Hepatology International (2019) 13:757–765
https://doi.org/10.1007/s12072-019-09972-1

ORIGINAL ARTICLE

Association of epicardial adipose tissue with non-alcoholic fatty liver disease: a meta-analysis

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Received: 19 December 2018 / Accepted: 26 July 2019 / Published online: 20 August 2019

Abstract

Background Increased epicardial adipose tissue (EAT) has been proposed as a risk factor for non-alcoholic fatty liver disease (NAFLD). The aim of this study was to investigate the association of EAT with NAFLD.

Methods The PubMed, EMBASE, and Cochrane databases were systematically reviewed by two independent investigators to identify relevant studies assessing the association of EAT thickness (EAT-t) and volume (EAT-v) with NAFLD. Comparisons between NAFLD subjects and controls were performed with meta-analysis and trial sequential analysis (TSA).

Results A total of thirteen case–control studies ($n = 2260$ patients) were included in the final analysis. The EAT was significantly increased in NAFLD patients compared with the controls (EAT, SMD: 0.73, 95% CI 0.51–0.94, $p < 0.001$; TSA-adjusted 95% CI 0.07–0.18; $p < 0.001$). When comparing the subgroups of NAFLD, the EAT-t in the severe-hepatic steatosis subgroup was thicker than that in the moderate subgroup (SMD: 1.43, 95% CI 0.15–2.71, $p = 0.029$). This study indicated that the EAT-t in the F3–4 fibrosis subgroup was thicker than that in the F0–2 fibrosis subgroup (SMD: 0.72, 95% CI 0.30–1.14, $p = 0.001$). The proportion of hypertension (OR = 1.64, 95% CI = 1.24–2.18, $p = 0.001$) and atherosclerotic cardiovascular disease (ASCVD) (OR = 1.66, 95% CI = 1.21–2.28, $p = 0.002$) was higher in the high-EAT-t group compared with the low-EAT-t group in NAFLD patients.

Conclusions The EAT was increased in the NAFLD subjects compared to the controls. The increase in the EAT was associated with the severity of steatosis, fibrosis and cardiovascular disease in patients with NAFLD. These findings provide new information regarding the development and progression of NAFLD.

Keywords Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Epicardial adipose tissue · Epicardial fat

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and causes a wide spectrum of types of hepatic damage, ranging from simple steatosis to cirrhosis [1, 2]. Abdominal ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI) are the most common methods for the diagnosis of NAFLD, though liver biopsy is the gold standard for the diagnosis of non-alcoholic steatohepatitis (NASH) and cirrhosis. It is estimated that NAFLD affects 25% of the general population [3]. It is predicted that liver cirrhosis and hepatocellular carcinoma caused by NAFLD will be overtaken by viral hepatitis in the future [4]. Therefore, it is important to elucidate the pathogenesis of NAFLD and reduce its occurrence. Previous studies have shown that the incidence of NAFLD is significantly higher in patients with obesity, dyslipidemia, and metabolic syndrome [5] than in healthy individuals, and insulin resistance, oxidative stress and inflammation are involved in the pathogenesis of NAFLD [6].

Epicardial adipose tissue (EAT) is visceral fat that is located between the myocardium and epicardium, and its thickness (EAT-t) can be measured with echocardiography

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12072-019-09972-1) contains supplementary material, which is available to authorized users.

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or its volume (EAT-v) can be measured with CT or MRI [7]. EAT secretes numerous cytokines, including adipocytokines, tumor necrosis factor alpha (TNF-α) and interleukins, which are associated with cardiovascular disease (CVD) and metabolic syndrome [7]. The associations of EAT with coronary artery disease, left ventricular dysfunction, atrial fibrillation, and metabolic syndrome have been demonstrated [8, 9]. NAFLD and EAT are both associated with insulin resistance and metabolic syndrome. Therefore, the relationship between EAT and NAFLD needs to be explored.

Previous studies have investigated the association of EAT-t and EAT-v with NAFLD [10–14]. Several studies reported that the EAT was increased in patients with NAFLD, and the increase of EAT was an independent risk factor for NAFLD [13–16]. However, another study showed no differences in the EAT between NAFLD patients and controls [17]. It remains controversial whether EAT is associated with NAFLD. In addition, it has also been reported that EAT plays a role in the incidence and progression of cardiovascular disease [18]. Therefore, we performed a meta-analysis that aimed to comprehensively evaluate the association of EAT with NAFLD.

Methods

Search strategy

We followed the protocols of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) to conduct the meta-analysis. A systematic search was performed with the following databases: PubMed, EMBASE, and Cochrane. To retrieve all the relevant literature with regard to this topic, we performed a search with the following expressions: [('epicardial adipose tissue') OR ('epicardial fat')] AND [('nonalcoholic fatty liver disease') OR ('nonalcoholic steatohepatitis')]. Only full-text, English language papers were considered for this meta-analysis. The search included literature published until June 16, 2018. The S1 file shows the complete database search strategy.

Inclusion and exclusion criteria

Observational studies investigating the association of NAFLD with EAT-t and EAT-v were considered for this meta-analysis. EAT-t was measured by echocardiography, and EAT-v was measured by CT or MRI. Only adults (> 18 years old) were included, and children were excluded. Abstracts, letters, case reports and studies without sufficient information were excluded. If the same sample was used in multiple publications, the most detailed report and/or the largest sample were included.

Data extraction and quality assessment

Potentially relevant articles were evaluated by two independent reviewers (Bin Liu and Yingrui Li) using a standardized form. Data were extracted from each study, including the sample size and mean ± standard deviation (SD) of the EAT-t or EAT-v. If the numeric data were not presented but were shown in a diagram, the Engauge Digitizer software version 10.9 was used for data extraction [19, 20]. When the median and range were presented in a study, secondary evaluations were conducted to calculate the mean and SD under the assumption of a normal distribution [21]. The methodological quality of all studies was assessed using the Newcastle–Ottawa Scale (NOS). The NOS consists of eight items regarding the quality of a study and mainly includes the study design, participant characteristics, possible biases, statistical evaluation and results. A score was given that ranged from 0 to 9, and studies with scores ≥ 7 were considered of high quality. Any disagreement was discussed and a consensus was reached.

Statistical analysis

We conducted a meta-analysis using the STATA package version 12 and conducted a trial sequential analysis (TSA) using the TSA software version 0.9.5.5 beta. The pooled standard mean difference (SMD) with 95% confidence intervals (CIs) was calculated using a fixed- or random-effects model according to the heterogeneity among the articles. If the I^2 statistic was ≤ 50%, a continuous-weighted fixed-effects model analysis was used. If not, the random-effects model was used. A formula was used when the mean value and standard deviation instead of median and range were needed [21]. Heterogeneity was assessed and quantified using the I^2 statistic among the studies. Meta-regression was used to evaluate the association between EAT and potential biological (age, gender, BMI, dyslipidemia, waist circumference, hypertension, metabolic syndrome, smoking and data sources) factors. The significance of the pooled SMD was evaluated with the Z test. $p < 0.05$ was regarded as significant.

Repeated significance testing of cumulative data increases the overall risk of type I errors in a conventional meta-analysis; however, 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. We searched for clinical studies in PubMed, EMBASE, and the Cochrane database, resulting in 59 records, and 13 observational case–control studies remained after exclusion [10–17, 22–26]. There were 2260 NAFLD subjects and 2280 controls in total. Of the included studies, eleven studies reported the relation between EAT-t and NAFLD, and two studies described the relationship between EAT-v and NAFLD. Five studies investigated the association of EAT-t with the severity of hepatic steatosis in NAFLD; two studies compared the EAT-t between non-NASH and NASH subgroups and between mild and severe liver fibrosis. Additionally, the association of CVD with EAT-t was evaluated in NAFLD patients in two studies. Steatosis was determined by imaging technology or a liver biopsy, and NASH and fibrosis were diagnosed with a liver biopsy. The NOS was used to evaluate the quality of the articles, and the scores showed the high quality of these articles (Table 1). A flowchart of the study selection is shown in Fig. 1. The characteristics of the included patients and controls are listed in Table 1.

Comparison of the epicardial adipose tissue between non-alcoholic fatty liver disease subjects and controls

The comparison of EAT was based on 2053 NAFLD subjects and 2280 healthy controls, and the meta-analysis indicated that EAT in NAFLD subjects significantly increased (SMD = 0.73, 95% CI 0.51–0.94, $p < 0.001$; Fig. 2a) compared to that in the healthy controls. TSA showed that the cumulative z-curve crossed the boundary for futility (TSA-adjusted 95% CI 0.07–0.18; $p < 0.001$; Fig. 2b). We conducted a meta-regression analysis to determine the impact of confounding factors on the results. The regression analysis showed that high-density lipoprotein (HDL) and triglyceride (TG) levels significantly affected EAT, suggesting that HDL ($p = 0.012$, $\text{tau}^2 = 0.089$, Adj R-squared = 49.85%, I^2-res = 86.79%) and TG ($p = 0.041$, $\text{tau}^2 = 0.106$, Adj R-squared = 86.68%, I^2-res = 35.97%) were the sources of heterogeneity. Other potential factors, including age, gender, BMI, hypertension, diabetes and data sources (Eastern or Western), did not have a significant effect on the results. We further assessed the effect of EAT on NAFLD according to the EAT measurement method, and the results showed that there were significant differences in EAT-t and EAT-v between NAFLD subjects and healthy controls (EAT-t: SMD = 0.77, 95% CI 0.53–1.01, $p < 0.001$; EAT-v: SMD: 0.51, 95% CI 0.18–0.83, $p < 0.001$; Fig. 2a).

Table 1 Characteristics of the included studies

Author (year)	Country	EAT-t/v	Control subjects (n); EAT t/v mean (SD)	All NAFLD subjects (n); EAT t/v mean (SD)	NOS score	Imaging system
Didem (2016)	Turkey	EAT-t	41; 0.4 (0.14) cm	37; 0.29 (0.07) cm	7	Echocardiography
Gianluca (2014)	Italy	EAT-t	62; 0.87 (0.10) cm	62; 0.75 (0.15) cm	9	Echocardiography
Yusuf (2011)	Turkey	EAT-t	54; 0.64 (0.13) cm	56; 0.54 (0.10) cm	7	Echocardiography
Anna (2016)	Italy	EAT-t	512; 0.55 (0.27) cm	647; 0.40 (0.29) cm	7	Echocardiography
Stavroula (2016)	Greece	EAT-t	57; 0.34 (0.16) cm	48; 0.34 (0.20) cm	7	Echocardiography
Murat (2014)	Turkey	EAT-t	100; 0.32 (0.06) cm	50;0.26 (0.04) cm	7	Echocardiography
Salvatore (2014)	Italy	EAT-t	–	147; 0.76 (0.25) cm	9	Echocardiography
M. Topuz (2014)	Turkey	EAT-t	71; 0.90 (0.19) cm	34; 0.58 (0.18) cm	7	Echocardiography
Yasar (2012)	Turkey	EAT-t	57; 0.58 (0.18) cm	30; 0.36 (0.17) cm	7	Echocardiography
Byung (2016)	Korea	EAT-t	677; 0.33 (0.10) cm	796; 0.31 (0.09) cm	7	Echocardiography
Kyoung (2017)	Korea	EAT-t	309; 0.66 (0.41) cm	463; 0.45 (0.34) cm	7	Echocardiography
Sharon (2017)	USA	EAT-v	62; 126.5 (80.9) ml	33; 85.4 (44.7) ml	6	CT
Marit (2014)	Finland	EAT-v	51; 808.7 (901.6) ml	24; 489.0 (388.0) ml	7	MRI

EAT, epicardial adipose tissue; EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume; NOS, Newcastle–Ottawa Scale

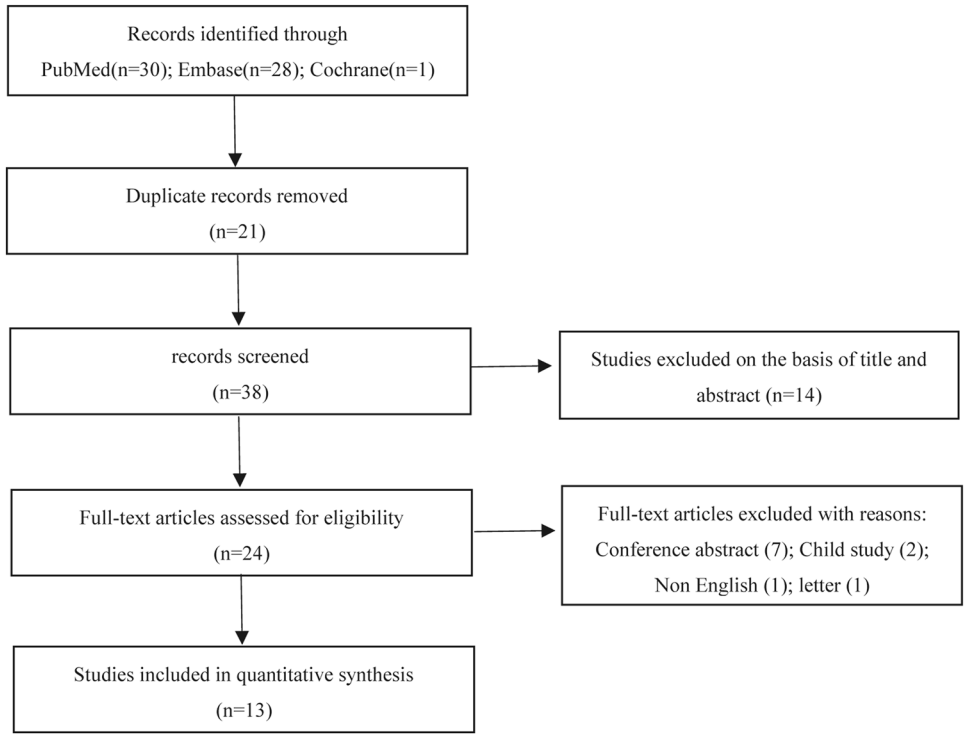

Fig. 1 Flowchart of the study selection

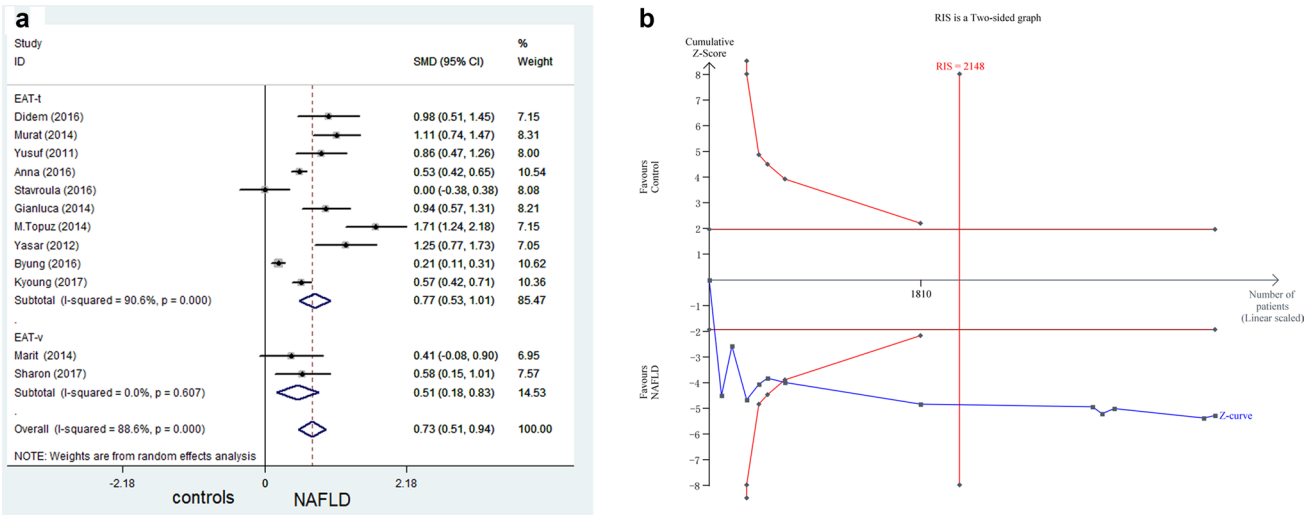

Fig. 2 Comparison of the epicardial adipose tissue between NAFLD subjects and controls. **a** Meta-analysis; **b** trial sequential analysis. EAT-t, epicardial adipose tissue thickness; EAT-v, epicardial adipose tissue volume

Relationship between the severity of liver steatosis and EAT-t

The NAFLD subjects were divided into the mild-, moderate- and severe-steatosis subgroups. We compared the NAFLD subgroups with respect to the controls and found that the EAT-t in the moderate and severe subgroups was significantly higher compared to that in the controls ((SMD: 1.00, 95% CI 0.49–1.51, $p < 0.001$); (SMD: 1.79, 95% CI 0.43–3.15, $p = 0.01$) for moderate and severe NAFLD, respectively) (Fig. 3), but no significant difference was found between the mild subgroup and controls (SMD: 0.71, 95% CI −0.14–1.55, $p = 0.101$; Fig. 3). When comparing the EAT-t among the subgroups of NAFLD, there was a significant SMD between the severe and moderate subtypes (SMD:1.43, 95% CI 0.15–2.71, $p = 0.029$;

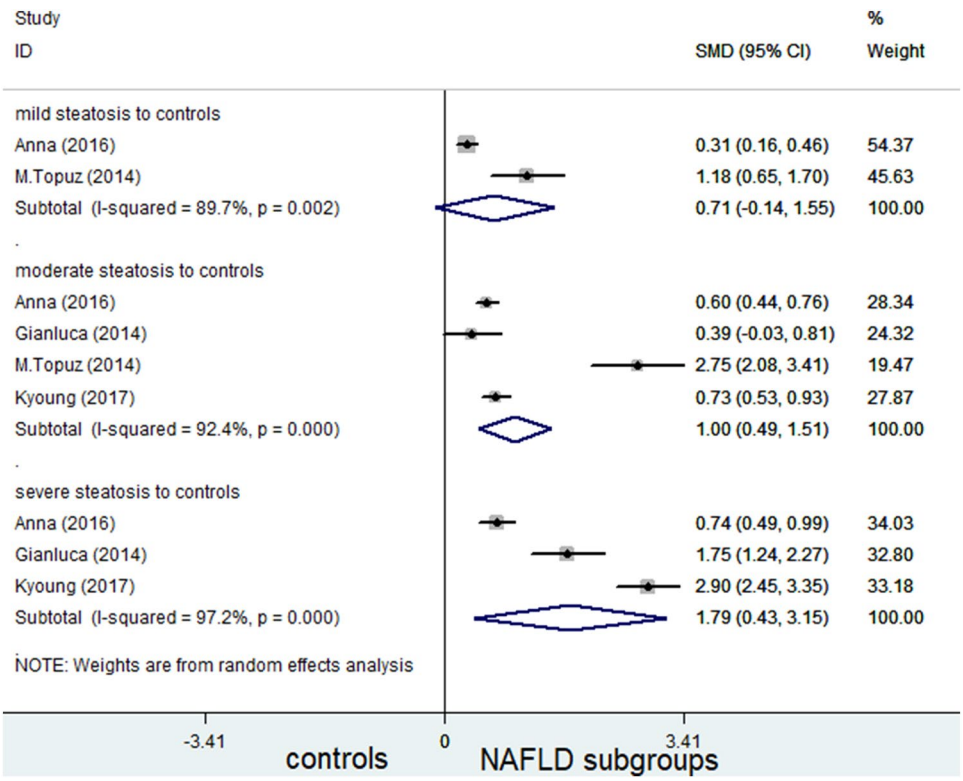

Fig. 3 Meta-analysis comparing the epicardial adipose tissue thickness of the mild-, moderate- and severe-hepatic steatosis subgroups to that of the controls. EAT-t, epicardial adipose tissue thickness

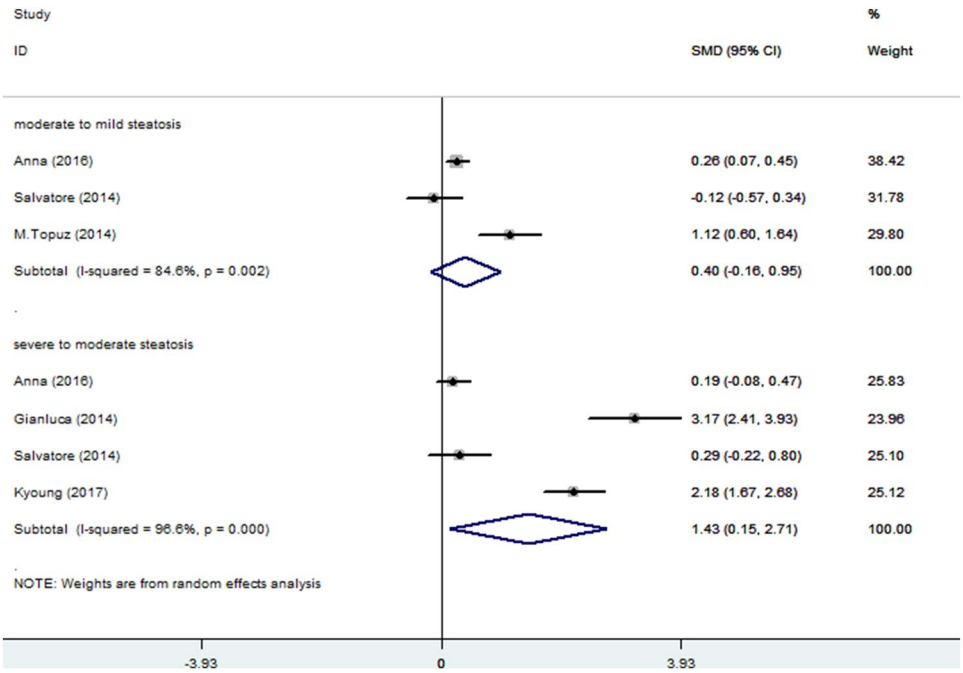

Fig. 4 Meta-analysis comparing the epicardial adipose tissue thickness among the mild-, moderate- and severe-hepatic steatosis subgroups in subjects with NAFLD. EAT-t, epicardial adipose tissue thickness

Fig. 4). However, no significant difference was found in the EAT-t between the moderate and mild subgroups (SMD = 0.40, 95% CI = − 0.16–0.95, $p = 0.164$; Fig. 4).

Relationship between histological liver damage (NASH and fibrosis) and EAT

We performed a meta-analysis to investigate the association of EAT with NASH and liver fibrosis in patients with NAFLD. There was no statistically significant difference in

the EAT-t between the NASH and non-NASH groups (SMD: 0.43, 95% CI −0.25–1.11, $p=0.215$; Fig. 5a). However, TSA indicated that the cumulative z curves did not cross any of the boundaries (TSA-adjusted 95% CI −0.23–0.48; $p<0.001$; Fig. 5b), and nearly 1000 patients would be needed to draw a definite conclusion. Interestingly, the analysis showed that the EAT-t was significantly thicker in the F3–F4 fibrosis group than in the F0–F2 fibrosis group (SMD = 0.72, 95% CI 0.30–1.14, $p=0.001$; Fig. 6a), which was confirmed by TSA (TSA-adjusted 95% CI 0.08–0.24; $p<0.001$; Fig. 6b).

Relationship between cardiovascular disease (CVD) and EAT in patients with NAFLD

Two studies investigated the association between CVD and EAT in patients with NAFLD. The NAFLD patients were divided into low- and high-EAT-t subgroups. The results showed that the proportion of hypertension (OR = 1.64, 95% CI = 1.24–2.18, $p=0.001$; Fig. 7) and atherosclerotic cardiovascular disease (ASCVD) (OR = 1.66, 95% CI = 1.21–2.28, $p=0.002$; Fig. 7) was higher in the high-EAT-t group compared with the low-EAT-t group.

Publication bias was not assessed because of the limited number of studies.

Discussion

This meta-analysis confirmed that NAFLD is associated with an increase in EAT. Furthermore, TSA indicated that the available samples were sufficient and the evidence was reliable. Regression analysis indicated that HDL and TG levels significantly affected the results. We did not find

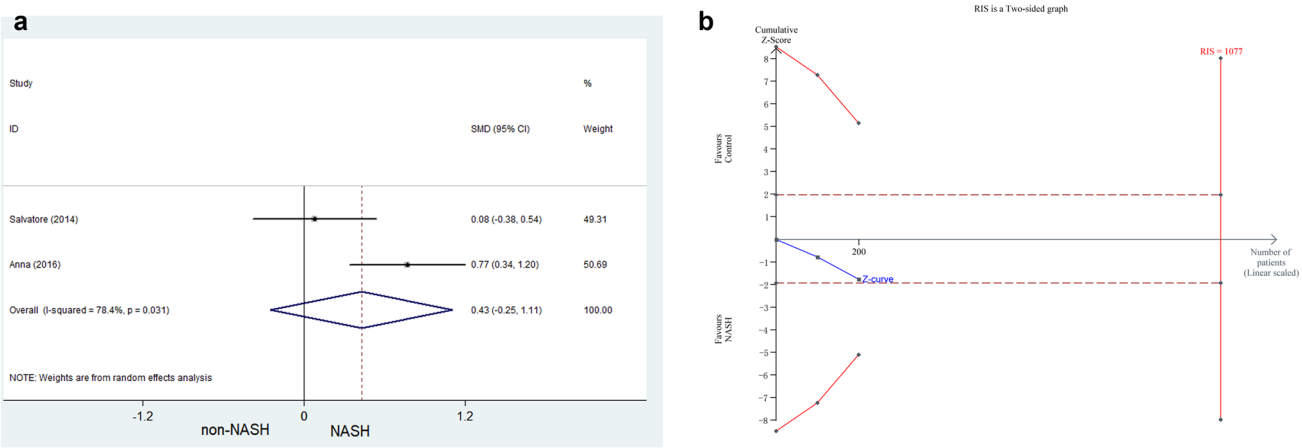

Fig. 5 Comparison of the epicardial adipose tissue thickness between non-NASH and NASH subgroups in subjects with NAFLD. **a** Meta-analysis; **b** trial sequential analysis. EAT-t, epicardial adipose tissue thickness

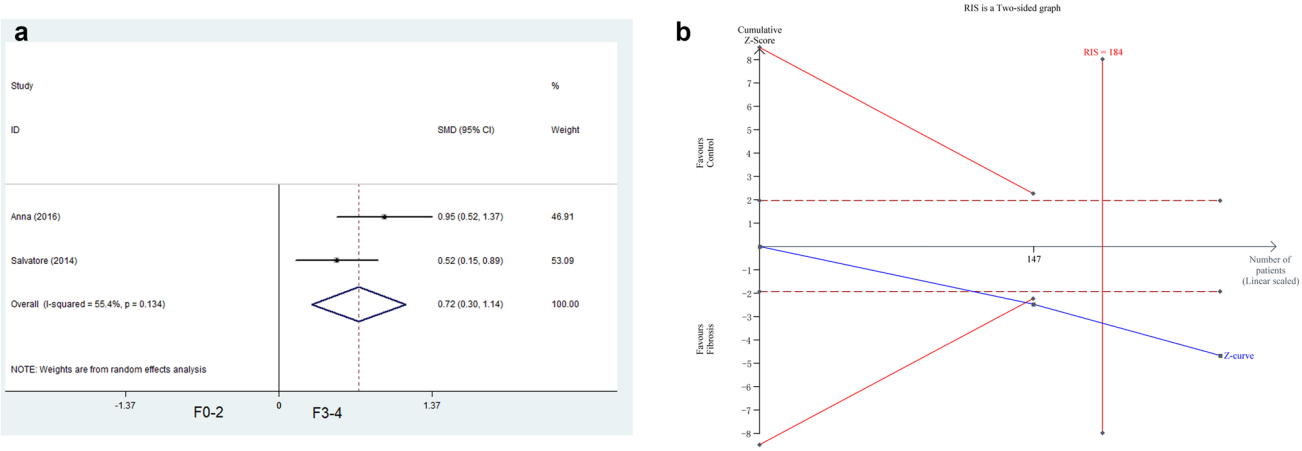

Fig. 6 Comparison of the epicardial adipose tissue thickness between F0–2 and F3–4 fibrosis subgroups in subjects with NAFLD. **a** Meta–analysis; **b** trial sequential analysis. EAT-t, epicardial adipose tissue thickness

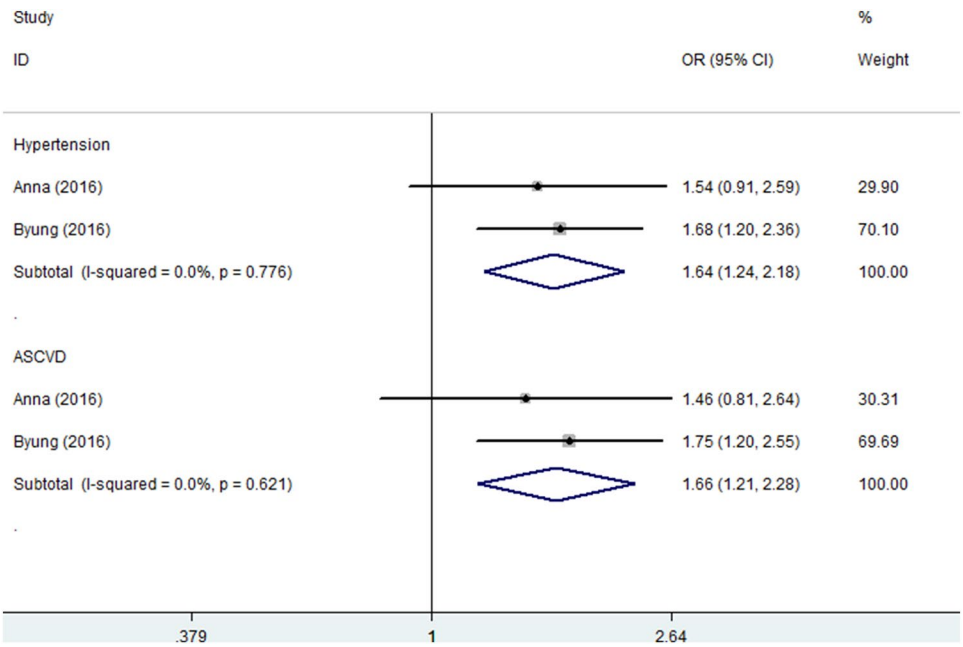

Fig. 7 The proportion of hypertension and ASCVD in the high-EAT-t group versus the low-EAT-t group in patients with NAFLD. EAT-t, epicardial adipose tissue thickness; ASCVD, atherosclerotic cardiovascular disease

an association between EAT-t and NASH. Interestingly, there was an association between EAT-t and liver steatosis, advanced fibrosis and cardiovascular disease in NAFLD patients.

NAFLD is the most common liver disease in clinical practice, which is caused by a large amount of fat that is deposited in the liver and is commonly associated with metabolic syndrome [13]. Although NAFLD is not immediately life threatening, it can lead to abnormal liver function, cirrhosis, and even liver failure [4]. Therefore, it is important to elucidate the pathogenesis and prevent the progression of NAFLD. EAT is able to act as an endocrine and paracrine organ and to secrete proinflammatory interleukins and adipokines, such as vaspin, TNF-α, interleukin 6, interleukin 17 and angiotensin [27], which are involved in the development and progression of diseases, including atherosclerosis, atrial fibrillation, hypertension, NAFLD and immune disease [7].

Our study indicated that the EAT was increased in patients with NAFLD compared with that in the controls, which was further confirmed by TSA. Additionally, we found that EAT-t was associated with the severity of liver steatosis. Some studies supported our finding that EAT-t increased with the severity of liver steatosis in NAFLD patients [11, 15, 25]. The parallel trend between EAT and liver steatosis suggests that ectopic fat may be simultaneously present in different organs, which is caused by metabolic disorders in individuals with insulin resistance. Interestingly, growing evidence indicates that EAT is associated with NAFLD and is not dependent on other potential confounding variables [10–13]. Iacobellis et al. found that EAT better predicts ultrasound-measured fatty liver than BMI or waist circumference in obese patients [11]. Cho et al. reported that EAT-t was an independent predictor of NAFLD and was associated with the severity of liver steatosis and fibrosis in NAFLD. Notably, this relationship was maintained after adjusting for clinical and metabolic risk factors, including age, BMI, waist circumference, hyperlipemia, blood pressure and smoking [15]. Therefore, we speculate that the increase in EAT might promote the incidence of NAFLD by secreting proinflammatory cytokines, including interleukins and adipokines [18, 23, 28]. However, more studies on the mechanism are needed to elucidate the association of EAT with NAFLD.

Additionally, we also investigated whether the EAT was associated with liver damage (including NASH and cirrhosis), and cardiovascular disease (including hypertension and ASCVD) in patients with NAFLD. However, we did not find a statistically significant difference in the EAT-t between the non-NASH and NASH subgroups. There were only two studies and 200 samples assessing the association of EAT with NASH [10, 12], and the TSA indicated that nearly 1000 samples are needed to draw a definitive conclusion. Therefore, more studies are needed to explore this association. Interestingly, we observed a significant association between EAT and advanced fibrosis and between EAT and atherosclerosis and hypertension in NAFLD patients, which supported the hypothesis that the cytokines and adipokines secreted by epicardial fat mediate the inflammatory response and lead to liver and vessel damage. A positive relationship has been demonstrated between EAT-t and the inflammatory marker IL-6 [17]. In addition, the inflammatory state in patients with NAFLD might act systemically and affect the homeostasis of different organs, as demonstrated for atherosclerosis and liver cirrhosis. Previous observations also suggested that there

was an association between epicardial fat and the presence and severity of NAFLD, carotid atherosclerosis, and coronary artery stenosis [3, 29]. The EAT was thicker in the patients with severe cirrhosis, coronary artery stenosis or left ventricular dysfunction. Thus, the NAFLD patients with thicker EAT may need a more intensive hepatic and cardiovascular follow-up and examinations. EAT may play an important role in the progression of NAFLD by secreting cytokines.

Study strengths and limitations

The current work has advantages. First, this is the first meta-analysis to investigate the association of EAT with NAFLD. Second, the present work takes into account the main potential biological factors that may act as confounders in the relationship between NAFLD and EAT. Third, the present work comprehensively evaluates the association of EAT with NAFLD, including hepatic steatosis, NASH, liver fibrosis and cardiovascular disease. Fourth, this work is based on thirteen high-quality studies and includes a large sample size. However, the current study also has potential limitations. There were a limited number of studies investigating the association of EAT with NASH, liver fibrosis, and cardiovascular disease.

Conclusion

In summary, our meta-analysis confirmed that EAT was associated with NAFLD. EAT was also associated with the severity of hepatic steatosis, liver fibrosis and cardiovascular disease in patients with NAFLD. The role of EAT in the pathogenesis of NAFLD is in the exploratory stage, and these potential mechanisms should be evaluated more extensively in the future.

Author contributions Conceived and designed the experiments: QS and BL. Collected the data: BL, Yingrui L, and Yu L. Analyzed the data: BL, Yuling Y, and Yajie L. Wrote the paper: BL. Revised the paper: BL, Yingrui L, Yuling Y, Aoran L, HR and QS.

Funding This study was funded by the National Natural Science Foundation of China (81770251) and the National Natural Science Foundation of China Youth Science Fund Project (81800254).

Compliance with ethical standards

Conflict of interest Bin Liu, Yingrui Li, Yu Li, Yajie Liu, Yuling Yan, Aoran Luo, Hong Ren and Qiang She declare thatthey have no competing interests.

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