Lipids in Health and Disease

REVIEW

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Linking abnormal fat distribution with HFpEF and diastolic dysfunction: a systematic review, meta-analysis, and meta-regression of observational studies

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Abstract

Background The global prevalence of obesity has escalated into a formidable health challenge intricately linked with the risk of developing cardiac diastolic disfunction and heart failure with preserved ejection fraction (HFpEF). Abnormal fat distribution is potentially strongly associated with an increased risk of cardiac diastolic dysfunction, and we aimed to scrutinize and elucidate the correlation between them.

Methods Following the Cochrane Handbook and PRISMA 2020 guidelines, we systematically reviewed the literature from PubMed, Embase, and Web of Science. We focused on studies reporting the mean and standard deviation (SD) of abnormal fat in HFpEF or cardiac diastolic dysfunction patients and the Pearson/Spearman correlation coefficients for the relationship between abnormal fat distribution and the risk of developing cardiac diastolic dysfunction. Data were standardized to the standard mean difference (SMD) and Fisher's z value for meta-analysis.

Results After progressive filtering and selection, 63 studies (43,113 participants) were included in the quantitative analyses. Abnormal fat distribution was significantly greater in participants with cardiac diastolic dysfunction than in controls [SMD 0.88 (0.69, 1.08)], especially in epicardial adipose tissue [SMD 0.99 (0.73, 1.25)]. Abnormal fat distribution was significantly correlated with the risk of developing cardiac diastolic dysfunction [E/E': 0.23 (0.18, 0.27), global longitudinal strain: r=-0.11 (-0.24, 0.02)]. Meta-regression revealed sample size as a potential heterogeneous source, and subgroup analyses revealed a stronger association between abnormal fat distribution and the risk of developing cardiac diastolic dysfunction in the overweight and obese population.

Conclusion Abnormal fat distribution was significantly associated with the risk of developing cardiac diastolic dysfunction.

Trial registration CRD42024543774.

Keywords Abnormal fat, Cardiac diastolic dysfunction, Heart failure with preserved ejection fraction, Systematic review, Meta-analysis

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Introduction

With the increasing popularity of sedentary lifestyles and high-calorie diets, obesity has become a serious social and public health problem [1]. In the United States, the incidence of overweight and obesity has escalated to 30.7% and 42.4%, respectively [2]. These alarming numbers are increasing and exerting a profound and detrimental impact on global health and economic stability [3]. A dose–response meta-analysis revealed a 41% heightened in the risk of developing heart failure with each 5 kg/m² body mass index (BMI) increment, whereas the Framingham Heart Study reported a 44% increase in the risk of developing heart failure with preserved ejection fraction (HFpEF) with each 4.7 kg/m² BMI increment [4, 5]. Obesity leads to impaired left ventricular diastolic function, myocardial stiffness, and reduced relaxation capacity, which results in volume expansion and elevated filling pressures. It is associated with abnormal fat distribution, resulting in excess systemic free fatty acid-mediated lipotoxicity and persistent microinflammation within cardiomyocytes [6–8]. Abnormal fat distribution refers to the abnormal deposition of fat in nonphysiological storage areas of the body, such as the liver, heart, pancreas, and skeletal muscle [9–11]. The connection between abnormal fat distribution and the risk of developing HFpEF is a burgeoning field in cardiovascular research. Studies have shown that visceral adipose tissue (VAT) and epicardial adipose tissue (EAT) are predictive of HFpEF and its associated cardiometabolic risks but not of heart failure with a reduced ejection fraction (HFrEF) [12, 13]. NAFLD induces HFpEF through inflammation and abnormal arteriovenous haemodynamics, resulting in three subtypes: obstructive, metabolic, and advanced liver fibrosis HFpEF [14].

With advancements and iterations in imaging technology, the methods for assessing abnormal fat distribution have become more abundant. However, previous research has often been limited to specific populations or types of abnormal fat distribution, and comprehensive comparisons and evaluations of the relationships between different abnormal fat deposits and the risk of developing cardiac diastolic dysfunction (CDD) are lacking. For example, a study by Wu et al. explored a strong association between EAT and the risk of developing atrial and ventricular dysfunction in HFpEF patients [15]. Similarly, Chong et al. reported a significant correlation between EAT thickness and volume and the risk of developing adverse cardiovascular outcomes, including myocardial infarction, coronary revascularization, and atrial fibrillation [16]. In addition, Cho et al. reported that EAT, rather than VAT, is associated with the risk of developing left ventricular geometry and function deterioration [17]. Considering the differences and limitations of previous studies, the aim of the current study was to conduct a meta-analysis of observational studies to provide a thorough review and investigation into the correlation between abnormal fat distribution and the risk of developing CDD.

Materials and methods

The study was guided by the Cochrane Handbook [18] and was registered in the PROSPERO (CRD42024543774). The study was guided by the 27-item checklist outlined in the PRISMA 2020 guidelines [19]. Data retrieval, extraction, and analysis were undertaken by FZY and WYJ. When disagreements occurred, a consensus was achieved through discussions with SQQ.

Search strategy and inclusion criterion

FZY and WYJ searched the PubMed, Embase, and Web of Science from establishment date to 10 May 2024, with language restrictions to English, and the search strategy involved a combination of subject terms plus free words, as described in Supplement Appendix S2.

The inclusion criteria were constructed according to the PECOS principles and studies were included based on the following criteria:

1) Participants: individuals diagnosed with HFpEF or CDD and were older than 18 years.
2) Exposure: abnormal fat (VAT, EAT, pericardial adipose tissue (PAT), nonalcoholic fatty liver disease (NAFLD)).
3) Outcomes: E/A, E/E', e, E, global circumferential strain (GCS), global longitudinal strain (GLS), the left ventricular end-diastolic volume (LVEDV) and left ventricular end-diastolic internal diameter (LVEDD).
4) Study design: observational clinical studies.

Studies were omitted based on the following criteria:

1) Reviews, abstracts, and case reports.
2) Publications in non-English languages; and.
3) Missing main outcomes.

Data extraction

Data were meticulously extracted and recorded in a standardized form via Microsoft Excel, capturing the following details: (1) basic information: first author, year, nationality/region, and study design; (2) baseline information: sample size, sex ratio, mean age, BMI, distribution of abnormal fat, and detection method; and (3) outcomes: reported quantitative measurements of abnormal fat (means with standard deviations (mean [SD])), correlation between abnormal fat distribution and the

risk of developing cardiac diastolic function (Pearson and Spearman coefficients).

Study quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of each study in the three dimensions: selectivity of the population, groups comparability, and outcome of the nonrandomized study. A cumulative score out of 9 was given, where scores of 7–9 signify high quality, 4–6 denote moderate quality, and below 4 indicates low quality [20].

Data analysis

Data processing

The extracted data included the mean (SD) and Pearson/Spearman correlation coefficients. To standardize the data and mitigate the effects of differing units, measurement techniques, and calculation methods, we transformed the continuous variables into Cohen's d standard mean differences (SMDs) with 95% confidence intervals (95% CIs). Additionally, we converted the Spearman correlation coefficients to their Pearson equivalents via the following formula [21, 22]:

$$r = \beta \times 0.98 - 0.05_r = \beta \times 0.98 - 0.05(-0.5 < \beta < 0); \quad r = \beta \times 0.98 + 0.05_r = \beta \times 0.98 + 0.05(\leq \beta < 0.50)$$

For data analysis, we translated the correlation coefficients into Z values via Fisher's z-transformation, which approximates a normal distribution, and calculated their standard deviations (standard errors, SEs). An inverse Fisher transformation was then applied to derive the correlation coefficients and 95% Cis [23, 24]. According to the established classification of correlation coefficients, we categorized absolute values into three ranges: below 0.3 for weak, from 0.3 to 0.7 for moderate, and above 0.7 for robust linear correlations [25]. Furthermore, we applied Cohen's criteria to define small, moderate, and large effect sizes for the SMD at thresholds of 0.2, 0.5, and 0.8, respectively [26].

Combined effect sizes

The statistical analyses were performed via Stata 17.0 (College Station, USA). Owing to considerable heterogeneity, a random-effects model with restricted maximum likelihood estimation and Cohen's statistic was used to synthesize the statistics. To identify the sources of heterogeneity, we conducted meta-regression and subgroup analyses, considering factors such as sample size, age, BMI, region, fat locations, detection methods, and study design.

Sensitivity analyses were executed via sequential elimination to identify and exclude the studies that exerted the most significant influence on the robustness of the findings. Publication bias was investigated via two complementary methods: (1) the contour-enhanced funnel plots, which were used to visually inspect the symmetry of the plot and the distribution intervals [27], and (2) the trim-and-fill method, which was used to iteratively determine whether the inclusion or exclusion of studies affected the direction of the results [28].

Results

Study screening process

The initial search yielded 2,132 articles. After removing duplicates, 1,536 articles remained. We then removed 1,424 irrelevant articles on the basis of their titles and abstracts. After a thorough review of the remaining 112 articles, we ultimately included 63 articles.(Fig. 1).

Description and quality assessment of the included studies

The systematic review encompassed 63 studies, comprising 43 cross-sectional studies, 9 case–control studies, and 11 cohort studies with a total of 43,113 participants. The mean age fluctuated within the range of 29 to 73 years, with an overall weighted average of 57.84 years. The BMI fluctuated within the range of 22 to 43.7 kg/m^2, with a weighted BMI of 27.08 kg/m^2. Abnormal fat included EAT ($n=31$), PAT ($n=8$), VAT ($n=15$), thigh adipose tissue ($n=1$), and NAFLD ($n=10$). (Table 1).

The quality assessment revealed that the NOS scores ranged from 7 to 9, indicating that all the studies were of high quality (Supplement Appendix S4).

Exploring the association between the risk of developing CDD and abnormal fat distribution based on the SMD

Fifteen studies reported quantitative measurements—such as thickness, area, or volume—of abnormal fat in participants presenting with CDD and included 4,533 participants (580 participants with CDD/HFpEF and 1106 controls). We calculate the combined effect size with the random-effects model and revealed a significant increase in abnormal fat distribution among CDD patients [SMD = 0.88(0.69, 1.08), $P<0.05$].

Subgroup analysis showed an association between EAT and CDD [SMD = 0.99(0.73, 1.25), $P<0.05$, $I^2=80.4\%$]. Similarly, VAT had a moderate effect size [SMD = 0.74(0.38, 1.10), $P<0.05$, $I^2=77\%$], and PAT had a smaller yet significant effect size [SMD = 0.51(0.18, 0.83), $P<0.05$] (Fig. 2).

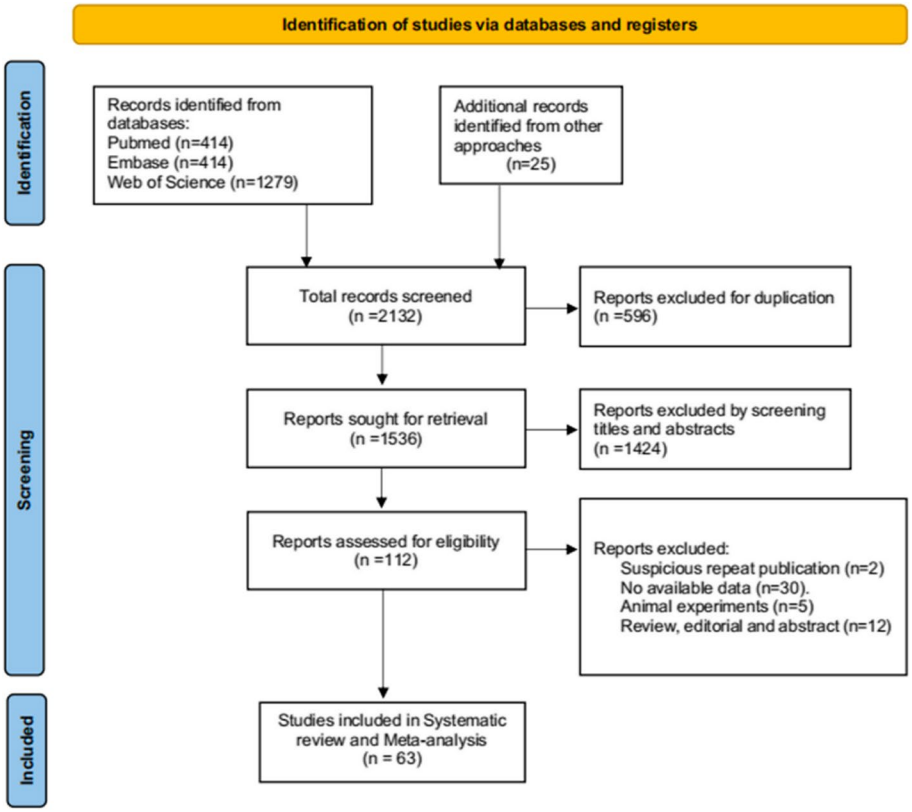

Fig. 1 Flowchart of study inclusion and screening

Exploring CDD and abnormal fat correlation via Pearson correlation

Mitral valve doppler ultrasound indices

Using tissue Doppler ultrasound to detect diastolic mitral flow velocities and motion velocities, abnormal fat distribution had a weak positive correlation with E/E' [$n=29$, $r=0.23$ (0.18, 0.27), $P<0.05$], whereas it had a weak positive correlation with E [$n=7$, r=-0.10(-0.24, 0.04), $P<0.05$)] and E/A [$n=16$, r=-0.29(-0.37, -0.21), $P<0.05$] and a weak negative correlation with E [$n=23$, r=-0.27(-0.35, -0.19), $P<0.05$] (Supplement Appendix S5).

An analysis of the different fat deposition locations revealed that NAFLD status had the strongest correlations with E/E' ($r=0.32$) and e (r=-0.24), whereas EAT showed a strong negative correlation with E/A (r=-0.32), and PAT similarly correlated negatively with with e ($r=0.32$) (Table 2).

Myocardial strain

The speckle tracking technique is a sophisticated method that enables the tracking of echo signals throughout the cardiac cycle and reflects quantitative myocardial ventricular motion. GLS indicates the relative change in the length of the left ventricular myocardium along its long axis from end-diastole to end-systole. Conversely, the GCS indicates the relative change in the circumferential direction. Abnormal fat distribution was weakly correlated with myocardial strain [GLS $n=17$, r=-0.11(-0.24, 0.02), $P<0.05$] [GCS $n=6$, r=-0.19(-0.34, -0.03), $P<0.05$] (Supplement Appendix S5).

An analysis of the different abnormal fat deposition locations revealed that NAFLD status had the strongest correlation with GLS (r=-0.18) and GCS (r=-0.34), whereas VAT had a weak negative correlation with GLS (r=-0.06) (Table 2).

LVEDd and LVEDV

Abnormal fat deposits had a weak positive correlation with LVEDd [$n=5$, $r=0.16$ (-0.05, 0.38), $P<0.05$)] and LVEDV [$n=9$, $r=0.10$ (-0.12, 0.31), $P<0.05$)] (Supplement Appendix S5).

An analysis of the different abnormal fat deposition locations revealed that NAFLD status had the strongest correlation with LVEDd ($r=0.24$). Moreover, EAT and VAT were positively correlated with the LVEDV ($r=0.31$), and surprisingly, NAFLD status was significantly negatively correlated with LVEDV (r=-0.31).

Table 1 Table of basic characteristics of included studies

First author Year	Region 1 = Asian 2 = Europe 3 = America 4 = Oceania	Design 1 = Cross-sectional study 2 = Case-control study 3 = Cohort study	Total sample	Mean age	BMI	Male%	Areas of ectopic fat 1 = Epicardial 2 = Pericardial 3 = Visceral 4 = Subcutaneous 5 = Thigh 6 = Fatty liver	Imagingmodality 1 = ultrasound 2 = DXA 3 = CT 4 = CMRI 5 = BIA 6 = PET-CT
Lin HH, 2013 [29]	1	1	149	57.8	24	75.84	134	1
Konishi M, 2012 [30]	1	1	229	69	23.7	59.00	2	3
Rao VN, 2018 [13]	3	3	1806	73.1	29.9	48.40	34	3
Chin JF, 2023 [31]	2	1	186	52.2	42.3	24.70	1	1
Choy M, 2023 [32]	1	3	1554	63.3	28.1	47.00	1	4
Koepp KE, 2020 [33]	1	1	338	64.5	24.8	58.00	1	1
Kardassis D, 2012 [34]	2	1	88	58.9	42.5	47.73	34	3
Pugliese NR, 2021 [35]	2	1	232	73	31.5	61.70	1	1
Hardt F, 2020 [36]	2	1	50	71	27	84.00	1	3
Takahari K, 2022 [37]	1	1	235	64.2	23.7	52.00	13	3
Rhee TM, 2019 [38]	1	1	338	64.5	24.8	58.00	1	1
Huynh K, 2022 [39]	3	1	2399	73	27.1	47.40	5	3
Qu YL, 2023 [40]	1	1	88	30.1	27.7	56.80	34	4
Yao F, 2023 [41]	1	1	1558	52.3	24	40.30	13	5
Ma W, 2021 [42]	1	1	1058	63.91	25.88	51.40	1	1
Tekin I, 2018 [43]	2	1	97	59	26.53	50.52	1	1
Park HE, 2014 [44]	1	3	1456	53	24	67.00	1	1
Chu CY, 2016 [45]	1	3	190	70	25.6	67.37	1	1
Peng DD, 2022 [46]	1	1	228	48.84	25.57	67.54	6	1
Chiu LS, 2020 [47]	3	1	2356	52	27.6	48.00	6	3
Lai YH, 2022 [48]	1	1	2161	48.3	25.69	63.50	1	1
Lee YH, 2018 [49]	1	1	308	56.9	23	55.00	6	6
VanWagner LB, 2015 [50]	3	3	2713	50.1	30.4	41.20	6	3
Min J, 2022 [51]	3	3	3032	57	27.2	47.00	2	3
Chiocchi M, 2023 [52]	2	1	93	66.4	27.9	73.10	1	3
Kostka F, 2024 [53]	2	1	1096	50.9	30.1	50.70	6	4
Hearon CM, 2023 [54]	3	1	71	49	39	21.13	1	4
Yoon HE, 2017 [55]	1	1	1028	50.6	24.8	75.10	3	5
Çetin M, 2013 [56]	2	1	127	50	30.1	67	1	1
Topuz M, 2017 [57]	2	1	250	69	28.3	76	1	1
Liu J, 2024 [12]	1	1	92	30	28.4	85.87	1	4
Huang S, 2023 [58]	1	1	260	52.3	22	51.54	6	4
Shao JW, 2024 [59]	1	2	62	42.94	35.78	58.1	1	4
Kim SA, 2017 [60]	1	1	152	62	25.2	50	1	1
Jin XY, 2022 [61]	1	2	248	64.6	29.2	54.8	1	1
Lin JL, 2021 [62]	1	2	252	65.8	26.5	35.3	1	1
Mahabadi AA, 2022 [63]	2	1	379	65.2	27.6	70.20	1	4
Dabbah S, 2014 [64]	2	1	73	52.3	30.7	82	1	1
Vural M, 2014 [65]	2	1	63	57.8	29.4	46	1	3
Ates K, 2022 [66]	2	2	60	71.6	32.79	10	1	1
Woerden G, 2021 [67]	2	1	102	70	29.5	51	1	4
Turak O, 2013 [68]	2	1	135	56.3	28.1	38.5	1	1

Table 1 (continued)

First author Year	Region 1 = Asian 2 = Europe 3 = America 4 = Oceania	Design 1 = Cross-sectional study 2 = Case-control study 3 = Cohort study	Total sample	Mean age	BMI	Male%	Areas of ectopic fat 1 = Epicardial 2 = Pericardial 3 = Visceral 4 = Subcutaneous 5 = Thigh 6 = Fatty liver	Imagingmodality 1 = ultrasound 2 = DXA 3 = CT 4 = CMRI 5 = BIA 6 = PET-CT
Fontes-Carvalho R, 2014 [8]	2	1	225	55.1	26.9	84	134	3
Coelho P, 2024 [69]	2	1	82	58	29.17	52	12	1
Hua N, 2014 [70]	3	1	60	42.4	35.9	0.00	2	4
Sawada N, 2020 [71]	1	1	340	56	23.5	71.8	34	1
Kosmala W, 2012 [72]	2	1	73	39.2	23.5	48	3	2
Nakanishi K, 2017 [73]	1	1	372	67	24.1	66.4	1	3
Zhou H, 2022 [74]	1	2	113	54.5	22.7	63.7	1	4
Wu CK, 2020 [75]	1	2	194	60.9	24.8	63.9	1	4
Chung GE, 2018 [76]	1	1	3300	60.7	24.6	62.9	6	1
Mantovani A, 2015 [77]	2	1	222	68.6	29.3	70.3	6	1
Wang QQ, 2018 [78]	1	2	40	61.9	24.74	50	6	1
Simon TG, 2017 [79]	3	3	65	50	43.7	56.92	6	1
Kenchaiah S, 2021 [80]	3	1	6785	60.2	26.7	47	2	3
Wolf P, 2016 [81]	4	1	31	29	23	61.3	2	4
Haykowsky MJ, 2018 [82]	3	2	161	66.5	39.3	73.9	12	4
Rao VN, 2021 [83]	3	3	2844	59.4	28	35	23	3
Neeland IJ, 2013 [84]	3	3	2710	41	27.5	48.1	3	4
Zhu J, 2023 [85]	1	2	89	56	25.54	49.44	1	4
Canepa M, 2013 [86]	3	3	843	67	26	55	34	3
Sawada N, 2019 [87]	1	1	213	56	24	71.8	34	3
Ying W, 2021 [88]	3	3	88	67.5	37.3	70.50	134	4

Subgroup analysis and meta-regression

Meta-regression was used to assess the trend of a potential effect modifier by statistically combining the results through an integrated and quantitative approach [89]. The results showed that sample size may be a covariate, with the associations of abnormal fat distribution with E/E' (Z=-2.68) and E/A (Z=-3.69) diminishing as the sample size increased. The strength of the association between abnormal fat distribution and the GCS score also tended to increase with age, BMI, and male sex (Supplement Appendix S7).

However, covariates in the meta-regression did not account for all of the observed heterogeneity, and subgroup analyses based on sample size, region, study design, age, BMI, and detection methods were conducted to detect heterogeneity. The aim was to delve deeper into the results, overcome the limitations associated with continuous variables, and identify the root causes of heterogeneity. The findings were as follows (Table 2):

1) In studies with larger sample sizes (>1000 participants), the correlation coefficients for the associations of abnormal fat distribution with E/E', E/A, and e' were approximately half those reported in smaller studies (<99 participants).
2) Compared with that in other demographic groups, the association between abnormal fat distribution and the risk of developing CDD was more pronounced in European populations (E/E' r=0.31, I^2=54.81%).
3) Compared with that in normal weight patients, in overweight or obese patients, abnormal fat distribution was strongly correlated with abnormal mitral Doppler findings (E/E' *r*=0.26, e *r*=-0.29) and impaired strain function (GLS *r*=-0.28, GCS *r*=-0.21).
4) When measured by ultrasound, abnormal fat distribution was significantly more strongly associated with the risk of developing CDD than other detection methods were.

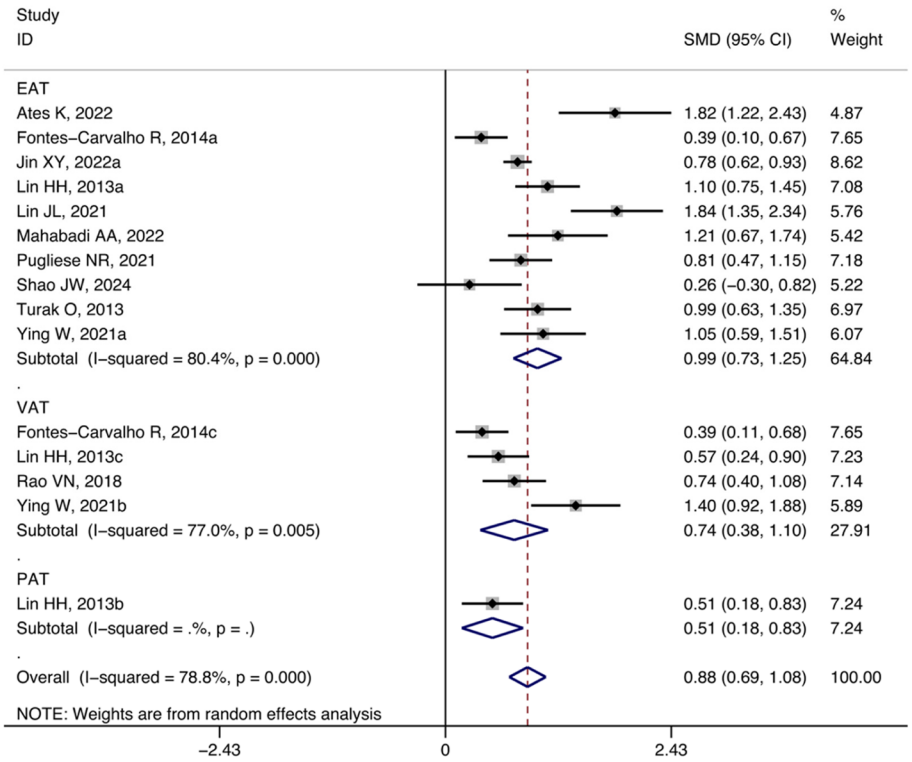

Fig. 2 Subgroup analysis linked abnormal fat distribution to CDD risk, based on the SMD

Sensitivity analysis

A sequential elimination sensitivity analysis was conducted to validate the results' robustness and reliability. During this process, the robustness of seven outcomes was affected. Upon eliminating those outlier studies and recalculating the combined effect sizes, no alteration was observed in the direction of the effects, which indicates the stability and dependability of the results. Notably, the large-sample studies conducted by Chiu et al. [47]. , Kostka et al. [53]. , and VanWagner et al. [50]. carried significant weight in the analysis and exerted a substantial influence on the combined effect sizes (Supplement Appendix S8).

Publication bias

The contour-enhanced plot classifies studies into three intervals: p values below 0.01, p values exceeding 0.05 0.05, and p values between 0.01 and 0.05. The central dark region, with p-values exceeding 0.05, indicates that the results of the studies in that area were not statistically significant. Most studies were symmetrical around the red estimated effect line (estimated θ_{IV}) or located in the black area. Nevertheless, a few studies showed asymmetry. By recombining the effect sizes via the trim-and-fill method, the direction of their estimates remained unchanged, suggesting that publication bias did not influence the robustness of the results (Supplement Appendix S9).

Discussion

Overview of results

The advent of sophisticated detection methods has ushered in a new era of noninvasive assessment of whole-body and regional fat distribution. This has led to an increase in interest among scientists and clinicians in adipose tissue, particularly its implications for cardiovascular health [90, 91]. To provide a systematic, exhaustive, and thorough review of the relationship between abnormal fat distribution and the risk of developing CDD, three electronic databases were searched, and 63 relevant articles were included (containing 43,113 participants).

According to these findings, two preliminary yet pivotal conclusions could be drawn. First, the quantification of abnormal fat (thickness, volume, or area) was elevated in participants with CDD or HFpEF compared with controls. Second, a noteworthy correlation was identified between abnormal fat distribution and the risk of developing CDD, and NAFLD and EAT appear to be most closely associated with CDD among different abnormal fat deposition locations.

Undoubtedly, considerable heterogeneity was uncovered in the present study, and meta-regression and

Table 2 Results of subgroup analysis

	E/E'			E			E/A		
	No.	Combined Effect Value	Heterogeneity	No.	Combined Effect Value	Heterogeneity	No.	Combined Effect Value	Heterogeneity
		r	I^2		r	I^2		r	I^2
Overall	29	0.23(0.18, 0.27)	83.79	7	-0.10(-0.24, 0.04)	44.13	16	-0.29(-0.37, -0.21)	73.54
Abnormal fat									
EAT	18	0.25	86.16	2	0.06	0	6	-0.35	21.99
PAT	2	0.17	69.99	3	-0.19	0	4	-0.27	0
VAT	7	0.18	39.66		0.00		3	-0.28	80.91
NAFLD	3	0.32	55.61	1	-0.24	76.17	1	-0.10	
Region									
Asia	15	0.18	74.94	1	0.06		2	-0.33	53.05
Europe	12	0.31	54.81	2	-0.01	0	7	-0.34	23.4
Americas	3	0.19	72.09	2	-0.26	79.82	4	-0.17	61.38
Oceania				1	-0.21		1	-0.25	
Design									
CSS	26	0.22	82.7	4	-0.14	54.52	13	-0.30	71.83
CC	1	0.40							
COH	3	0.20	0.08	2	-0.07	76.17	1	-0.17	
Sample group									
< 99	8	0.29	55.25	5	-0.17	0	7	-0.29	0
100 ~ 999	14	0.27	54.24	1	0.06		5	-0.33	72.65
> 1000	8	0.14	83.26				2	-0.20	96.44
Age group									
< 45	1	0.35		2	-0.26	0	2	-0.29	0
45 ~ 59	19	0.22	88.41	3	-0.11	51.32	10	-0.30	78.95
60 ~ 74	10	0.22	73.16	1	0.06		2	-0.21	41.8
BMI group(kg/m^2)									
< 24.9	11	0.19	74.67	1	-0.21		3	-0.32	23.73
25 ~ 29.9	15	0.26	88.24	3	0.04	0	6	-0.31	85.1
> 30	4	0.21	0	2	-0.26	0	5	-0.27	0
Detection methods									
Ultra-sound	14	0.26	82.96	4	-0.03	35.89	7	-0.34	23.4
DXA	1	0.35							
CT	7	0.19	34.51				3	-0.22	91.68
CMRI	4	0.28	61.51	2	-0.26	0	3	-0.30	0.00
BIA	3	0.09	82.29				1	-0.29	
PET-CT	1	0.17							
	e			**GLS**			**LVEDd**		
	No.	Combined Effect Value	Heterogeneity	No.	Combined Effect Value	Heterogeneity	No.	Combined Effect Value	Heterogeneity
		Pearson r	I^2		Pearson r	I^2		Pearson r	I^2
Overall	23	-0.27(-0.35, -0.19)	94.75	17	-0.11(-0.24, 0.02)	94.75	5	0.16(-0.05, 0.38)	95.84
Abnormal fat									
EAT	15	-0.27	90.93	10	-0.10	96.56	4	0.14	97.1
PAT	3	-0.31	93.91						
VAT	3	-0.26	76.97	2	-0.06	85.01			
NAFLD	2	-0.20	96.75	5	-0.18	97.97	1	0.24	
Region									
Asia	9	-0.23	92.31	10	-0.04	96.54	5	0.16	95.84
Europe	10	-0.32	88.85	5	-0.26	90.86			

Table 2 (continued)

Americas	4	-0.24	93.47	2	-0.09	99.61			
Design									
CSS	19	-0.26	94.34	13	-0.15	96.26	2	0.08	93.89
CC	1	-0.46		1	0.14	92.44	1	0.08	
COH	3	-0.28	0.02	3	-0.31	93.28	2	0.25	97.08
Sample group									
< 99	6	-0.39	86.99	4	-0.06	88.57	1	0.08	
100 ~ 999	10	-0.26	78.21	7	-0.13	94.63	2	0.13	79.73
> 1000	7	-0.20	95.43	6	-0.11	97.71	2	0.21	99.44
Age group									
< 45				1	-0.37	0	1	0.08	
45 ~ 59	17	-0.30	96.23	11	-0.05	98.57	1	0.24	
60 ~ 74	6	-0.17	77.28	5	-0.20	83.21	3	0.15	98.44
BMI group(kg/m^2)									
< 24.9	5	-0.25	92.51	6	-0.04	95.32			
25 ~ 29.9	14	-0.29	95.96	8	-0.09	97.62	4	0.62	
> 30	4	-0.21	66.78	3	-0.28	97.09	1	0.08	
Detection methods									
Ultra-sound	12	-0.30	94.26	5	-0.17	94.10	3	0.06	87.45
DXA									
CT	6	-0.25	90.22	3	-0.05	98.76			
CMRI	3	-0.28	87.87	7	-0.11	96.49	2	0.35	52.98
BIA	2	-0.09	74.69	2	-0.06	0.01			
	LVEDV			**GCS**					
	No.	Combined Effect Value	Heterogeneity	No.	Combined Effect Value	Heterogeneity			
		Pearson r	I^2		Pearson r	I^2			
Overall	7	0.06(-0.21, 0.33)	96.52	6	-0.19(-0.34, -0.03)	82.38			
Abnormal fat									
EAT	3	0.13	89.78	4	-0.18	80.5			
VAT	3	0.13	89.81	1	-0.08				
NAFLD	1	-0.31		1	-0.34				
Region									
Asia	2	0.25	51.32	2	-0.28	0			
Europe	4	0.07	95.64	4	-0.14	91.49			
Americas	1	-0.22							
Design		0.00							
CSS	5	0.14	94.49	6	-0.18	82.38			
CC	1	-0.02							
COH	1	-0.22							
Sample group									
< 99	4	0.12	72.24	3	-0.12	74.21			
100 ~ 999	1	0.51		2	-0.31	0			
> 1000	2	-0.26	88.47	1	-0.08				
Age group									
< 45	3	0.05	85.12	2	-0.28	0			
45 ~ 59	2	0.05	92.77	1	-0.08				
60 ~ 74	2	0.19	96.18	3	-0.16	88.92			
BMI group(kg/m^2)									
25 ~ 29.9	4	0.14	95.78	5	-0.21	73.35			

Table 2 (continued)

> 30	3	-0.05	82.61	1	-0.08	
Detection methods						
CT	2	0.03	82.32	1	0.21	
CMRI	5	0.07	98.58	5	-0.23	73.12

EAT Epciardial adipose tissue, *VAT* Visceral adipose tissue, *NAFLD* Nonalcoholic fatty liver disease, *CSS* Cross-sectional study, *CC* Case-control study, *COH* Cohort study, *BMI* Body mass index, *CMRI* Cardiac magnetic resonance imaging, *CT* Computed tomography, *DXA* Dual-energy X-ray absorptiometry, *BIA* Bioelectrical impedance analysis, *PET-CT* Positron emission tomography-computed tomography, *GLS* Global longitudinal strain, *GCS* Global circumferential strain, *LVEDV* Left ventricular end-diastolic volume index, *LVEDD* Left ventricular end-diastolic internal diameter, *No*. number

subgroup analyses were employed to dissect potential effect modifiers. Meta-regression identified sample size as a significant modifier that impacts the correlation between abnormal fat distribution and diastolic function, including the E/E' ratio and E/A. Studies with larger cohorts enhance the statistical robustness, minimize sampling error, and bolster the generalizability and credibility of the findings [92]. Subgroup analysis is a powerful tool that can be used to combine similar studies and identify sources of heterogeneity, distinguishing between clinical and assay-related heterogeneity [93]. Notably, the findings differed for different regions of abnormal fat. For example, EAT and NAFLD demonstrated robust negative correlations with diastolic function indices such as E/A and e', whereas the correlation between VAT and diastolic function was weaker. Furthermore, a pronounced correlation between abnormal fat distribution and the risk of developing CDD was discovered, particularly in overweight or obese populations. This finding is consistent with previous findings that the obese phenotype is associated with severe diastolic dysfunction and all-cause mortality [94].

Abnormal fat distribution and potential mechanisms of CDD

Adipose tissue is a metabolically active endocrine organ that elicits local and systemic responses through the production of chemical messengers such as adipokines, proinflammatory cytokines, and chemokines. It communicates with all tissues and organs in autocrine, paracrine, and endocrine manners [95, 96]. Adipose tissue can be categorized into brown adipose tissue (BAT) and white adipose tissue (WAT) on the basis of structural, phenotypic, and functional grounds [97, 98]. WAT is composed of clusters of unilocular adipocytes that are pivotal for fat storage and mobilization and are intricately connected to lipid metabolism. The size of white adipocytes and their metabolic turnover rate are key factors in determining insulin sensitivity and cardiovascular metabolic abnormalities [99].

Abnormal fat can be deposited in various locations in the body and poses a threat to metabolic homeostasis and cardiovascular health. EAT is located between the myocardium and the pericardium and is composed of adipocytes, stromal cells, and resident inflammatory cells [100]. EAT transmits adipokines and cytokines to influence cardiomyocytes through a shared microcirculation, and its hypertrophic expansion exerts a direct compressive effect on the myocardium [101, 102]. Advanced transcriptomics and proteomics have revealed the gene profiles of EAT involved in processes such as inflammation, thrombosis, and extracellular matrix remodelling [103]. Furthermore, proteomic analysis of EAT among HFpEF patients revealed that its biological processes are predominantly related to lipid metabolism disorders, inflammation, and mitochondrial dysfunction [104]. However, the correlations between different fat distributions and cardiovascular metabolic risk are not uniform. The Framingham Heart Study established a link between abnormal fat distribution, systemic inflammation, and cardiometabolic burden, with VAT emerging as a significant predictor of cardiovascular risk and PAT being correlated with coronary atherosclerosis [105–107]. Kranendonk et al. characterized PAT by its small adipocyte volume, dense capillary network, and elevated levels of inflammatory adipokines (such as epidermal growth factor, neurotrophic factors, IL-17, and monocyte chemotactic protein-1). In contrast, VAT is strongly associated with insulin resistance and metabolic syndrome [108]. The latest research suggests that NAFLD has a more significant association with HFpEF than with HFrEF on the basis of comorbid risk factors such as metabolic disorders, obesity and diabetes [29, 30]. Individuals with NAFLD first experience a reduction in myocardial energy metabolism, including decreased glucose utilization, triglyceride deposition, and a decreased phosphocreatine: ATP ratio, which subsequently affects cardiac structure, including an enlarged left atrium, increased cardiac mass, and ultimately diastolic dysfunction [31]. Therefore, we systematically summarized the relevant clinical trials to clarify the effect of abnormal fat distribution on diastolic function.

Strengths and limitations

The results may provide some guidance for clinical practice. First, the findings suggest that abnormal fat may

be a novel biomarker for the dynamic identification of HFpEF, and physicians can incorporate these biomarkers into their clinical assessments. Moreover, physicians and nursing staff can develop or recommend preventive strategies, such as lifestyle changes, dietary modifications, and physical activity, to reduce abnormal fat distribution among populations with cardiovascular disease.

However, this study still has limitations that cannot be resolved at present. 1). Study definition limitations: Many studies have concentrated on abnormal fat distribution, yet many have failed to distinguish between EAT and PAT. 2). Data heterogeneity and sensitivity: The results exhibited significant heterogeneity, with meta-regression and subgroup analysis indicating differences in fat distribution and sample size as likely causes. Although the sensitivity analysis revealed some irregularities, the overall direction of the effect remained consistent even after the studies were sequentially removed. Nevertheless, this continues to provoke inquiries regarding the reliability and credibility of the outcomes.

Conclusion

According to the available evidence, excessive accumulation of abnormal fat influences the risk of developing CDD. However, the persistent heterogeneity across studies prevents us from establishing a robust conclusion. Consequently, additional clinical data is needed to bolster and solidify the conclusions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02266-y.

Supplementary Material 1.

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Authors' contributions
Study design and writing the review were done by Zhenyue Fu and Yajiao Wang; the literature search was done by Shuqing Shi and Yumeng Li; Bingxuan Zhang were responsible for data calculation, Zhenyue Fu and Yuxin Wang were responsible for translation, and HuaqinWu and Qingqiao Song did the secondary revision of the literature.

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Availability of data and materials
Supplementary materials.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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