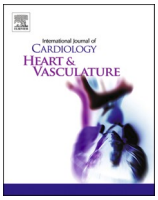
IJC Heart & Vasculature 54 (2024) 101444

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature



Association of epicardial fat with cardiac structure and function and exercise capacity in heart failure with preserved ejection fraction: A systematic review and meta-analysis

Hidekatsu Fukuta [a,*], Toshihiko Goto [b], Takeshi Kamiya [c]

[a] Core Laboratory, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[b] Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[c] Department of Medical Innovation, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

ARTICLE INFO

Keywords:
Heart failure
Preserved ejection fraction
Epicardial fat
Adipose tissue
Meta-analysis

ABSTRACT

Background: Studies have reported the association of epicardial adipose tissue (EAT) with cardiac structure and function as well as exercise capacity in patients with heart failure with preserved ejection fraction (HFpEF), yielding inconsistent results. We aimed to conduct a *meta*-analysis of studies on the association of EAT with cardiac structure and function and exercise capacity in HFpEF patients.

Methods and Results: We searched studies examining the association of EAT quantified by echocardiography, computed tomography, or magnetic resonance imaging (MRI) with cardiac structure and function or exercise capacity in HFpEF patients through PubMed, Web of Science, and Scopus. In cases of significant heterogeneity ($I^2 > 50$ %), data were pooled using a random-effects model; otherwise, a fixed-effects model was used. We identified five echocardiography studies (n = 825) and six MRI studies (n = 562), but found no computed tomography studies. In the echocardiography studies, EAT thickness correlated positively with left ventricular (LV) mass ($P_{random} < 0.01$) and negatively with LV global longitudinal strain ($P_{random} < 0.01$) and peak exercise oxygen uptake ($P_{fix} < 0.001$). In the MRI studies, EAT volume correlated positively with LV mass ($P_{fix} < 0.01$), left atrial volume ($P_{fix} < 0.001$), and the ratio of LV early diastolic mitral inflow to early diastolic mitral annular velocity (E/e'; $P_{random} < 0.01$) and negatively with LV ejection fraction ($P_{fix} < 0.01$) and LV global longitudinal strain ($P_{fix} < 0.001$).

Conclusion: Our *meta*-analysis indicates a potential association of increased EAT with altered cardiac structure and function and exercise intolerance in HFpEF patients. However, our *meta*-analysis included only two or three studies for each outcome and thus further studies are necessary to confirm our findings.

1. Introduction

Nearly half of patients with heart failure (HF) in the community have preserved ejection fraction (EF), and the mortality and morbidity of patients with HF with preserved EF (HFpEF) are high [1–4]. Patients with HFpEF are often elderly and their primary chronic symptom is severe exercise intolerance that results in a reduced quality of life [5,6]. There is much evidence that altered cardiac structure and function are associated with the pathophysiology of HFpEF and contribute importantly to exercise intolerance in HFpEF patients [4,7–12].

Visceral adipose tissue is the largest fat deposit in the human body, and is associated with cardiovascular disease and its risk factors including diabetes, insulin resistance, hypertension, and dyslipidemia [13–15]. Epicardial adipose tissue (EAT) is defined as a fat deposit localized between the myocardial surface and the visceral layer of the pericardium [16]. Similar to visceral adipose tissue, EAT is associated with cardiovascular disease and its risk factors [14,15]. Although EAT comprises less than one-tenth the volume of visceral adipose tissue, it surrounds the coronary arteries and myocardium and thus may exert a local effect on the coronary arteries and cardiac structure and function, in addition to its systemic effect [14–17].

Recent studies have reported that increased EAT is associated with impaired cardiac structure and function and exercise intolerance in HFpEF patients [18–33]. In some studies, however, the associations did

* Corresponding author at: Core Laboratory, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho Mizuho-ku, Nagoya 467-8601, Japan.
E-mail address: fukuta-h@med.nagoya-cu.ac.jp (H. Fukuta).

https://doi.org/10.1016/j.ijcha.2024.101444
Received 22 March 2024; Received in revised form 12 May 2024; Accepted 8 June 2024
Available online 14 June 2024

not reach statistical significance. The inconsistent results may have been due to limited statistical power and/or variations in imaging modalities used to quantify EAT. Accordingly, we aimed to perform a systematic review and *meta*-analysis of studies on the association of EAT with cardiac structure and function as well as exercise capacity in HFpEF patients.

2. Methods

This study has been registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols with the registration number of INPLASY 202420071 (https://www.doi.org;DOI: https://doi.org/10.37766/inplasy2024.2.0071). The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement [34].

2.1. Search strategy

Studies examining the association of EAT with cardiac structure and function or exercise capacity in HFpEF patients published until April 30, 2024 were identified using PubMed, Web of Science, and Scopus. For the search of eligible studies, the following keywords and Medical Subject Headings were used:

#1"epicardial adipose tissue" OR "epicardial fat" OR "pericardial adipose tissue" OR "pericardial fat" OR "cardiac adipose tissue" OR "cardiac fat" OR "subepicardial adipose tissue" OR "subepicardial fat" OR "heart fat" OR "heart adipose tissue".

#2 "heart failure with preserved ejection fraction" OR "heart failure with normal ejection fraction" OR "diastolic heart failure".

#1 AND #2 for outcomes of interest.

Literature search was also conducted by manual screening of reference lists of relevant reviews and retrieved articles.

Two researchers (HF and TG) independently performed the literature search. We initially reviewed the titles and abstracts of each study, and if a study was considered relevant, we proceeded to read the full text. Disagreements were resolved by consensus.

2.2. Selection criteria

Inclusion criteria of studies for the present *meta*-analysis were: (1) examined HFpEF patients; (2) quantified EAT using echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI); (3) measured cardiac structure and function or assessed exercise capacity; and (4) described the relationships of EAT with cardiac structure and function and exercise capacity. Only articles published in the English language were included.

2.3. Outcomes

The primary outcomes of interest were cardiac structure and function. Measures of cardiac structure or function which have been reported to be associated with the pathophysiology and/or prognosis in HFpEF patients were extracted [4,35–38]. Regarding measures of cardiac structure, left ventricular (LV) mass and left atrial (LA) volume were extracted. As to measures of LV systolic function, LV ejection fraction (LVEF) and LV global longitudinal strain were extracted. As to measures of LV diastolic function, early diastolic mitral annular velocity (e') and the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity (E/e') were extracted given the linear relationships of e' and E/e' with the LV diastolic dysfunction grade. Regarding measures of right ventricular (RV) function, RV ejection fraction (RVEF), RV fractional area change, tricuspid annular systolic velocity, tricuspid annular plane systolic excursion, and RV global longitudinal strain were extracted. The secondary outcome of interest was exercise capacity assessed as peak exercise oxygen uptake (VO_2) by expired gas analysis or 6-minute walk distance.

2.4. Data extraction

Two reviewers (HF and TG) independently extracted relevant data from the retrieved articles, including authors, study design, number of participants, used modalities to quantify EAT, clinical outcomes of interest, and information on the methodological quality (selection of cohorts, assessment of outcome, etc.). Disagreements were resolved by consensus.

2.5. Quality assessment

The quality of the included studies was assessed using the revised and validated version of the Methodological Index for Non-Randomized Studies (MINORS) [39]. The global ideal score is 24 for comparative studies and 16 for non-comparative studies.

2.6. Statistical analysis

To assess the association of EAT with cardiac structure and function or exercise capacity, correlation coefficients between EAT and indices of cardiac structure and function or exercise capacity were synthesized. When the relationship of EAT with cardiac structure and function or exercise capacity was reported as a standardized regression coefficient, the value was converted into a correlation coefficient using a validated method [40]. The analyses were performed when at least two studies reported a correlation coefficient between EAT and indices of outcomes of interest. For each outcome, heterogeneity was assessed using the I^2 statistic; $I^2 > 50$ % was considered significant. When there was significant heterogeneity, data were pooled using a random-effects model; otherwise a fixed-effects model was used. The pooled analyses were performed separately for each modality for assessing EAT. When more than two studies were included for each outcome, funnel plots were generated to assess publication bias. A two-tailed $P < 0.05$ was considered statistically significant. For these analyses, Comprehensive Meta Analysis Software version 2 (Biostat, Englewood, NJ, USA) was used.

3. Results

3.1. Search results and characteristics

The study identification and selection process are summarized in Fig. 1. Electronic database searches revealed five echocardiography studies quantifying EAT (n = 825) and six MRI studies quantifying EAT (n = 562). No CT studies quantifying EAT were found.

The characteristics of the included studies are presented in Tables 1 and 2. All included studies were non-comparative studies. The study by Jin et al. [28] was divided into two sub-studies due to the inclusion of derivation and validation cohorts (Table 1). The definition of preserved EF varied among the studies, ranging from > 40 % to ≥ 50 %. In all echocardiography studies, the evaluation of cardiac structure and function was conducted using echocardiography (Table 1). In all MRI studies, the evaluation of cardiac structure and function was performed through MRI, except for the assessment of LV diastolic function, which was examined using echocardiography (Table 2).

The characteristics of the patients in the included studies are summarized in Sup. Tables 1 and 2. EAT volume varied widely probably due to differences in volume calculation methodologies across the studies (Sup. Table 2).

3.2. Qualitative analysis of echocardiography studies

3.2.1. Cardiac structure

Three studies examined the relationship between EAT thickness and

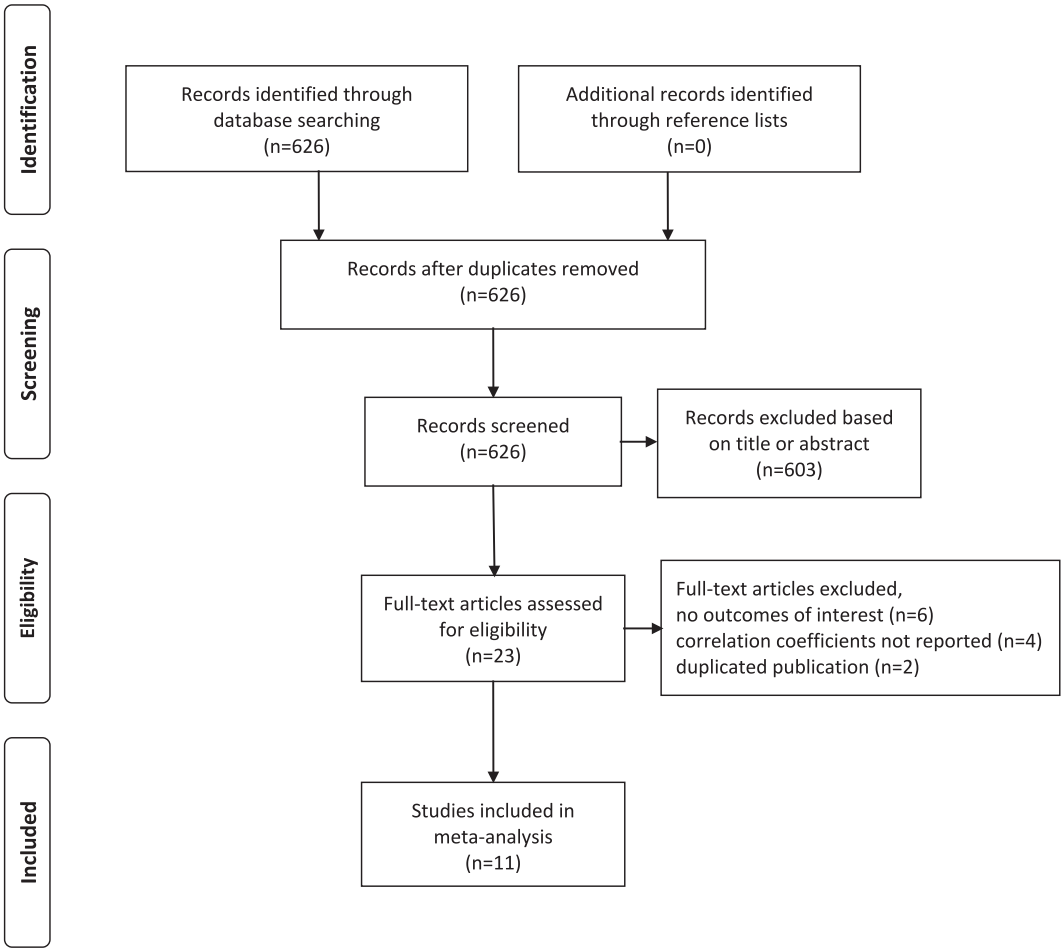


Fig. 1. Selection process for studies included in our *meta*-analysis.

LV mass index [21,26,27]. A significant positive correlation between EAT thickness and LV mass index was observed in two studies [26,27], while no significant correlation was found in one study [21]. One study examined the relationship between EAT thickness and left atrial volume index but found no significant correlation [21].

3.2.2. *LV systolic function*

Two studies examined the relationship between EAT thickness and LVEF but found no significant correlation [21,26]. Three studies examined the relationship between EAT thickness and LV global longitudinal strain [26,28]. A significant negative correlation between EAT thickness and LV global longitudinal strain was observed in two studies [26,28], with no significant correlation found in one study, which was the derivation cohort of the study by Jin et al.[28].

3.2.3. *LV diastolic function*

Two studies examined the relationships of EAT thickness with E/e' and e' [21,26]. A significant positive correlation of EAT thickness with E/e' and a significant negative correlation of EAT thickness with e' were observed in one study [26], while no significant correlations were found in the other study [21].

3.2.4. *RV function*

One study examined the relationship between EAT thickness and RV fractional area change but found no significant correlation [21]. No studies reported the relationship of EAT with RVEF, tricuspid annular systolic velocity, tricuspid annular plane systolic excursion, or RV global longitudinal strain.

3.2.5. *Exercise capacity*

Three studies examined the relationship between EAT thickness and peak VO_2, all of which found a significant negative correlation [20,21,27]. No studies reported the relationship of EAT with the 6-minute walk distance.

3.3. *Qualitative analysis of MRI studies*

3.3.1. *Cardiac structure*

Three studies examined the relationship between EAT volume and LV mass index [18,22,32]. A significant positive correlation between EAT volume and LV mass index was observed in one study [22], while no significant correlation was found in the other two studies [18,32]. Two studies examined the relationship between EAT volume and left atrial volume index, both of which found a significant positive correlation [18,22].

3.3.2. *LV systolic function*

Three studies examined the relationship between EAT volume and LVEF [18,22,32]. A significant negative correlation between EAT volume and LVEF was observed in two studies [18,22], while no significant correlation was found in the other study [32]. Three studies examined the relationship between EAT volume and LV global longitudinal strain, all of which found a significant negative correlation [18,31,33].

3.3.3. *LV diastolic function*

Three studies examined the relationship between EAT volume and E/e' [18,22,33]. A significant positive correlation of EAT volume with E/e' was observed in two studies [18,33], while no significant correlation

Table 1
Characteristics of echocardiography studies.

Study, year	Study design	Definition of preserved EF	No. of patients	Method of quantifying EAT	Cardiac structure and function outcomes*	Exercise capacity outcomes	Summary of findings	Multivariate analysis	Quality
Koepp, 2020 [20]	Retrospective	EF ≥ 50 %	169	EAT thickness	…	Peak VO_2	EAT thickness correlated negatively with peak VO_2.	No	8
Gorter, 2020 [21]	Retrospective	EF > 45 %	75	EAT thickness	LV mass index, Left atrial volume index, LVEF, e', E/e', RV fractional area change	Peak VO_2	EAT thickness correlated negatively with peak VO_2. EAT thickness did not correlate with LV mass, left atrial volume index, LVEF, e', E/e', or RV fractional area change.	No	6
Lin, 2021 [26]	Retrospective	EF > 45 %	51	EAT thickness	LV mass index, LVEF, e', E/e', LV global longitudinal strain	…	EAT thickness correlated positively with LV mass and E/e' and negatively with LV global longitudinal strain. EAT thickness did not correlate with LVEF or e'.	Yes#	6
Pugliese, 2021 [27]	Prospective	EF ≥ 50 %	188	EAT thickness	LV mass index	Peak VO_2	EAT thickness correlated positively with LV mass and negatively with peak VO_2.	No	8
Jin, 2022 [28]	Prospective (derivation cohort)	EF ≥ 50 %	99	EAT thickness	LV global longitudinal strain	…	EAT thickness did not correlate with LV global longitudinal strain.	No	8
Jin, 2022 [28]	Retrospective (validation cohort)	EF ≥ 50 %	243	EAT thickness	LV global longitudinal strain	…	EAT thickness correlated negatively with LV global longitudinal strain.	No	6

EAT indicates epicardial adipose tissue; EF, ejection fraction; e', early diastolic mitral annular velocity; E/e', the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity; LV, left ventricular; peak VO_2, peak exercise oxygen uptake; RV, right ventricular.
Quality was assessed by the MINORS score. The global ideal score is 16 for non-comparative studies.
*Evaluated using echocardiography.
#Adjusted for age, sex, body mass index, hypertension, diabetes, dyslipidemia, prior cardiovascular diseases, and estimated glomerular filtration rate.

was found in the other study [22]. One study examined the relationship between EAT volume and e' but found no significant correlation [18].

3.3.4. RV function

Two studies examined the relationship between EAT volume and RV global longitudinal strain but found no significant correlation [18,33]. One study examined the relationship between EAT volume and RVEF but found no significant correlation [18]. No studies reported the relationship of EAT with RV fractional area change, tricuspid annular systolic velocity, or tricuspid annular plane systolic excursion.

3.3.5. Exercise capacity

One study examined the relationships of EAT volume with peak VO_2 and 6-minute walk distance and found significant positive correlations [19].

3.4. Quantitative analysis of echocardiography studies

The correlations of EAT thickness with cardiac structure and function and exercise capacity on echocardiography studies are shown in Fig. 2. EAT thickness significantly correlated with LV mass (pooled correlation coefficient [95 % CI] = 0.196 [0.053, 0.331], $P_{random} < 0.01$; $I^2 = 59.6$ %), LV global longitudinal strain (−0.265 [-0.425, −0.088], $P_{random} < 0.01$; $I^2 = 78.7$ %), and peak VO_2 (−0.370 [-0.454, −0.280], $P_{fix} < 0.001$; $I^2 = 0$ %), but not with LVEF (0.065 [-0.044, 0.173], $P_{fix} = 0.245$; I2 = 0 %), E/e' (0.199 [-0.186, 0.532], $P_{random} = 0.311$; $I^2 = 88.8$ %), or e' (−0.262 [-0.599, 0.155], $P_{random} = 0.215$; $I^2 = 90.5$ %). Funnel plots for each outcome are shown in Sup. Fig. 1.

3.5. Quantitative analysis of MRI studies

The correlations of EAT volume with cardiac structure and function on MRI studies are shown in Fig. 3. EAT volume significantly correlated with LV mass (pooled correlation coefficient [95 % CI] = 0.174 [0.048, 0.294], $P_{fix} < 0.01$; $I^2 = 0$ %), left atrial volume (0.268 [0.142, 0.386], $P_{fix} < 0.001$; $I^2 = 0$ %), LVEF (−0.207 [-0.325, −0.082], $P_{fix} < 0.01$; $I^2 = 0$ %), LV global longitudinal strain (−0.245 [-0.353, −0.131], $P_{fix} < 0.001$; $I^2 = 0$ %), and E/e' (0.171 [0.056, 0.282], $P_{random} < 0.01$; $I^2 = 74.8$ %), but not with RV global longitudinal strain (−0.162 [-0.326, 0.011], $P_{fix} = 0.06$; $I^2 = 0$ %). Funnel plots for each outcome are shown in Sup. Fig. 2.

4. Discussion

In the present study, we conducted a *meta*-analysis of studies examining the relationship between EAT and cardiac structure and function and exercise capacity in HFpEF patients. In the echocardiography studies, greater EAT thickness was associated with increased LV mass and reduced LV global longitudinal strain and peak VO_2. Similarly, in the MRI studies, a higher EAT volume was associated with increased LV mass, left atrial volume, and E/e' as well as reduced LVEF and LV global longitudinal strain. Thus, our findings indicate that increased EAT is associated with abnormal cardiac structure and function as well as exercise intolerance in HFpEF patients.

A previous *meta*-analysis of studies evaluating the association of EAT volume quantified by CT with cardiac structure and function reported that EAT volume was associated with altered cardiac structure and function, including LV hypertrophy, left atrial dilation, and LV diastolic dysfunction [41]. However, the study populations in the previous *meta*-analysis primarily comprised community-dwelling subjects and patients referred for cardiovascular risk stratification or cardiac CT due to suspected coronary artery disease. The present *meta*-analysis is significant in extending the reported association of EAT with abnormal cardiac structure and function to HFpEF patients. Furthermore, our *meta*-analysis is important in demonstrating the association of EAT with exercise intolerance in HFpEF patients.

Although our *meta*-analysis does not elucidate the precise mechanisms underlying the observed correlation between EAT and impaired

Table 2
Characteristics of MRI studies.

Study, year	Study Design	Definition of preserved EF	No. of Patients	Method of quantifying EAT	Cardiac structure and function outcomes*	Exercise capacity outcomes	Summary of findings	Multivariate analysis	Quality
van Woerden, 2018 [18]	Prospective	EF > 40 %	64	EAT volume	LV mass index, Left atrial volume index, LVEF, LV global longitudinal strain, e', E/e', RV global longitudinal strain, RVEF	…	EAT volume correlated positively with left atrial volume and E/e' and negatively with LVEF and LV global longitudinal strain. EAT volume did not correlate with LV mass, e', RV global longitudinal strain, or RVEF.	No	8
Haykowsky, 2018 [19]	Prospective	EF ≥ 50 %	100	EAT volume	…	Peak VO_2, 6-minute walk distance	EAT volume correlated positively with peak VO_2 and 6-minute walk distance	No	10
Wu, 2020 [22]	Prospective	EF ≥ 50 %	163	EAT volume	LV mass index, Left atrial volume index, LVEF, E/e'	…	EAT volume correlated positively with LV mass and left atrial volume index and negatively with LVEF. EAT volume did not correlate with E/e'.	No	10
Nakamori, 2023[31]	Retrospective	EF ≥ 50 %	150	EAT volume	LV global longitudinal strain, RV global longitudinal strain	…	EAT volume correlated negatively with LV global longitudinal strain and RV global longitudinal strain.	Yes†	8
Shao 2024 [32]	Prospective	EF ≥ 50 %	17	EAT volume	LV mass index, LVEF	…	EAT volume did not correlate with LV mass index or LVEF.	No	10
Schulz 2024 [33]	Prospective	EF ≥ 50 %	68	EAT volume	LV global longitudinal strain, E/e', RV global longitudinal strain	…	EAT volume correlated negatively with LV global longitudinal strain. EAT volume did not correlate with E/e' or RV global longitudinal strain.	Yes‡	8

EAT indicates epicardial adipose tissue; EF, ejection fraction; e', early diastolic mitral annular velocity; E/e', the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity; LV, left ventricular; peak VO_2, peak exercise oxygen uptake; RV, right ventricular.
Quality was assessed by the MINORS score. The global ideal score is 16 for non-comparative studies.
*Evaluated using MRI, except for LV diastolic function (e' and E/e') which was evaluated using echocardiography.
†Adjusted for age, sex, and body mass index.
‡Adjusted for age, body mass index, diabetes, dyslipidemia, and sex.

cardiac structure and function and exercise intolerance in HFpEF patients, several plausible explanations exist. First, EAT is known to modulate the secretion of systemic adipokines. Increased EAT volume has been linked to elevated leptin secretion and diminished adiponectin levels [42]. This dysregulation in adipokine profile has been associated with LV hypertrophy and LV dysfunction [43–47], which are common finding in HFpEF patients [4].

Second, coronary artery disease and coronary microvascular dysfunction may serve as a connecting mechanism between EAT and the altered cardiac structure and function observed in HFpEF patients. Many studies have reported the association of EAT with the severity of coronary artery disease [16 17]. Moreover, it is becoming increasingly apparent that EAT is linked with coronary microvascular dysfunction [16,17]. Numerous studies have documented the frequent occurrence of coronary artery disease and coronary microvascular dysfunction in HFpEF patients [48,49].

Third, prior research, including our own, has demonstrated a significant association between EAT and aortic stiffness [50–52]. Increased epicardial fat can exacerbate aortic stiffening, leading to elevated pulse wave velocity and early wave reflections in the central aorta [53]. These alterations in vascular dynamics contribute to delayed LV relaxation, thereby elevating diastolic filling pressure, especially during times of increased heart rate such as exercise [54–56]. Additionally, reduced aortic pressure in diastole may compromise coronary perfusion, potentially causing subendomyocardial ischemia, thereby exacerbating cardiac dysfunction, particularly in HFpEF patients with coronary artery disease [57].

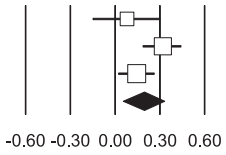
Moreover, reduced levels of circulating natriuretic peptides, attributed to enhanced expression of natriuretic peptide clearance receptors in adipose tissue, may serve as a potential intermediary between increased EAT deposition and cardiac dysfunction. Natriuretic peptides play pivotal roles in maintaining cardiovascular homeostasis, exerting natriuretic, vasorelaxant, and antifibrotic effects, thus mitigating cardiac hypertrophy and fibrosis [58].

Taken together, the interplay between EAT, coronary artery disease and microvasculature dysfunction, adipokines, vascular stiffness, and natriuretic peptide levels likely contributes to the development and progression of the cardiac structural and functional abnormalities observed in HFpEF patients. However, further mechanistic investigations are warranted to fully elucidate these complex pathways and potential therapeutic targets.

There are several limitations to the present study. First, the limited number of studies included in our *meta*-analysis and inconsistencies in the reporting of outcomes of interest resulted in a *meta*-analysis with only two or three studies for each outcome. Our findings demonstrated statistical significance when all included studies individually yielded significant findings, yet failed to achieve significance when these studies did not. This highlights a limitation of our study and emphasizes the need for caution in interpreting our findings. Second, not all reported correlation coefficients were adjusted for potential confounders. The observed associations of EAT with altered cardiac structure and function and exercise intolerance might reflect these potential confounders. Third, several studies included in our *meta*-analysis defined preserved EF as an EF of greater than or equal to 40 % or 45 %, which is inconsistent with the definition of preserved EF in the diagnostic criteria of HFpEF [59,60].

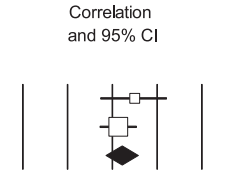
(a) LV mass

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Gorter 2020	0.080	-0.150	0.301	0.680	0.496
Pugliese 2021	0.320	0.185	0.443	4.511	0.000
Lin 2021	0.145	0.022	0.264	2.304	0.021
I^2 = 59.6%	0.196	0.053	0.331	2.675	0.007



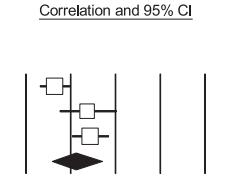
(b) LVEF

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Gorter 2020	0.150	-0.080	0.365	1.282	0.200
Lin 2021	0.040	-0.084	0.163	0.632	0.528
I^2 = 0%	0.065	-0.044	0.173	1.164	0.245



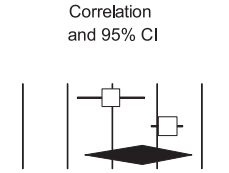
(c) LV global longitudinal strain

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Lin 2021	-0.408	-0.506	-0.300	-6.836	0.000
Jin 2022 Derivation cohort	-0.190	-0.373	0.008	-1.885	0.059
Jin 2022 Validation cohort	-0.170	-0.290	-0.045	-2.659	0.008
I^2 = 78.7%	-0.265	-0.425	-0.088	-2.910	0.004



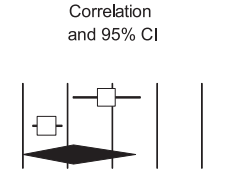
(d) E/e'

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Gorter 2020	-0.010	-0.236	0.217	-0.085	0.932
Lin 2021	0.371	0.259	0.473	6.148	0.000
I^2 = 88.8%	0.199	-0.186	0.532	1.014	0.311



(e) e'

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Gorter 2020	-0.040	-0.265	0.189	-0.340	0.734
Lin 2021	-0.441	-0.535	-0.336	-7.471	0.000
I^2 = 90.5%	-0.262	-0.599	0.155	-1.239	0.215



(f) Peak VO_2

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Koepp 2020	-0.300	-0.453	-0.130	-3.391	0.001
Gorter 2020	-0.430	-0.599	-0.225	-3.902	0.000
Pugliese 2021	-0.390	-0.505	-0.261	-5.601	0.000
I^2 = 0%	-0.370	-0.454	-0.280	-7.542	0.000

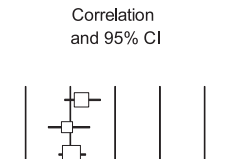
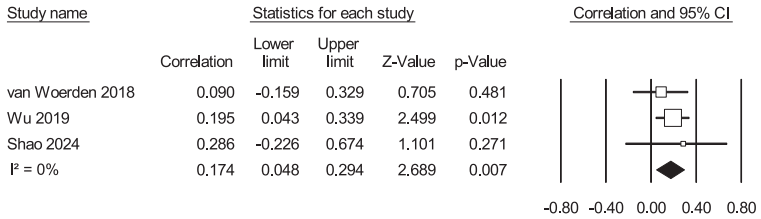
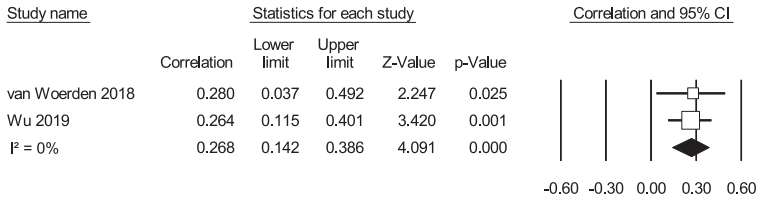


Fig. 2. Forest plots showing the correlation coefficients of epicardial adipose tissue thickness with left ventricular (LV) mass (a), LV ejection fraction (EF; b), LV global longitudinal strain (c), the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity (E/e'; d), early diastolic mitral annular velocity (e'; e), and peak VO_2 (f) in echocardiography studies.

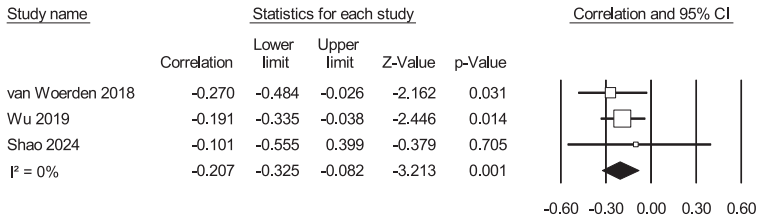
(a) LV mass



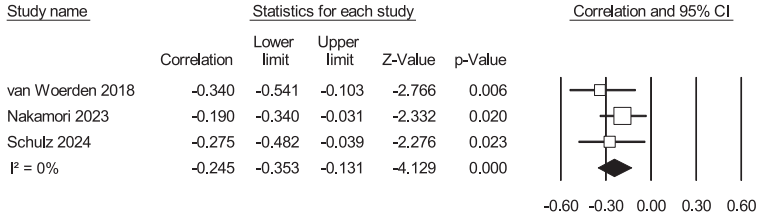
(b) Left atrial volume



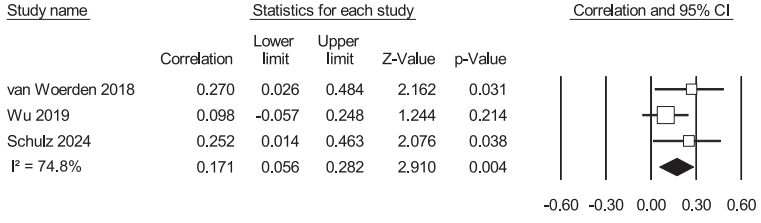
(c) LVEF



(d) LV global longitudinal strain



(e) E/e'



(f) RV global longitudinal strain

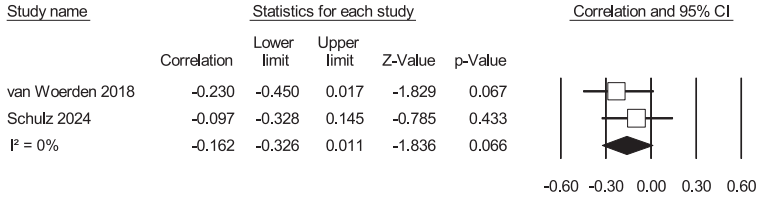


Fig. 3. Forest plots showing the correlation coefficients of epicardial adipose tissue volume with left ventricular (LV) mass (a), left atrial volume (b), LV ejection fraction (EF; c), LV global longitudinal strain (d), the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity (E/e'; e), and right ventricular (RV) global longitudinal strain (f) in MRI studies.

5. Conclusion

Our *meta*-analysis indicates a potential association of epicardial fat with altered cardiac structure and function and exercise intolerance in HFpEF patients. However, it is important to note that our *meta*-analysis was limited by the inclusion of only two or three studies for each outcome. Therefore, further research is necessary to validate our findings. Nevertheless, our findings underscore the need for further research to elucidate the pathophysiological mechanisms linking epicardial fat to abnormal cardiac structure and function and exercise intolerance in HFpEF patients. This exploration has the potential to inspire the development of innovative treatments tailored to this patient population.

6. Systematic review registration

INPLASY 202420071

CRediT authorship contribution statement

Hidekatsu Fukuta: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Toshihiko Goto:** Writing – review & editing, Data curation. **Takeshi Kamiya:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101444.

References

[1] R.S. Vasan, S.M.G. Larson, E.J. Benjamin, et al., Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction, J. Am. Coll. Cardiol. 33 (1999) 1948–1955.
[2] T.E. Owan, D.O. Hodge, R.M. Herges, et al., Trends in prevalence and outcome of heart failure with preserved ejection fraction, N Engl J Med 355 (2006) 251–259.
[3] M. Tsuchihashi-Makaya, S. Kinugawa, H. Yokoshiki, et al., Beta-blocker use at discharge in patients hospitalized for heart failure is associated with improved survival, Circ J 74 (2010) 1364–1371.
[4] M.A. Pfeffer, A.M. Shah, B.A. Borlaug, Heart Failure With Preserved Ejection Fraction In Perspective, Circ Res 124 (2019) 1598–1617.
[5] D.W. Kitzman, W.C. Little, P.H. Brubaker, et al., Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure, JAMA 288 (2002) 2144–2150.
[6] Y.N.V. Reddy, A. Rikhi, M. Obokata, et al., Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity, Eur J Heart Fail 22 (2020) 1009–1018.
[7] D.W. Kitzman, M.B. Higginbotham, F.R. Cobb, et al., Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism, J Am Coll Cardiol 17 (1991) 1065–1072.
[8] M.R. Zile, C.F. Baicu, W.H. Gaasch, Diastolic heart failure–abnormalities in active relaxation and passive stiffness of the left ventricle, N Engl J Med 350 (2004) 1953–1959.
[9] M.R. Zile, J.S. Gottdiener, S.J. Hetzel, et al., Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction, Circulation 124 (2011) 2491–2501.
[10] C.S. Lam, V.L. Roger, R.J. Rodeheffer, et al., Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 115 (2007) 1982–1990.
[11] M.R. Zile, B. Kjellstrom, T. Bennett, et al., Effects of exercise on left ventricular systolic and diastolic properties in patients with heart failure and a preserved ejection fraction versus heart failure and a reduced ejection fraction, Circ Heart Fail 6 (2013) 508–516.
[12] M.T. Maeder, B.R. Thompson, H.P. Brunner-La Rocca, D.M. Kaye, Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction, J Am Coll Cardiol 56 (2010) 855–863.
[13] C.S. Fox, J.M. Massaro, U. Hoffmann, et al., Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study, Circulation 116 (2007) 39–48.
[14] G.A. Rosito, J.M. Massaro, U. Hoffmann, et al., Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study, Circulation 117 (2008) 605–613.
[15] A.A. Mahabadi, J.M. Massaro, G.A. Rosito, et al., Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study, Eur Heart J 30 (2009) 850–856.
[16] M. Konwerski, A. Gasecka, G. Opolski, et al., Role of Epicardial Adipose Tissue in Cardiovascular Diseases, A Review, Biology (basel) 11 (2022) 355.
[17] G. Iacobellis, Epicardial adipose tissue in contemporary cardiology, Nat Rev Cardiol 19 (2022) 593–606.
[18] G. van Woerden, T.M. Gorter, B.D. Westenbrink, et al., Epicardial fat in heart failure patients with mid-range and preserved ejection fraction, Eur J Heart Fail 20 (2018) 1559–1566.
[19] M.J. Haykowsky, B.J. Nicklas, P.H. Brubaker, et al., Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction, JACC Heart Fail 6 (2018) 640–649.
[20] K.E. Koepp, M. Obokata, Y.N.V. Reddy, et al., Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction, JACC Heart Fail 8 (2020) 657–666.
[21] T.M. Gorter, G. van Woerden, M. Rienstra, et al., Epicardial Adipose Tissue and Invasive Hemodynamics in Heart Failure With Preserved Ejection Fraction, JACC Heart Fail 8 (2020) 667–676.
[22] C.K. Wu, J.K. Lee, J.C. Hsu, et al., Myocardial adipose deposition and the development of heart failure with preserved ejection fraction, Eur J Heart Fail 22 (2020) 445–454.
[23] G. van Woerden, D.J. van Veldhuisen, T.M. Gorter, et al., Importance of epicardial adipose tissue localization using cardiac magnetic resonance imaging in patients with heart failure with mid-range and preserved ejection fraction, Clin Cardiol 44 (2021) 987–993.
[24] J. Tromp, J.A. Bryant, X. Jin, et al., Epicardial fat in heart failure with reduced versus preserved ejection fraction, Eur J Heart Fail 23 (2021) 835–838.
[25] W. Ying, K. Sharma, L.R. Yanek, et al., Visceral adiposity, muscle composition, and exercise tolerance in heart failure with preserved ejection fraction, ESC Heart Fail 8 (2021) 2535–2545.
[26] J.L. Lin, K.T. Sung, Y.H. Lai, et al., Epicardial Adiposity in Relation to Metabolic Abnormality, Circulating Adipocyte FABP, and Preserved Ejection Fraction Heart Failure, Diagnostics (basel) (2021) 11.
[27] N.R. Pugliese, F. Paneni, M. Mazzola, et al., Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure, Eur J Heart Fail 23 (2021) 1858–1871.
[28] X. Jin, C.L. Hung, W.T. Tay, et al., Epicardial adipose tissue related to left atrial and ventricular function in heart failure with preserved versus reduced and mildly reduced ejection fraction, Eur J Heart Fail 24 (2022) 1346–1356.
[29] A. Venkateshvaran, U.L. Faxen, C. Hage, et al., Association of epicardial adipose tissue with proteomics, coronary flow reserve, cardiac structure and function, and quality of life in heart failure with preserved ejection fraction: insights from the PROMIS-HFpEF study, Eur J Heart Fail 24 (2022) 2251–2260.
[30] G. van Woerden, D.J. van Veldhuisen, O.C. Manintveld, et al., Epicardial Adipose Tissue and Outcome in Heart Failure With Mid-Range and Preserved Ejection Fraction, Circ Heart Fail 15 (2022) e009238.
[31] S. Nakamori, S. Kucukseymen, J. Rodriguez, et al., Obesity-Related Differences in Pathomechanism and Outcomes in Patients With HFpEF. JACC, Advances 2 (2023) 100730.
[32] J.W. Shao, B.H. Chen, K. Abu-Shaban, et al., Epicardial adipose tissue in obesity with heart failure with preserved ejection fraction: Cardiovascular magnetic resonance biomarker study, World J Cardiol 16 (2024) 149–160.
[33] A. Schulz, S.J. Backhaus, T. Lange, et al., Impact of epicardial adipose tissue on cardiac function and morphology in patients with diastolic dysfunction, ESC Heart Fail, 2024.
[34] D. Moher, L. Shamseer, M. Clarke, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst Rev 4 (2015) 1.
[35] J. Webb, L. Fovargue, K. Tondel, et al., The Emerging Role of Cardiac Magnetic Resonance Imaging in the Evaluation of Patients with HFpEF, Curr Heart Fail Rep 15 (2018) 1–9.
[36] C. Tschope, M. Senni, Usefulness and clinical relevance of left ventricular global longitudinal systolic strain in patients with heart failure with preserved ejection fraction, Heart Fail Rev 25 (2020) 67–73.
[37] T.M. Gorter, E.S. Hoendermis, D.J. van Veldhuisen, et al., Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis, Eur J Heart Fail 18 (2016) 1472–1487.
[38] V. Anastasiou, A.S. Papazoglou, D.V. Moysidis, et al., The prognostic value of right ventricular longitudinal strain in heart failure: a systematic review and meta-analysis, Heart Fail Rev 28 (2023) 1383–1394.
[39] K. Slim, E. Nini, D. Forestier, et al., Methodological index for non-randomized studies (minors): development and validation of a new instrument, ANZ J Surg 73 (2003) 712–716.
[40] R.A. Peterson, S.P. Brown, On the use of beta coefficients in meta-analysis, J Appl Psychol 90 (2005) 175–181.
[41] J. Mancio, D. Azevedo, M. Fragao-Marques, et al., Meta-Analysis of Relation of Epicardial Adipose Tissue Volume to Left Atrial Dilation and to Left Ventricular Hypertrophy and Functions, Am J Cardiol 123 (2019) 523–531.

[42] G. Iacobellis, D. Corradi, A.M. Sharma, Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart, Nat Clin Pract Cardiovasc Med 2 (2005) 536–543.
[43] S.J. Hong, C.G. Park, H.S. Seo, et al., Associations among plasma adiponectin, hypertension, left ventricular diastolic function and left ventricular mass index, Blood Press 13 (2004) 236–242.
[44] F. Sam, T.A. Duhaney, K. Sato, et al., Adiponectin deficiency, diastolic dysfunction, and diastolic heart failure, Endocrinology 151 (2010) 322–331.
[45] H. Fukuta, N. Ohte, K. Wakami, et al., Relation of plasma levels of adiponectin to left ventricular diastolic dysfunction in patients undergoing cardiac catheterization for coronary artery disease, Am J Cardiol 108 (2011) 1081–1085.
[46] R. Fontes-Carvalho, J. Pimenta, P. Bettencourt, et al., Association between plasma leptin and adiponectin levels and diastolic function in the general population, Expert Opin Ther Targets 19 (2015) 1283–1291.
[47] V.P. Puurunen, E.S. Lepojarvi, O.P. Piira, et al., High plasma leptin levels are associated with impaired diastolic function in patients with coronary artery disease, Peptides 84 (2016) 17–21.
[48] C.J. Rush, C. Berry, K.G. Oldroyd, et al., Prevalence of Coronary Artery Disease and Coronary Microvascular Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction, JAMA Cardiol 6 (2021) 1130–1143.
[49] D. D'Amario, R. Laborante, E. Bianchini, et al., Impact of coronary microvascular dysfunction in heart failure with preserved ejection fraction: a meta-analysis, ESC Heart Fail, 2024.
[50] F. Natale, M.A. Tedesco, R. Mocerino, et al., Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives, Eur J Echocardiogr 10 (2009) 549–555.
[51] B.J. Kim, B.S. Kim, J.H. Kang, Echocardiographic epicardial fat thickness is associated with arterial stiffness, Int J Cardiol 167 (2013) 2234–2238.
[52] K. Hachiya, H. Fukuta, K. Wakami, 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 30 (2014) 1393–1398.
[53] M.F. O'Rourke, G. Mancia, Arterial stiffness, J Hypertens 17 (1999) 1–4.
[54] M. Hori, M. Inoue, M. Kitakaze, et al., Altered loading sequence as an underlying mechanism of afterload dependency of ventricular relaxation in hearts in situ, Jpn Circ J 49 (1985) 245–254.
[55] F. Kohno, T. Kumada, M. Kambayashi, et al., Change in aortic end-systolic pressure by alterations in loading sequence and its relation to left ventricular isovolumic relaxation, Circulation 93 (1996) 2080–2087.
[56] G.D. Buckberg, D.E. Fixler, J.P. Archie, J.I. Hoffman, Experimental subendocardial ischemia in dogs with normal coronary arteries, Circ Res 30 (1972) 67–81.
[57] W.J. Paulus, W. Grossman, T. Serizawa, et al., Different effects of two types of ischemia on myocardial systolic and diastolic function, Am J Physiol 248 (1985) H719–H728.
[58] R. Sarzani, M. Allevi, C. Di Pentima, et al., Role of Cardiac Natriuretic Peptides in Heart Structure and Function, Int J Mol Sci 23 (2022).
[59] C.W. Yancy, M. Jessup, B. Bozkurt, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J Am Coll Cardiol 62 (2013) e147–e239.
[60] P. Ponikowski, A.A. Voors, S.D. Anker, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 37 (2016) 2129–2200.