Association of Epicardial Adipose Tissue with Essential Hypertension: A Meta-Analysis

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Abstract

Background and aims: Increased epicardial adipose tissue (EAT) has been proposed as a risk factor for essential hypertension (EH). The aim of this study was to investigate the association of EAT with EH.

Methods and results: PubMed, EMBASE, and Cochrane databases were systematically reviewed to identify relevant studies assessing the association of EAT thickness (EAT-t) and volume (EAT-v) with EH. There were 39 observational studies and 8,983 subjects included in the meta-analysis. The analysis indicated that hypertensive patients had a higher mean of EAT-t (SMD=0.64, 95% CI: 0.44-0.83, p<0.001) and EAT-v (SMD: 0.69, 95% CI:0.34-0.1.05, p<0.001) than normotensive individuals. Accordingly, we calculated pooled odds ratio (OR) and 95% confidence intervals (CI) for the association of EAT with EH, and the results showed that EAT-t (OR: 1.59, 95% CI: 1.09–2.33, P<0.001) and EAT-v (OR: 1.82, 95% CI: 1.33–2.19, P<0.001) were associated with essential hypertension. Additionally, higher mean of EAT-t (SMD=0.85, 95% CI=0.49-0.1.21, p<0.001) and EAT-v (SMD=0.83, 95% CI=0.31-1.34, p=0.002) were found in non-dipper hypertensive patients than those in dipper patients, but we didn't find significant difference in EAT-t among patients with different grades of hypertension. We also investigated the association of EAT with complications in hypertensive patients, and the results showed that EAT was increased in patients with arteriosclerotic cardiovascular disease (ASCVD) or cardiac hypertrophy and dysfunction than those without.

Conclusions: The increase in EAT was associated with the occurrence and complications of EH. The findings provide new information regarding the occurrence and complications of EH.

Introduction

Essential hypertension (EH) is a major global health problem and seriously threatens to human health[1], which is an independent risk factor for stroke, congestive heart failure, end-stage renal failure and mortality[2]. It is believed that the heredity, environment, age, obesity, and lifestyle is related to the occurrence of EH[3]. However, the pathogenesis of EH is still not clear. The metabolic changes including insulin resistance, dyslipidemia, and fat accumulation are frequently associated with high blood pressure[4]. Interestingly, there is growing evidence showing that not only the amount of adipose tissue but also its distribution plays an important role in occurrence of hypertension[5–7].

Epicardial adipose tissue (EAT) covers three-quarters of the human heart surface and locates between the myocardium and epicardium[8]. EAT is newly regarded as a metabolically active organ and composed of adipocytes, inflammatory cells, and stromal cells, which is known to have endocrine and paracrine functions[8]. It secretes numerous cytokines including adipocytokines, chemokines and interleukins, mediating unfavorable metabolism and proinflammatory activities[9], which is involved in the pathophysiology of obesity-related heart diseases, including coronary artery disease, heart failure, atrial fibrillation, and carotid plaque[10]. There is growing evidence suggesting the association between EAT and EH[11–15]. EAT was increased in patients with EH compared with normotensive individuals[16–18], and the

incidence of hypertension was increased in subjects with higher amount of EAT[12]. Furthermore, studies reported that EAT was also associated with secondary hypertension[19,20]. However, another study found no difference in EAT between patients with essential hypertension and controls[21]. There is a controversy over the association between EAT and essential hypertension. Therefore, it is necessary to perform a meta-analysis to evaluate the association of EAT with EH.

In this meta-analysis, we firstly aimed to evaluate the association of EAT thickness (EAT-t) and volume (EAT-v) with EH. Then we performed a subgroup analysis by grade of hypertension and impaired circadian blood pressure patterns. At last, we assessed the association of EAT with cardiac hypertrophy and dysfunction and arteriosclerotic cardiovascular disease (ASCVD) in patients with EH.

Methods

Search strategy

Article's search was performed independently by two researchers (XZ and BL). The protocols of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was followed to conduct the meta-analysis. This systematic search was applied to PubMed, EMBASE, and Cochrane databases. In order to retrieve all the literature related to this topic, we performed a search using the following expressions: [('epicardial adipose tissue') OR ('epicardial fat')] AND [('hypertension') OR ('high blood pressure')]. The search included articles published until February 06, 2021.

Inclusion And Exclusion Criteria

Only English full-size of articles were considered for this meta-analysis. These observational studies investigating the association of essential hypertension with EAT-t (by echocardiography, CT or MRI) and EAT-v (by CT or MRI) were eligible for this meta-analysis, and researches on secondary hypertension were excluded. Diagnosis of the EH was based on systolic blood pressure (SBP) ≥ 140 mmHg, and /or diastolic blood pressure (DBP) ≥ 90 mmHg. Literature were excluded if they investigated the association of EAT with the special patient populations: on long-term hemodialysis chronic kidney disease, renal artery stenosis, aortic coarctation, primary aldosteronism, pheochromocytoma, cushing syndrome, acromegaly, drug-induced hypertension. Children' (< 18-years-old) studies are also excluded. If the same sample was used in multiple publications, the most detailed report and/or the largest sample were included. Non-dipper hypertension was defined as less than 10% decrease in either SBP or DBP during night-time record over ambulatory blood pressure monitoring (ABPM). The subjects were diagnosed with normotensive, pre-hypertension, or hypertensive according to the Seventh Report of the Joint National Committee[22]. In the sub-group analysis of EAT with the degree of hypertension, hypertensive patients are classified into three groups according to the grade of hypertension: grade 1 hypertension, grade 2 hypertension, and grade 3 hypertension.

Data Extraction And Quality Assessment

Potentially relevant articles were evaluated by two independent reviewers (JD and XZ) using a standardized form. Data were extracted from the included study, including the sample size, mean and standard deviation (SD). We tried our best to contact the author via email to get the data which was not shown in the article. The methodological quality of all studies was assessed using the Newcastle–Ottawa scale (NOS). A score ranged from 0 to 9, and studies with a score ≥ 7 were considered high quality. Any disagreement between reviewers was discussed and resolved by consensus.

Statistical analysis

STATA package version 12 was used to conduct the meta-analysis. The pooled standard mean difference (SMD) with 95% confidence intervals (CIs) and odds ratio (OR) with 95% CI were calculated using a fixed- or random-effects model according to the heterogeneity among the articles. Heterogeneity was assessed and quantified using the I^2 statistic among the included studies. If the I^2 statistic was ≤ 50%, a fixed-effects model was used to calculate the data. If not, a random-effects model was used. The risk of publication bias was determined by the symmetry of the funnel plot. The significance of the OR and SMD were evaluated with the Z-test. A two-side of P value < 0.05 was considered significant.

Repeated significance testing of cumulative data increases the overall risk of type I errors in a conventional meta-analysis. However, trial sequential analysis (TSA) can reduce the risk of type I errors and adjust the 95% CI of the SMD with the O'Brien-Fleming α-spending function. Moreover, TSA can estimate the required information size (RIS) to achieve preset levels of power, construct a monitoring boundary, and calculate futility in a cumulative meta-analysis. The RIS with the boundary infers whether further trials are needed. We conducted a TSA with a 5% risk of a type I error, as well as the α-spending adjusted 95% CI for repetitive significance testing. TSA was used in our meta-analysis to determine whether the evidence was reliable and conclusive.

Results

Characteristics of the included studies

This study followed the protocols specified in the PRISMA statement, and PRISMA checklist was shown in supplement 1 file. A total of 794 studies initially identified after searching the database of PubMed, Embase, and the Cochrane. 47 observational studies matched our eligibility criteria and 39 remained after exclusion for reasons: non-English(n = 1), reported the studies from the same original database (n = 2), secondary hypertension (n = 2), comprised insufficient data (n = 3). A flowchart of the study selection was shown in Fig. 1. The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the articles, and these studies were assessed as high-quality publications (median: 8; 25th and 75th percentile: 7 and 9). Accordingly, A total of 8,983 subjects were included in this study. There were 18 studies comparing EAT thickness and/or volume between EH patients and normotensive subjects[11–14,16–18,21,23–32], including 13

studies reported EAT-t, 3 studies reported EAT-v, and 2 articles reported both EAT-t and EAT-v between the two groups. There were 16 studies dividing the subjects (including hypertensive and normotensive subjects) into two groups according to EAT thickness or volume[14,33–47]. Seven studies compared the difference of EAT between non-dipper and dipper hypertension[13,18,27,32,48–50]. Two studies investigated the association of EAT-t with the grade of hypertension[12,30]. Additionally, four studies reported the association of cardiac remodeling and function with EAT[15,26,51,52],and three studies provided data addressing the association of ASCVD with EAT in hypertensive patients[15,28,53].

The association of epicardial adipose tissue thickness and volume with essential hypertension

There were 18 studies compared the EAT-t and EAT-v between 3258 hypertensive patients and 1928 normotensive controls. We performed a meta-analysis of comparing EAT-t and EAT-v between hypertensive and normotensive, and the results showed that both EAT-t (EAT-t: SMD = 0.64, 95% CI: 0.44–0.83, p < 0.001; Fig. 2A) and EAT-v (EAT-v: SMD: 0.69, 95% CI:0.34 − 0.1.05, p < 0.001; Fig. 2A) were significantly increased in hypertensive compared to those in normotensive. TSA showed that the cumulative z-curve crossed the boundary for futility (TSA adjusted 95% CI: 0.72–1.55; p < 0.001; Fig. 2B) and a definite conclusion can be drawn. A total of 4795 subjects (normotensive subjects and hypertensive patients) were divided into two groups according to EAT thickness or volume in sixteen studies, and we investigated the association of EAT-t and EAT-v with hypertension. The meta-analysis indicated that EAT-t (OR: 1.59, 95% CI: 1.09–2.33, P < 0.001; Fig. 3A) and EAT-v (OR: 1.82, 95% CI: 1.33–2.19, P < 0.001; Fig. 3A) were strongly associated with the occurrence of EH. The TSA confirmed that the results were reliable (TSA-adjusted 95% CI: 1.31–2.21; p < 0.001; Fig. 3B).

Comparison of the epicardial adipose tissue thickness and volume between dipper and non-dipper hypertension

Six studies compared the EAT-t and one study compared the EAT-v between dipper and non-dipper hypertension. We performed a meta-analysis to compare EAT-t and EAT-v between dipper and non-dipper hypertension. The results showed that both EAT-t (SMD = 0.85, 95% CI = 0.49 − 0.1.21, p < 0.001; Fig. 4) and EAT-v (SMD = 0.83, 95% CI = 0.31–1.34, p = 0.002; Fig. 4) were increased in non-dipper hypertensive patients than those in dipper hypertensive patients.

Comparison of the epicardial adipose tissue thickness among the grades of hypertension

Two studies compared the epicardial adipose tissue thickness among the patients with different grades of hypertension. We performed a meta-analysis to compare EAT-t between grade 1 and grade 2 hypertension and between grade 2 and grade 3 hypertension. However, there was no significant differences in EAT-t among the patients with different grades of essential hypertension (grade 1 to grade 2: SMD = 0.23, 95% CI=-0.13-0.59, p = 0.211; grade 2 to grade 3: SMD = 0.09, 95% CI=-0.15-0.33, p = 0.452; Fig. 5).

The association of epicardial adipose tissue with arteriosclerotic cardiovascular disease and cardiac morphology and function in hypertensive patients

We also investigate the association of EAT with the complication in EH. We compare the EAT-t in EH patients with normal and abnormal cardiac morphology. Higher mean of EAT-t (SMD = 0.85, 95% CI = 0.71–0.99, $p < 0.001$; Fig. 6A) was found in patients with cardiac hypertrophy and dysfunction than that in patients with normal cardiac morphology and function. Additionally, we also compared the EAT in EH patients with and without arteriosclerotic cardiovascular disease (ASCVD), and the results showed that EAT-t (SMD = 0.37, 95% CI = 0.23–0.52, $p < 0.025$; Fig. 6B) was increased in hypertensive patients with ASCVD than those without.

Heterogeneity And Publication Bias

There were significant differences in EAT thickness and volume mean values among individual studies ($I^2 = 86\%$, $p < 0.001$). Similarly, we found significant differences in the association of EAT with essential hypertension among individual studies ($I^2 = 70.4\%$, $p < 0.001$). Therefore, a random-effects model was used to analyze the data. Publication bias about the mean of EAT between essential hypertension and controls were assessed and shown in Fig. 7A. The publication bias reporting the association of EAT with essential hypertension were determined and shown in Fig. 7B. The results showed that there was no significant publication bias.

Discussion

This meta-analysis indicated that hypertensive patients have higher thickness and larger volume of EAT than that in normotensive individuals, and the increase of EAT accumulation was related to the occurrence of EH. The TSA confirmed that the available samples were sufficient and a definite conclusion can be drawn. Additionally, the increase of EAT was associated with impaired circadian blood pressure patterns, but not with the grades of essential hypertension. Interestingly, higher means of EAT-t and EAT-v were found in EH patients with the complications (including cardiac hypertrophy and dysfunction and arteriosclerotic cardiovascular disease) than those without.

EH often leads to coronary heart disease, stroke, congestive heart failure, and peripheral vascular disease[54]. However, the pathogenesis of EH has not been fully elucidated. Human EAT has recently been recognized as a metabolically active organ, which can secret free fatty acid, adiponectin, and pro- and anti-inflammatory cytokines[8]. Thus, EAT seems critical for the homeostasis, function, and diseases of the heart, which has been recognized as a new risk for essential hypertension. Donatas et. al reported that EAT volume is an independent risk factor for essential hypertension and can be used to identify hypertensive after adjusting for age, BMI, and dyslipidemia[12]. However, there is controversy over the association of EAT with the occurrence of essential hypertension. Other studies didn't find differences in EAT thickness or volume between hypertensive patients and normotensive individuals[21].

We performed the meta-analysis and found a relation between EAT and EH. In addition, we also found the EAT-t and EAT-v were increased in non-dipper hypertensive patients than those in dipper. However, the mechanisms of EAT lead to high blood pressure are still unclear. The increase of EAT may result in increased secretion of numerous pro-inflammatory mediators and vasoactive peptides, including fatty acid transport protein (FATP), interleukin (IL) -6, macrophage chemotactic factor-1(MCP-1) and CD36 [55–57]. These molecules can create an inflammatory environment and activate the renin-angiotensin system, which may increase arterial blood pressure. Additionally, EAT was positively correlated with indices of insulin resistance and glucose intolerance, which may lead to high blood pressure by affecting insulin resistance and glucose tolerance[58]. Finally, secretion of free fatty acids by EAT may excessively activate cardiac autonomic nervous system and subsequently increase arterial blood pressure[59]. The activation of cardiac autonomic nervous system may also associate with impaired circadian blood pressure patterns.

There is significant difference in EAT thickness in the normotensive individuals, prehypertensive and hypertensive groups after adjustment for confounding factors including age, gender, high-density lipoprotein, waist circumference, and body mass index[24]. Patients with higher degrees of hypertension showed the potential of increased EAT thickness[12]. Therefore, we assessed the association of EAT accumulation with the degree of hypertension. However, we didn't find the relation between EAT and the grades of essential hypertension, which may be due to limited studies. More studies are needed to investigate the association between EAT accumulation and the degree of essential hypertension.

Previous studies have reported a strong association of increased EAT with heart failure, myocardial infarction and peripheral atherosclerosis[10]. The occurrence of hypertension accompanied by the increase of EAT accumulation have been demonstrated in this study. Furthermore, we also found that EAT were associated with arteriosclerotic cardiovascular disease (ASCVD) and cardiac hypertrophy and dysfunction in hypertensive patients. Mayumi et al. constructed the adipose tissue-cardiomyocyte coculture model and suggested that EAT may be related to the lipotoxic of cardiomyocytes via unknown factors plus fatty acid transport protein (FATP) and CD36[57]. The increase of EAT accumulation may result in more pro-inflammatory and lipotoxic cytokines secretion, which can directly diffuse into the myocardium and lead to myocardial hypertrophy and cardiac dysfunction[60]. In addition, the plasma proatherogenic cytokines (IL-6, MCP-1, CD36, FATP-4) secreted by EAT might damage the vascular structure and promote coronary and peripheral atherosclerosis[61]. EAT thickness can be easily measured by echocardiography with a non-invasive way, which might be used as cardiovascular risk stratification in hypertensive patients. Though the mechanisms of EAT on cardiac dysfunction and atherosclerosis are not clear enough, the hypertensive patients with more EAT accumulation may need more intensive cardiovascular follow-up.

Strengths And Limitations

The present work has its own advantages. First, this is the first meta-analysis to investigate the association of EAT with EH. Second, the present work comprehensively evaluates the association of EAT

with EH, including circadian blood pressure patterns, degree of hypertension, and complications. Third, high quality studies and a large sample size are included in this meta-analysis. However, the this work also has its limitations. First, the study only analyzes the relation between EAT and hypertension without considering other possible biological factors including age, BMI, insulin resistance and lipidemia. Second, there were limited number of studies comparing EAT-t among different degree of hypertensive patents.

Conclusion

In summary, our meta-analysis demonstrated that EAT ectopic deposition was associated with the occurrence and complications of EH. The role of EAT in the pathogenesis of EH is in the exploratory stage, and the potential mechanism needs to be investigated in detail research.

Declarations

Author Contributions: Conceptualization: XZ and BL; Methodology: XZ, BL and YL; Collecting and analyzing the data: BL, XZ and YL; Writing, reviewing & editing the draft: XZ, QS and BL.

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References

1. Amberbir A, et al. Systematic Review of Hypertension and Diabetes Burden, Risk Factors, and Interventions for Prevention and Control in Malawi: The NCD BRITE Consortium. Global heart. 2019;14:109–18. doi:10.1016/j.gheart.2019.05.001.
2. Katsanos AH, et al. Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials. Hypertension. 2017;69:171–9. doi:10.1161/hypertensionaha.116.08485.
3. Lee HA, Park H. Diet-Related Risk Factors for Incident Hypertension During an 11-Year Follow-Up: The Korean Genome Epidemiology Study. Nutrients 10, doi:10.3390/nu10081077 (2018).
4. Kusters YH, et al. Independent tissue contributors to obesity-associated insulin resistance. JCI insight 2, doi:10.1172/jci.insight.89695 (2017).
5. Bochaliya RK, Sharma A, Saxena P, Ramchandani GD, Mathur G. To Evaluate the Association of Neck Circumference with Metabolic Syndrome and Cardiovascular Risk Factors. J Assoc Phys India. 2019;67:60–2.
6. Malden D, et al. Body Fat Distribution and Systolic Blood Pressure in 10,000 Adults with Whole-Body Imaging: UK Biobank and Oxford BioBank. Obesity. 2019;27:1200–6. doi:10.1002/oby.22509.

7. Chen Y, Liang X, Zheng S, Wang Y, Lu W. Association of Body Fat Mass and Fat Distribution With the Incidence of Hypertension in a Population-Based Chinese Cohort: A 22-Year Follow-Up. Journal of the American Heart Association 7, doi:10.1161/jaha.117.007153 (2018).
8. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab. 2011;22:450–7. doi:10.1016/j.tem.2011.07.003.
9. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. Obesity reviews: an official journal of the International Association for the Study of Obesity. 2007;8:253–61. doi:10.1111/j.1467-789X.2006.00293.x.
10. Berg G, Miksztowicz V, Morales C, Barchuk M. Epicardial Adipose Tissue in Cardiovascular Disease. Adv Exp Med Biol. 2019;1127:131–43. doi:10.1007/978-3-030-11488-6_9.
11. Erdogan G, et al. Assessment of epicardial adipose tissue thickness in patients with resistant hypertension. Blood pressure monitoring. 2016;21:16–20. doi:10.1097/mbp.0000000000000149.
12. Austys D, et al. Epicardial Adipose Tissue Accumulation and Essential Hypertension in Non-Obese Adults. Medicina 55, doi:10.3390/medicina55080456 (2019).
13. Kim BJ, et al. Epicardial Fat Thickness and Neutrophil to Lymphocyte Ratio are Increased in Non-Dipper Hypertensive Patients. Journal of cardiovascular ultrasound. 2016;24:294–302. doi:10.4250/jcu.2016.24.4.294.
14. Graeff DB, et al. Epicardial fat thickness: distribution and association with diabetes mellitus, hypertension and the metabolic syndrome in the ELSA-Brasil study. Int J Cardiovasc Imaging. 2016;32:563–72. doi:10.1007/s10554-015-0810-z.
15. Korkmaz L, et al. Relation of epicardial adipose tissue with arterial compliance and stiffness in patients with hypertension. Angiology. 2014;65:691–5. doi:10.1177/0003319713502120.
16. Mohammadzadeh M, et al. Assessing the Relation of Epicardial Fat Thickness and Volume, Quantified by 256-Slice Computed Tomography Scan, With Coronary Artery Disease and Cardiovascular Risk Factors. Arch Iran Med. 2018;21:95–100.
17. Kim SA, Kim MN, Shim WJ, Park SM. Epicardial adipose tissue is related to cardiac function in elderly women, but not in men. Nutrition metabolism cardiovascular diseases: NMCD. 2017;27:41–7. doi:10.1016/j.numecd.2016.11.001.
18. Kim DJ, et al. Association among epicardial fat, heart rate recovery and circadian blood pressure variability in patients with hypertension. Clinical hypertension. 2015;21:24. doi:10.1186/s40885-015-0034-5.
19. Karoli R, et al. Assessment of noninvasive risk markers of subclinical atherosclerosis in premenopausal women with previous history of gestational diabetes mellitus. Heart views: the official journal of the Gulf Heart Association. 2015;16:13–8. doi:10.4103/1995-705x.152995.
20. Iacobellis G, et al. Epicardial Fat Thickness and Primary Aldosteronism. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme* **48**, 238–241, doi:10.1055/s-0035-1559769 (2016).

21. Shim IK, Cho KI, Kim HS, Heo JH, Cha TJ. Impact of Gender on the Association of Epicardial Fat Thickness, Obesity, and Circadian Blood Pressure Pattern in Hypertensive Patients. *Journal of diabetes research* 2015, 924539, doi:10.1155/2015/924539 (2015).
22. Chobanian AV, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension (Dallas, Tex.*: 1979) **42**, 1206–1252, doi:10.1161/01.HYP.0000107251.49515.c2 (2003).
23. Dicker D, Atar E, Kornowski R, Bachar GN. Increased epicardial adipose tissue thickness as a predictor for hypertension: a cross-sectional observational study. J Clin Hypertens (Greenwich). 2013;15:893–8. doi:10.1111/jch.12201.
24. Sironi AM, et al. Early hypertension is associated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat. Hypertension. 2008;51:282–8. doi:10.1161/hypertensionaha.107.098640.
25. Hell MM, et al. Epicardial adipose tissue volume but not density is an independent predictor for myocardial ischemia. J Cardiovasc Comput Tomogr. 2016;10:141–9. doi:10.1016/j.jcct.2016.01.009.
26. Seker T, Turkoglu C, Harbalioglu H, Gur M. Epicardial Fat Thickness is Associated with Abnormal Left Ventricle Geometry in Newly Diagnosed Hypertension. Acta Cardiologica Sinica. 2018;34:280–7. doi:10.6515/acs.201805_34(3).20171209a.
27. Ertas F, et al. Increased echocardiographic epicardial fat thickness is related to impaired diurnal blood pressure profiles. Blood pressure. 2012;21:202–8. doi:10.3109/08037051.2011.649538.
28. Homsi R, et al. Interrelations of Epicardial Fat Volume, Left Ventricular T1-Relaxation Times and Myocardial Strain in Hypertensive Patients: A Cardiac Magnetic Resonance Study. J Thorac Imaging. 2017;32:169–75. doi:10.1097/rti.0000000000000264.
29. Chang S, Lee W, Kwag B, Chung YH, Kang IS. Maximal pericoronary adipose tissue thickness is associated with hypertension in nonobese patients with acute or chronic illness. Korean J Intern Med. 2017;32:668–74. doi:10.3904/kjim.2016.118.
30. Haberka M, et al. Obesity, Visceral Fat, and Hypertension-Related Complications. Metab Syndr Relat Disord, doi:10.1089/met.2018.0062 (2018).
31. Turak O, et al. [Relation between epicardial adipose tissue thickness and blood pressure levels in prehypertension]. Turk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir. 2014;42:358–64. doi:10.5543/tkda.2014.35477.
32. Derya MA, Demir V, Ede H. Relationship between neutrophil/lymphocyte ratio and epicardial fat tissue thickness in patients with newly diagnosed hypertension. J Int Med Res. 2018;46:940–50. doi:10.1177/0300060517749130.
33. Lu C, Jia H, Wang Z. Association between epicardial adipose tissue and adverse outcomes in coronary heart disease patients with percutaneous coronary intervention. Bioscience reports 39, doi:10.1042/bsr20182278 (2019).
34. Sato F, et al. Association of Epicardial, Visceral, and Subcutaneous Fat With Cardiometabolic Diseases. Circulation journal: official journal of the Japanese Circulation Society. 2018;82:502–8.

doi:10.1253/circj.CJ-17-0820.

35. et al. Association of systemic inflammation with epicardial fat and coronary artery calcification.*Inflammation research: official journal of the European Histamine Research Society… et al.]* **64**, 313–319, doi:10.1007/s00011-015-0809-x (2015).
36. Sarin S, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. The American journal of cardiology. 2008;102:767–71. doi:10.1016/j.amjcard.2008.04.058.
37. Nabati M, Favaedi M, Kheirgoo M, Yazdani J, Dabirian M. Correlation between epicardial fat thickness and aortic valve sclerosis. Asian Cardiovasc Thorac Ann. 2018;26:188–95. doi:10.1177/0218492318760692.
38. Fracanzani AL, et al. Epicardial Adipose Tissue (EAT) Thickness Is Associated with Cardiovascular and Liver Damage in Nonalcoholic Fatty Liver Disease. PloS one. 2016;11:e0162473. doi:10.1371/journal.pone.0162473.
39. Nasri A, Najafian J, Derakhshandeh SM, Madjlesi F. Epicardial fat thickness and severity of coronary heart disease in patients with diabetes mellitus type II. ARYA atherosclerosis. 2018;14:32–7. doi:10.22122/arya.v14i1.1552.
40. Borekci A, et al. Epicardial fat thickness in stable coronary artery disease: its relationship with high-sensitive cardiac troponin T and N-terminal pro-brain natriuretic peptide. Coron Artery Dis. 2014;25:685–90. doi:10.1097/mca.0000000000000140.
41. Vural M, et al. Evaluation of the relationship between epicardial fat volume and left ventricular diastolic dysfunction. Japanese journal of radiology. 2014;32:331–9. doi:10.1007/s11604-014-0310-4.
42. Hajsadeghi F, et al. Increased epicardial adipose tissue is associated with coronary artery disease and major adverse cardiovascular events. Atherosclerosis. 2014;237:486–9. doi:10.1016/j.atherosclerosis.2014.09.037.
43. Ertem AG, et al. Is there a relationship between serum paraoxonase level and epicardial fat tissue thickness? *Anadolu kardiyoloji dergisi: AKD = the*. Anatolian journal of cardiology. 2014;14:115–20. doi:10.5152/akd.2014.4742.
44. Tran KV, et al. Micro-RNAs Are Related to Epicardial Adipose Tissue in Participants With Atrial Fibrillation: Data From the MiRhythm Study. Frontiers in cardiovascular medicine. 2019;6:115. doi:10.3389/fcvm.2019.00115.
45. Hachiya K, et al. Relation of epicardial fat to central aortic pressure and left ventricular diastolic function in patients with known or suspected coronary artery disease. Int J Cardiovasc Imaging. 2014;30:1393–8. doi:10.1007/s10554-014-0472-2.
46. Biere L, et al. Relation of Quantity of Subepicardial Adipose Tissue to Infarct Size in Patients With ST-Elevation Myocardial Infarction. The American journal of cardiology. 2017;119:1972–8. doi:10.1016/j.amjcard.2017.03.024.

47. Albuquerque FN, et al. Usefulness of epicardial adipose tissue as predictor of cardiovascular events in patients with coronary artery disease. The American journal of cardiology. 2012;110:1100–5. doi:10.1016/j.amjcard.2012.06.003.
48. Zhou L, et al Epicardial adipose tissue volume a diagnostic study for independent predicting disorder of circadian rhythm of blood pressure in patients with essential hypertension. *Cellular and molecular biology (Noisy-le-Grand, France)* **62**, 1–7 (2016).
49. Sengul C, et al. Epicardial fat thickness is associated with non-dipper blood pressure pattern in patients with essential hypertension. *Clinical and experimental hypertension (New York, N.Y.: 1993)* **34**, 165–170, doi:10.3109/10641963.2011.577488 (2012).
50. Bakirci EM, et al. New inflammatory markers for prediction of non-dipper blood pressure pattern in patients with essential hypertension: Serum YKL-40/Chitinase 3-like protein 1 levels and echocardiographic epicardial adipose tissue thickness. *Clinical and experimental hypertension (New York, N.Y.*: 1993) **37**, 505–510, doi:10.3109/10641963.2015.1013122 (2015).
51. Borekci A, et al. Epicardial fat thickness as associated with left ventricular myocardial performance in patients with newly diagnosed hypertension. Turk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir. 2015;43:705–13. doi:10.5543/tkda.2015.95902.
52. Turak O, et al. Increased echocardiographic epicardial fat thickness and high-sensitivity CRP level indicate diastolic dysfunction in patients with newly diagnosed essential hypertension. Blood pressure monitoring. 2013;18:259–64. doi:10.1097/MBP.0b013e3283651d19.
53. Pierdomenico SD, et al. Prediction of carotid plaques in hypertensive patients by risk factors, left ventricular hypertrophy, and epicardial adipose tissue thickness. Heart vessels. 2013;28:277–83. doi:10.1007/s00380-012-0240-y.
54. Sorrentino MJ. The Evolution from Hypertension to Heart Failure. Heart Fail Clin. 2019;15:447–53. doi:10.1016/j.hfc.2019.06.005.
55. Mazurek T, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003;108:2460–6. doi:10.1161/01.cir.0000099542.57313.c5.
56. Fosshaug LE, et al. Altered Levels of Fatty Acids and Inflammatory and Metabolic Mediators in Epicardial Adipose Tissue in Patients With Systolic Heart Failure. J Card Fail. 2015;21:916–23. doi:10.1016/j.cardfail.2015.07.014.
57. Anan M, et al. A promising culture model for analyzing the interaction between adipose tissue and cardiomyocytes. Endocrinology. 2011;152:1599–605. doi:10.1210/en.2010-1106.
58. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab. 2005;90:6300–2. doi:10.1210/jc.2005-1087.
59. Paolisso G, et al. Elevated plasma fatty acid concentrations stimulate the cardiac autonomic nervous system in healthy subjects. Am J Clin Nutr. 2000;72:723–30. doi:10.1093/ajcn/72.3.723.
60. Erdogan T, et al. Epicardial adipose tissue is independently associated with increased left ventricular mass in untreated hypertensive patients: an observational study. Anadolu kardiyoloji dergisi: AKD = the Anatolian journal of cardiology. 2013;13:320–7. doi:10.5152/akd.2013.099.

61. Domienik-Karlowicz J, et al. Emerging measurements of atherosclerosis: extra-media thickness, epicardial adipose tissue, and periarterial adipose tissue intima media adventitia index in morbidly obese patients undergoing bariatric surgery. Wideochirurgia i inne techniki maloinwazyjne = Videosurgery other miniinvasive techniques. 2019;14:249–54. doi:10.5114/wiitm.2019.84678.

Supplementary

Supplemental Files 1 and 2 are not available with this version.

Figures

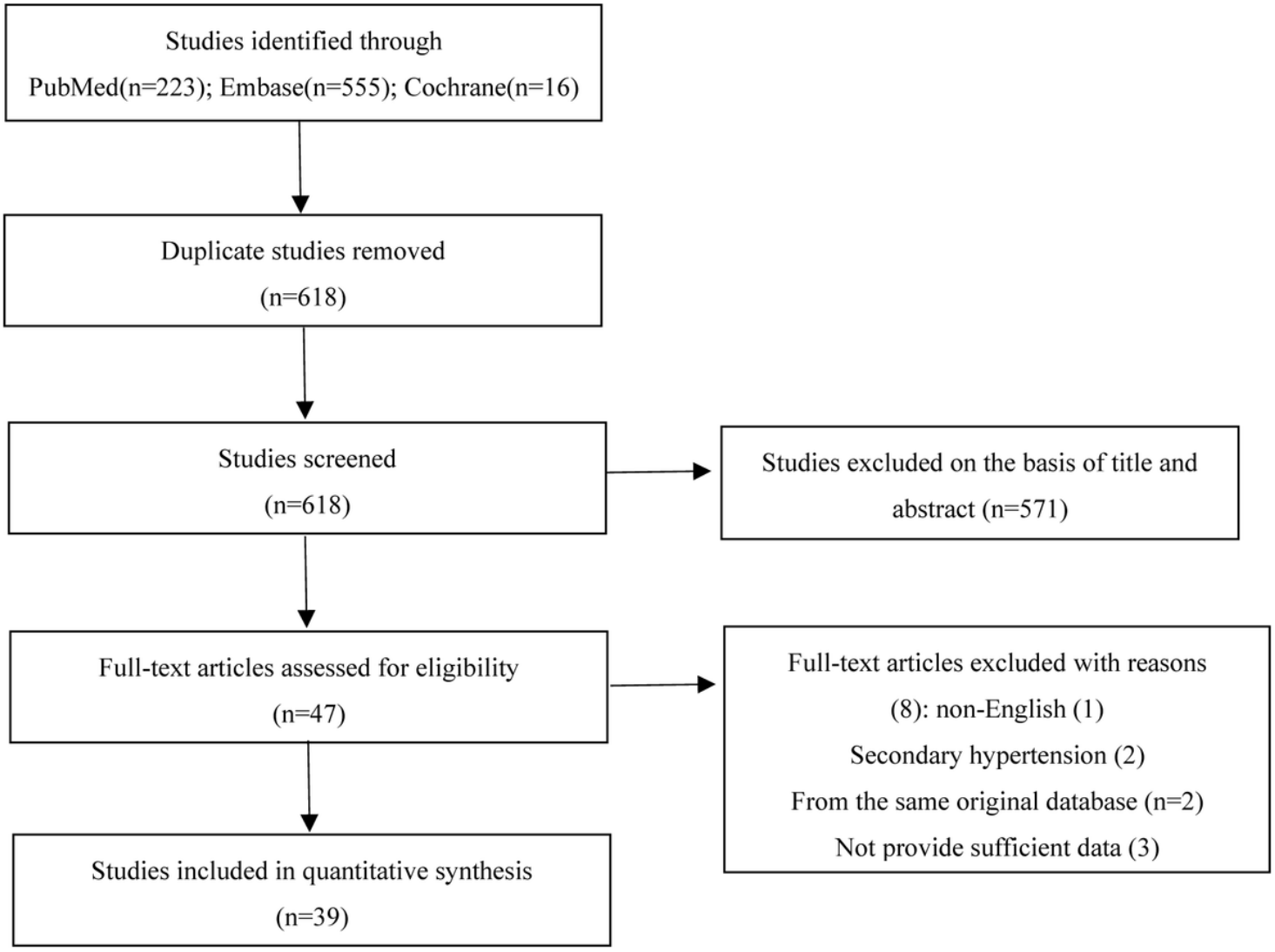

Figure 1

Flowchart of the study selection

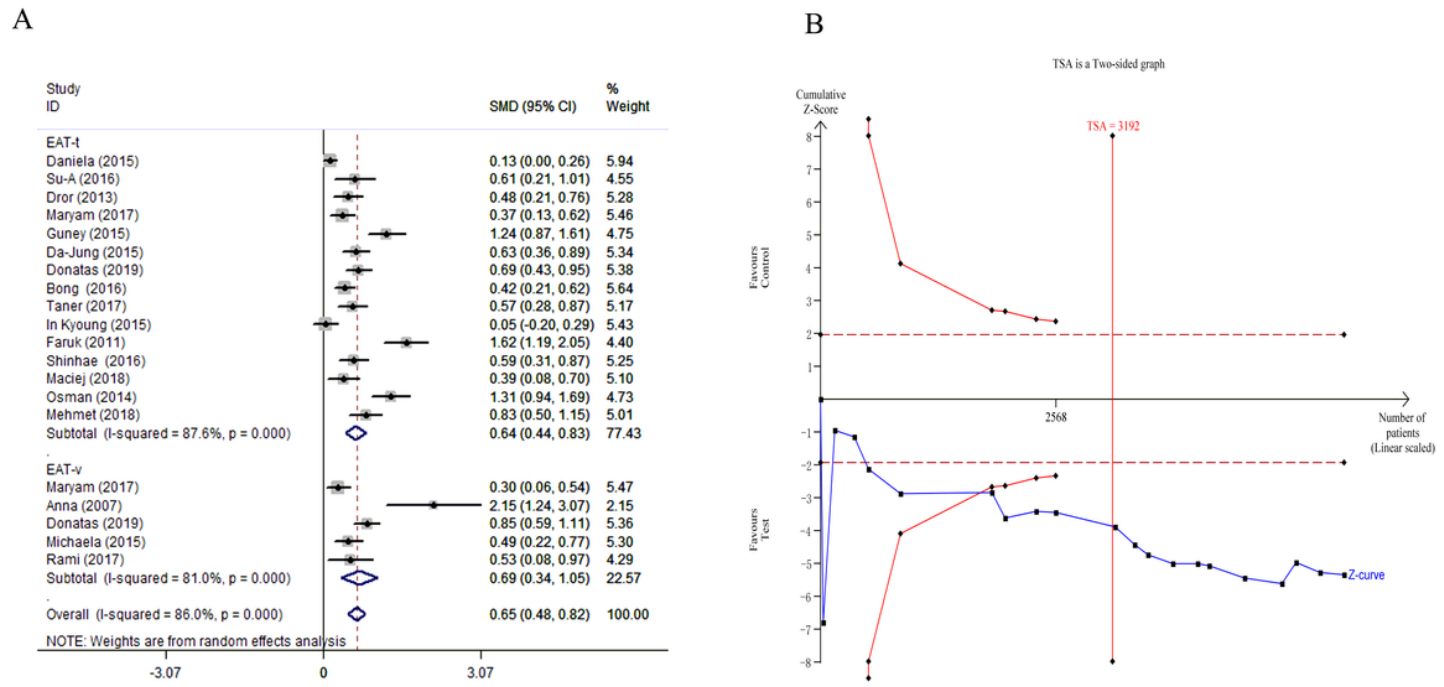

Figure 2

Comparison of the epicardial EAT-t and EAT-v between essential hypertensive (EH) patients and normotensive individuals. (A) Meta–analysis; (B) trial sequential analysis. EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume

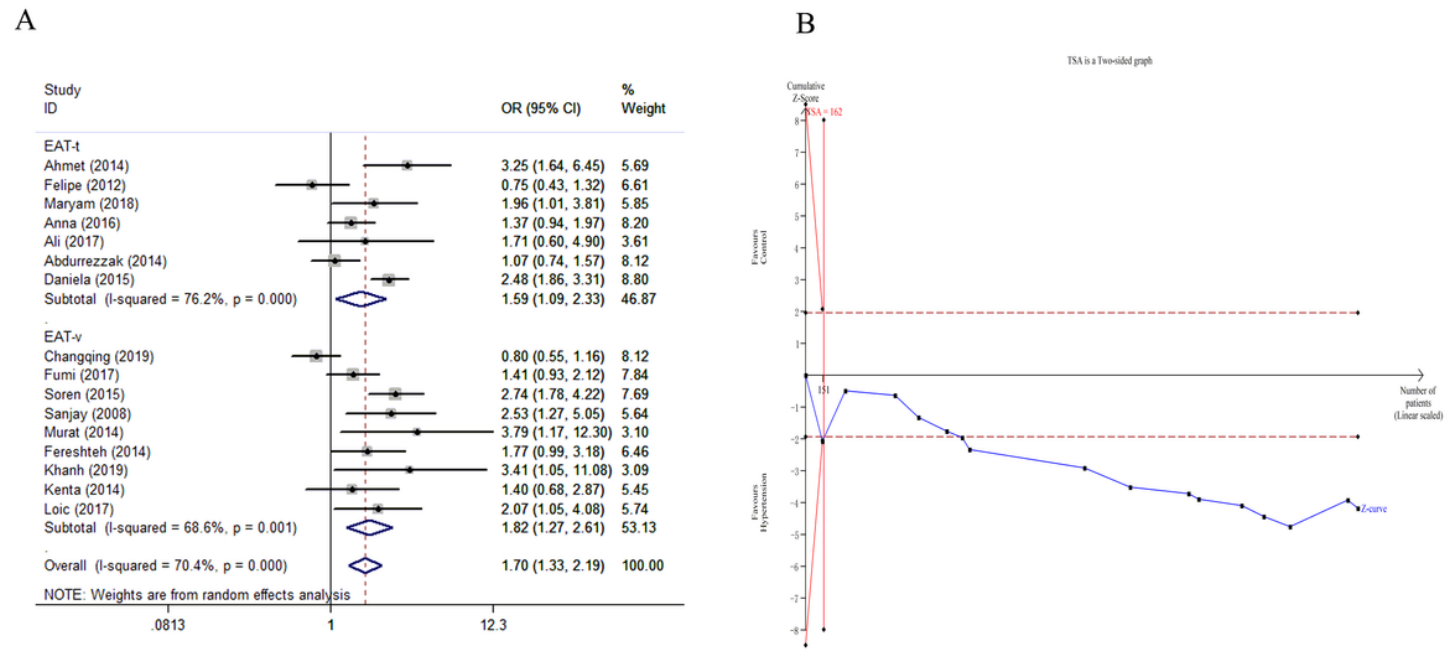

Figure 3

Analyzing the association of EAT-t and EAT-v with the occurrence of essential hypertension (EH). (A) Meta–analysis; (B) trial sequential analysis. EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial

adipose tissue volume

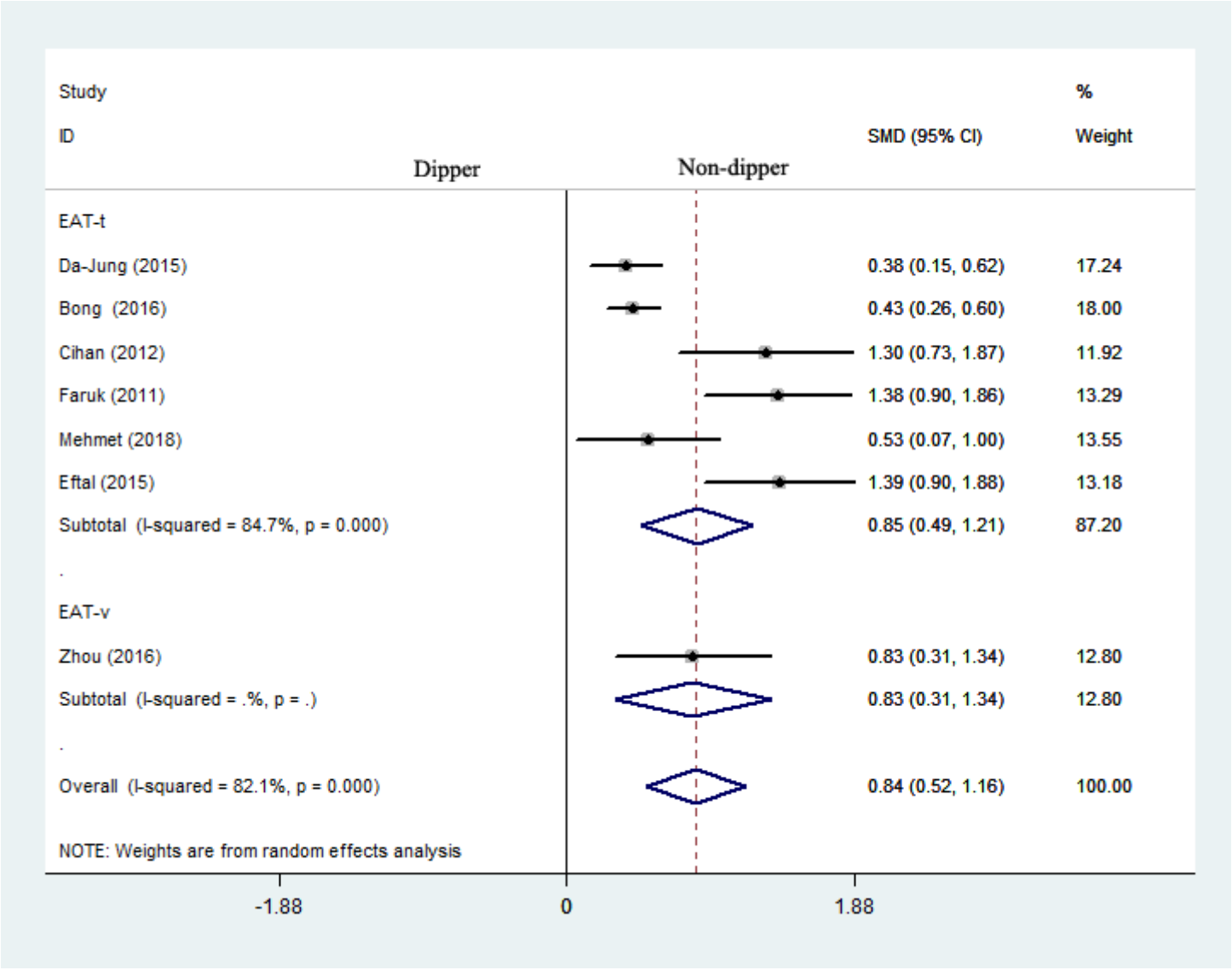

Figure 4

Meta–analysis comparison of the EAT-t and EAT-v between dipper and non-dipper subgroups in patients with essential hypertension (EH). EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume

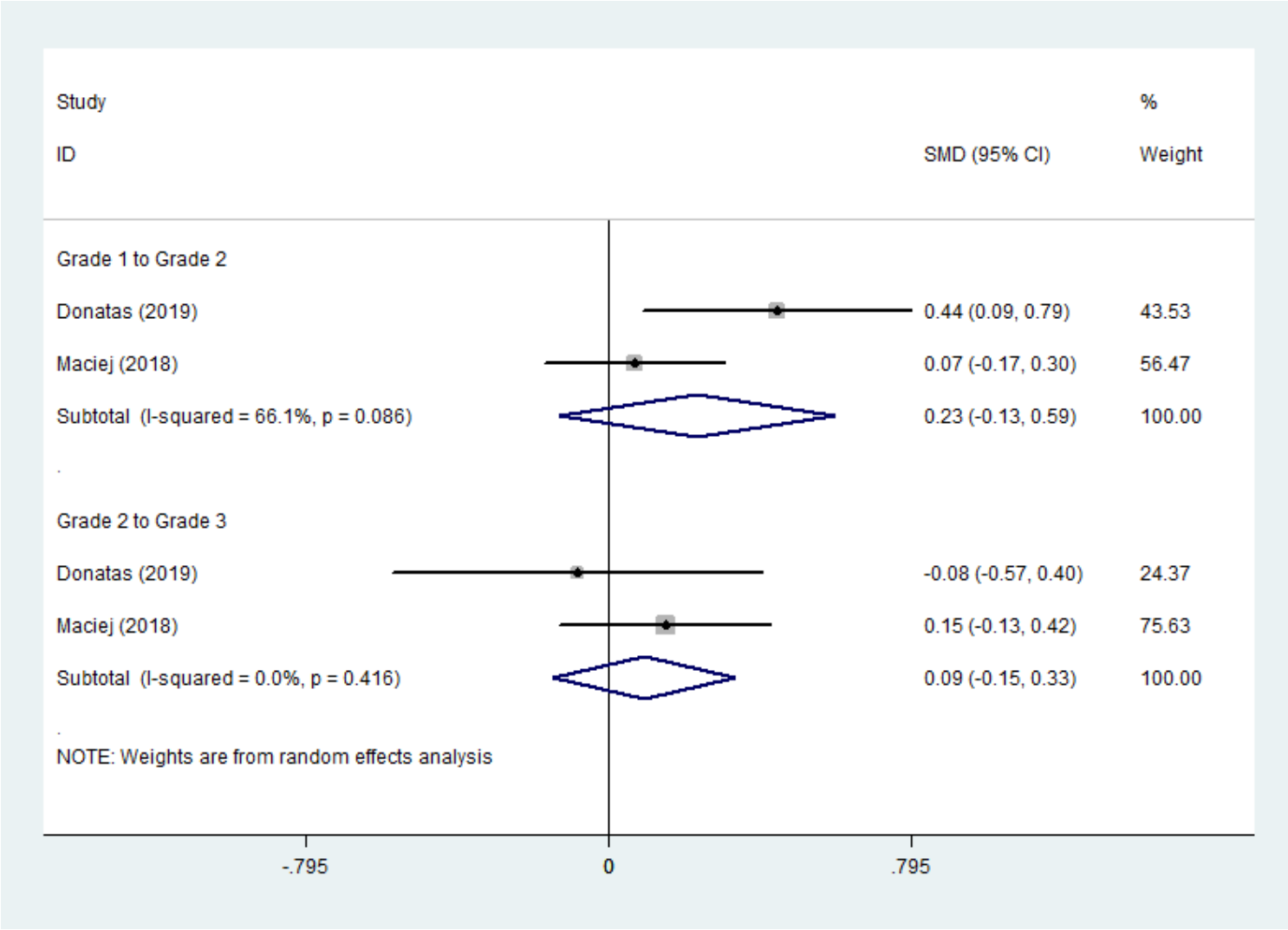

Figure 5

Meta-analysis comparing the EAT-t among the grade 1, grade 2 and grade 3 essential hypertension (EH) subgroups. EAT-t, epicardial adipose tissue thickness

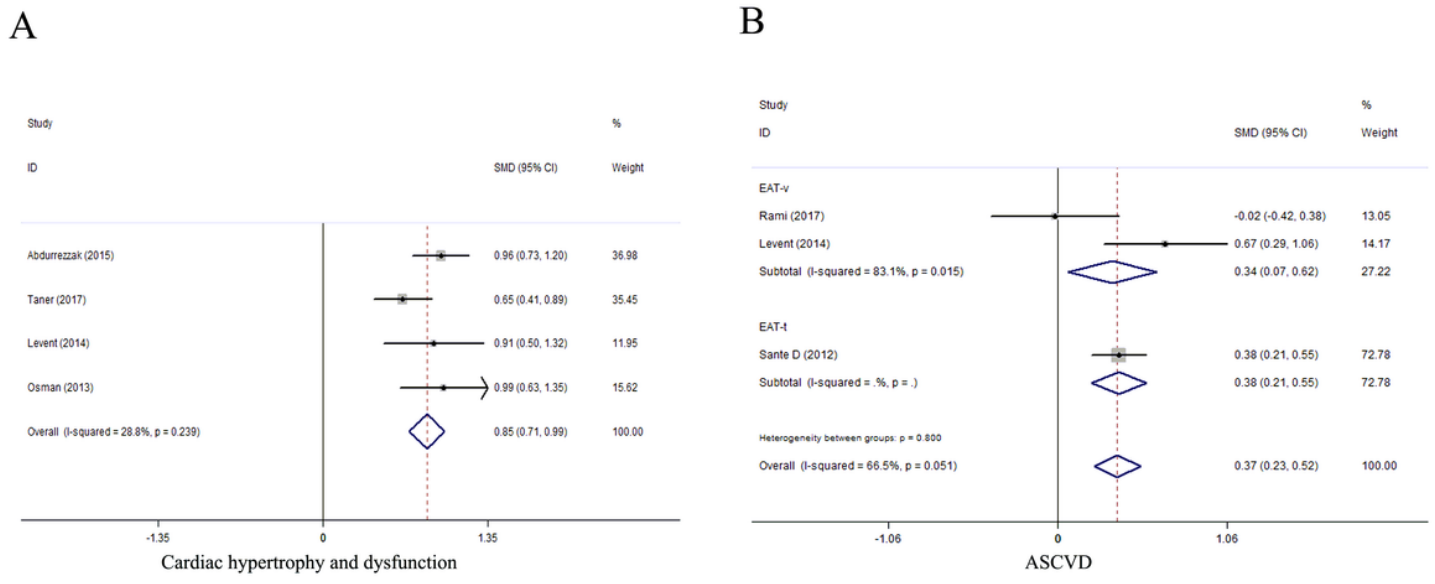

Figure 6

(A) Meta–analysis comparing the EAT-t and EAT-v between in essential hypertensive patients (EH) with normal and abnormal cardiac structure and function. (B) Meta–analysis comparing the EAT-t between essential hypertensive (EH) patients with and without arteriosclerotic cardiovascular disease. EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume

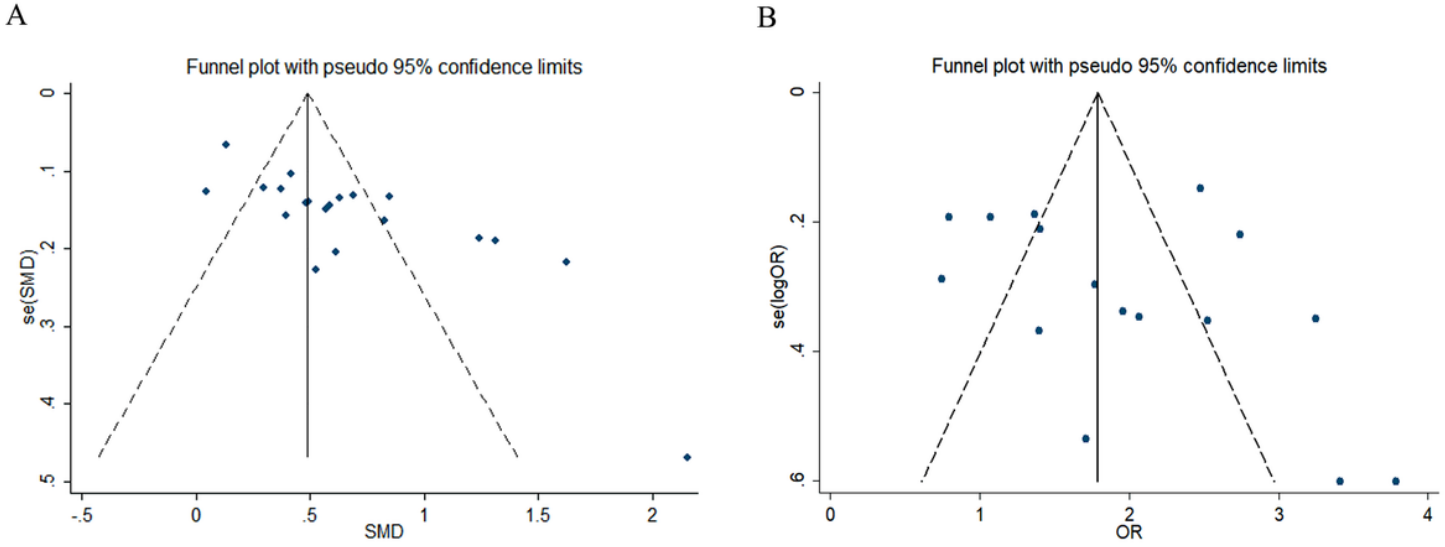

Figure 7

(A) Funnel plot of studies included in bias analysis with regard to the mean of EAT-t and-v between hypertensive patients (EH) and normotensive individuals; (B) Funnel plot of studies included in bias analysis with regard to the association of EAT-t and-v with the occurrence of EH. EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume