

Association of Volumetric Epicardial Adipose Tissue Quantification and Cardiac Structure and Function

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Background—Epicardial adipose tissue (EAT) is in immediate apposition to the underlying myocardium and, therefore, has the potential to influence myocardial systolic and diastolic function or myocardial geometry, through paracrine or compressive mechanical effects. We aimed to review the association between volumetric EAT and markers of myocardial function and geometry.

Methods and Results—PubMed, Medline, and Embase were searched from inception to May 2018. Studies were included only if complete EAT volume or mass was reported and related to a measure of myocardial function and/or geometry. Meta-analysis and meta-regression were used to evaluate the weighted mean difference of EAT in patients with and without diastolic dysfunction. Heterogeneity of data reporting precluded meta-analysis for systolic and geometric associations. In the 22 studies included in the analysis, there was a significant correlation with increasing EAT and presence of diastolic dysfunction and mean e' (average mitral annular tissue Doppler velocity) and E/e' (early inflow / annular velocity ratio) but not E/A (ratio of peak early (E) and late (A) transmitral inflow velocities), independent of adiposity measures. There was a greater EAT in patients with diastolic dysfunction (weighted mean difference, 24.43 mL; 95% confidence interval, 18.5–30.4 mL; $P < 0.001$), and meta-regression confirmed the association of increasing EAT with diastolic dysfunction ($P = 0.001$). Reported associations of increasing EAT with increasing left ventricular mass and the inverse correlation of EAT with left ventricular ejection fraction were inconsistent, and not independent from other adiposity measures.

Conclusions—EAT is associated with diastolic function, independent of other influential variables. EAT is an effect modifier for chamber size but not systolic function. (*J Am Heart Assoc.* 2018;7:e009975. DOI: 10.1161/JAHA.118.009975.)

Key Words: diastolic function • epicardial fat • systolic dysfunction

Epicardial adipose tissue (EAT) has been widely studied as a potential contributor to cardiovascular pathological characteristics. Much of this research has focused on its effect on coronary atherosclerosis,¹ but there are unique properties of EAT that may lead to an effect on myocardial function. EAT shares direct anatomic contact with the myocardium without fascial interruption² and, therefore, may exhibit local

compressive forces, resulting in alteration of myocardial function and geometry. In addition, the shared blood supply of the coronary circulation to both the myocardium and surrounding EAT may predispose paracrine effects on the neighboring myocardium with such inflammatory cytokines as MCP-1 (monocyte chemoattractant), interleukin- β , interleukin-6, tumor necrosis factor- α , and leptin.² Persisting inflammation may lead to collagen deposition and subsequent impaired left ventricular (LV) relaxation and further effects on diastolic and systolic function. Furthermore, there is an association between EAT and release of free fatty acids, as well as their myocardial consumption.³ The relationship between obesity, visceral fat, and EAT may also explain effects on myocardial function, chamber size, and mass.

Several methods have been used for measurement of EAT, including echocardiography, cardiac computed tomography (CT), and cardiac magnetic resonance imaging (MRI). Echocardiography may overestimate or underestimate total EAT volume because of single-plane assessment and the effects of probe angulation on linear measurement. Single-slice area measurements on CT or MRI are also limited by being only single-plane measures. Recently, we have demonstrated the

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Accompanying Tables S1 through S3 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009975>

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Clinical Perspective

What Is New?

- Increasing epicardial adipose tissue volume is associated with diastolic dysfunction, independent of other markers of adiposity.
- Epicardial adipose tissue is an effect modifier for left ventricle chamber geometry.
- Epicardial adipose tissue is not associated with systolic function.

What Are the Clinical Implications?

- Epicardial adipose tissue may represent an important target for therapy associated with diastolic dysfunction.

superiority of volumetric EAT assessment in comparison to 2-dimensional linear echocardiographic EAT thickness.⁴ We, therefore, sought the association of full-volume quantification of EAT (assessed by cardiac CT or cardiac MRI) with myocardial function, as assessed by transthoracic echocardiography, full R-R interval cardiac CT, or cardiac MRI.

Methods

Search Method

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the trial was registered with PROSPERO (CRD 42017038400). The search was conducted in MEDLINE, EMBASE, and PubMed databases, ending in March 2018. References of eligible articles were hand searched for additional articles. Searches were restricted to human studies, and conference abstracts were included. A study search flowchart is presented in Figure 1, and the specific search term strategy is given in Table S1. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Our inclusion criteria were as follows: patients undergoing cardiac CT (CT angiography or calcium score) or MRI with volumetric assessment of EAT (either volume or mass), with cardiac imaging for assessment of myocardial function parameters (full cardiac cycle cardiac CT or MRI or echocardiography), or measurement of myocardial geometry (LV mass, LV volumes, and left atrium size) by validated methods.

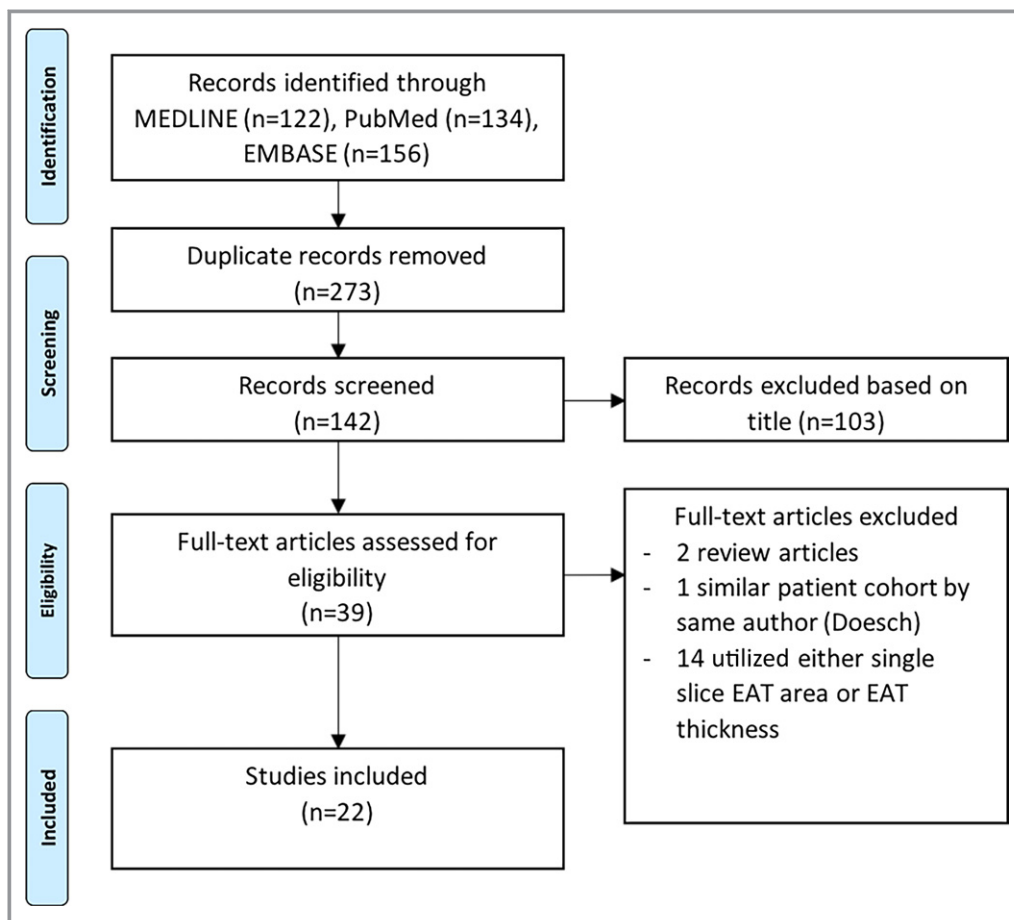


Figure 1. Search strategy. EAT indicates epicardial adipose tissue.

Assessment of diastolic function was restricted to studies using echocardiography. Exclusion criteria included the following: any study with linear measurement of EAT thickness, single-slice area measures of EAT, measures of myocardial lipid content not differentiated from EAT, and measurement of paracardial adipose tissue (ie, fat beyond the parietal pericardium). Two authors (N.N. and R.G.M.) independently reviewed the abstracts from the search to meet the inclusion criteria, and discrepancies were resolved by consensus. Probable overlap of the patient cohort with a similar study led to exclusion of the smaller study.⁵

Evaluation of Full-Volume EAT

EAT was regarded as adipose tissue enclosed within the visceral pericardium, and mean values (indexed and nonindexed) were recorded.

Evaluation of Cardiac Function

Included studies measured myocardial performance based on echocardiography or MRI. Measures of diastolic function included the following: transmitral flow for peak early (E) and late (A) inflow velocities and their ratio (E/A); deceleration time; septal, lateral, and/or average myocardial annular velocities on tissue Doppler imaging (e'); early inflow/annular velocity ratio (E/ e'); pulmonary vein flow to calculate the time difference between the atrial reversal wave and mitral A-wave duration; and the isovolumic relaxation time. Diastolic class grade was recorded if reported: normal, grade 1 (impaired relaxation), grade 2 (pseudonormal), and grade 3 (restrictive). Measures of systolic performance assessed included LV ejection fraction, cardiac output, stroke volume, and global longitudinal strain, if recorded. Measures of cardiac structure included LV mass, LV end-diastolic and end-systolic volumes, and left atrial size.

Statistical Analysis

Data on univariable correlations are presented because this was the most consistent measure seen in included studies. Where multivariable regression was performed, adjusted study estimates and model covariates are reported. Meta-analysis was performed for the weighted mean difference in EAT volume between groups with and without diastolic dysfunction. Meta-regression of weighted mean difference as an effect size and the combined mean EAT in included studies were performed with the moment-based estimate of between-study variance and a permutation test using 1000 Monte Carlo simulations to moderate for potentially spurious results, as previously described.⁶ Precision of pooled estimates is reported as 95% confidence intervals, and heterogeneity is reported by the I^2 statistic. The Newcastle Ottawa Scale was used to assess risk of bias (Tables S2 and S3). Statistical analysis was performed using StataMP 14.0 (StataCorpLP, College Station, TX).

Results

Study Selection

A brief outline summary of the 22 studies (18 published and 4 conference papers) included in this review is presented in Table 1.^{3,7–28}

Association of EAT With LV Diastolic Function

There were 11 studies that investigated the relationship between EAT and diastolic parameters, with 5 specifying adherence to an iteration of the American Society of Echocardiography diastolic guidelines.²⁹ EAT was associated with diastolic parameters, including peak mitral annular tissue Doppler velocities (e' septal, e' lateral, or e' mean) and transmitral flow (early [E] and late [A] diastolic peak flow velocities and their ratio [E/A]) (Table 2).^{9,13–16,18,20–24,29–32} Although some studies did perform comprehensive Doppler measures, such as isovolumic relaxation times, deceleration times, and pulmonary vein Doppler, the association with EAT individually with each parameter was not described. The classification of patients with diastolic dysfunction was available in 5 studies. Most patients (26%–38% of total cohort) had grade 1 diastolic dysfunction, with fewer qualifying as grade ≥ 2 (2%–28%).

In the 5 studies that measured differences in EAT between groups, EAT was significantly greater in the diastolic dysfunction group compared with patients with normal diastolic function (weighted mean difference, 24.4 mL; 95% confidence interval, 18.5–30.4 mL; $P < 0.001$; $I^2 = 28\%$) (Figure 2).^{15,16,20,21,23,26} Meta-regression, performed evaluating the weighted mean difference (effect size) against the mean EAT volume, demonstrated a nominally increasing presence of diastolic dysfunction with increasing EAT values ($\beta = 0.17$, $SEE = 0.09$, $P = 0.06$). This was statistically significant after Monte Carlo permutation testing, $P = 0.001$ (Figure 3).

Mean E/e' values were positively correlated with EAT (r value range, 0.21–0.34; $P < 0.05$), and mean e' values were inversely correlated (r value range, -0.26 to -0.44 ; $P < 0.05$); in all but one study, no consistent association was seen with the E/A ratio (r value range, -0.40 to 0.08). Increasing EAT was an independent predictor of diastolic dysfunction, e' and E/e' independent of age, sex, and measures of adiposity (Table 2). No independent association was identified with the E/A ratio. In 6 studies, hypertension was also an adjusted covariate in the model, and increasing EAT remained a predictor of altered diastolic parameters.

Association of EAT With Systolic Function

Of 10 studies describing the association of EAT with systolic parameters, LV function was evaluated with MRI in 5 and echocardiography in 4 (Table 3).^{3,10,11,16,18,19,22,27} One study

Table 1. Study Characteristics

First Author	Year	Country	Study Type	Population	Sample Size	EAT Method	EAT Value
Bakkum ⁸	2015	the Netherlands	Cross-sectional	Suspected CAD	208	PET-CT	113.8±48.1 cm ³
Cavalcante ⁹	2012	United States	Cross-sectional	Self-referred screening	110	MDCCT	Men, 101±51 cm ³ Women, 67±40 cm ³
Al Chekake ⁷	2010	United States	Case-control	AF and controls	273	MDCCT	Sinus rhythm, 76.1±36.3 mL; AF, 101.6±44.1 mL
Doesch ¹¹	2012	Germany	Case-control	Established CAD	158 Cases and 40 controls	MRI	Control, 31±8 g/m ² ; CAD, 29±10 g/m ² ; CAD and EF <50%, 26±8 g/m ² ; CAD and EF >50%, 36±11 g/m ²
Doesch ¹²	2013	Germany	Case-control	DCM	112 Cases and 48 controls	MRI	Control, 62.1±14.4 g; DCM, 47.2±15.2 g; control, 66±15.3 mL; DCM, 50.2±16.2 mL; control, 31.7±5.6 g/m ² ; DCM, 24±7.5 g/m ² ; control, 33.5±6.4 mL/m ² ; DCM, 25.5±8 mL/m ²
Doesch ¹⁰	2010	Germany	Case-control	CHF (LVEF <35%) (ICM=36; DCM=30)	66 Cases and 31 controls	MRI	Control, 71±13 mL; CHF, 46±11 mL; control, 36±5 mL/m ² ; CHF, 24±5 mL/m ² ; control, 67±13 g; CHF, 43±11 g; control, 34±4 g/m ² ; CHF, 22±5 g/m ²
Ede ¹³	2014	Turkey	Cross-sectional	Suspected CAD	106	MDCCT	38±31 cm ³
Faustino ^{14*}	2011	Portugal	Cross-sectional	Not specified	78	MDCCT	Threshold of 44.1 mL defined by ROC curve (72% sensitivity and 50% specificity) for diastolic dysfunction
Fernando ^{15*}	2015	United States	Cross-sectional	AF before ablation	20	MRI	125.7±56.7 mL
Fontes-Carvalho ¹⁶	2014	Portugal	Cross-sectional	Postmyocardial infarction	225	MDCCT	113.6±43.2 cm ³
Fox ¹⁷	2009	United States	Cross-sectional	Substudy of Framingham	997	MDCCT	Women, 108±41 cm ³ ; men, 136.5±54.4 cm ³
Hachiya ¹⁸	2014	Japan	Cross-sectional	Suspected CAD	134	MDCCT	77.1±29.6 cm ³ /m ²
Khawaja ¹⁹	2011	United States	Cross-sectional	Suspected CAD	381	MDCCT	Normal LVEF, 114.5±98.5 cm ³ ; LVEF <55%, 83.5±67.1 cm ³
Konishi ²⁰	2012	Japan	Cross-sectional	Suspected CAD	229	MDCCT	Diastolic dysfunction, 184±61 cm ³ ; normal function, 154±58 cm ³
Lai ²¹	2015	Taiwan	Cross-sectional	Self-referred screening	318	MDCCT	80.6±33 mL
Liu ²²	2011	United States	Cross-sectional	Blacks	1402	MDCCT	Men, 79.8±37.1 mL; women, 67.1±29.0 mL
Longenecker ^{23*}	2016		Cross-sectional	Patients with HIV	46 HIV+ and 23 HIV-	MDCCT	HIV+ with DD, median of 120 (74–143) mL; HIV+ with normal function, median of 72 (54–100) mL; HIV-, not specified

Continued

Table 1. Continued

First Author	Year	Country	Study Type	Population	Sample Size	EAT Method	EAT Value
Ng ²⁴	2016	Australia	Cross-sectional	Suspected CAD	130	MDCCT	Total, 97.5±43.7 cm ³ , men, 103.7±39.5 cm ³ , women, 90.9±47.4 cm ³
Ruberg ³	2010	United States	Cross-sectional	Obese with metabolic syndrome	28 Cases and 18 controls	MRI	Controls, 85±66 mL; subjects, 161±88 mL; controls, 1.1±0.7 mL/g; subjects, 2.0±1.1 mL/g
Vanni ^{25*}	2015	Italy	Case-control	Not specified	19 NAFLD and 9 controls	MRI	NAFLD, 228.1±112.9 mL; controls, 66.8±25.2 mL
Vural ²⁶	2014	Turkey	Case-control	Suspected CAD	63	CACS	137±56 cm ³
Wu ²⁷	2015	Taiwan	Cross-sectional	Compensated CHF	50 Cases and 20 controls	MRI	Control, 45.8 (39.4–50.3) mL; CHF+VT/VF, 51.5 (46.6–59.8) mL; CHF and no VT/VF, 44.0 (33.9–48.3) mL
Yamashita ^{28*}	2012	Japan	Cross-sectional	Suspected CAD	286	MDCCT	EAT, 71.6±37.9 (10.5–179.9) mL

Values are mean±SD or mean (range). AF indicates atrial fibrillation; CACS, coronary artery calcium score; CAD, coronary artery disease; CHF, congestive heart failure; DCM, dilated cardiomyopathy; DD, diastolic dysfunction; EAT, epicardial adipose tissue; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; MDCCT, multidetector computed tomography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; PET-CT, positron emission tomography-computed tomography; ROC, receiver operating characteristic; VT/VF, ventricular tachycardia/ventricular fibrillation.

*This is a conference abstract.

reported associations between EAT and global longitudinal strain, a subclinical measure of myocardial function.²⁴ Only one described an independent effect of EAT on LV ejection fraction (LVEF) by echocardiography.¹⁹ No univariable correlation with LVEF was reported in the MRI studies.^{10–12} Of the 6 studies reporting multivariable regression analysis, an independent association with LVEF was observed in 2 studies: one study was performed in patients with established coronary artery disease (CAD) stratified by LVEF and compared with normal controls (hazard ratio, 0.48; 95% confidence interval, 0.28–0.68; $P<0.01$),¹¹ and the other study was performed in patients undergoing investigation for suspected CAD with reduced LVEF compared with normal LVEF (values not reported).¹⁹

The only consistent feature across all studies appeared to be a relative decrease in EAT as LVEF decreased. In studies that included control groups (ie, normal LVEF), no association of EAT with EF was identified in the control group. One study demonstrated a significant inverse correlation with EAT (normalized to LV mass) with cardiac output and stroke volume (but not LVEF)³ in obese patients (r value, -0.46) but not in corresponding controls.

In studies focusing specifically on patients with reduced LVEF, EAT was reduced compared with those with preserved LVEF. Doesch et al¹¹ demonstrated that patients with CAD and preserved LVEF had greater EAT (36 ± 11 g/m²) than normal controls without CAD (31 ± 8 g/m²), and both had greater EAT than patients with CAD with LVEF $<50\%$ (28 ± 8 g/m²; $P<0.01$). A population with presumed ischemic cardiomyopathy (CAD with reduced LVEF) also reported a stepwise decrease in EAT volume with reducing grades of LVEF.¹⁹ This stepwise decrease was not found in a different study by Doesch et al¹² in patients with dilated cardiomyopathy against normal controls, although EAT was reduced overall compared with normal controls.

In the study related to strain analysis,²⁴ there was a positive correlation with EAT and impaired 3-dimensional global longitudinal strain ($r=0.601$, $P<0.001$) that remained significant on multivariable regression (standardized $\beta=0.512$, $P<0.001$), independent of markers of obesity and diabetes mellitus.

Association of EAT With Chamber Measures

There were 14 studies with data relating to a measure of myocardial geometry. All modalities of echocardiography, CT, and MRI were represented, with most values indexed to body surface area, unless otherwise specified. Some studies avoided indexation because body weight or other adiposity measures were used in regression models and, therefore, raw measures were used to prevent collinearity.

The most often reported univariable correlation coefficient was for EAT and LV mass or indexed mass and was always

Table 2. EAT and Diastolic Function

First Author	Diastolic Function Reference	Subgroup Characteristics		Diastolic Parameter: Correlations			Multivariable Regression Comments
		DD	Normal Function	E/A	e'	E/e'	
Cavalcante ⁹	ASE ²⁹	Grade 1 (n=29, 26%) Grade 2 (n=11, 10%)	n=70, 64%		Averaged 0.44*	0.34*	Multivariate model outcomes of grade 1 or higher DD, mean e', and mean E/e': EAT was an independent predictor (model included 10-y Framingham Risk Score, metabolic syndrome, subclinical CAD, and LV mass index), β range, -0.02 to 0.04 (all $P < 0.05$). Indexed EAT was found to increase clinical model for prediction of DD (adjusted $R^2=0.16$ vs 0.24 ; $P=0.004$) and mean e' (adjusted $R^2=0.17$ vs 0.27 ; $P=0.001$) (ie, indexed EAT represents 8%–10% of the variation of predictors for DD)
Ege ¹³	Lang et al ³²	Grade 1 (n=39, 37%) Grade 2 (n=10, 9%) Grade 3 (n=2, 2%)	n=55, 52%	-0.404			
Faustino ^{14†}	Not specified	46 Patients with DD and EAT >44.1 mL	32 Patients with no DD and EAT <44.1 mL				EAT not significant on multivariable regression (results and covariates not reported). Relationship of EAT with DD by ROC AUC of 0.66 ($P=0.02$)
Fernando ^{15†}	Not specified	EAT=164±118 mL (E/E' >15)	EAT=114±54 mL (E/E' <15)		-0.48*	0.22	On multivariable regression adjusted for age, BMI, LA volume, hypertension, and CAD, EAT associated with abnormal myocardial relaxation (OR, not specified; $P=0.04$)
Fontes-Carvalho ¹⁶	ASE ²⁹	EAT=116.7±67.9 cm ³ Grade 1 (n=57, 28%) Grade 2 (n=58, 28%) Grade 3 (n=10, 5%)	EAT=93.0±52.3 cm ³ n=80 (39%)		e' Septal, -0.26^* e' lateral, -0.28^*	0.25*	On multivariable regression adjusted for hypertension, age, sex, and other markers of adiposity (SAT, VAT, waist/height ratio, and fat mass %), EAT remained significantly predictive of E/e' (β , 0.19 [0.06–0.32]; $P < 0.01$), as did e' septal and e' lateral
Hachiya ¹⁸	ASE ²⁹			-0.05	-0.31*	0.24*	Definition of diastolic dysfunction not specified. On different multivariate models, e' inversely correlated with EAT (standardized β range, -0.30 to -0.36 ; all $P < 0.05$) but not E/e' (standardized β , 0.23; $P=0.06$), except when adjusted for age, sex, and BMI (model 1) and medication use (model 2) (standardized β range, 0.25–0.31; all $P < 0.05$)
Konishi ²⁰	Defined as E/e' >10	EAT=184±61 cm ³ n=141 (62%)	EAT=154±58 cm ³ n=88 (38%)			0.21*	On multivariable regression with age, hypertension, male sex, diabetes mellitus, and abdominal obesity, there was an independent effect of EAT on DD: OR, 2.09 (1.15–3.79; $P=0.02$) for EAT per 100 cm ³

Continued

Table 2. Continued

First Author	Diastolic Function Reference	Subgroup Characteristics		Diastolic Parameter Correlations			Multivariable Regression Comments
		DD	Normal Function	E/A	e'	E/e'	
Lai ²¹	Lang et al ³²	EAT=86.79±31.77 n=100	EAT=67.32±31.95 n=218		-0.38*	0.284*	On multivariable regression adjusted for age, sex, BMI, systolic blood pressure, LV mass index, hypertension, diabetes mellitus, hyperlipidemia, and smoking, EAT was significantly associated with E/A (β, -0.002), * E' (β, -0.02), * E/E' (β, 0.02), * and diastolic dyssynchrony (β, 0.197), * ROC-derived optimal cutoff for DD was 67.3 mL (ROC, 0.712; sensitivity, 73%; specificity, 62%)
Liu ²²	Gottdiener et al ³¹			Men, -0.12* women, -0.12*			On multivariable linear regression adjusted for age, height, smoking, alcohol, blood pressure, eGFR, hemoglobin, total physical activity score, medications, VAT, and weight, E/A no longer became significant (regression co-efficient, -0.01±0.02 [P=0.41] in women and -0.0±0.02 [P=0.64] in men) (described as pericardial fat volume)
Longenecker ^{23†}	Not specified	Grade 1 (n=29 [HIV+, n=19; HIV-, n=10]) Grade 2 (n=2 [HIV+, n=1; HIV-, n=2])	n=38 (HIV+) n=26 and n=12 (HIV-)	-0.392*			On multivariable regression adjusted for age, BMI, and sex, EAT remained independently associated with diastolic dysfunction (OR, 1.35; 95% CI, 1.02-1.79) per 10-mL increase (described as pericardial fat volume)
Ng ²⁴	Not specified					e' Septal, -0.263*; e' lateral, -0.285*	
Vural ²⁶	Alnabhan et al ³⁰	EAT=164.4±54 cm ³ Grade 1 (n=24, 38%) Grade 2 (n=4, 6%) Grade 3 (n=1, 1.5%)	EAT=114.1±46.6 cm ³ n=34 (56%)			-0.437*	On multivariable regression adjusted for age, blood pressure, BMI, waist circumference, and cholesterol, EAT was an independent predictor of DD (OR, 1.03 [1.01-1.06]; P=0.006). ROC-derived optimal cutoff for DD, 129.6 cm ³ (ROC curve, 0.758)

Correlations represent the correlation co-efficient. Values are mean±SD or mean (range). ASE indicates American Society of Echocardiography; AUC, area under the curve; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; DD, diastolic dysfunction; e', average mitral annular tissue Doppler velocity; E/e', early inflow / annular velocity ratio; E/A, ratio of peak early (E) and late (A) transmitral inflow velocities; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; OR, odds ratio; ROC, receiver operating characteristic; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. *P value for univariate correlation is significant at <0.05. †Study is a conference abstract.

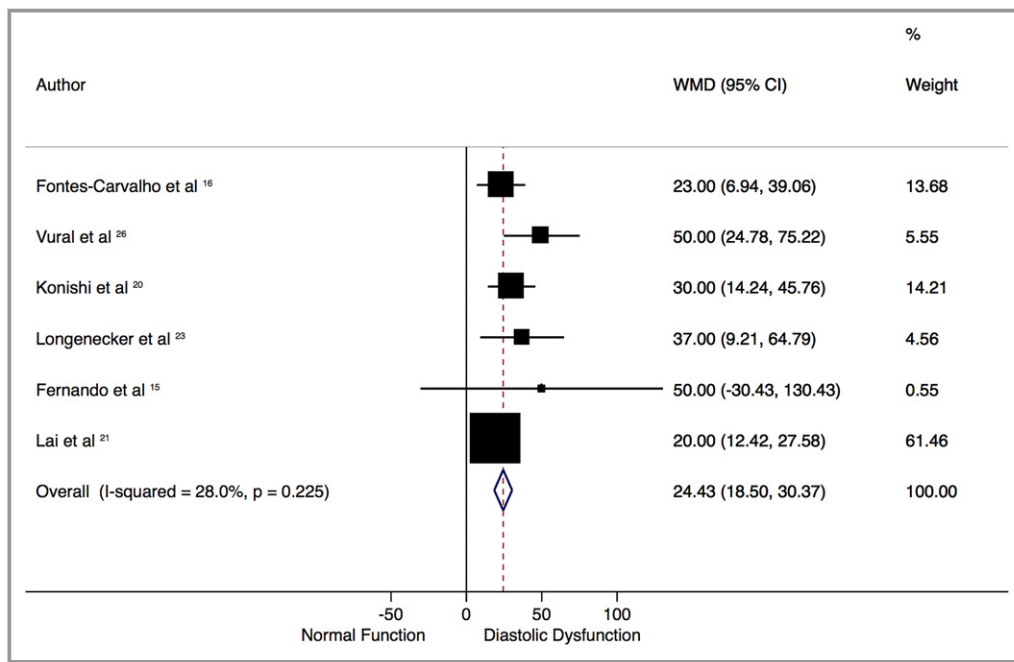


Figure 2. Mean difference of epicardial adipose tissue (EAT) volume in patients with and without diastolic dysfunction. Forest plot demonstrates the weighted mean difference (WMD; in mL) of EAT in studies with and without diastolic dysfunction, according to a random-effect model. Those with diastolic dysfunction have significantly greater EAT volumes. There is mild heterogeneity, as seen by the I^2 statistic of 28%. CI indicates confidence interval.

statistically significantly positively correlated in the diseased patient group (not controls), with ranges from $r=0.19$ to $r=0.42$ ($P<0.05$). Only studies by Doesch et al^{11,12} measured LV end-diastolic diameter and found a consistent association with EAT (r value range, 0.22–0.42; $P<0.05$). Similar findings were seen for LV end-diastolic and end-systolic volume. Left atrial size was measured either as volume or diameter and demonstrated significant univariable associations with EAT (Table 4).*

An inconsistent association was seen with measures of adiposity in relation to EAT and cardiac structure. In patients with reduced LVEF, indexed EAT appears to be associated with indexed LV end-diastolic mass independent of BMI (Table 4).^{10–12} One study assessing patients with suspected CAD and normal LVEF demonstrated that EAT correlated best with LV mass (nonindexed) in the nonobese cohort only ($\beta=0.23$, $P<0.001$).⁸ Finally, in 2 observational studies, an independent association of EAT with LV mass (nonindexed), adjusted for body weight, was only seen in women (Table 4).^{17,22}

Discussion

This review of 21 studies has demonstrated the emerging body of work relating EAT to myocardial structure and

function. Increasing EAT is associated with the following: (1) an increasing prevalence of diastolic dysfunction; (2) a concomitant increase in LV mass; and (3) no consistent association with markers of systolic function. However, these

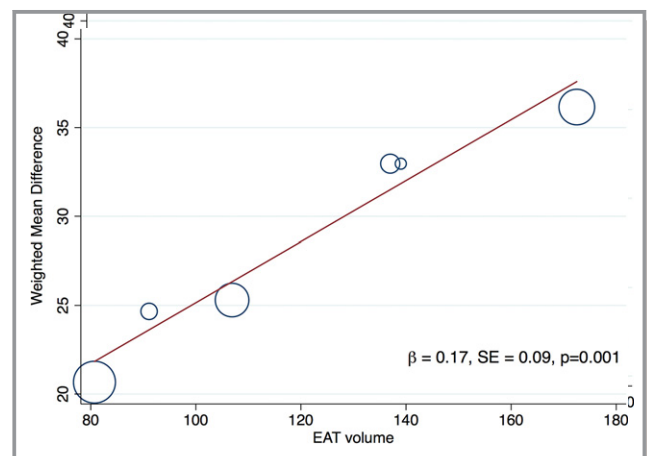


Figure 3. Meta-regression of the effect of increasing epicardial adipose tissue (EAT) volume on the weighted mean difference (effect size) of EAT in patients with and without diastolic dysfunction. Meta-regression bubble plot depicts increasing differences in mean EAT volume in patients with diastolic dysfunction as EAT increases. Circles represent the weight of each study. β coefficient is from meta-regression with associated SEE; P value is from Monte-Carlo testing (1000 simulations) and demonstrates a significant association ($P=0.001$).

*References 3, 7–12, 17, 18, 20, 22, 24, 25, 28.

Table 3. EAT and Systolic Function

First Author	Method	Group	EAT Value	Systolic Measure	r Value (Univariate)	Multivariable Regression Comment
Doesch ¹¹	MRI	CAD and EF >50% (n=44) CAD and EF <50% (n=114) Combined CAD (n=158) Controls (n=40)	36±11 g/m ² 26±8 g/m ² 29±10 g/m ² 31±8 g/m ²	LVEF	0.171 0.137 0.574* Not specified	On multivariable regression adjusted for BMI, NYHA classes I and III, atrial fibrillation, LV-EDVI, LV-ESVI, LV-EDD, LVRI, and LGE%, LVEF was an independent predictor of indexed EAT (HR, 0.478 [0.28–0.675]; <i>P</i> <0.01) [†]
Doesch ¹²	MRI	Control (n=48) DCM (n=112)	31.7±5.6 g/m ² 24±7.5 g/m ²	LVEF LVEF	0.069 0.085	No correlation with LVEF and EAT (<i>P</i> =0.37)
Fontes-Carvalho ¹⁶	Echocardiography			LVEF	−0.07	
Hachiya ¹⁸	Echocardiography			LVEF	0.22*	Significant association on multivariate regression models adjusted for hypertension, diabetes mellitus, dyslipidemia, previous CAD or revascularization, and medication use (standardized β range, 0.16–0.22; all <i>P</i> <0.05) but not adjusted for age, sex, or BMI (standardized β, 0.13; <i>P</i> >0.05)
Khawaja ¹⁹	Echocardiography	Normal (n=321) EF <55% (n=60) EF 35%–55% (n=43) EF <35% (n=17)	114.5±98.5 cm ³ 83.5±67.1 cm ³ 96.0±73.9 cm ³ 52.2±29.7 cm ³			Multivariate analysis revealed LVEF and triglyceride levels predicted EAT (values and covariates not reported)
Liu ²²	Echocardiography	Women Men		LVEF LVEF	−0.04 0.03	Not significant on multivariable regression in either sex (adjusted for age, height, smoking, alcohol, blood pressure, eGFR, hemoglobin, total physical activity score, medications, VAT, and weight: regression coefficient, −0.3±0.4 [<i>P</i> =0.51] in women and 0.2±0.6 [<i>P</i> =0.72] in men). Note: described as pericardial fat volume.
Ruberg ³	MRI	Obese Control		CO SV LVEF CO SV LVEF	−0.46* Inverse* Not correlated Not correlated Not correlated Not correlated	Values are normalized to LV mass (mL/g)
Wu ²⁷	MRI			LVEF	Not correlated	

Values are mean±SD or *r* value correlation coefficients, unless otherwise stated. BMI indicates body mass index; CAD, coronary artery disease; CO, cardiac output; DCM, dilated cardiomyopathy; EAT, epicardial adipose tissue; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LGE%, percentage of late gadolinium enhancement; LV, left ventricular; LV-EDD, LV end-diastolic diameter; LV-EDVI, LV end-diastolic volume index; LV-ESVI, left ventricular end-systolic volume index; LVRI, LV remodeling index; MRI, magnetic resonance imaging; NYHA, New York Heart Association; SV, stroke volume; VAT, visceral adipose tissue.

**P*<0.05.

[†]Directly quoted values from source article.

correlations were no more than moderate; no coefficient exceeded 0.50.

Protective Functions of EAT

EAT has a high fatty acid content and can both release and scavenge excess free fatty acids to regulate myocardial

energy production.² In addition, EAT secretes anti-inflammatory cytokines, such as adiponectin, adrenomedullin, and omentin, which have antiatherogenic effects; EAT also regulates vascular tone and cardiac remodeling.³³ There is a thermogenic role for EAT in providing heat for the myocardium in times of hypoxic or ischemic stress.³³ However, the presence of numerous proinflammatory

Table 4. EAT and Chamber Geometry

Author	Modality	Subgroup	LV-EDD	LA Size (Diameter/Volume)	LVEDMI	LV-EDVI	LV-ESVI	LVRI	Comment
Bukkam ⁸	CT				0.42 ^{*,†}				On multivariable regression adjusted for traditional cardiovascular risk factors, CACS and BMI, EAT was not a significant predictor of LV mass in obese patients, but only in nonobese patients ($\beta=0.23$, $P<0.0001$)
Cavalcante ⁹	Echocardiography				0.41 [*]				Measure not included in multivariate analysis
Al Chekake ⁷	CT and echocardiography			0.25/0.24					
Doesch ¹¹	MRI	EF <50% (n=44) EF >50% (n=114) Combined (n=158)	0.076 0.011 0.272 [*]		0.336 [*] 0.305 [*] 0.019	0.201 [*] 0.043 0.16 [*]	0.089 0.056 0.262 [*]	0.137 0.202 0.344 [*]	On multivariable regression including LVEF, BMI, NYHA classes I and III, atrial fibrillation, LV-EDVI, LV-ESVI, LV-EFF, LVRI, and LGE%, best correlates to indexed EAT were LVEF, BMI, LV-ESVI (HR, 0.48; $P<0.01$), and LV-EDD (HR, -0.238 ; $P=0.01$). In subgroup analysis by EF <50% or >50%, full model not described; however, no association with LVEDMI in LVEF >50% but association seen in LVEF >50% (HR, 0.105; $P=0.01$)
Doesch ¹²	MRI	Control (n=48) DCM (n=112)	0.01 0.22 [*]		0.346 [*] 0.417 [*]	0.007 0.251 [*]	0.0001 0.239 [*]	0.204 0.116	Increased EAT mass with increasing LVEDMI in DCM, but less values than healthy control group. Greater mass seen in DCM with hypertrophy vs nonhypertrophy (31.7 ± 5.6 vs 24.4 ± 7.1 g/m ² ; $P=0.01$). On multivariable regression only, LVEDMI independently correlated with indexed EAT, as was seen in healthy controls (adjusted for age and BMI [value not reported]).
Doesch ¹⁰	MRI	Control CHF	NR 0.42 [*]		0.36 [*] 0.59 [*]				Increased EAT mass in CHF with increasing LVEDMI; however, higher levels of EAT in controls compared with CHF (34 ± 4 vs 22 ± 5 g/m ² ; $P<0.01$). On multivariate regression adjusted for LVEF, LV-EDD, RVEF, and LVEDMI, only LVEDMI independently associated with indexed EAT ($P=0.0001$)
Fox ¹⁷	MRI	Women Men		0.28 [*] 0.37 [*]	0.35 ^{*,†} 0.19 ^{*,†}	0.2 ^{*,†} 0.07 [‡]			On multivariable regression adjusted for age, height, smoking, alcohol, menopause, hormone replacement therapy, blood pressure, hypertension therapy, and weight, only in women, LVM (adjusted regression coefficient, 1.66; $P=0.01$), and in men, LA diameter (adjusted regression coefficient, 0.8; $P=0.002$) were independent predictors of pericardial fat volume
Hachiya ¹⁸	Echocardiography				0.28 [*]				Measure not included in multivariate analysis

Continued

Table 4. Continued

Author	Modality	Subgroup	LV-EDD	LA Size (Diameter/Volume)	LVEDMI	LV-EDVI	LV-ESVI	LVRI	Comment
Konishi ²⁰	Echocardiography			0.32*	0.23*				Measure not included in multivariate analysis
Liu ²²	Echocardiography	Women Men		0.3* 0.11	0.24* [‡] 0.21* [‡]				On multivariable regression adjusted for age, height, smoking, alcohol, blood pressure, eGFR, hemoglobin, total physical activity score, medications, VAT, and weight, only in women, LVM (adjusted regression coefficient, 4.1±1.8; P=0.03) and LA diameter (adjusted regression coefficient, 0.4±0.2; P=0.03) were independent predictors of pericardial fat volume
Ng ²⁴	Echocardiography					-0.09	0.08		
Ruberg ³	MRI					Not			
Vanni ^{25§}	MRI	Cases					0.46*		Inversely correlated with EF No other analysis specified
Yamashita ^{26§}	CT			0.25*					

Values are mean±SD or r value correlation coefficients, unless otherwise stated. BMI indicates body mass index; CACS, coronary artery calcium score; CHF, congestive heart failure; CT, computed tomography; DCM, dilated cardiomyopathy; EAT, epicardial adipose tissue; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LA, left atrial; LGE%, percentage of late gadolinium enhancement; LV, left ventricular; LV-EDVI, LV end-diastolic volume index; LV-EDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVEDMI, LV end-diastolic mass index; LV-EDVI, LV end-diastolic volume index; LV-ESVI, LV end-systolic volume index; LVRI, LV remodeling index; MRI, magnetic resonance imaging; NR, not reported; NYHA, New York Heart Association; RVEF, right ventricular EF; VAT, visceral adipose tissue.

*P < 0.05.

[†]Value is for LV mass on CT, nonindexed and time in cardiac cycle not specified.

[‡]Represents a nonindexed measure.

[§]Study is a conference abstract.

^{||}Value is for end-systolic LV diameter.

cytokines within EAT may lead to a potential imbalance of harmful versus protective cytokines and disruption of myocardial function. Higher levels of these molecules (eg, tumor necrosis factor- α , interleukin-6, interleukin-1, and MCP-1) are seen in patients with CAD or heart failure. It is uncertain whether the trigger for the imbalance of cytokines is a cause of the pathological characteristics or a consequence, and a potential reciprocal or bidirectional role has been proposed.²

EAT and Diastolic Dysfunction

Adipose tissue can modulate the cardiovascular system by mechanisms including sympathetic activation, adipokine secretion, and myocardial oxidative stress.^{34,35} EAT is regarded as a visceral fat depot. Visceral fat is metabolically active and is a determinant of diastolic function.³⁶ The adipokines within EAT can all affect diastolic function through persistent inflammation and subsequent collagen turnover,³⁷ impaired microvascular relaxation, or a direct toxic effect on the myocardium.^{38,39} The loss of protective effects of adiponectin can also modify diastolic function.⁴⁰

Mechanical effects may arise from myocardial compression of EAT because it lies within a fixed pericardial sac,¹⁷ inducing a similar mechanism as pericardial constriction. Hachiya et al demonstrated an independent correlation of EAT with aortic pulse pressure as another mechanism of diastolic dysfunction that may be mediated by the association of EAT with aortic stiffness and, therefore, increased pulse wave velocity and early wave reflection.¹⁸ Increased pressure in late systole may cause slower LV relaxation and subsequent diastolic dysfunction, as well as compromise coronary perfusion, especially if there is underlying CAD leading to impaired LV relaxation.⁴¹

EAT is associated with obesity, which itself is independently associated with diastolic dysfunction.⁴² Obese patients often have elevated EAT volumes,¹⁷ and indexed EAT has modest incremental value for diastolic dysfunction over traditional covariates, such as metabolic syndrome, subclinical CAD, and LV mass index.⁹ Although the results from our analysis demonstrate that EAT had an independent effect on diastolic function parameters over adiposity measures, adiposity measures varied considerably and included BMI, bioimpedance testing, area of visceral adipose tissue or subcutaneous adipose tissue, or indexed EAT, which accounts for body weight. This heterogeneity needs further explanation to adequately isolate the effect of obesity and EAT on diastolic function. The lack of an association of EAT with E/A ratio may be confounded by the effects of age, proportion of patients with CAD, measurement in patients with normal LVEF, and the U-shaped relationship of E/A ratio with diastolic function that makes it difficult to assess without the addition of other variables.⁴³

The evaluation of diastolic function is challenging and influenced by a patient's filling status, the presence of CAD,

diabetes mellitus, obesity, as well as "normal" changes seen in the ageing patient. Although most studies aim to account for these factors in multivariable regression models, no more than association can be interpreted, and causality cannot be proved. Statistically, there may be implications of collinearity of obesity measures and EAT in multivariable models.

EAT and Systolic Dysfunction

Our study noted weak and inconsistent associations of EAT and systolic parameters. In the single study that evaluated EAT and longitudinal strain as a marker of subclinical myocardial dysfunction, there was a strong association noted independent of confounders, such as obesity and diabetes mellitus.²⁴ This is a notable finding; however, causality remains unproved and requires further assessment in larger-scale studies as a possible marker of the syndrome of heart failure with preserved ejection fraction. Various hypotheses have been developed to relate EAT and systolic function. In studies of patients with ischemic and dilated cardiomyopathy, there has been a consistent signal of reducing EAT with reducing LVEF, with less EAT also seen compared with normal controls or those with normal LVEF.^{10–12,19} As myocardium becomes progressively dysfunctional, the role of EAT as a source of energy or cytokine homeostasis may become less necessary, contributing to EAT depletion. Conversely, in obese patients, there was no association with EAT (normalized to cardiac mass) and LVEF, and there was a negative correlation with MRI-derived cardiac output as EAT increased.³ The proposed mechanism is from mechanical restriction of myocardial expansion from EAT in diastole that may lead to less ventricular filling and, therefore, reduced cardiac output.³ A further mechanism may involve the effects of a direct cytokine release, as seen in patients with decompensated heart failure, but no studies have applied this in the context of EAT volume.

EAT and Chamber Measures

Postmortem and experimental studies^{44,45} have demonstrated a constant ratio of epicardial fat/ventricular myocardium, regardless of underlying pathological characteristics of hypertrophy, ischemia, or normal muscle. Furthermore, the increase in fat mass parallels LV hypertrophy, although healthy controls have higher quantities of EAT.¹⁰ Similar findings are seen when evaluating the LV remodeling index (ratio of mass/end-diastolic volume), where an inverse correlation is noted with LVEF and the EAT/LV remodeling index ratio. LVEF is inversely correlated with EAT and linearly correlated with LV remodeling index, suggesting that remodeling is not compensated by an adequate increase in EAT.¹⁰

Obesity has shown a positive relationship with increased LV mass and EAT, yet the impact of obesity on myocardial

geometry may outweigh the local effects of ectopic fat because associations attenuated after adjustment for other adiposity measures, including body weight.¹⁷ From a mechanistic perspective, the association of EAT with central obesity and visceral adipose tissue might result in greater LV afterload and subsequent increased LV output, therefore leading to LV remodeling.⁸ As LV remodeling progresses, LV diameter, volume, and mass increase, which may then deplete EAT stores¹² and result in a vicious cycle of reduced protective benefits on the heart and further dysfunction. However, the independent association of EAT with LV mass is limited to nonobese subjects.⁸ Associations of EAT with the incidence of CAD have been described in nonobese people⁴⁶ and could contribute to the so-called obesity paradox.⁴⁷

Limitations

We acknowledge several limitations in our study. EAT measurement by different modalities may lead to differences between studies. Some reported EAT indexed to Body Surface Area (BSA) (therefore accounting for weight), and some reported raw values using weight as a covariate in multivariable models. Such normalization, as opposed to normalization to height, may obscure the contribution of obesity to differences in chamber volumes and mass, which are associated with EAT. Not all studies adjusted for hypertension in multivariable models, which is also associated with obesity and diastolic function. Variations in the reference literature on measures of diastolic function also lead to difficulties with comparing studies. The differences in regional location of EAT were not available in most studies and, therefore, the effect of EAT distribution was not assessable. The level of heterogeneity and variable study end points precluded detailed meta-analysis.

Conclusions

Despite small and heterogeneous studies, there is clear evidence of a consistent effect of volumetric EAT on myocardial diastolic function and chamber measurements; however, robust data are lacking to make causal inferences. These findings are observed despite adjustment for common confounders, such as adiposity. No consistent effect is seen with respect to systolic parameters. Further longitudinal studies are necessary to generate quantitative summary measures as well as develop potential targets for treatment.

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Disclosures

None.

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Supplemental Material

Table S1. Example MEDLINE search strategy.

#	Searches	Results
1	exp Adipose Tissue/ or epicardial fat.mp.	79789
2	epicardial adipose tissue.mp.	417
3	epicardial fat volume.mp.	56
4	pericardial adipose tissue.mp.	58
5	pericardial fat.mp.	242
6	pericardial fat volume.mp.	31
7	1 or 2 or 3 or 4 or 5 or 6	79916
8	exp Myocardial Contraction/ or exp Heart Failure/ or exp Heart Ventricles/ or exp Echocardiography, Doppler/ or exp Ventricular Dysfunction, Left/ or exp Diastole/ or exp Ventricular Function, Left/ or diastolic function.mp.	260853
9	diastolic dysfunction.mp.	6262
10	systolic function.mp.	9152
11	exp Myocardial Contraction/ or myocardial function.mp.	75943
12	myocardial performance.mp.	2269
13	mitral annular velocities.mp.	154
14	ejection fraction.mp.	44097
15	8 or 9 or 10 or 11 or 12 or 13 or 14	282014
16	exp Tomography, X-Ray Computed/ or cardiac ct.mp.	337987
17	coronary calcium score.mp. or exp Tomography, X-Ray Computed/	337983
18	exp Multidetector Computed Tomography/ or ccta.mp.	4630
19	16 or 17 or 18	338169
20	exp Magnetic Resonance Imaging/	346308
21	cardiac mri.mp.	1739
22	ectopic fat.mp.	396
23	7 or 22	80055
24	20 or 21	346580
25	15 and 19 and 23	53
26	15 and 23 and 24	78
27	25 or 26	122

Table S2. Newcastle - Ottawa Scale for Assessment of Cross-sectional Studies.

First Author	Year	Selection			Non - respondent s	Comparability	Outcome		Total
		Representativeness of the sample	Sampl e size	Ascertainment of exposure		Outcome groups comparable	Assessment of outcome	Correct statistical test	
Bakkum ¹	2015	*	-	**	*	*	*	*	7
Cavalcante ²	2012	*	-	**	*	**	**	*	9
Ede ³	2014	*	-	**	*	**	**	*	9
Faustino ⁴	2011	*	-	**	-	**	*	*	7
Fernando ⁵	2015	*	-	**	-	**	*	*	7
Fontes-carvalho ⁶	2014	*	-	**	*	**	**	*	9
Fox ⁷	2009	*	*	**	*	**	**	*	10
Hachiya ⁸	2014	*	-	**	*	*	*	*	7
Khawaja ⁹	2011	*	-	**	-	**	**	*	8
Konishi ¹⁰	2012	*	-	**	*	-	*	*	6
Lai ¹¹	2015	*	-	**	*	**	*	*	8
Liu ¹²	2011	*	*	**	*	**	*	*	10
Longenecker ¹³	2016	*	-	**	*	**	*	*	8
Ng ¹⁴	2016	*	-	**	*	**	*	*	8
Ruberg ¹⁵	2010	*	-	**	*	*	**	*	8
Wu ¹⁶	2015	*	-	**	*	*	**	*	8
Yamashita ¹⁷	2012	*	-	**	*	**	*	*	8

Table S3. Newcastle - Ottawa Scale for Assessment of Case Control Studies.

First Author	Year	Selection			Comparability		Exposure		Total	
		Representativeness of the sample	Adequate case definition?	Selection of controls	Definition of controls	Controls and cases comparable	Ascertainment of exposure	Same method of ascertainment for cases and controls		Non-response rate
Chekakie ¹⁸	2010	*	*	*	*	**	*	*	*	9
Doesch ¹⁹	2012	*	*	*	*	**	*	*	*	9
Doesch ²⁰	2013	*	*	*	*	**	**	*	*	10
Doesch ²¹	2010	*	*	*	*	**	**	*	*	10
Vanni ²²	2015	*	*	*	*	*	*	*	*	8
Vural ²³	2014	*	*	*	*	**	**	*	*	10

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