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Original Research

Site-Specific Associations of Regional Adipose Tissue With Cardiac Remodeling in Middle-Aged and Older Adults

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Abstract

Background: Obesity is characterized not only by excess body fat but also by a heterogeneous distribution of adipose tissue, and different fat depots may contribute unequally to cardiovascular risk. However, whether these depots are differentially associated with cardiovascular remodeling remains unclear. This study therefore aimed to investigate the site-specific associations of epicardial adipose tissue (EAT), abdominal visceral adipose tissue (VAT), and abdominal subcutaneous adipose tissue (SAT) with cardiovascular remodeling. **Methods:** The retrospective, cross-sectional observational study enrolled 587 middle-aged and older adults (median age 66 years, interquartile range 60–78) at Peking Union Medical College Hospital in China. Regional adipose tissue volumes were quantified by computed tomography (CT). Cardiac structure was assessed via echocardiography. Systemic inflammation was measured by serum C-reactive protein (CRP). Correlation analysis, multiple regression analysis, and mediation analyses were performed to elucidate independent associations after adjusting traditional risk factors and potential mechanistic pathways. **Results:** After adjustment for covariates, EAT was independently associated with left ventricular posterior wall thickness ($b = 0.18$, $p = 0.024$), whereas SAT was independently associated with left atrial diameter ($b = 0.71$, $p = 0.005$). VAT showed no independent association with cardiac chamber dimensions but was linked to aortic remodeling. Mediation analyses indicated that serum CRP significantly mediated the indirect associations between both EAT and VAT with aortic diameter ($p < 0.001$ for indirect effect). **Conclusions:** Regional adipose deposits exert distinct effects on cardiac remodeling. The specific association between EAT and ventricular myocardium suggests potential local paracrine mechanisms, while SAT is specifically linked to atrial enlargement. Visceral fat may be involved in aortic dilation primarily through systemic inflammation. These findings highlight the necessity of targeting specific adipose deposits and managing inflammation to mitigate cardiovascular aging.

Keywords: epicardial adipose tissue; body fat distribution; ventricular remodeling; inflammation; intra-abdominal fat; subcutaneous fat

1. Introduction

Aging is associated with profound changes in body composition, characterized by a redistribution of adipose tissue from subcutaneous to visceral and ectopic deposits [1,2]. This age-related accumulation of visceral and epicardial fat is closely linked to metabolic dysregulation. While obesity is a known cardiovascular risk factor [3,4], excessive adiposity is intricately linked to adverse cardiac remodeling, including left ventricular hypertrophy, atrial enlargement, and aortic dilation, which predispose individuals to heart failure, atrial fibrillation, and aortic aneurysms [5,6]. Although the body mass index (BMI) has served as a convenient index of obesity, it is increasingly recognized as an imprecise metric [7,8]. Individuals with similar BMI may exhibit heterogeneous cardiovascular and metabolic manifestations.

Emerging evidence highlights that the distribution of adipose tissue is a key determinant of cardiovascular health [1,5]. Rather than acting merely as energy storage, adipose tissue is an active metabolic endocrine organ with distinct functional characteristics depending on its deposition [9,10]. Visceral adipose tissue (VAT) is metabolically active and pro-inflammatory, whereas subcutaneous adipose tissue (SAT) acts as a benign "metabolic sink" for excess energy [11]. Of particular interest, epicardial adipose tissue (EAT), shares the same microcirculation with the myocardium [12]. Given this anatomical contiguity, the paracrine effect of EAT may contribute to local inflammation and fibrosis more than systemic obesity [13].

Despite growing interest in regional adiposity, knowledge gaps remain regarding how specific fat deposits affect cardiac structures. Most prior studies have been limited to generalized obesity or focused on single adipose deposits. Therefore, the present study aims to explore the site-specific impacts of EAT, VAT, and SAT on cardiac and aortic remodeling in a Chinese population. Specifically, we investigated the independent association of each adipose tissue volume with ventricular, atrial, and aortic dimensions. Furthermore, we explored the potential effect of systemic inflammation on the "heart-adiposity crosstalk" to elucidate the underlying mechanisms.

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2. Patients and Methods

2.1 Study Population and Data Collection

A total of 587 participants aged ≥45 years were enrolled in the study at Peking Union Medical College Hospital. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Peking Union Medical College Hospital (I-23PJ1278). Written informed consent was obtained from all participants prior to enrollment. The study flowchart is presented in **Supplementary Fig. 1**.

The exclusion criteria included: (1) severe cardiac diseases (including myocardial infarction, severe valvular heart disease, cardiomyopathy, atrial fibrillation, heart failure, or a history of cardiac surgery); (2) active infections; (3) malignancies; (4) major surgery or trauma within 3 months.

All participants underwent comprehensive clinical evaluations, including demographic data collection, medical history, physical examinations, laboratory tests, computed tomography, and echocardiography. Demographic survey and physical examinations included age, gender, height, weight, and blood pressure. Body surface area (BSA) was calculated using Stevenson's formula, which is validated specifically for the East Asian population: BSA (m^2) = 0.0061 × height (cm) + 0.0128 × weight (kg) − 0.1529. Comorbidities such as hypertension and diabetes were recorded. Biochemical tests included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), lipoprotein(a) (Lp(a)), free fatty acids (FFA), glycated hemoglobin A1c (HbA1c), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

2.2 Quantification of Regional Adipose Tissue

All participants underwent Computed tomography (CT) scans performed on a dual-source computed tomography scanner system (Somatom Definition Flash, Siemens, Forchheim, Germany) without contrast enhancement. The Volume Soft workstation (Syngo, Siemens, Forchheim, Germany) was utilized to measure the volume of regional adipose tissue. Adipose tissue was semi-automatically identified and segmented based on a range of −190 to −30 Hounsfield Units (HU) in the traced region [14]. Manual tracing was performed to ensure accurate delineation. The volume of the fat was measured in voxels and converted into cubic centimeters. For the assessment of abdominal adipose tissue, the anatomical region was defined by the superior and inferior boundaries corresponding to the diaphragmatic dome and the upper margin of the iliac crest, respectively [15]. Adipose tissue located within the peritoneal cavity was classified as abdominal visceral adipose tissue (VAT), while tissue outside the peritoneum was classified as abdominal subcutaneous adipose tissue (SAT). Epicardial adipose tissue (EAT) was defined as adipose tissue located between the myocardium and the visceral pericardium [16,17]. The pericardial contours were manually traced from the pulmonary artery bifurcation to the diaphragm. All assessments were performed by trained radiologists blinded to the participants' clinical information. To ensure the reliability of measurements, a subset of 30 participants was randomly selected for re-evaluation by the same radiologist and a second independent observer. The intra- and inter-observer intraclass correlation coefficients (ICCs) for EAT, VAT, and SAT volumes ranged from 0.92 to 0.96, indicating excellent reproducibility.

2.3 Echocardiography

Echocardiographic examinations were performed with two-dimensional guided M-mode echocardiography obtained in the parasternal short and long-axis views following the guidelines of the American Society of Echocardiography. The following variables were measured: ascending aortic diameter (AOD), aortic root diameter (AOR), left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), mitral early/late diastolic flow velocity ratio (E/A), interventricular septum thickness (IVS), left ventricular posterior wall thickness (LVPW), main pulmonary artery diameter (MPA), and right ventricular diameter (RVD). Left ventricular mass (LVM) was calculated using the Devereux equation: LVM (g) = 0.8 × 1.04 × [(LVEDD + IVS + LVPW)^3 − LVEDD^3] + 0.6. Left ventricular mass index (LVMI) (g/m^2) was calculated by dividing LVM by body surface area (BSA).

2.4 Statistical Analysis

2.4.1 Descriptive Statistics and Normality Testing

The Kolmogorov-Smirnov test was used for the normality test. Continuous variables with normal distribution were expressed as means ± standard deviations (SD) and compared using one-way analysis of variance (ANOVA). Non-normally distributed variables were presented as medians with interquartile ranges (IQR), and group differences were analyzed by the Mann-Whitney U test or the Kruskal-Wallis test. Categorical variables were expressed as frequencies (percentages) and compared using the Chi-square test or Fisher's exact test.

2.4.2 Processing of Missing Data

Missing data were present in several variables: Lp(a) and FFA (n = 2 each), CRP (n = 3), EAT (n = 4), BSA, mean arterial pressure (MAP), and LVMI (n = 7 each), and E/A (n = 19), with missing proportions ranging from 0.34% to 3.24%. To maximize statistical power and minimize bias, we performed multiple imputation by the chained equation (MICE) method with 5 replications, implemented via the mi package in R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Sensitivity analysis compar-

ing the original and imputed datasets is detailed in **Supplementary Table 1**. All subsequent regression analyses were performed on each of the five imputed datasets separately, and the resulting parameter estimates (e.g., b coefficients and 95% Confidence Intervals) were pooled according to Rubin's Rules.

2.4.3 Correlation and Collinearity

Spearman correlation analysis was performed to explore the bivariate associations between variables. To ensure the stability of the regression models, multicollinearity was assessed using the variance inflation factor (VIF). Variables with a VIF $\geq$5 were considered to indicate significant multicollinearity and were excluded from the models.

2.4.4 Simple and Multiple Regression Analyses

Simple linear regression analysis was conducted to identify potential risk factors significantly associated with the outcome variables. Variables with $p < 0.05$ in the simple linear analysis were selected for further multiple regression analysis. Hierarchical linear regression analysis was performed to evaluate the independent association between regional adipose tissue and cardiac remodeling after sequentially adjusting for confounders. Model 1 was unadjusted. Model 2 was adjusted for demographic factors (e.g., age, gender, BSA, and hypertension). Model 3 was further adjusted for other regional adipose tissue. Model 4 was further adjusted for cardiometabolic markers (e.g., LDL-C and CRP) that were significant in the simple linear analyses. The parameter estimate b was used to denote the unstandardized regression coefficient, while SE represented the standard error.

2.4.5 Mediation Analysis

Mediation analysis was conducted using the PROCESS v4.2 macro in SPSS. The direct effect reflects the influence of regional fat on cardiac structure, whereas the indirect effects represent the impact through mediation variables. To evaluate the robustness of the results and generate 95% confidence intervals, a bootstrap method with 5000 resampling iterations was employed.

2.4.6 Statistical Analyses

Statistical analyses were conducted with SPSS (version 26.0, IBM, Armonk, NY, USA), and R (version 4.2.0). A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline Characteristics of the Study Population

The clinical and echocardiographic characteristics of the 587 participants are summarized in Table 1. The study population had a mean age of 68.95 years and was predominantly male (86.71%), with a high prevalence of hypertension (58.60%) and diabetes (24.87%). Overall, the cohort exhibited preserved left ventricular systolic function (mean LVEF 69.0%) but impaired diastolic function (median E/A ratio 0.8).

When stratified by EAT tertiles, participants in the highest tertile were significantly older, had higher BSA, and showed a greater prevalence of hypertension and diabetes (all $p < 0.05$). Increasing EAT volume was associated with worse cardiometabolic profiles, including higher TG and HbA1c, lower HDL-C, and significantly elevated systemic inflammation (CRP: Low 0.49 vs. High 0.82 mg/L; $p < 0.001$). Regarding cardiac structure, a clear trend of adverse remodeling was observed; ventricular wall thickness (IVS, LVPW), left ventricular mass (LVM), left atrial diameter (LAD), and aortic dimensions (AOD, AOR) all increased significantly across EAT tertiles (all $p < 0.001$). Notably, cardiac systolic function (LVEF, LVFS) and right heart dimensions (MPA, RVD) remained comparable across groups ($p > 0.05$), suggesting that EAT accumulation is specifically linked to subclinical structural remodeling rather than functional failure.

3.2 Correlation Analysis Among Cardiac Structure, Regional Fat, and Cardiometabolic Markers

Spearman correlation analysis was conducted to evaluate the correlations between the regional adipose tissue volumes and the echocardiographic parameters (Fig. 1A, **Supplementary Table 2**). A strong and consistent pattern of positive correlations was observed between EAT and VAT and indices of cardiac structural remodeling, including LAD, IVS, LVPW, LVM, AOD, and AOR. Abdominal subcutaneous fat tissue (SAT) was also positively correlated with LAD, IVS, and LVPW, but showed no significant association with aortic dimensions or LVM. SAT showed a significant negative correlation with the LVMI ($p < 0.05$). None of the adipose tissue volumes showed a significant correlation with systolic (LVEF, LVFS) or diastolic function (E/A ratio).

The relationships between circulating cardiometabolic biomarkers and cardiac structure were also assessed (Fig. 1B, **Supplementary Table 3**). HDL-C, LDL-C, and TC demonstrated inverse correlations with LAD, IVS, LVPW, AOD, and AOR. Notably, CRP exhibited a positive and significant correlation with all measured structural parameters. HbA1c was positively correlated with ventricular wall thickness (IVS and LVPW), while FFA was positively associated with AOD. No significant associations were observed for TG or Lp(a) with any of the structural parameters.

3.3 Simple Linear Analysis of Risk Factors for Cardiac and Aortic Remodeling

To identify potential predictors of cardiac and aortic structural remodeling, a series of simple linear regression analyses were performed (Fig. 2, **Supplementary Table**

Table 1. Clinical characteristics of the study population.

Characteristics	Total (n = 587)	Low EAT (n = 196)	Mid EAT (n = 196)	High EAT (n = 195)	*p* value
Age, years	68.95 ± 11.30	66.57 ± 10.82	68.36 ± 11.49	71.95 ± 10.95	<0.001
Male, n (%)	509 (86.71)	163 (83.2)	165 (84.2)	181 (92.8)	0.008
BSA, m^2	1.81 ± 0.16	1.76 ± 0.16	1.79 ± 0.15	1.87 ± 0.15	<0.001
MAP, mmHg	92.37 ± 10.49	91.55 ± 10.70	92.32 ± 10.72	93.25 ± 10.02	0.277
Hypertension, n (%)	344 (58.60)	91 (46.4)	118 (60.2)	135 (69.2)	<0.001
Diabetes, n (%)	146 (24.87)	32 (16.3)	51 (26.0)	63 (32.3)	0.001
Laboratory tests					
TC, mmol/L	4.28 ± 0.92	4.39 ± 0.91	4.32 ± 0.95	4.14 ± 0.89	0.025
LDL-C, mmol/L	2.75 ± 0.84	2.77 ± 0.83	2.80 ± 0.89	2.66 ± 0.81	0.238
HDL-C, mmol/L	1.33 ± 0.32	1.42 ± 0.37	1.30 ± 0.29	1.26 ± 0.28	<0.001
TG, mmol/L	1.28 (0.95–1.76)	1.17 (0.88–1.61)	1.32 (0.96–1.76)	1.39 (1.03–2.01)	0.002
Lp(a), mg/L	70.0 (33.0, 186.0)	91.5 (38.0–231.0)	58.5 (29.0–159.2)	73.0 (30.0–182.5)	0.056
FFA, µmol/L	388.0 (293.0, 511.0)	363.5 (272.2–505.2)	381.5 (281.2–497.0)	413.0 (317.0–531.5)	0.048
HbA1c, %	5.99 ± 0.85	5.88 ± 0.77	5.97 ± 0.71	6.12 ± 1.02	0.018
CRP, mg/L	0.57 (0.29, 1.25)	0.49 (0.23–1.04)	0.50 (0.26–0.95)	0.82 (0.43–1.71)	<0.001
ESR, mm/h	6 (2, 10)	7.0 (2.0–9.0)	6.0 (2.0–10.0)	6.0 (3.0–10.0)	0.692
Echocardiographic parameters					
AOD, mm	35.10 ± 3.58	34.59 ± 3.50	34.46 ± 3.27	36.26 ± 3.69	<0.001
AOR, mm	34.32 ± 3.19	34.02 ± 3.13	33.76 ± 2.96	35.17 ± 3.31	<0.001
LAD, mm	37.89 ± 4.72	36.85 ± 4.69	37.63 ± 4.26	39.20 ± 4.91	<0.001
LVEDD, mm	47.36 ± 3.39	47.43 ± 3.43	47.13 ± 3.17	47.53 ± 3.57	0.484
IVS, mm	8.95 ± 1.21	8.74 ± 1.32	8.80 ± 1.16	9.29 ± 1.08	<0.001
LVPW, mm	8.81 ± 1.00	8.61 ± 1.04	8.65 ± 0.99	9.18 ± 0.87	<0.001
LVEF, %	69.0 ± 4.0	69.0 ± 5.0	69.0 ± 5.0	69.0 ± 4.0	0.627
LVFS, %	39.0 ± 4.0	39.0 ± 4.0	39.0 ± 4.0	39.0 ± 3.0	0.963
LVM, g	143.54 ± 30.62	139.64 ± 31.47	139.08 ± 29.17	151.93 ± 29.59	<0.001
LVMI, g/m^2	79.66 ± 16.96	79.16 ± 17.72	78.19 ± 16.12	81.64 ± 16.89	0.117
E/A	0.8 (0.7, 1.0)	0.84 (0.70–1.00)	0.80 (0.70–1.00)	0.80 (0.70–1.00)	0.131
MPA, mm	22.99 ± 2.00	23.02 ± 1.81	23.02 ± 1.78	22.92 ± 2.38	0.858
RVD, mm	22.06 ± 4.03	22.11 ± 4.58	22.02 ± 3.62	22.05 ± 3.83	0.971
Adiposity volume					
SAT, 1000 mL	2.31 (1.74, 2.94)				
VAT, 1000 mL	2.63 (1.83, 3.49)				
EAT, 100 mL	0.95 (0.61, 1.43)				

Continuous variables are presented as mean ± SD for normally distributed data and median (interquartile range) for skewed data. Categorical variables are presented as n (%). Abbreviations: BSA, body surface area; MAP, mean arterial pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein (a); FFA, free fatty acids; HbA1c, glycosylated hemoglobin A1c; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AOD, ascending aortic diameter; AOR, aortic root diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVM, left ventricular mass; LVMI, left ventricular mass index; E/A, mitral early/late diastolic flow velocity ratio; IVS, interventricular septum thickness; LVPW, left ventricular posterior wall thickness; MPA, main pulmonary artery diameter; RVD, right ventricular diameter; SAT, abdominal subcutaneous adipose tissue; VAT, abdominal visceral adipose tissue; EAT, epicardial adipose tissue. Data were missing for several variables: BSA, MAP, and LVMI (n = 7); Lp(a) and FFA (n = 2); CRP (n = 3); EAT (n = 4), and E/A (n = 19). SAT, VAT, EAT values are presented as ×1000 mL, ×1000 mL, ×100 mL, respectively.

4). TC was excluded from the analysis to mitigate multicollinearity due to its strong correlation with LDL-C.

Among regional adipose tissue, both EAT and VAT showed consistent, significant, and positive associations with all five echocardiographic parameters, including AOD, AOR, LAD, IVS, and LVPW. SAT was significantly associated with LAD and IVS, but showed no significant relationship with aortic dimensions or LVPW. The lipid profiles, HDL-C and LDL-C were consistently and negatively associated with all cardiac and aortic parameters. FFA was

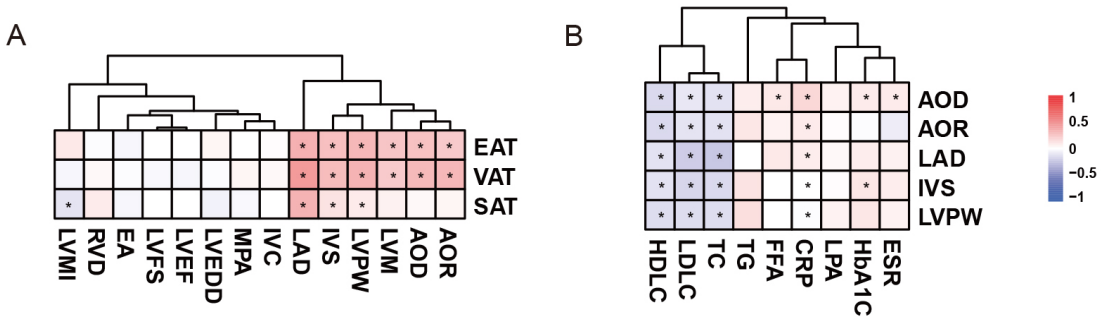


Fig. 1. Correlation heatmap of cardiac structure, regional fat, and laboratory tests. (A) The association between cardiac structure and regional fat distribution; (B) The association between cardiac structure and metabolic profiles. Abbreviations: SAT, abdominal subcutaneous adipose tissue; VAT, abdominal visceral adipose tissue; EAT, epicardial adipose tissue; AOD, ascending aortic diameter; AOR, aortic root diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVM, left ventricular mass; LVMI, left ventricular mass index; E/A, mitral early/late diastolic flow velocity ratio; IVS, interventricular septum thickness; LVPW, left ventricular posterior wall thickness; MPA, main pulmonary artery diameter; RVD, right ventricular diameter; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein (a); FFA, free fatty acids; HbA1c, glycosylated hemoglobin A1c; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVC, inferior vena cava. *$p < 0.05$.

significantly associated with LAD ($p = 0.043$) and showed a borderline association with AOD ($p = 0.051$), whereas Lp(a) was not significantly associated with any parameter. Among the inflammatory and metabolic markers, CRP showed a highly significant and positive correlation with AOD ($p < 0.001$). HbA1C showed significant positive associations with AOD ($p = 0.048$), IVS ($p = 0.023$), and LVPW ($p = 0.029$).

3.4 Independent Associations of Regional Adipose Tissue and Cardiac Structure

To investigate the independent associations between regional adipose tissue and cardiac and aortic structural parameters, multiple regression analyses were conducted using four sequential models (Table 2, **Supplementary Table 5**). In the unadjusted model (Model 1), EAT was significantly and positively associated with AOD, AOR, LAD, IVS, and LVPW (all $p < 0.001$). After adjustment for age, gender, BSA, and hypertension (Model 2), the associations of EAT with AOD, AOR, LAD, and IVS became non-significant, whereas the association with LVPW remained statistically significant. In the fully adjusted model (Model 4), EAT remained an independently significant risk factor of LVPW (b = 0.18, $p = 0.024$), indicating that for every 100 mL increase in EAT, the thickness of LVPW increased by 0.18 mm.

In terms of VAT, significant positive associations were observed with all five echocardiographic parameters in Model 1 (all $p < 0.001$). However, after adjustment for demographic and clinical covariates (Model 2), VAT remained only associated with LAD (b = 0.45, $p = 0.010$), while associations with AOD, AOR, IVS, and LVPW were no longer significant. In Models 3 and 4, after further adjustment for other regional adipose tissue and cardiometabolic markers, no significant associations were found between VAT and cardiac parameters including AOD after full adjustment.

Regarding SAT, positive associations were initially found with LAD and IVS (LAD: b = 1.43, $p < 0.001$; IVS: b = 0.14, $p = 0.012$). SAT showed a persistent positive association with LAD even in the fully adjusted model (Model 4: b = 0.71, $p = 0.005$), suggesting that for every 1000 mL increase in SAT, the LAD increased by 0.71 mm.

In addition, as detailed in **Supplementary Table 5**, CRP was observed as an independent positive risk factor of AOD (b = 0.17, $p = 0.004$), while LDL-C demonstrated an independent negative association with LAD (b = −0.527, $p = 0.010$).

3.5 Mediation Analysis

Based on the multiple regression results, we further explored potential mediation pathways (Fig. 3, **Supplementary Tables 6,7**). Mediation analysis revealed a significant indirect role of CRP in visceral adipose tissue to AOD (Fig. 3A, **Supplementary Table 6**), EAT was robust and significantly positively correlated with CRP (b = 0.443, $p < 0.001$), which in turn was positively associated with AOD (b = 0.182, $p < 0.001$). Bootstrap analysis (5000 resamples) confirmed a significant indirect effect of CRP (b = 0.080; 95% CI: 0.055, 0.111) even after adjusting for the covariates of age, BSA, and hypertension, while neither the total effect ($p = 0.228$) nor the direct effect of EAT on AOD ($p = 0.663$) were statistically significant. A similar pattern was observed for the VAT-AOD association (Fig. 3B and **Supplementary Table 6**). VAT was significantly associated with elevated CRP (b = 0.314, $p < 0.001$), and CRP maintained its positive association with AOD (b = 0.187, p

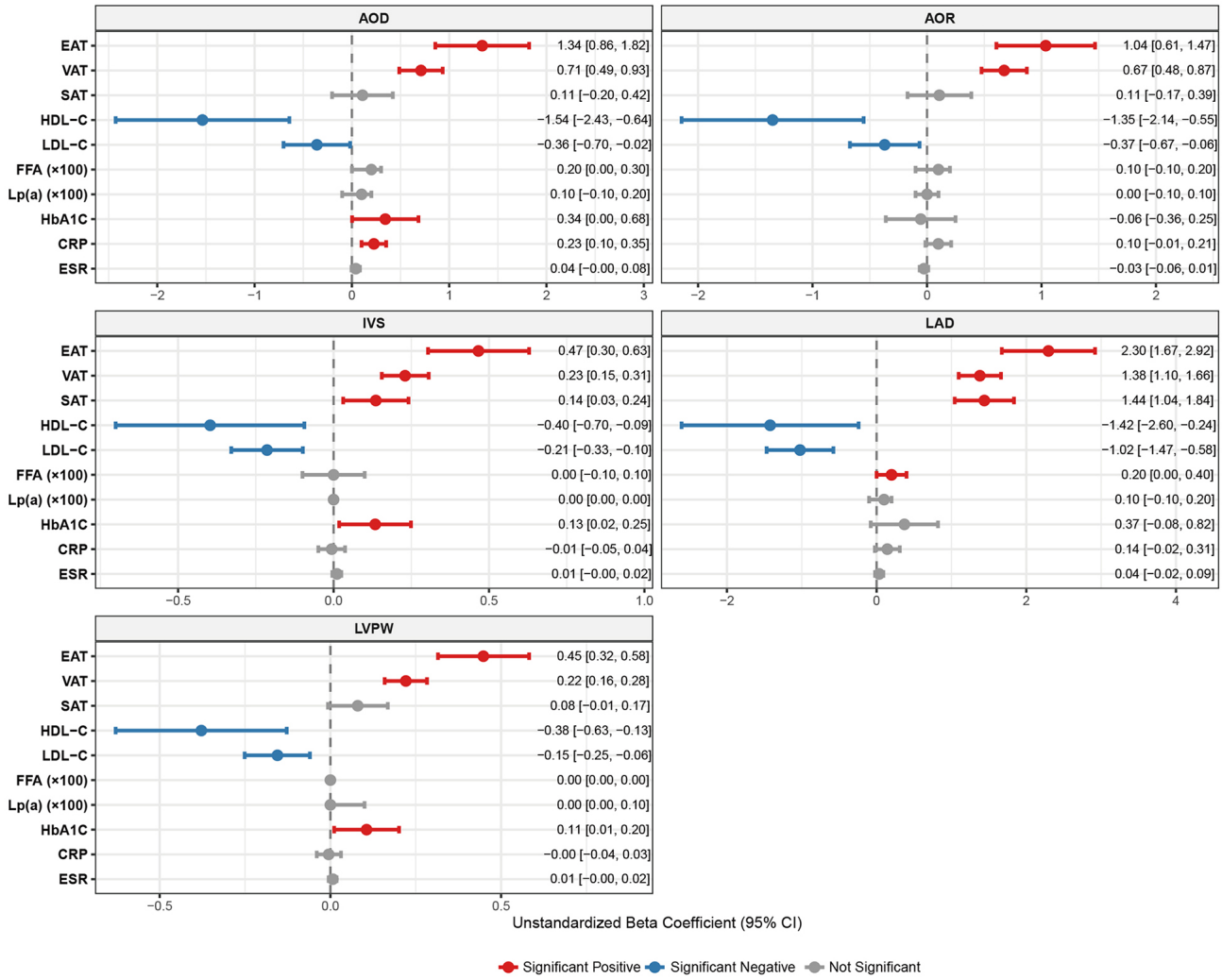


Fig. 2. Forest plot of simple linear regression analysis. Unstandardized b coefficients and 95% confidence intervals are shown for the association between each risk factor and cardiac structural parameters. Red color indicates a significant positive association ($p < 0.05$, b >0). Blue indicates a significant negative association ($p < 0.05$, b <0). Gray indicates no statistical significance ($p \geq 0.05$). To ensure visual comparability, the coefficients and confidence intervals for FFA and Lp(a) were multiplied by 100 (presented as per 100 units change). CI, confidence interval.

< 0.001). The indirect effect of VAT on AOD via CRP was statistically significant (b = 0.059; 95% CI: 0.044, 0.076, $p < 0.001$), while the direct association between VAT and AOD was not significant ($p = 0.171$). These findings suggest that systemic inflammation serves as a key mediating role in the association between VAT and aortic dilation.

We also tested whether LDL-C mediated the relationship between adipose tissue and LAD (**Supplementary Table 7**). The analysis showed that although adipose tissue and LDL-C were associated with LAD, the indirect effects of SAT, VAT, or EAT on LAD via LDL-C were not statistically significant.

4. Discussion

In this study, we demonstrate that regional adipose tissue deposits exert distinct, site-specific effects on cardiac remodeling. First, EAT was identified as an independent risk factor of LVPW, highlighting its local, direct impact on ventricular remodeling. Second, SAT, rather than visceral fat, was independently associated with left atrial enlargement. Third, CRP demonstrated a significant indirect effect on the relationship between VAT and aortic dilation. Collectively, these results suggest that anatomical proximity and systemic inflammatory status play divergent roles in the complex “heart-adiposity crosstalk”.

EAT is a unique visceral adipose tissue located directly between the myocardium and the visceral pericardium, characterized by the absence of a fascia barrier and a shared microcirculation with the underlying myocardium [12,18]. This anatomical contiguity facilitates a complex “heart-adiposity crosstalk” through paracrine and vasocrine pathways. Under physiological conditions, EAT acts as

Table 2. Multiple regression model of regional adipose tissue and cardiac and aortic structure.

Predictor/Model	AOD	AOR	LAD	IVS	LVPW
	b (SE)	b (SE)	b (SE)	b (SE)	b (SE)
EAT					
Model 1	1.35 (0.25)***	1.04 (0.22)***	2.31 (0.32)***	0.47 (0.08)***	0.45 (0.07)***
Model 2	0.17 (0.26)	0.02 (0.23)	0.55 (0.33)	0.16 (0.09)	0.18 (0.07)*
Model 3	0.22 (0.28)	0.08 (0.25)	0.41 (0.36)	0.17 (0.10)	0.18 (0.08)*
Model 4	0.16 (0.28)	0.08 (0.25)	0.41 (0.36)	0.17 (0.10)	0.18 (0.08)*
VAT					
Model 1	0.71 (0.11)***	0.67 (0.10)***	1.38 (0.14)***	0.23 (0.04)***	0.22 (0.03)***
Model 2	–0.02 (0.14)	–0.07 (0.12)	0.45 (0.18)*	0.02 (0.05)	0.03 (0.04)
Model 3	–0.06 (0.15)	–0.08 (0.13)	0.19 (0.21)	–0.01 (0.06)	–0.01 (0.04)
Model 4	–0.17 (0.16)	–0.11 (0.14)	0.23 (0.21)	–0.02 (0.06)	–0.02 (0.04)
SAT					
Model 1	—	—	1.43 (0.20)***	0.14 (0.05)*	—
Model 2	—	—	0.80 (0.24)**	–0.02 (0.07)	—
Model 3	—	—	0.72 (0.25)**	–0.01 (0.07)	—
Model 4	—	—	0.71 (0.25)**	–0.01 (0.07)	—

Hierarchical regression analysis was conducted with cardiac and aortic structural indicators as dependent variables and regional adipose tissue volume as independent variables. The parameter estimate b represents the unstandardized coefficient; SE represents standard error. Model 1 was unadjusted. Model 2 was adjusted for age, gender, BSA, and hypertension. Model 3 additionally included other regional adipose tissue identified as significant in simple linear analyses. Model 4 further included cardiometabolic markers significant in simple linear analyses. Abbreviations: ascending aortic diameter (AOD), aortic root diameter (AOR), left atrial diameter (LAD), interventricular septum thickness (IVS), left ventricular posterior wall thickness (LVPW). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

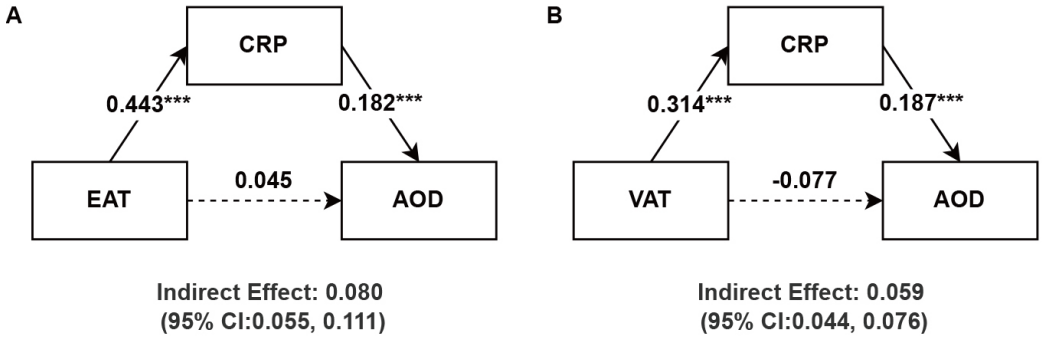


Fig. 3. Mediation analysis of CRP on the association between adipose tissue and AOD. (A) Path diagram of the mediation model in which C-reactive protein (CRP) mediates the association between epicardial adipose tissue (EAT) and aortic diameter (AOD). (B) Path diagram of the mediation model in which CRP mediates the association between visceral adipose tissue (VAT) and AOD. In each panel, arrows represent the direct, indirect, and total effects, with the corresponding path coefficients shown alongside. *** $p < 0.001$. CRP, C-reactive protein; EAT, epicardial adipose tissue; VAT, visceral adipose tissue; AOD, aortic diameter.

a "double-edged sword" with significant cardioprotective properties [18]. It serves as a metabolic buffer that provides immediate energy to the myocardium by supplying free fatty acids and secretes anti-inflammatory adipokines, such as adiponectin and adrenomedullin [12,18]. Moreover, EAT possesses dynamic brown-fat-like thermogenic features that can protect the heart during unfavorable conditions like ischemia or hypoxia [18].

However, the biological role of EAT is highly dependent on its phenotype, which shifts with aging and excessive adiposity. In middle-aged and older adults, EAT undergoes a functional transition from a thermogenic, protective organ to a pro-inflammatory white adipose tissue depot [18]. This phenotypic switch involves a decrease in brown adipocytes and a reciprocal increase in the secretion of pro-inflammatory and pro-fibrotic cytokines, including interleukin-6 (IL-6), tumor necrosis factor (TNF), and activin A [12,18,19]. These bioactive mediators can subsequently activate pro-fibrotic signaling pathways, thereby driving adverse cardiac remodeling [13]. The robust and

independent association between EAT and LVPW in our study supports this "paracrine hypothesis", suggesting that in our population, EAT exerts a specific, local cardiotoxic effect on the ventricular myocardium. By contrast, abdominal visceral adipose tissue (VAT), representing generalized visceral fat, showed no significant independent effect on LVPW after adjusting for confounders, further emphasizing the unique role of EAT.

Recognizing EAT as a modifiable risk factor offers promising therapeutic avenues [20]. Notably, EAT expresses GLP-1 receptors, whereas subcutaneous fat does not, providing a biological basis for the direct effect of Glucagon-like peptide-1 receptor agonists (GLP-1RA) on EAT reduction [21,22]. Targeting EAT with GLP-1RA or Sodium-glucose co-transporter 2 inhibitors (SGLT2i) may therefore represent a precise therapeutic strategy to restore EAT's physiological properties and promote the regression of left ventricular hypertrophy [23,24].

SAT is traditionally regarded as a benign "metabolic sink", capable of buffering excess caloric intake and protecting against metabolic dysregulation [25,26]. However, an unexpected but significant finding in our study was the independent association between SAT and LAD, even after adjusting for BSA. Left atrial enlargement is a well-established precursor to atrial fibrillation [27]. As a thin-walled structure, the left atrium is particularly sensitive to chronic volume overload. Obesity, characterized by substantial SAT expansion, is associated with increased blood volume and cardiac output [28], thereby serving as a recognized risk factor for left atrial enlargement [11,29]. We hypothesize that the hemodynamic burden associated with SAT expansion contributes to chronic volume overload, which may facilitate atrial remodeling. Conversely, SAT was negatively associated with LVMI in correlation analysis, suggesting a potential protective effect. This dual role implies that clinicians should not categorize SAT as absolutely benign or harmful. Future studies are needed to clarify the balance between SAT's metabolic and hemodynamic contributions.

A novel insight from our study is the significant indirect effect of CRP on the association between VAT and aortic dilation. While the direct association between VAT and AOD was not statistically significant after full adjustment, the identified indirect pathway through systemic inflammation is robust. This "indirect-only mediation" suggests that the biological impact of VAT on the aorta is primarily channeled through systemic inflammation. It is plausible that other unmeasured factors or counteracting mechanisms might obscure a direct VAT-AOD relationship, making the inflammatory pathway a crucial, albeit specific, mediator. This mechanistic pathway is supported by the American College of Cardiology (ACC), which emphasized the critical role of inflammation in the pathogenesis of cardiovascular diseases (CVD) [30]. Adipose tissue is a major source of circulating inflammatory mediators, including IL-6 and TNF-α, which stimulate CRP production [19,31]. Chronic inflammation is known to upregulate matrix metalloproteinases (MMPs) and accelerate elastin degradation in the arterial wall [32], a process that affects structural integrity and predisposes to aorta dilation. Our data imply that managing systemic inflammation may be crucial for preventing aortic remodeling, particularly in patients with excessive adiposity. This finding aligns with the concept of "inflammaging", a hallmark of biological aging where age-related visceral adiposity drives chronic low-grade inflammation, subsequently impairing vascular integrity [33]. While we used CRP and ESR as inflammatory markers, future studies incorporating specific cytokines (e.g., IL-6, adiponectin) could also provide further mechanistic insights.

We also observed an inverse association between cholesterol levels (LDL-C, HDL-C) and cardiac structural parameters, a pattern consistent with the "lipid paradox" [34]. This relationship is often attributed to polypharmacy, selection bias (such as the exclusion of those with severe cardiac diseases), and other confounding factors [34]. It is noteworthy that the majority of our participants exhibited lipid profiles within the normal range (median LDL-C: 2.63 mmol/L). This may limit the generalizability of our findings to patients with hyperlipidemia and warrants cautious interpretation.

A critical observation from our results is the dissociation between structural and functional cardiac parameters. While regional fat depots were significantly and independently associated with adverse structural indices, these associations did not extend to functional parameters (e.g., LVEF, E/A ratio). Consistent with the Frank-Starling mechanism, the heart likely undergoes compensatory structural remodeling prior to functional impairment. Given that our study excluded participants with severe cardiac disease, this dissociation may suggest that we captured an early, subclinical stage of cardiovascular pathology. Consequently, integrating CT-based assessment of EAT and SAT volumes into primary cardiovascular prevention strategies may offer earlier risk stratification than relying on functional parameters via echocardiography.

Our findings support a shift from BMI-based assessment toward CT-quantified regional fat for superior cardiovascular risk stratification, particularly in Asian populations. Depot-specific strategies are warranted: targeting EAT reduction (e.g., via GLP-1RA or SGLT2i) may effectively prevent ventricular hypertrophy, while managing SAT expansion is key to mitigating atrial remodeling [35]. Furthermore, the mediating role of inflammation in the VAT-aorta relationship suggests that anti-inflammatory therapy is crucial for preventing aortic dilation. Future research should prioritize prospective, longitudinal cohorts to validate these findings and interventional studies to explore whether targeting EAT or systemic inflammation can effectively reverse adverse cardiac remodeling in this population.

5. Limitations

Several limitations of this study should be acknowledged. First, the cross-sectional design of our study precludes the determination of causal relationships. Second, our study cohort exhibited a male predominance (86.71% male). Given the sexual dimorphism in adipose tissue distribution, this may limit the generalizability to the female population [36]. Third, despite our rigorous adjustments, the possibility of residual confounding cannot be entirely ruled out. Specifically, detailed information regarding medication history (e.g., statins, RAAS inhibitors) and certain lifestyle factors, such as smoking status and alcohol consumption, were not incorporated in the analysis. Although severe cardiac diseases were excluded (including myocardial infarction, severe valvular heart disease, cardiomyopathy, atrial fibrillation, heart failure, or a history of cardiac surgery), the potential influence of comorbidities, such as coronary artery disease (CAD), or arrhythmias remains a limitation.

6. Conclusions

Our study demonstrates that regional adipose deposits exert distinct, site-specific effects on cardiac remodeling. Specifically, EAT appears to exert a local cardiotoxic effect on ventricular wall thickness, consistent with a paracrine mechanism, whereas SAT is primarily associated with atrial enlargement, indicative of systemic volume overload. In addition, chronic systemic inflammation is a key mediator of aortic remodeling. Assessment and targeting of regional adipose tissue distribution, rather than focusing on general weight loss, may be essential for the precise understanding and management of cardiovascular disease.

Availability of Data and Materials

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author Contributions

XZ: Conceptualization, Methodology, Formal analysis, Investigation, Writing–original draft, Visualization. Funding acquisition. GW: Conceptualization. Methodology. Formal analysis. Investigation. Writing–review & editing. XN: Conceptualization, Supervision, Project administration, Writing–review & editing. HL: Conceptualization. Data curation, Resources. Writing–review & editing, Funding acquisition. All the authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Ethics Committee of the Peking Union Medical College Hospital (I-23PJ1278). All participants provided written informed consent. The study was carried out in accordance with the guidelines of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM49635.

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