

Review Article

The Predictive Value of Epicardial Fat Tissue Volume in the Occurrence and Development of Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Received 30 May 2022; Revised 20 August 2022; Accepted 26 August 2022; Published 29 September 2022

Academic Editor: Carlo Lavallo

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Background. Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. Although fat is currently considered to be a risk factor for AF and a pathogenic link between epicardial fat tissue (EFT) and AF has been speculated, there are currently few clinical studies and literature data domestically or abroad. **Objective.** This study conducted a meta-analysis of observational case series studies to verify the relationship between atrial fibrillation and EFT and to strengthen the predictive value of EFT in the occurrence, development, and postablative recurrence of AF. **Methods.** We conducted a systematic search of the literature in electronic databases until December 2021 and supplemented this through manual searches of individual studies, reviewed articles, and reference lists in conference proceedings. This study conducted a meta-analysis to compare the differences between different populations, such as healthy participants and AF patients, healthy subjects and AF subtype cases, and paroxysmal and persistent AF with AF recurrence and without AF recurrence after ablation. **Results.** Following the retrieval of 828 articles, only 22 articles were selected as research results. Accordingly, the meta-analysis results show that the volume of EFT in AF is greater than that in healthy subjects (MD = 39.34 ml, 95% CI = 27.11, 51.58); persistent AF is greater than paroxysmal AF (MD = 14.37 ml, 95% CI = 7.46, 21.27); and recurrence after ablation is greater than without recurrence (MD = 14.37 ml, 95% CI = 7.46, 21.27). **Conclusion.** The results of this study further confirm the connection between EFT and AF and that EFT has a certain predictive value for the occurrence and development of AF.

1. Introduction

AF is the most common clinically sustained cardiac arrhythmia and a significant contributor to cardiovascular morbidity and mortality, with increasing morbidity and prevalence worldwide. The currently estimated prevalence of AF in adults is between 2% and 4% [1]. Therefore, it is very important to find one or more predictive indicators for AF. Regarding the treatment of AF, although catheter ablation is currently the best treatment option for the control of symptomatic AF while being more effective than

antiarrhythmic drug therapy to maintain sinus rhythm, there is nevertheless a high rate of postoperative recurrence of AF (approximately 30%-50%) and difficulty in predicting rhythmic outcomes after catheter ablation of AF in individual patients [2].

Previous studies have demonstrated a close link between AF and EFT, but the mechanism by which fat causes AF remains unclear. Some studies have pointed out that fat is associated with diastolic dysfunction, atrial inflammation, myocardial deposition, and atrial systolic function disorders, which may lead to atrial structural remodeling (including

diffuse atrial fibrosis and dilation) and electrophysiological abnormalities (including conduction slowing and shortening of the atrial effective refractory period) [3–5]. As a special visceral fat tissue, EFT is not only anatomically close to the myocardium but can also produce a variety of cytokines with proinflammatory effects. Atrial fibrosis is a central pathophysiological feature of AF [4].

It has been suggested that EFT has an additional role in modulating different triggers, including metabolic and biochemical triggers, that contribute to the development of AF. The interaction between AF and EFT is both structural and functional, with atrial structural abnormalities, adipocyte infiltration, and atrial fibrosis predisposing myocardial tissue to arrhythmia [6]. To date, there have been systematic reviews and meta-analyses on the relationship between EFT and AF, but the research results contained in the articles are few [7, 8]. This study contains more findings and comprehensively describes the predictive value of EFT in the occurrence, development, and recurrence after ablation of AF.

2. Methods

2.1. Search Strategy. The PubMed, Cochrane Library, Embase, and CNKI databases were manually searched for relevant literature. Searches were performed using the following keywords: “atrial fibrillation, arrhythmia, heart, fat tissue, epicardial fat, and epicardial adipose.” Titles and abstracts were screened to exclude irrelevant articles. In addition, the references of all ultimately included articles were reviewed to prevent any relevant articles from being missed.

2.2. Qualification Criteria. There were no language restrictions on the included articles. The criteria for inclusion in the manuscript were as follows: (1) the article reported the total volume of EFT with statistical indicators, (2) the total volume of EFT was measured by CT or MRI, (3) there were healthy subjects and an AF group or AF ablation treatment group, and (4) at least one of the following major confounders was reported: age, sex, hypertension, and body mass index (BMI). Studies published as conference abstracts were considered eligible for inclusion; however, case reports and review clauses were not.

2.3. Assessment of Study Quality. These articles were independently assessed by two experienced clinical staff and discussed and revised in the event of disagreement. The STROBE statement was used to assess the methodological quality of the included studies, and STROBE contained 22 items with which to assess the quality of the information reported in different sections of the study, including presentation, study design and setting, statistical evaluation, results, and discussion [9]. The STROBE judgment results for all included studies were summarized on a scale between 0 and 22. In case of discrepancies, quality assessments were performed by 2 different graders and a 3rd grader. For meeting abstracts, another type of STROBE checklist was

used, which contained 12 items to include when reporting observational studies published as meeting abstracts.

2.4. Statistical Methods. Random-effects meta-analysis was used to estimate the differences in total EFT volume among the different populations. RevMan 5.3 and Stata 15.1 were used for statistical analysis in this study, and the results were represented by forest plots. Since the included studies were all measurement data, mean difference (MD) and 95% confidence intervals (CIs) were used to evaluate whether there was a significant difference in EFT volume between different populations. At the significance level $\alpha = 0.1$, the heterogeneity test adopted was the X^2 test, $P \geq 0.1$, with $I^2 \leq 50\%$ indicating that the heterogeneity was small and for which the fixed-effect model (FED) would be used; otherwise, the random-effect model (RED) would be used. Subgroup analysis and drawing a funnel plot were used to assess potential publication bias.

3. Results

A total of 831 literature search results were recorded. After 213 copies of the records were removed, 550 of the remaining 618 records were not related to the subject. After evaluating the full text of the remaining 68 studies, 46 of them were excluded. Finally, the results of 22 published studies were included in this study. Finally, 5 different meta-analyses were performed to assess the association of EFT volume with AF. Flowchart of study selection is reported in Figure 1. The characteristics of the included studies are reported in Table 1.

3.1. Comparison of EFT Volume in Healthy Participants and AF Cases. Analysis of 5495 healthy controls and 1470 AF subjects using a random-effects model showed that the MD was -39.34 ml (95% confidence interval (CI) = $-51.58, -27.11$), indicating that the EFT volume was higher in AF cases. From this comparison, relative heterogeneity between studies was observed (I -squared = 91% $P < 0.00001$) (Figure 2(a)). Inclusion of potential confounding factors for supplementation, such as sex, incidence of type 2 diabetes, and hypertension, did not result in a reduction in supplementation heterogeneity. After excluding individual studies one by one, the combined MD values were all within the 95% CI ($-51.58, -27.11$), and the MD values ranged from -41.66 (95% CI = $-54.33, -28.98$) to -35.32 (95% CI = $-41.59, -25.46$). The results obtained in this study were relatively stable (Figure 3(a)).

3.2. Comparison of Total EFT Volume in Healthy Subjects and AF Subtype Cases. A comparison of total EFT volume between 667 patients in sinus rhythm and 619 patients with paroxysmal AF (PAF) using a random-effects model showed an MD of -22.74 ml (95% confidence interval (CI) = $-29.73, -15.74$). From this comparison, relative heterogeneity between studies was observed (I -squared = 73% $P < 0.00001$) (Figure 2(b)). After excluding

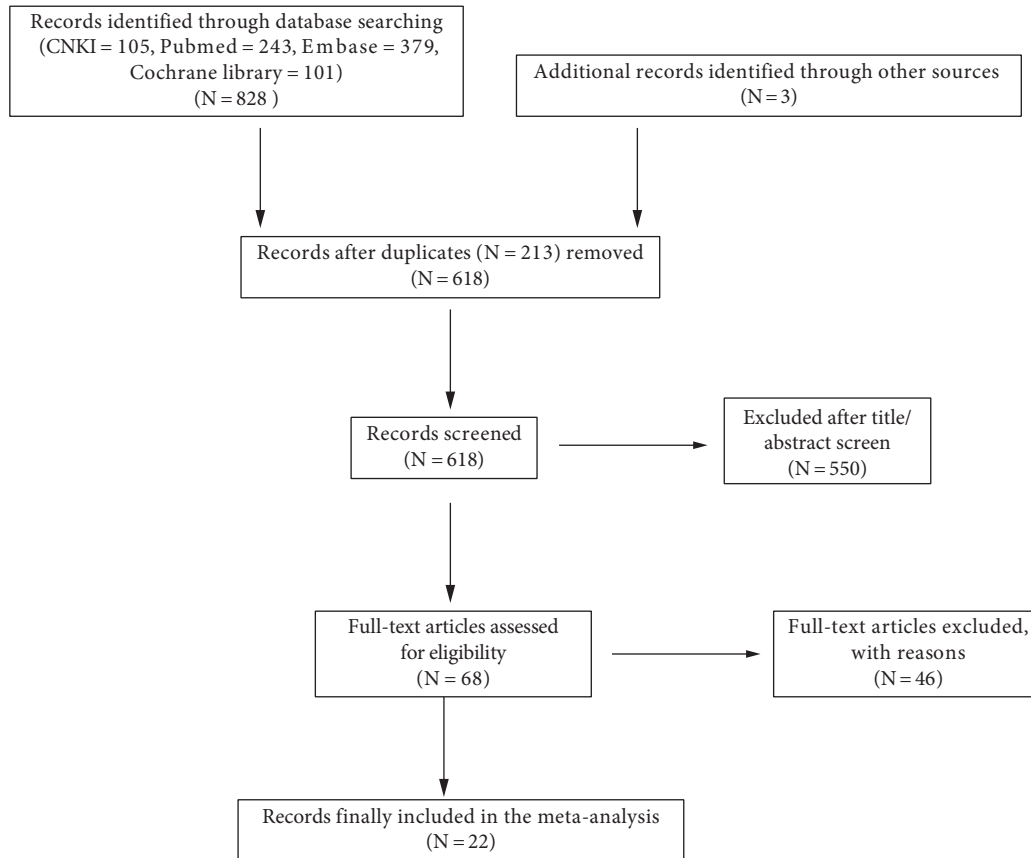


FIGURE 1: Flow chart of study selection.

individual studies one by one, the combined MD values were all within the 95% CI (-29.73, -15.74), and the MD values ranged from -24.61 ml (95% CI = -31.69, -17.54) to -20.21 ml (95% CI = -26.33, -14.08) (Figure 3(b)). When comparing healthy subjects ($n = 667$) and patients ($n = 371$) with persistent AF (PeAF), the MD was -38.40 ml (95% CI = -47.70, -29.10), and relative heterogeneity between studies was also observed (I -squared = 77% $P < 0.00001$) (Figure 2(c)). After excluding individual studies one by one, the combined MD values were all within the 95% CI (-47.70, -29.10), and the MD values ranged from -41.00 ml (95% CI = -51.56, -30.45) to -34.01 ml (95% CI = -41.74, -26.31) (Figure 3(c)). The above results show that the results obtained in this study were relatively stable and that the total EFT volume was significantly higher in AF.

3.3. Comparison of Total EFT Volume in Paroxysmal AF and Persistent AF. Notably, when comparing patients with PAF ($n = 1084$) and PeAF ($n = 610$), a significant MD of -14.37 ml (95% CI = -21.27, -7.46) was found, showing that the EFT volume was higher in PeAF cases. From this comparison, relative heterogeneity between studies was observed (I -squared = 66% $P < 0.0001$) (Figure 2(d)). After excluding individual studies one by one, the combined MD values were all within the 95% CI (-21.27, -7.46), and the MD values ranged from -15.94 ml (95% CI = -24.35, -7.54)

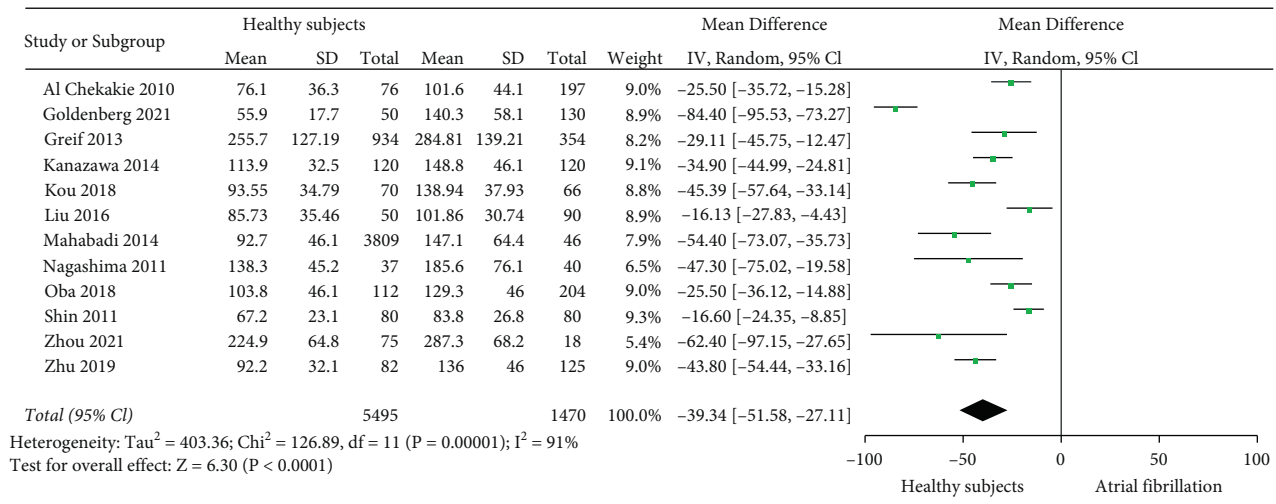
to -10.16 ml (95% CI = -14.53, -5.78), showing that the results were relatively stable (Figure 3(d)).

3.4. Comparison of AF Recurrence and Nonrecurrence after Ablation. The comparison of total EFT volume between the two groups of patients with ($n = 523$) and without ($n = 1266$) AF recurrence after ablation using a random-effects model showed an SDM of -19.77 ml (95% CI = -30.83, -8.71), indicating that EFT volume was higher in AF recurrence patients. In addition, relative heterogeneity between studies was observed (I -squared = 77% $P = 0.0005$) (Figure 2(e)). After excluding individual studies one by one, the combined MD values were all within the 95% CI (-30.83, -8.71), and the MD values ranged from -22.41 ml (95% CI = -34.43, -10.39) to -17.15 ml (95% CI = -27.54, -6.75), showing that the results were relatively stable (Figure 3(e)).

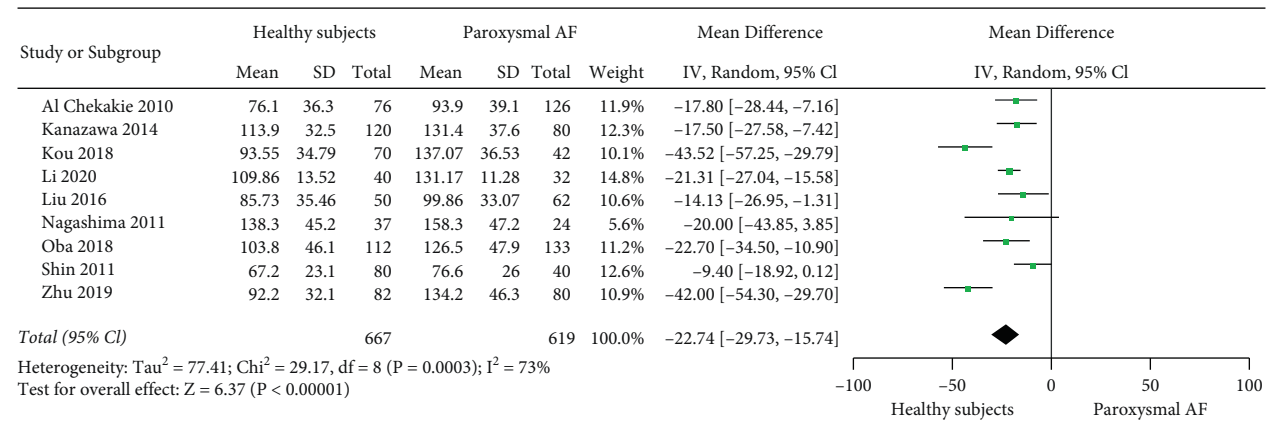
3.5. Quality Assessment and Publication Bias. The quality of the studies in the current meta-analysis was variable; the lowest STROBE (22 items) score was 13, and the highest was 20; the lowest STROBE (12 items) score was 4, and the highest was 5. This meta-analysis was not affected by publication bias according to the Egger test for the following comparisons: (1) the group of healthy participants and AF cases, $P = 0.283$ (Figure 4(a)); (2) the group of healthy participants and paroxysmal AF cases, $P = 0.544$ (Figure 4(b)); (3) the group of healthy participants and

TABLE 1: Characteristics of the included studies.

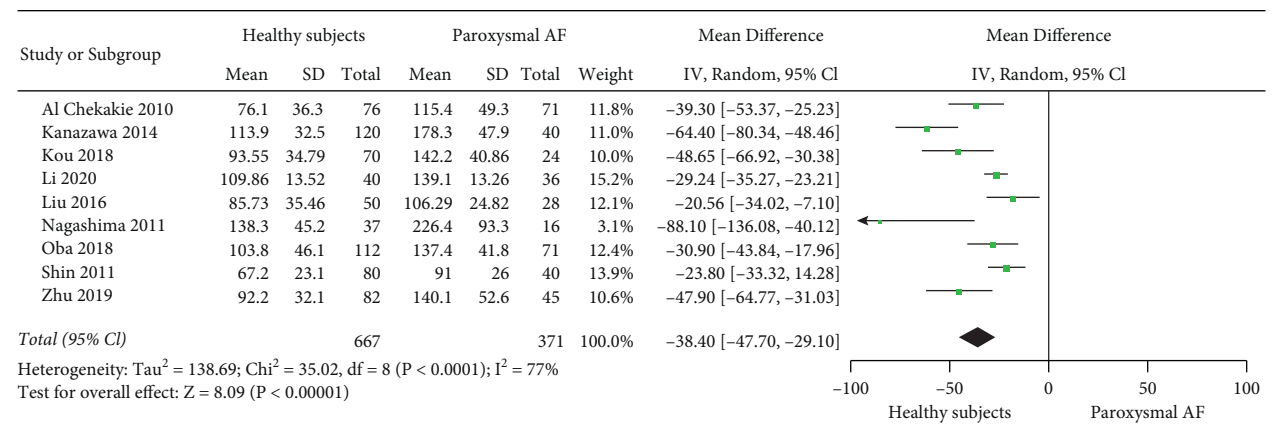
Reference year	Country	Healthy subjects (n) EFTV (M±SD)	All AF subjects (n) EFTV (M±SD)	PAF subjects (n) EFTV (M±SD)	PeAF subjects (n) EFTV (M±SD)	AF recurrence (n) EFTV (M±SD)	No AF recurrence (n) EFTV (M±SD)	Imaging system	Quality score
Al Chekatie et al. [10] 2010	USA	76.10 ± 36.30 n = 76	101.60 ± 44.10 n = 197	93.90 ± 39.10 n = 126	115.40 ± 49.30 n = 71	N/A	N/A	CT	15/22
Goldenberg et al. [11] 2021	Israel	55.90 ± 17.70 n = 50	140.30 ± 58.10 n = 130	N/A	N/A	130.70 ± 54.20 n = 103	175.00 ± 54.40 n = 27	CT	20/22
Greif et al. [12] 2013	Germany	255.70 ± 127.19 n = 934	284.81 ± 139.21 n = 354	N/A	N/A	N/A	N/A	CT	16/22
Hammache et al. [13] 2021	France	N/A	N/A	N/A	N/A	88.60 ± 37.20 n = 128	91.40 ± 40.50 n = 261	CT	20/22
Kanazawa et al. [14] 2014	Japan	113.90 ± 32.50 n = 120	148.80 ± 46.10 n = 120	131.40 ± 37.60 n = 80	178.30 ± 47.90 n = 40	N/A	N/A	CT	14/22
Kim et al. [15] 2014	Korea	N/A	N/A	100.67 ± 43.07 n = 450	108.13 ± 46.88 n = 215	99.44 ± 42.51 n = 489	113.19 ± 48.11 n = 176	CT	17/22
Maeda et al. [16] 2018	Germany	N/A	N/A	N/A	N/A	126.00 ± 44.00 n = 157	141.00 ± 53.00 n = 61	CT	13/22
Mahabadi et al. [17] 2014	Japan	92.70 ± 46.10 n = 3809	147.10 ± 64.40 n = 46	N/A	N/A	N/A	N/A	CT	19/22
Nagashima et al. [18] 2011	Japan	138.30 ± 45.20 n = 37	185.60 ± 76.10 n = 40	158.3 ± 47.2 n = 24	226.40 ± 93.30 n = 16	153.50 ± 42.70 n = 25	239.00 ± 90.20 n = 15	CT	18/22
Nakatani et al. [19] 2015	Japan	N/A	N/A	N/A	N/A	123.00 ± 56.00 n = 45	107.0 ± 64.00 n = 10	CT	17/22
Nakatani et al. [20] 2020	Japan	N/A	N/A	N/A	N/A	116.00 ± 34.00 n = 34	103.00 ± 43.00 n = 10	CT	18/22
Oba et al. [21] 2018	Japan	103.80 ± 46.10 n = 112	129.30 ± 46.00 n = 204	126.5 ± 47.90 n = 133	134.70 ± 41.80 n = 71	N/A	N/A	CT	16/22
Romanov et al. [22] 2021	Japan	N/A	N/A	159.60 ± 42.20 n = 15	187.60 ± 62.10 n = 15	N/A	N/A	CT	15/22
Shin et al. [23] 2011	Korea	67.20 ± 23.10 n = 80	83.80 ± 26.80 n = 80	76.60 ± 26.00 n = 40	91.00 ± 26.00 n = 40	N/A	N/A	CT	18/22
Zhou et al. [24] 2021	China	224.90 ± 64.80 n = 75	287.3 ± 68.2 n = 18	NA	NA	N/A	N/A	MRI	19/22
Zhu et al. [25] 2019	China	92.20 ± 32.10 n = 82	136.00 ± 46.00 n = 125	134.20 ± 46.30 n = 80	140.1 ± 52.6 n = 45	N/A	N/A	CT	14/22
Chikka et al. [26] 2012	Japan	N/A	N/A	N/A	N/A	145.00 ± 37.00 n = 26	200.00 ± 62.00 n = 112	CT	5/12
Kawakam et al. [27] 2008	Japan	N/A	N/A	N/A	N/A	109.50 ± 34.90 n = 61	147.30 ± 35.80 n = 34	CT	4/12
Masaharu et al. [28] 2015	USA	N/A	N/A	N/A	N/A	94.50 ± 35.20 n = 24	98.50 ± 45.70 n = 29	CT	21/22
Liu et al. [29] 2016	China	85.73 ± 35.46 n = 50	101.86 ± 30.74 n = 90	99.86 ± 33.07 n = 62	106.29 ± 24.82 n = 28	95.49 ± 28.60 n = 41	119.15 ± 28.66 n = 21	CT	18/22
Kou et al. [30] 2018	China	93.55 ± 34.79 n = 70	138.94 ± 37.93 n = 66	137.07 ± 36.53 n = 42	142.20 ± 40.86 n = 24	N/A	N/A	CT	19/22
Li et al. [31] 2020	China	109.86 ± 13.52 n = 40	NA	131.17 ± 11.28 n = 32	139.10 ± 13.26 n = 36	N/A	N/A	CT	17/22



(a)



(b)



(c)

FIGURE 2: Continued.

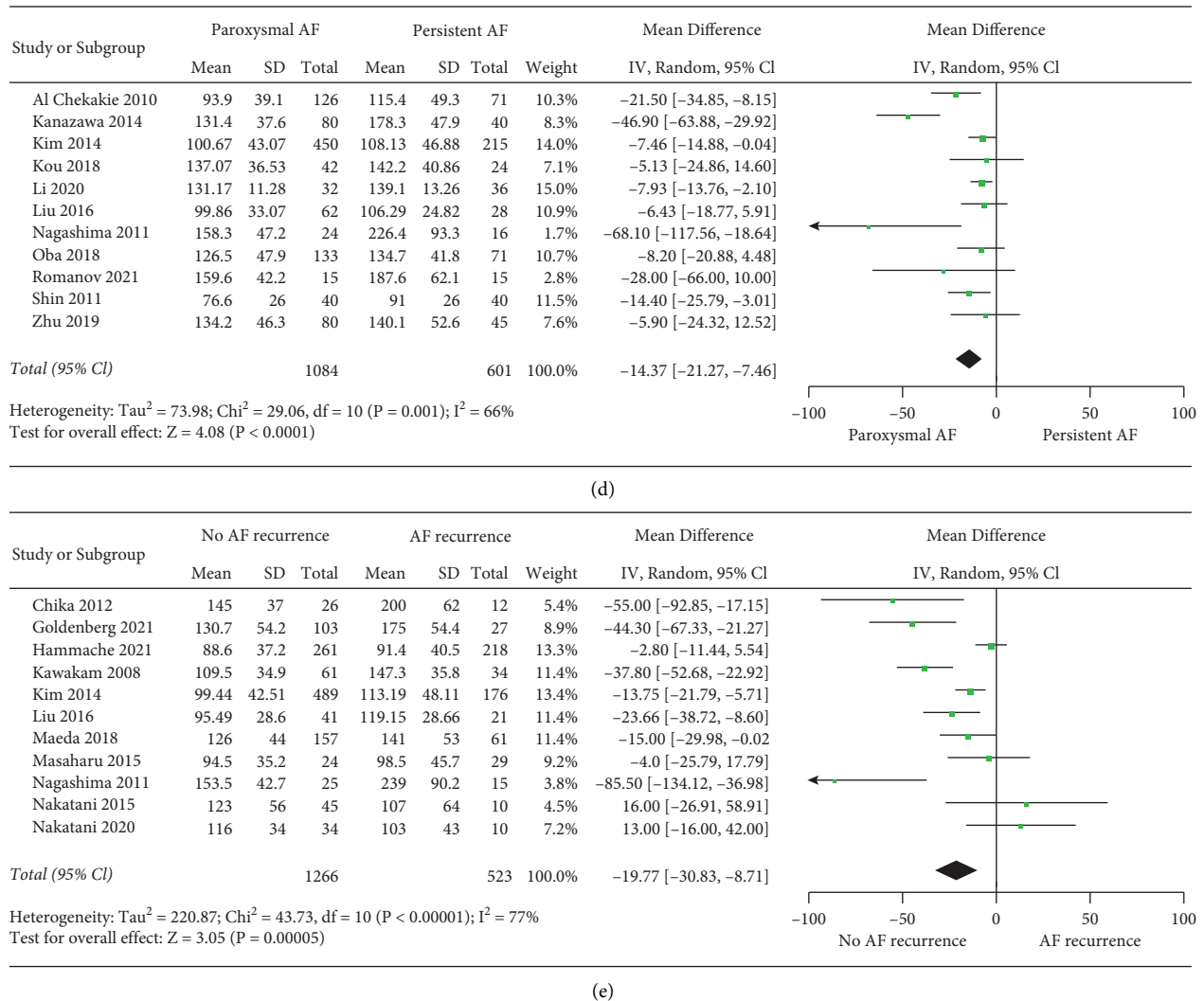


FIGURE 2: Forest map of EFT volume differences among different populations: (a) healthy participants and all AF cases; (b) healthy participants and paroxysmal atrial fibrillation; (c) healthy participants and persistent atrial fibrillation; (d) paroxysmal atrial fibrillation and persistent atrial fibrillation; and (e) recurrent and nonrecurrent patients after ablation.

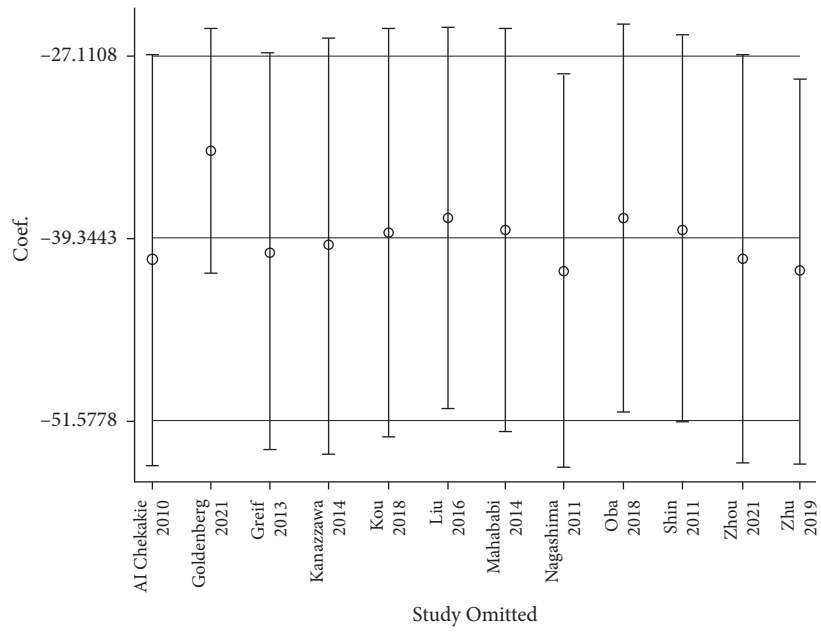
persistent AF cases, $P = 0.045$ (Figure 4(c))—therefore, we carried out a cut-and-fill analysis, and the MD value and orientation were unchanged (Figure 4(c)); (4) the group of PAF and PeAF cases, $P = 0.07$ (Figure 4(d)); and (5) the AF recurrence group and the AF nonrecurrence after ablation group, $P = 0.229$ (Figure 4(e)).

4. Discussion

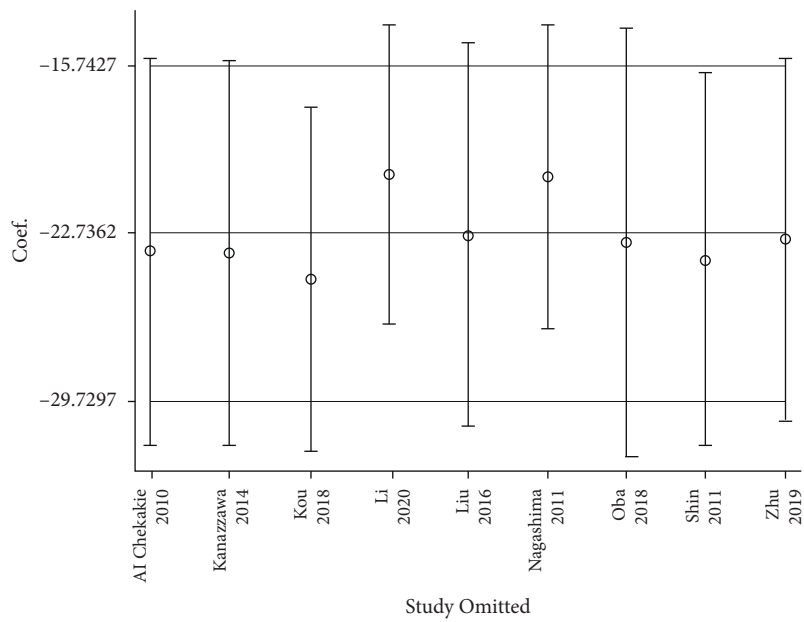
4.1. Main Findings. This study further strengthens the link between EFT volume and AF. Since different subtypes of AF exist and since AF presents differently at different stages of development, it is difficult to predict the recurrence rate of patients with AF after radiofrequency ablation. Consequently, this study conducted a meta-analysis to determine the relationship between EFT and AF. The results of this study found that patients with AF had greater EFT volume than those with sinus rhythm and that patients with persistent AF had greater EFT volume than those with

paroxysmal AF. In addition, the EFT volume of patients with AF recurrence after ablation was greater than that of patients without AF recurrence. These results further indicate that EFT is related not only to the occurrence of AF but also to the severity of AF, which strengthens the value of EFT volume as an imaging indicator in clinical work. However, further well-designed studies are still needed for more accurate assessments.

4.2. Link between AF and EFT. In recent years, a number of risk factors and conditions associated with AF have been identified, such as coronary heart disease, hypertension, heart failure, diabetes, smoking, age, and obesity [32]. However, the exact pathophysiological mechanism of the occurrence and progression of AF is unknown and may be related to inflammation, oxidative stress, endothelial dysfunction, microvascular dysfunction, hypercoagulability, epicardial fat tissue disturbance, atrial stretch,



(a)



(b)

FIGURE 3: Continued.

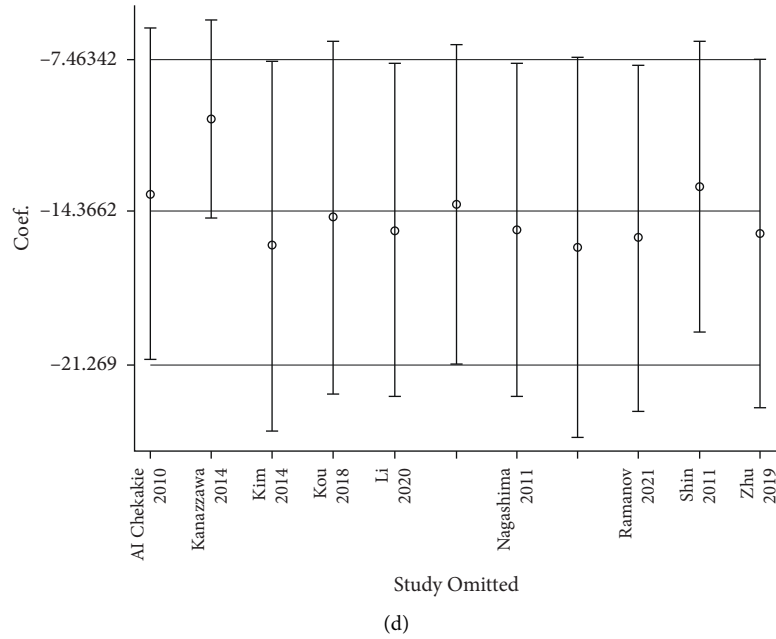
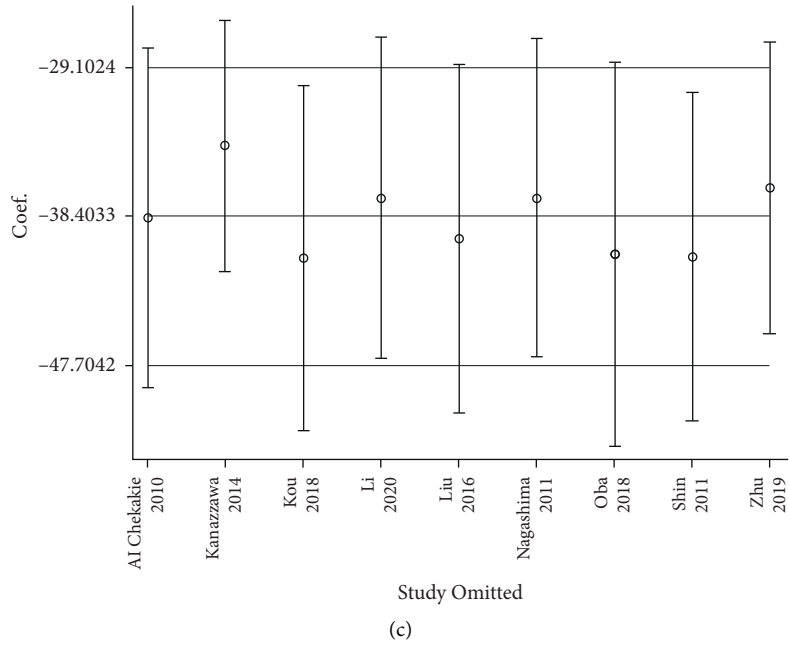
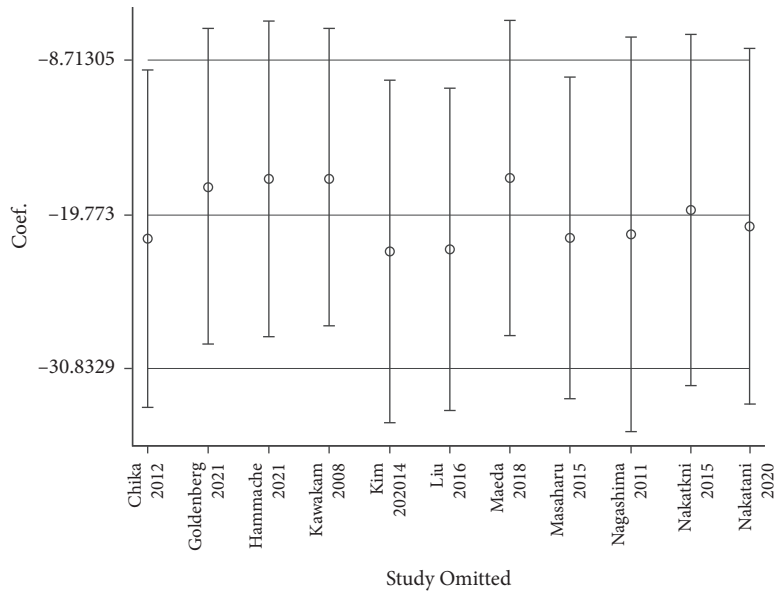
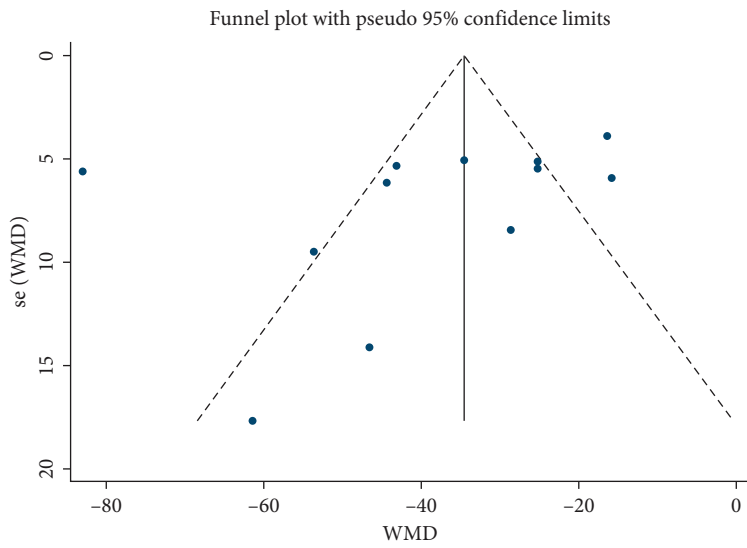


FIGURE 3: Continued.



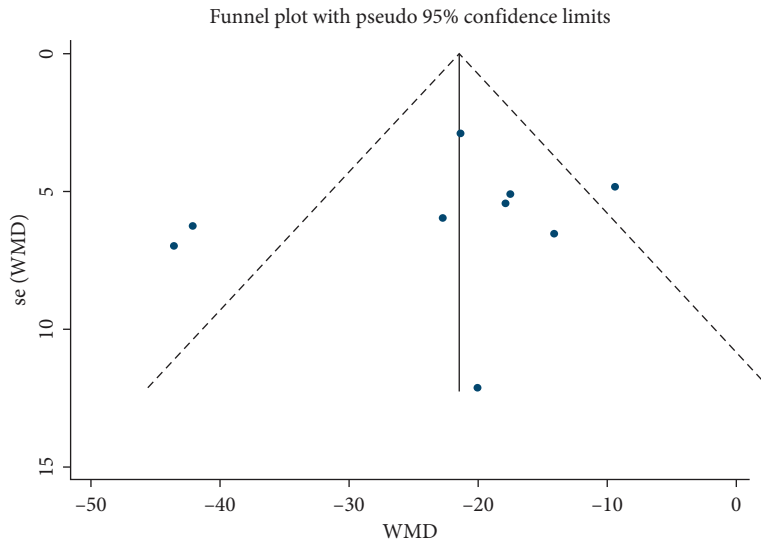
(e)

FIGURE 3: Sensitivity analysis plot of EFT volume differences among different populations: (a) healthy participants and all AF cases; (b) healthy participants and paroxysmal atrial fibrillation; (c) healthy participants and persistent atrial fibrillation; (d) paroxysmal atrial fibrillation and persistent atrial fibrillation; and (e) recurrent and nonrecurrent patients after ablation.

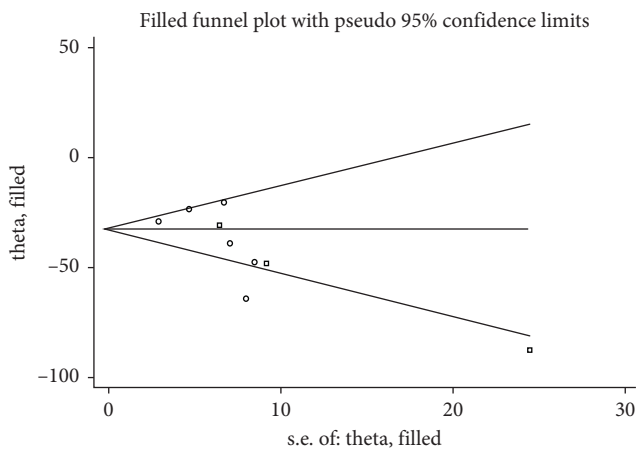
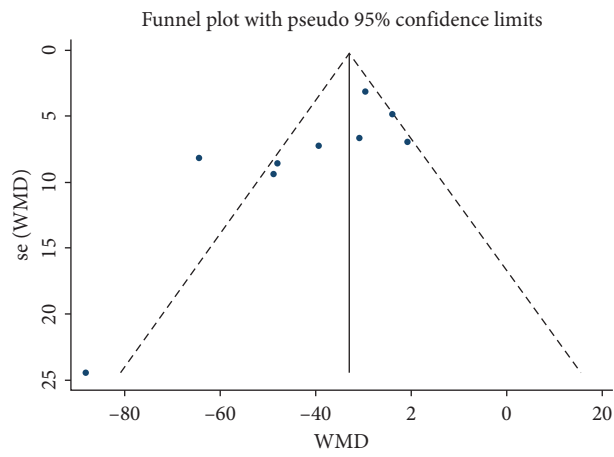


(a)

FIGURE 4: Continued.



(b)



(c)

FIGURE 4: Continued.

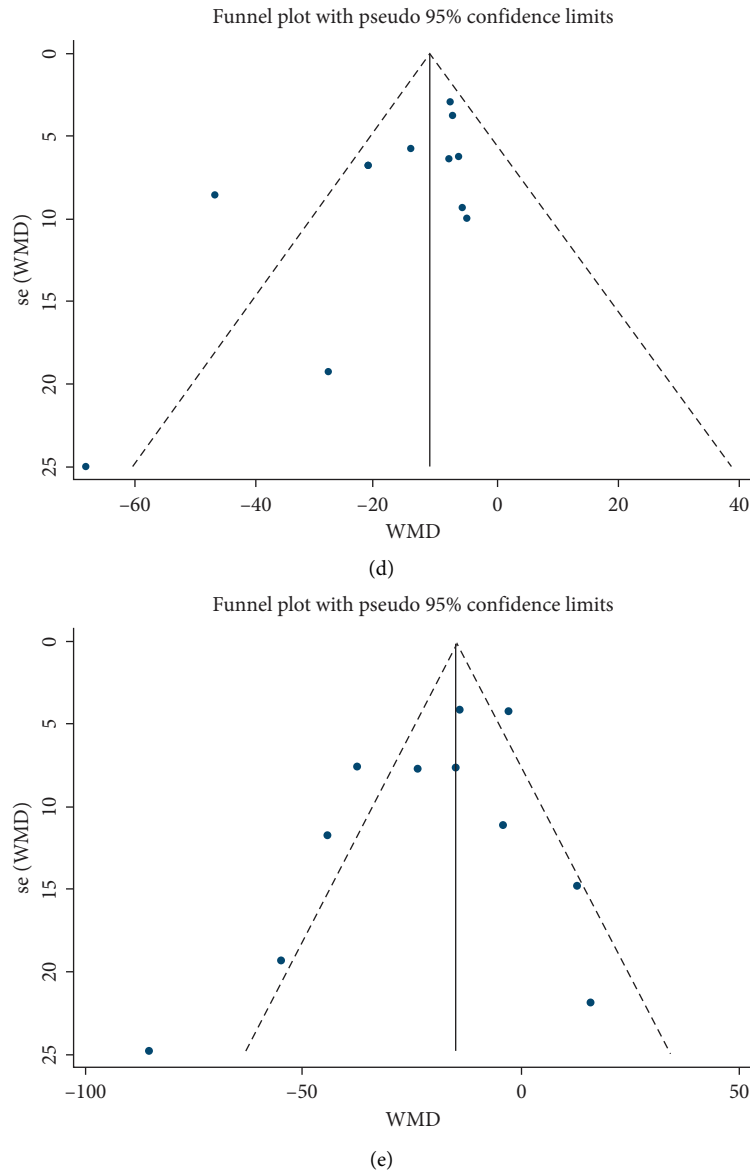


FIGURE 4: Funnel plot of EFT volume differences among different populations: (a) healthy participants and all AF cases; (b) healthy participants and paroxysmal atrial fibrillation; (c) healthy participants and persistent atrial fibrillation; (d) paroxysmal atrial fibrillation and persistent atrial fibrillation; and (e) recurrent and nonrecurrent patients after ablation.

electrophysiology, or conduction function changes [33, 34]. Among these risk factors and mechanisms, the role played by EFT has received increasing attention. Many studies have shown that EFT is closely related to the occurrence and development of AF. The presence of other cardiovascular risk factors (age, hypertension, diabetes, and obesity) known to be associated with AF did not attenuate the relationship between AF and EFT volume [35].

Regarding the pathophysiological mechanism, some studies suggest that EFT may affect the atrial stroma through multiple pathways, such as inflammatory pathways, cardiac structural remodeling, and inducing atrial fibrosis. Atrial fibrosis has become an important pathophysiological factor in AF and has been linked to AF recurrence, resistance to therapy and complications. Epicardial adipocytes in contact

with cardiomyocytes can not only infiltrate the myocardium but also secrete a large number of cytokines (IL-6, IL-4, IL-1, leptin, TNF- α , extracellular vesicles, etc.) regulating myofibroblast and myocyte physiology [36]. These cytokines are protective in a healthy heart against inflammation and fibrosis; however, adipokines secreted by adipocytes may be converted to proinflammatory and profibrotic cytokines and are associated with the production of reactive oxygen species [37]. In addition, EFT can also promote the occurrence of AF by affecting sympathetic nerve excitability, and autonomic nervous system dysfunction may also alter the endocrine activity of adipocytes in a feedback response [38]. Some studies have demonstrated that epicardial adipocytes are sensitive to catecholamine stimulation, which can activate the secretion of cytokines from these cells to the neighboring

tissue. Atrial fibrosis is tightly associated with EFT, but the exact mechanism by which atrial myocytes and fibroblasts are associated with EFT is not fully understood [39].

4.3. Link between AF Severity and EFT. The severity of AF can be reflected by the duration of atrial fibrillation and the type of AF. We usually think that PeAF is often more harmful than PAF because PeAF is more likely to cause more serious clinical problems, such as heart failure. The main pathological mechanism of AF is atrial fibrosis, and PeAF is usually considered more severe fibrosis than PAF. As mentioned above, EFT can promote the progression of atrial fibrosis by secreting proinflammatory factors and direct infiltration. Previous studies have also shown that the volume of EFT and AF burden have a dose-dependent relationship, which is consistent with our finding that patients with PeAF have greater EFT volume than patients with PAF [21]. Therefore, we believe that EFT volume can reflect the severity of AF to some extent.

4.4. Link between Recurrence of AF and EFT. Currently, catheter ablation is an effective therapy to maintain sinus rhythm, but it is unfortunate that a long history of AF and severe atrial fibrosis can increase the probability of AF recurrence. As mentioned above, EFT promotes the occurrence of atrial fibrosis and increases AF burden through direct infiltration, secretion of adipocytokines, induction of inflammatory responses, etc. In addition, previous research has shown that resistin (an adipocytokine) and high-sensitivity c-reactive protein (an indicator of inflammation) are higher in patients with AF recurrence after catheter ablation [40, 41]. Our study shows that patients with AF recurrence after catheter ablation have a greater EFT volume. Therefore, we believe that EFT volume has some predictive value for the recurrence of AF after catheter ablation.

4.5. Recent Research and Treatment Progress. EFT is responsive to glucagon-like peptide 1 receptor agonists (GLP1A) and sodium glucose cotransporter 2 inhibitors (SGLT2i). As recently demonstrated, GLP-1A and SGLT2i provide weight loss and cardiovascular protection beyond diabetes control [42]. In addition, classic RAS blockers, such as angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor inhibitors (ARBs), may prevent AF by affecting the accumulation of EFT, especially in patients with heart failure and known left heart failure [43].

4.6. Limitations. Given the heterogeneity, this study used a random-effects model in the EFT meta-analysis. Then, we conducted a subgroup analysis on the three confounding factors of sex, hypertension, and diabetes, in which hypertension and diabetes did not markedly reduce the heterogeneity. The number of studies, no language restrictions on the included articles, BMI, age, and errors in manual measurements of EFT volume may all be sources of heterogeneity. However, most of the articles did not explicitly

give detailed data related to BMI and age, so further analysis could not be carried out.

5. Conclusion

The EFT volume is associated with AF and has some predictive value in the occurrence, development, and recurrence of AF. More research is necessary to better understand the link between AF and epicardial fat tissue.

Data Availability

The data are available from the first author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Qiankun Fan and Yingge Zhan contributed equally to this work.

Acknowledgments

This study was supported by Key Science and Technology Research Program of Hebei Provincial Health Commission (20210065, 20201164), Hebei provincial Government Funded Specialty Capacity Building and Specialty Leader Training Project (LS202109), and Natural Science Foundation of Hebei Province (H2020206124) provided funds for labor fees, article revisions, publishing fees, and other expenses for the article.

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