to obesity. Obesity also promotes systemic inflammation because of a shift from a protective profile to an imbalanced production of proinflammatory, pro-oxidant, and profibrotic adipokines; EAT can act as a transducer of this chronic systemic inflammatory state. However, in this work, we showed that EAT accumulation can also affect cardiac structure and function independently of body mass index (BMI), suggesting that EAT may be a key determinant of myocardial remodeling in nonobese subjects affecting the clinical course of other chronic inflammatory conditions, such as rheumatoid arthritis, psoriasis, and human immunodeficiency infection. It is well established that systemic inflammatory responses in these disorders are associated with increased EAT and accelerated coronary atherosclerosis, independently of BMI.
BMI = body mass index; CAD = coronary artery disease; EAT = epicardial adipose tissue; LA = left atrium; LV = left ventricle.

function, faster progression to symptoms, and increased late mortality.[34]

During diastole, LV pressure is nearly identical to LA pressure. Consequently, the increment in LV filling pressures is paralleled by atria dilation and fibrosis. This LA-LV interaction seems to explain only partially the positive association between EAT and LA dilation. We systematically reviewed studies including LV mass in the regression models and in all of them, EAT volume was still associated with increased LA size, suggesting that EAT, in particular, periatrial EAT, may directly affect LA remodelling.[14,17] We found 6 studies specifically addressing the association of periatrial EAT with LA size and function; these studies reported a positive association of periatrial EAT accumulation with LA dilation and impaired function, independently of BMI,[13,20,21,23] obstructive CAD,[9,23] and LV mass[9,13,20,21] or LV ejection fraction.[20,23] Interestingly, even when total EAT volume was included in the regression models, periatrial EAT accumulation remained associated with LA parameters.[21,22] These findings suggest that periatrial EAT may be different than total EAT, which is in agreement with the observation that pericoronary, periatrial, and periventricular EAT have distinctive transcriptomic signatures.[35]

None of the studies have shown a significant effect in LV ejection fraction or S′ velocity.[14,15,18] In a sole study analyzing the systolic function of LV using global 3D-speckle tracking echocardiography, EAT was associated with systolic function impairment.[12] One can speculate that, at the cellular level, EAT might be associated with subtle systolic myocardial impairment, which could not have been detected at the organ or tissue levels, using LV ejection fraction or tissue Doppler velocities, respectively. However, 3D-speckle tracking echocardiography has been inconsistent and difficult to interpret across studies, and thus, the findings of Ng et al. should be interpreted with caution.

EAT volume was associated with the presence of coronary stenosis and myocardial ischemia and predicted the incidence of major adverse cardiovascular events.[6]

Moreover, even in the absence of visible coronary stenosis, EAT was associated with impaired coronary microvascular function, which may, in turn, negatively impair myocardial perfusion and function. In this work, we found 5 studies in which confounding by CAD was controlled.[9,12,17,24,26] These studies suggested that EAT may lead to LV hypertrophy,[26] LA dilation,[9] diastolic[12,17] and systolic dysfunction,[12] irrespective of the presence of CAD. These results highlight that, although CAD is one intermediate step in the pathway between EAT and abnormalities of cardiac structure and function, EAT may also modulate cardiac remodeling by CAD-independent mechanisms.

Major strengths of this work rely on the efforts of combining a growing body of evidence to answer a well-defined research question with broad eligibility criteria. Beyond the drawbacks inherent to this type of analysis (i.e., we did not have access to individual patient data from all studies reviewed and we based on published information only), we found a high level of heterogeneity between studies due to variability in the parameters chosen to characterize the heart structure and function, and in the methods of assessing them. Despite the high number of publications, few studies provided association measures able to be combined through a meta-analysis.

In conclusion, in this systematic review and meta-analysis, EAT volume was independently associated with LA dilation, LV hypertrophy, and diastolic dysfunction. Exploring the mechanistic pathways behind these associations will increase our understanding of the pathophysiology of diastolic dysfunction and render new therapeutic targets on the treatment of heart failure with preserved ejection fraction and atrial fibrillation. Future studies are needed to clarify the association between EAT and systolic function.

Disclosures

The authors have declared no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.10.020.

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