CHEST

Epicardial Adipose Tissue as an Independent Risk Factor for Mortality in Pulmonary Arterial Hypertension

Breanne E. McCarthy, MD; Rui Feng, PhD; Drew A. Torigian, MD; Yubing Tong, PhD; Jason S. Fritz, MD; Jasleen K. Minhas, MD; Jeremy A. Mazurek, MD; K. Akaya Smith, MD; Harold I. Palevsky, MD; Steven C. Pugliese, MD; Natalie Z. Homer, PhD; Margaret R. MacLean, PhD; Jayaram K. Udupa, PhD; and Nadine Al-Naamani, MD

BACKGROUND: Increased epicardial adipose tissue (EAT) has adverse effects in cardiovascular diseases, independent of BMI. Estrogen levels may affect EAT accumulation. Little is known about the predictors and potential impact of EAT in pulmonary arterial hypertension (PAH).

RESEARCH QUESTION: Is EAT associated with estrogen levels, disease severity, and mortality in PAH?

STUDY DESIGN AND METHODS: We conducted a retrospective cohort study of patients with PAH enrolled in the Penn Pulmonary Hypertension registry and used chest CT scans to quantify EAT. Serum estrone and estradiol levels were also measured.

RESULTS: A total of 221 patients were included in the analysis, with median follow-up of 88 months. Mean age was 55.1 years, 74.7% were female, mean BMI was 27.20 kg/m^2, and the most common PAH etiology was connective tissue disease-associated PAH (43.0%) followed by idiopathic or heritable PAH (35.3%). Median EAT volume was 52.1 mL/m^2. Of the 102 patients with a follow-up chest CT scan, EAT increased over time in 74 (71.8%). High EAT volume (hazard ratio, 2.62; 95% CI, 1.62-4.24; $P < .001$) and greater accumulation of EAT over time (hazard ratio, 1.09; 95% CI, 1.01-1.17; $P = .03$) were both independently associated with worse survival. Patients with high EAT volume had lower serum estrone (13.70 vs 30.60 pg/mL; $P = .009$) and estradiol (6.05 vs 19.40 pg/mL; $P = .002$) levels compared with those with low EAT volume.

INTERPRETATION: In patients with PAH, high EAT and a greater rate of accumulation of EAT volume were independently associated with worse survival. Higher EAT volume was also associated with lower estrogen levels. The association of EAT volume with survival was independent of BMI and disease severity, suggesting that EAT may be a marker for a unique PAH phenotype. Future research should investigate the role of EAT-modifying therapies in PAH and consider incorporating EAT into PAH risk models.

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KEY WORDS: epicardial adipose tissue; estrogen; pulmonary arterial hypertension; sex hormones; survival

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ABBREVIATIONS: EAT = epicardial adipose tissue; E1 = estrone; E2 = estradiol; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; RV = right ventricular

AFFILIATIONS: From the Departments of Medicine (B. E. M., J. S. F., J. K. M., J. A. M., K. A. S., H. I. P., S. C. P., and N. A.-N.), Biostatistics, Epidemiology, and Informatics (R. F.), and Radiology (D. A. T., Y. T., and J. K. U.), Perelman School of Medicine at the University

Take-Home Points

Study Question: Is epicardial adipose tissue (EAT) associated with disease severity and mortality in pulmonary arterial hypertension (PAH), and is there an association between EAT and estrogen levels?

Results: EAT was inversely associated with estrogen levels; high EAT volume and greater accumulation of EAT over time were associated with worse survival in PAH, and this association was independent of BMI and disease severity.

Interpretation: EAT may be a marker for a unique, pro-inflammatory PAH phenotype and may be a future therapeutic target.

Obesity is associated with an increased incidence of cardiovascular disease and worse outcomes. A growing body of evidence has suggested that ectopic fat deposition contributes to obesity-mediated poor cardiovascular outcomes.[1-4] Obesity is increasingly prevalent in patients with pulmonary arterial hypertension (PAH), a condition characterized by progressive pulmonary vasculopathy and right ventricular (RV) dysfunction.[5-8] Metabolic factors such as insulin resistance and dyslipidemia have been previously implicated in the pathogenesis of PAH[9-11]; however, the potential impact of ectopic fat has not been extensively studied in PAH.

Epicardial adipose tissue (EAT) is located between the myocardium and visceral pericardium. EAT is a unique visceral fat depot that usually provides cardioprotective effects for the adjacent myocardium through numerous beneficial thermogenic, metabolic, and mechanoprotective functions.[4,12,13] Various pathologic conditions may lead to a deleterious, pro-inflammatory EAT phenotype; this transition has been hypothesized to contribute to the pathogenesis of cardiovascular disease.[12,14-16] Increased EAT volume, independent of BMI, has been associated with adverse outcomes in many cardiovascular diseases, including heart failure with preserved ejection fraction,[16,17] coronary artery disease,[18,19] and atrial fibrillation.[20,21] EAT increases with aging.[4,13] Estrogen levels may also affect fat accumulation, as there are both sex-based differences in adipose tissue distribution[22-24] and fat depot-based differences in estrogen metabolism (between visceral vs subcutaneous depots).[25] In a randomized controlled trial of hormone therapy in early menopause, conjugated estrogen slowed the rate of EAT accumulation compared with placebo, suggesting a possible role for estrogens.[26] A recent study in patients with PAH suggested that EAT has a U-shaped association with worse RV function.[27] However, the predictors of EAT, the potential effect of changes in EAT over time, and the influence of sex hormones on EAT in PAH have not previously been studied.

Using chest CT scans to quantify EAT, the current study investigated the following: (1) predictors of high EAT and how EAT changes over time; (2) the impact of EAT on survival; and (3) whether estrogen levels were associated with EAT in patients with PAH. We hypothesized that increased EAT in PAH leads to worse survival and may be associated with disease severity. We also hypothesized that lower estrogen levels would be associated with higher EAT.

Study Design and Methods

We conducted a retrospective cohort study of patients with PAH enrolled in the Penn Pulmonary Hypertension registry between January 1, 2007, and December 31, 2015. Patients with PAH are enrolled in the registry at the time of their initial evaluation at our center. We included all patients who had chest CT imaging available during their initial PAH evaluation. For patients who had completed their initial PAH evaluation at another institution, CT images from the outside institution were obtained with patient consent and uploaded to our medical imaging system for review. Also included was the first follow-up chest CT scan if performed at least 1 year following the initial CT scan. The study was approved by the University of Pennsylvania Institutional Review Board (approved protocols: 833725, 706091, 803002, and 829924).

of Pennsylvania, Philadelphia, PA; Mass Spectrometry Core (N. Z. H.), Edinburgh Clinical Research Facility, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh; and the Strathclyde Institute of Pharmacy and Biomedical Sciences (M. R. M.), University of Strathclyde, Glasgow, Scotland.

Some of these data were previously presented in abstract form at the American Thoracic Society Meeting, May 19-24, 2023, Washington, DC, and the American Thoracic Society Meeting, May 17-22, 2024, San Diego, California.

CORRESPONDENCE TO: Nadine Al-Naamani, MD; email: Nadine.Al-Naamani@pennmedicine.upenn.edu

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Clinical Variables and Vital Statistics

Baseline demographic characteristics (age, sex, race and ethnicity, BMI, and PAH etiology), World Health Organization functional class, 6-minute walk distance, diagnostic right heart hemodynamics, and echocardiographic data were recorded at time of enrollment into the registry. Race and ethnicity were obtained from the electronic medical record.

Patients were categorized as having low, intermediate, or high risk for 1-year mortality at time of enrollment in the registry using the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 score.[28] The REVEAL Lite 2 score was calculated by using a minimum of 5 variables. Scores were classified as low (0-5), intermediate (6-7), or high ($\geq$ 8) risk.

Patients were followed up using the medical record and Social Security Death Index. Patients were followed up from initial enrollment in the registry until either death or censorship on May 31, 2022, whichever occurred first.

EAT Volume Measurement

CT scans were de-identified to ensure blinding of researchers to clinical information and outcomes. CT scans were included if the axial scan slice thickness was $\leq$ 5 mm and the thorax was not truncated on the scan. Using a standardized anatomic space approach that has been described previously,[29] EAT was delineated automatically. Automated EAT contours were then manually reviewed and corrected on each axial slice from the most basal slice of the heart to the superior slice of the heart, which was defined at the bifurcation of the pulmonary artery. EAT was defined as the adipose tissue located between the visceral layer of the pericardium and the myocardium (Fig 1). EAT volume was defined as the volume of EAT determined by volumetric assessment (milliliters) divided by the body surface area (square meters).

Serum Estrogen Measurement

Phlebotomy was performed following enrollment if the patient consented to blood draw. Plasma specimens were stored at −80 °C. Serum estrone (E1) and estradiol (E2) levels were measured using liquid chromatography tandem mass spectrometry according to previously described methods.[30]

Statistical Analysis

Patients were classified as having either "low" ($<$ 100 mL/m^2) or "high" ($\geq$ 100 mL/m^2) EAT volume, a cutoff used in prior studies of EAT.[17,31,32] Continuous data are summarized as mean and SD or median and interquartile range, as appropriate. Discrete data are summarized as numbers and percentages. Pearson correlation was used to test the association between age, BMI, and EAT volume. The association between potential predictors and EAT volume was assessed using multivariable logistic regression models adjusted for age, sex, and BMI. For individuals who had follow-up CT imaging, a rate of change was calculated as the difference between the EAT volume measured on follow-up imaging and the baseline EAT volume, divided by the time between the 2 CT scans (milliliters per year). The relationship between potential predictors and the rate of change of EAT volume were assessed by using multivariable linear regression models with similar adjustments. Pearson correlation was used to examine the association between EAT volume and E1 and E2 levels. Generalized additive models with Loess smoothing functions were used to plot the relationship between estrogen levels and EAT volume. In a sensitivity analysis, we refitted the models for 2 female subgroups: those

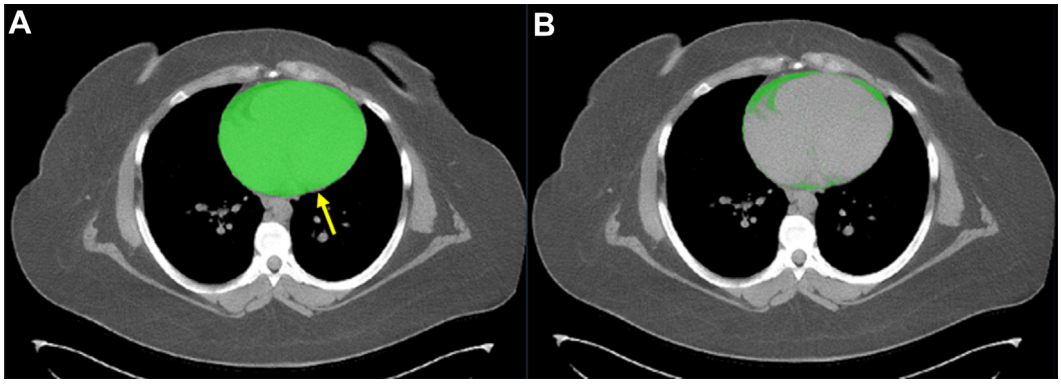

Figure 1 – *A, B, Delineation of epicardial adipose tissue on chest CT scan. A, Automated mask delineation of heart and epicardial adipose tissue deep to the pericardium with manual correction on axial CT chest image. Surrounding paracardial fat (arrow) is excluded. B, Axial CT slice showing epicardial adipose tissue delineated, after removal of non-epicardial adipose tissue and myocardium from original mask.*

aged < 40 years (assumed to be premenopausal) and those aged ≥ 55 years (assumed to be postmenopausal).

The association between EAT volume and overall survival was assessed by using Kaplan-Meier, log-rank test, and multivariable Cox proportional hazards regression models. The proportional hazards assumption was assessed by using Schoenfeld and martingale residuals. Time was defined as the time from initial CT scan to death, last follow-up, or the study data lock on May 31, 2022, or whichever occurred first. We tested for interactions between EAT volume and age, sex, and BMI. To assess the association of the rate of change of EAT volume with survival, inverse probability weighting was used to control for selection bias for participants who had follow-up imaging. Inverse probability weighting was determined from a model that included age, sex, BMI, PAH etiology, and REVEAL Lite 2 score. Multivariable Cox proportional hazards regression analysis was conducted by using this weighted follow-up cohort, adjusting this model for the same covariates as the survival model for baseline EAT.

All analyses were conducted in R version 4.3.1 (2023-06-16; R Foundation for Statistical Computing).

Results

A total of 453 patients were enrolled in the Penn Pulmonary Hypertension registry between 2007 and 2015, of whom 290 (64%) had chest CT images available for review. Of these, 69 (24%) patients were excluded due to poor-quality scans or truncation of the thorax on CT imaging. The final cohort included 221 participants, with median follow-up of 88 months (range, 46-127 months) (Fig 2). The baseline characteristics of participants are presented in Table 1. The median EAT volume was 52.1 mL/m^2 (Q1-Q3, 31.0-76.8), and 30 (13.6%) had high EAT volume. The mean age was 55.1 years, with the high EAT volume group being significantly older than the low EAT volume group (53.7 vs 63.8 years). Most (74.7%) of the cohort was female, and the majority (60.2%) were non-Hispanic White followed by non-Hispanic Black (30.3%). The most common etiology was connective tissue disease-associated PAH (43.0%) followed by idiopathic or heritable PAH (35.3%) (Table 1). There were no significant differences in sex, race and ethnicity, or PAH etiology between the high and low EAT volume groups. Mean BMI was 27.20 kg/m^2 with no significant difference between groups. There were also no significant differences in echocardiographic or hemodynamic parameters between patients with high vs low EAT volume. A total of 103 patients (47%) had a follow-up chest CT scan included with a median of 64 months (Q1-Q3, 33-101 months) between baseline and follow-up scan. A total of 142 participants were alive and censored at the end of the study.

Predictors of High EAT Volume

EAT volume was positively associated with age when EAT volume was analyzed as a continuous variable

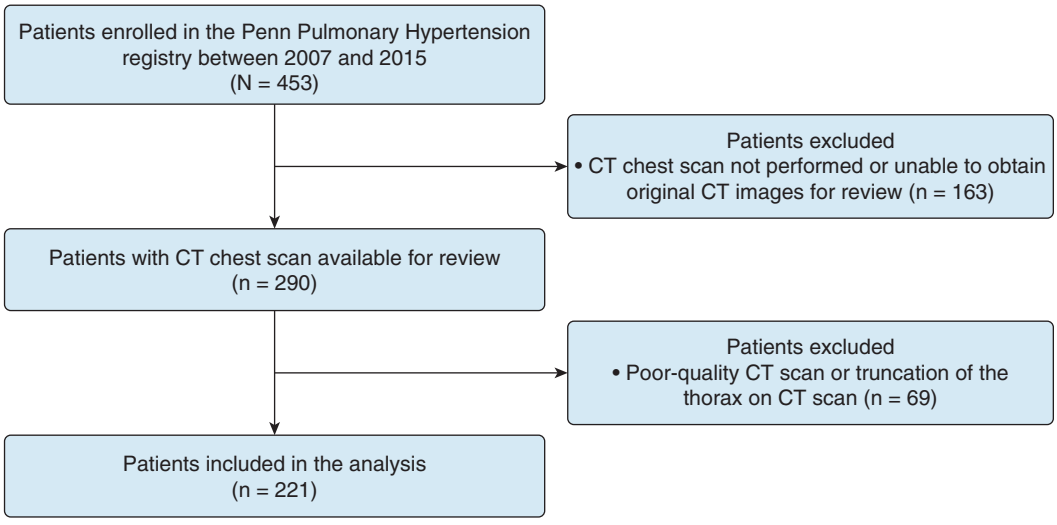

Figure 2 – *Participant inclusion flow diagram.*

TABLE 1] Baseline Characteristics of Study Participants

Characteristic	Entire Cohort (N = 221)	EAT < 100 mL/m^2 (n = 191)	EAT ≥ 100 mL/m^2 (n = 30)	*P* Value[a]
Age, y	55.1 ± 16.1	53.7 ± 16.1	63.8 ± 12.9	.001
Sex				.39
Female	165 (74.7)	145 (75.9)	20 (66.7)	
Male	56 (25.3)	46 (24.1)	10 (33.3)	
Race and ethnicity				.43
Asian	4 (1.8)	3 (1.6)	1 (3.3)	
Hispanic	12 (5.4)	12 (6.3)	0 (0)	
Non-Hispanic Black	67 (30.3)	59 (30.9)	8 (26.7)	
Non-Hispanic White	133 (60.2)	112 (58.6)	21 (70.0)	
Other or more than one race	5 (2.3)	5 (2.6)	0 (0)	
PAH etiology				.87
Idiopathic or heritable PAH	78 (35.3)	67 (35.1)	11 (36.7)	
Drug- and toxin-associated PAH	4 (1.8)	4 (2.1)	0 (0)	
Connective tissue disease-associated PAH	95 (43.0)	80 (41.9)	15 (50.0)	
Congenital heart disease-associated PAH	13 (5.9)	12 (6.3)	1 (3.3)	
HIV-associated PAH	9 (4.1)	8 (4.2)	1 (3.3)	
Portopulmonary hypertension	22 (10.0)	20 (10.5)	2 (6.7)	
BMI, kg/m^2	27.2 (24.1-32.3)	27.2 (24.1-32.2)	26.9 (24.1-32.6)	.96
WHO functional class (n = 56)				.69
I	3 (5.4)	3 (5.8)	0 (0)	
II	12 (21.4)	11 (21.2)	1 (25.0)	
III	30 (53.6)	27 (51.9)	3 (75.0)	
IV	11 (19.6)	11 (21.2)	0 (0)	
6-minute walk distance, m (n = 181)	311.0 (203.0-408.0)	320.5 (206.3-414.0)	270.0 (180.5-331.0)	.12
REVEAL Lite 2 risk category				.57
Low	42 (19.0)	37 (19.4)	5 (16.7)	
Intermediate	85 (38.5)	74 (38.7)	11 (36.7)	
High	94 (42.5)	80 (41.9)	14 (46.7)	
Echocardiogram findings				
Right atrial dilation (n = 203)	158 (77.8)	139 (78.1)	19 (76.0)	.99
Right ventricular dilation (n = 211)	163 (77.3)	145 (79.2)	18 (64.3)	.13
Right ventricular hypertrophy (n = 104)	44 (42.3%)	41 (46.6)	3 (18.8)	.07
Right ventricular dysfunction (n = 189)	137 (72.5)	117 (72.7)	20 (71.4)	.99
Estimated pulmonary artery systolic pressure, mm Hg (n = 186)	73 (55-89)	73 (55-89)	67 (52-83)	.53
Left ventricular dysfunction (n = 196)	25 (12.8)	22 (12.9)	3 (11.5)	.99
Left ventricular hypertrophy (n = 177)	79 (44.6)	68 (44.2)	11 (47.8)	.92
Pericardial effusion (n = 191)	68 (35.6)	56 (34.1)	12 (44.4)	.41

(Continued)

TABLE 1] *(Continued)*

Characteristic	Entire Cohort (N = 221)	EAT < 100 mL/m^2 (n = 191)	EAT ≥ 100 mL/m^2 (n = 30)	*P* Value[a]
Paradoxical motion of septum (n = 136)	116 (85.3)	103 (85.8)	13 (81.2)	.91
Right heart catheterization				
Mean right atrial pressure, mm Hg (n = 215)	9.00 (5.00-13.5)	9.00 (5.00-13.0)	11.0 (4.80-15.0)	.19
Mean pulmonary arterial pressure, mm Hg (n = 92)	46.0 (36.8-55.0)	47.0 (36.0-55.0)	45.0 (37.0-51.0)	.45
Pulmonary capillary wedge pressure, mm Hg (n = 216)	10.0 (7.00-15.0)	10.0 (7.00-15.0)	12.0 (8.00-19.0)	.13
Cardiac output, L/min (n = 216)	4.20 (3.51-5.40)	4.20 (3.50-5.57)	4.13 (3.70-4.86)	.58
Cardiac index, L/min/m^2 (n = 216)	2.40 (1.90-2.90)	2.40 (1.90-2.90)	2.40 (1.90-2.58)	.39
Pulmonary vascular resistance, Wood units (n = 217)	7.68 (5.17-11.7)	7.72 (5.01-11.82)	7.22 (5.86-9.81)	.65
Epicardial adipose tissue volume, mL/m^2	52.1 (31.0-76.8)	45.8 (28.7-67.3)	122.3 (108.6-145.9)	< .001
Serum estrone level, pg/mL (n = 117)	28.80 (16.7-54.7)	30.60 (17.50-60.20)	13.70 (8.08-34.08)	.009
Serum estradiol level, pg/mL (n = 117)	17.30 (6.70-59.7)	19.40 (7.20-67.80)	6.05 (3.43-19.23)	.002
Use of estrogen-containing product[b]	7 (3.17)	6 (2.71)	1 (0.52)	1.00

Data are presented as mean ± SD, no. (%), or median (quartile 1-quartile 3). EAT = epicardial adipose tissue; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; WHO = World Health Organization.
[a]*P* values for comparison between low (< 100 mL/m^2) vs high (≥ 100 mL/m^2) EAT volume.
[b]Includes patients using either hormone replacement therapy or estrogen-containing oral contraceptives.

($r = 0.38$; $P < .001$) (e-Fig 1A), with no difference between male and female participants. Higher age was significantly associated with having high EAT volume (OR per 1 year increase, 1.05; 95% CI, 1.02-1.08; $P = .002$) (e-Table 1). There was no statistically significant association between EAT volume and BMI ($r = 0.09$; $P = .19$) (e-Fig 1B); higher BMI was not associated with odds of high EAT volume (OR, 1.00; 95% CI, 0.95-1.06; $P = .87$). This lack of association between EAT and BMI was similar for male and female participants. Sex and REVEAL Lite 2 risk score were not significantly associated with odds of high EAT volume. Of the hemodynamic measurements from baseline right heart catheterization, only pulmonary capillary wedge pressure was significantly associated with high EAT volume (OR, 1.07; 95% CI, 1.00-1.14; $P = .04$). No echocardiographic parameters were associated with odds of high EAT volume.

EAT and Estrogen Levels

The median serum E1 level and median serum E2 level for the cohort were 28.80 pg/mL (Q1-Q3, 16.70-54.70) and 17.30 pg/mL (Q1-Q3, 6.70-59.70), respectively (Table 1). There were significant differences in mean serum estrogen levels between the 2 EAT volume groups, with the high EAT volume group having both lower serum E1 (13.70 vs 30.60 pg/mL; $P = .009$) and E2 (6.05 vs 19.40 pg/mL; $P = .002$) levels compared with the low EAT volume group. Both E1 ($r = -0.24$; $P = .0.01$) and E2 ($r = -0.26$; $P = .004$) were weakly negatively correlated with EAT volume. We found no significant nonlinearity between EAT volume and either E1 or E2 (Fig 3).

Of 165 female participants included in the overall analysis, 34 (21%) were < 40 years old, and 89 (54%) were ≥ 55 years old. Forty-two female participants (25%) were excluded because they were aged within the 40- to 54-year-old range. Median serum E1 and E2 levels grouped according to sex and menopausal status are summarized in e-Table 2. There was a significant difference in E1 ($P = .009$) and E2 ($P = .002$) levels according to sex in both the high and low EAT volume groups (Fig 4), but there was no significant interaction between E1 or E2 and sex ($P = .99$ for both). This relationship between EAT volume and estrogen, with higher EAT volume associated with lower E1 and E2 levels, was similar for female participants < 40 years old, female participants ≥ 55 years old, and male participants.

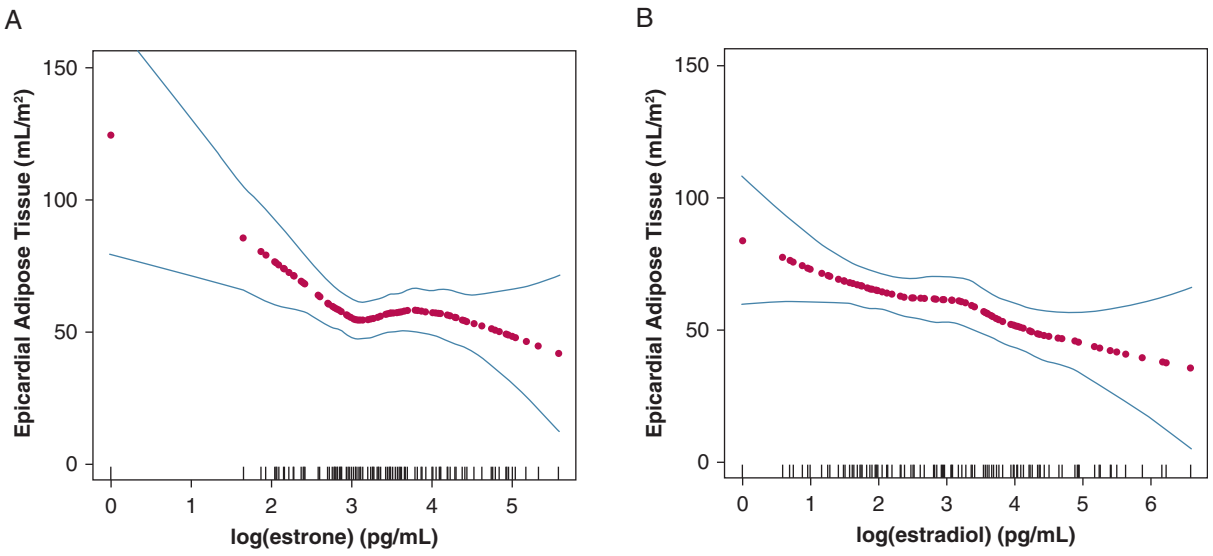

Figure 3 – *A, B, Nonlinear interaction between epicardial adipose tissue volume and serum estrogen. A, Generalized additive model for the nonlinear interaction between epicardial adipose tissue volume with serum estrone. B, Generalized additive model for the nonlinear interaction between epicardial adipose tissue volume with serum estradiol. Thick dotted lines indicate smoothed regression lines; solid outer lines indicate 95% CIs.*

Change in EAT Over Time

There was no significant difference in baseline demographic characteristics, PAH etiology, World Health Organization functional class, 6-minute walk distance, or REVEAL Lite 2 risk category between participants who had a follow-up chest CT and those who only had a baseline CT scan (e-Table 3). The group that had follow-up imaging had a lower median EAT volume than the group that had only baseline imaging (45.34 [Q1-Q3, 27.99-66.64] mL/m^2 vs 63.60 [Q1-Q3, 35.05-85.21] mL/m^2; $P = .002$). For those with follow-up imaging, mean EAT volume increased from 59.7 $\pm$39.4 mL/m^2 at baseline to 81.3 $\pm$52.2 mL/m^2 at follow-up. In total, 51 patients (49.5%) had an increase in EAT volume by at least 1 SD compared with baseline (e-Table 4, Fig 5).

There was no significant association between rate of change in EAT volume and baseline EAT volume, age, PAH etiology, hemodynamic parameters on right heart catheterization, or echocardiographic measurements (Table 2). Male sex (22.74 mL/year; $P = .005$), BMI (β per 1 kg/m^2 increase, –1.07 mL/year; $P = .02$), and

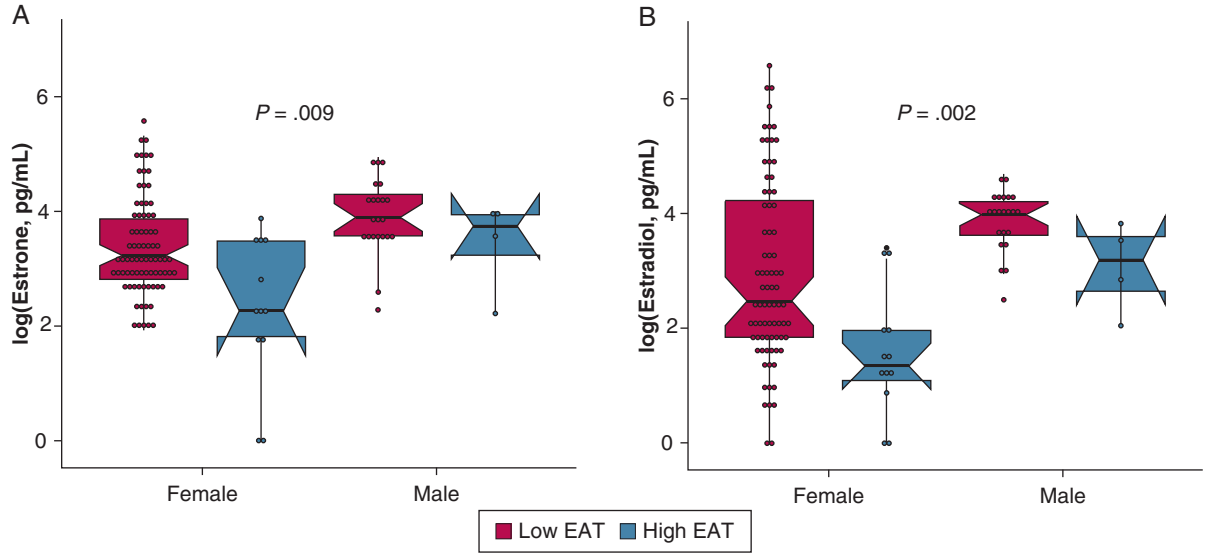

Figure 4 – *A, B. Association of EAT volume and sex with serum estrogen. A, Interaction between low vs high EAT volume and sex with serum estrone level. B, Interaction between low vs high EAT volume and sex with serum estradiol level. EAT = epicardial adipose tissue.*

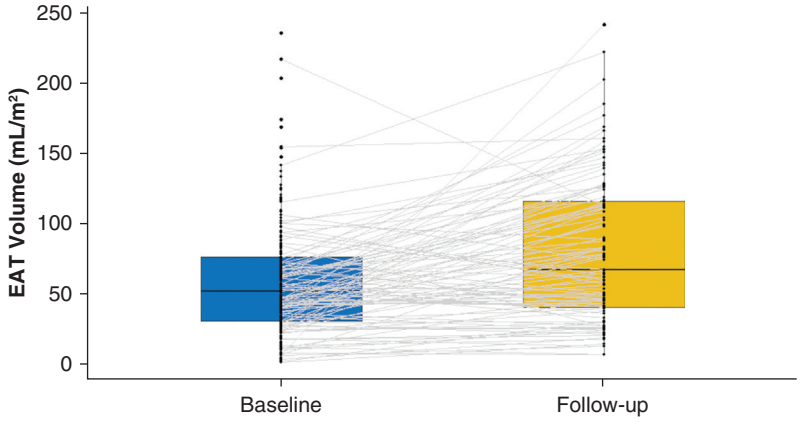

Figure 5 – *Change in EAT volume from baseline to follow-up for participants with follow-up chest CT imaging. Box plots show the distribution of EAT volume at baseline and at follow-up. The central line within each box represents the median; the edges of the box indicate the interquartile range (25th to 75th percentiles). Each gray line represents the change in EAT volume for a single participant. EAT = epicardial adipose tissue.*

higher right atrial pressure (β per 1 mm Hg increase, 2.04 mL/year; $P = .001$) were significantly and independently associated with the rate of change in EAT volume.

EAT Volume and Survival

High EAT volume was significantly associated with worse survival both compared with low EAT volume (Fig 6) and when EAT volume was analyzed as a continuous variable (e-Table 5). This association persisted following multivariable adjustments for age, sex, BMI, PAH etiology, and REVEAL Lite 2 risk score (hazards ratio, 2.62; 95% CI; 1.62-4.24; $P < .001$) (e-Table 6). A higher rate of increase in EAT volume was also associated with worse survival following multivariable adjustment (hazards ratio, 1.09; 95% CI, 1.01-1.17; $P = .03$) (e-Table 7).

Discussion

In patients with PAH, EAT volume was strongly associated with age, whereas it was not correlated with BMI. High EAT volume was associated with lower serum estrogen levels. Higher EAT volume was significantly and independently associated with worse survival, while a greater rate of accumulation of EAT over time was also associated with worse survival in patients with PAH.

EAT volume increases with age.[13,33] Under normal physiologic conditions, EAT possesses cardioprotective, brown fat-like activity.[4] However, with aging, EAT loses its cardioprotective functions and becomes more pro-inflammatory.[4,13] Our findings are consistent with prior literature showing that EAT volume was positively associated with age and that it increased over time in most patients.[13,33,34] The current study provides further evidence of increased EAT accumulation with aging; however, the rate of accumulation and properties of EAT may vary across different populations and should be explored further. We also found that the relationship between EAT volume and survival was independent of age, suggesting that the accumulation of EAT over time with aging does not entirely explain the association with worsened survival in patients with PAH. Instead, this may indicate that the properties of EAT are a significant contributor to this relationship between EAT and survival.

The association between visceral adipose tissue and cardiovascular disease varies by sex, with a stronger association in female participants than in male participants despite the latter group having a greater volume of visceral fat.[3,35] In experimental models, the transition of EAT to a less cardioprotective phenotype that occurs with aging is more prominent in female rats compared with male rats.[13] EAT has also been associated with worse cardiovascular outcomes in male participants and postmenopausal female participants but not in premenopausal female participants.[36,37] Adipose distribution differs according to sex, with premenopausal female individuals accumulating subcutaneous adipose tissue while male individuals preferentially accumulate visceral adipose tissue.[24,36] Following menopause, there is an increasing shift to visceral adipose tissue, a change that parallels the increased cardiovascular disease risk seen in postmenopausal female individuals.[36,38] Some data suggest that EAT volume increases in postmenopausal female individuals[23,36] and that administering exogenous estrogen in early menopause attenuates EAT accumulation.[26] In the current cohort, lower serum E1 and E2 levels were found in patients with PAH who had higher EAT volume. However, no sex-based interactions were observed: the association between low estrogen levels and high EAT volume was consistent across male and female participants, including when female

TABLE 2] Predictors of the Rate of Change of Epicardial Adipose Tissue Volume Over Time

Model and Variables	β (SE)	*P* Value
Univariable models		
Baseline EAT volume, per 1 mL/m^2 increase	−0.15 (0.10)	.13
REVEAL Lite 2 risk score, per 1 unit increase	2.93 (1.42)	.04
Age, per 1 year increase	−0.14 (0.22)	.55
Male sex	18.28 (8.3)	.03
BMI per 1 kg/m^2 increase	−0.69 (0.41)	.10
Invasive hemodynamics		
Right atrial pressure, per 1 mm Hg increase	1.27 (0.54)	.02
Mean pulmonary artery pressure, per 1 mm Hg increase	0.01 (0.23)	.95
Pulmonary capillary wedge pressure, per 1 mm Hg increase	0.58 (0.47)	.23
Cardiac output, per 1 mL/min increase	0.07 (2.14)	.97
Cardiac index, per 1 mL/min/m^2	−0.13 (4.38)	.98
Pulmonary vascular resistance, per 1 Wood unit increase	0.11 (0.60)	.85
Echocardiographic findings		
Right atrial dilation	−11.17 (8.06)	.17
Right ventricular dilation	1.05 (8.00)	.90
Right ventricular hypertrophy	−14.92 (10.47)	.16
Right ventricular dysfunction	2.65 (7.58)	.73
PAH etiology		.52
Idiopathic/heritable PAH	Reference	
Drug- and toxin-associated PAH	45.37 (34.49)	
Connective tissue disease-associated PAH	−3.28 (7.56)	
Congenital heart disease-associated PAH	−7.46 (18.00)	
HIV-associated PAH	2.59 (18.00)	
Portopulmonary hypertension	15.11 (12.78)	
Adjusted model		
Baseline EAT volume, per 1 mL/m^2 increase	−0.15 (0.10)	.15
Age, y	−0.03 (0.23)	.88
Male sex	22.74 (7.91)	.005
Body mass index, per 1 kg/m^2 increase	−1.07 (0.44)	.02
REVEAL Lite 2 risk score, per 1 unit increase	1.72 (1.49)	.25
Right atrial pressure, mm Hg	2.04 (0.61)	.001
Cardiac index, L/min/m^2	4.03 (4.18)	.34

Results describe predictors of rate of change of EAT volume per year (milliliters per year). EAT = epicardial adipose tissue; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management.

participants were analyzed according to menopausal status. Our data suggest a potential link between estrogen and EAT in PAH, but this theory requires further investigation.

Obesity is a risk factor for and affects outcomes in PAH.[6,9] Obesity is a heterogeneous disease, and there is growing recognition that BMI is a suboptimal measure of individual body composition. Excess visceral adipose tissue is associated with cardiovascular disease, irrespective of BMI.[1-3] As such, specific obesity phenotypes, including differential adipose tissue distribution, may be more important markers for overall cardiovascular risk than BMI alone. At the cellular level, accumulation of excess visceral fat is associated with adipose tissue dysfunction, resulting in systemic inflammation, increased lipolysis, local tissue hypoxia, mitochondrial dysfunction and oxidative stress, and altered adipokine secretion that lead to endothelial dysfunction, vascular remodeling, and metabolic dysfunction.[12,14,15,38] Alterations in EAT have been hypothesized to contribute to the pathogenesis of cardiovascular disease through direct paracrine and autocrine effects.[4,12,14,15,38] This has potential therapeutic implications, with agents such as sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide 1 receptor agonists having been shown to both reduce EAT volume and restore its cardioprotective phenotype.[39-43]

We found no significant correlation between EAT and BMI; that is, those with high BMI were not more likely to have high EAT volume. In our cohort, higher EAT volume and a greater rate of accumulation of EAT over time were both independently associated with worse survival. In community-dwelling adults, pericardial fat has also been linked to increased all-cause mortality,[44] suggesting that cardiac fat analysis might provide

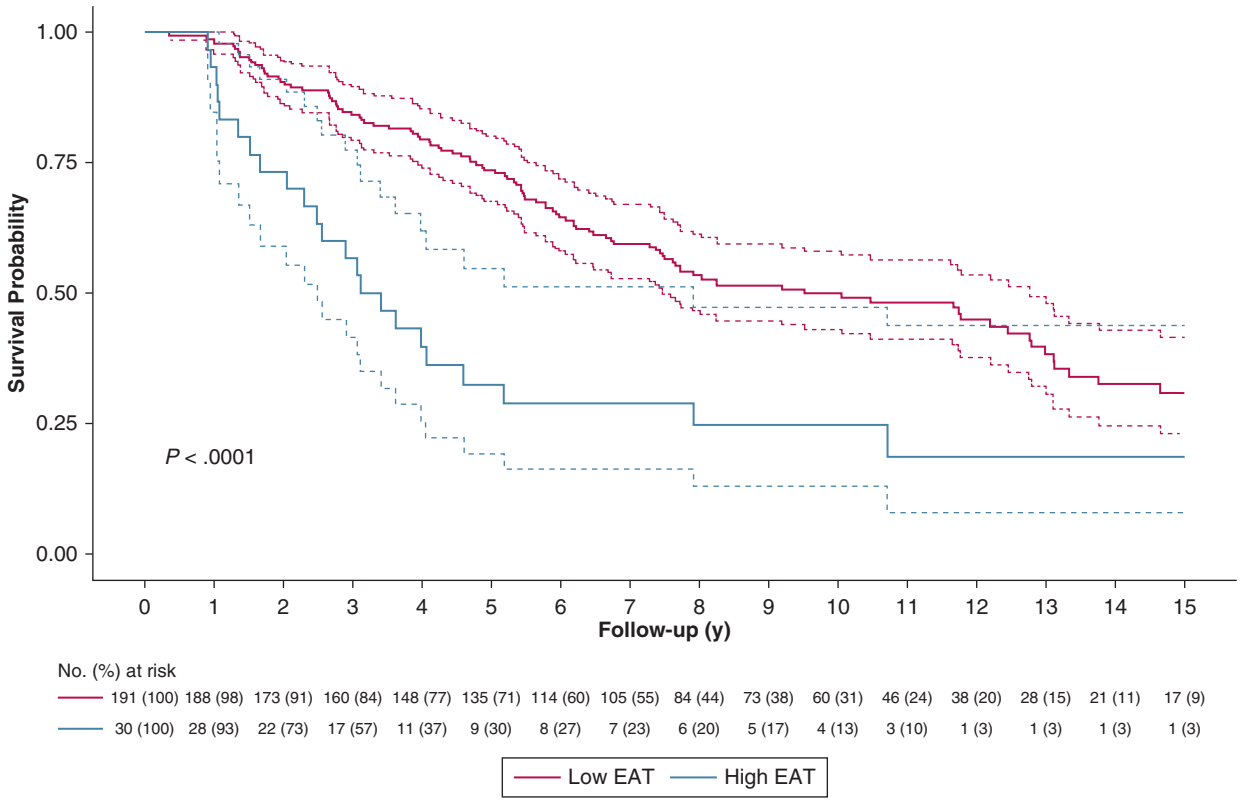

Figure 6 – *EAT volume and survival. Kaplan-Meier estimate of survival for patients with low (< 100 mL/m^2) and high (≥ 100 mL/m^2) EAT volume. Confidence bands indicating 95% CIs are shown. EAT = epicardial adipose tissue.*

valuable risk assessment not only in PAH but also in other populations. Importantly, finding that EAT volume is associated with survival independent of BMI suggests that EAT may provide information about a unique PAH phenotype. EAT may therefore be a marker for a more pro-inflammatory PAH phenotype and may serve as a more useful risk factor than BMI in PAH. A recent PAH study found a U-shaped association of EAT volume with worse RV function and survival.[27] The current study found a more linear relationship between EAT volume (analyzed as a continuous variable) and survival and did not find an association between EAT volume and right heart echocardiographic parameters. It is possible that these differences could be related to a higher BMI in the current cohort, or they may instead suggest that the impact of EAT on survival in PAH may involve distinct mechanism(s) beyond RV dysfunction.

The current study had some limitations. Selection bias is a concern because not all patients had a CT scan of adequate quality available. However, this is one of the larger cohorts in PAH to quantify EAT on baseline and follow-up imaging, and there was no significant difference in baseline characteristics between included and excluded participants (e-Table 8). The CT scans in this study were clinical scans and did not follow a standardized research protocol, introducing differences in technique and resolution that may have led to measurement error. Manual revisions of automated EAT contours were completed by anonymized reviewers to minimize this risk. However, this is also a strength, as it shows the feasibility of measuring epicardial fat on clinical CT scans as part of routine care, particularly with the development of artificial intelligence models to quantify EAT.

Although the current study is one of the largest exploring EAT measured on CT imaging, it was not sufficiently powered to examine differences in EAT volume according to PAH etiology. We also did not have adjudicated cause of death for our cohort. However, knowing that the majority of patients with PAH die of PAH-related causes,[45] the associations between EAT and all-cause mortality in the current study would likely also hold for cardiovascular-specific mortality. Finally, because blood samples were not available for all patients, the study may have been underpowered to fully explore

the association between serum estrogen levels, sex, and EAT. Nonetheless, the associations between EAT and estrogen found in this study are hypothesis generating and warrant further investigation.

Interpretation

We found that, in patients with PAH, higher EAT volume and a greater rate of accumulation of EAT were independently associated with worse survival. Higher EAT volume was also associated with lower estrogen levels independent of sex. Whether modulation of EAT through diet or medications might improve outcomes in PAH remains to be determined. Future research is needed to investigate the role of EAT-modifying therapies in PAH, as well as to consider the incorporation of EAT measurement into PAH risk models. Ultimately, this study adds to a growing body of literature investigating the role of the metabolic syndrome, body composition, and epicardial fat in PAH.

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References

1. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol*. 2013;62(10):921-925.
2. Neeland IJ, Turer AT, Ayers CR, et al. Body fat distribution and incident cardiovascular disease in obese adults. *J Am Coll Cardiol*. 2015;65(19):2150-2151.
3. Lee JJ, Pedley A, Hoffmann U, Massaro JM, Levy D, Long MT. Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: the Framingham Heart Study. *Am J Med*. 2018;131(6):684-692.e612.
4. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol*. 2022;19(9):593-606.
5. Poms AD, Turner M, Farber HW, Meltzer LA, McGoon MD. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. *Chest*. 2013;144(1):169-176.
6. Frank RC, Min J, Abdelghany M, et al. Obesity is associated with pulmonary hypertension and modifies outcomes. *J Am Heart Assoc*. 2020;9(5):e014195.
7. Min J, Feng R, Badesch D, et al. Obesity in pulmonary arterial hypertension (PAH): the Pulmonary Hypertension Association Registry (PHAR). *Ann Am Thorac Soc*. 2021;18(2):229-237.
8. Thenappan T, Ryan JJ, Archer SL. Evolving epidemiology of pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2012;186(8):707-709.
9. Hansmann G, Wagner RA, Schellong S, et al. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-γ activation. *Circulation*. 2007;115(10):1275-1284.
10. Brunner NW, Skhiri M, Fortenko O, et al. Impact of insulin resistance on ventricular function in pulmonary arterial hypertension. *J Heart Lung Transplant*. 2014;33(7):721-726.
11. Heresi GA, Aytekin M, Newman J, Didonato J, Dweik RA. Plasma levels of high-density lipoprotein cholesterol and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;182(5):661-668.
12. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol*. 2018;71(20):2360-2372.
13. Iacobellis G. Aging effects on epicardial adipose tissue. *Front Aging*. 2021;2:666260.
14. Salgado-Somoza A, Teijeira-Fernández E, Fernández ÁL, González-Juanatey JR, Eiras S. Proteomic analysis of epicardial and subcutaneous adipose tissue reveals differences in proteins involved in oxidative stress. *Am J Physiol*. 2010;299(1):H202-H209.
15. Dozio E, Vianello E, Briganti S, et al. Increased reactive oxygen species production in epicardial adipose tissues from coronary artery disease patients is associated with brown-to-white adipocyte trans-differentiation. *Int J Cardiol*. 2014;174(2):413-414.
16. Van Woerden G, Van Veldhuisen DJ, Westenbrink BD, De Boer RA, Rienstra M, Gorter TM. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: mechanisms, management and modern perspectives. *Eur J Heart Fail*. 2022;24(12):2238-2250.
17. Van Woerden G, Van Veldhuisen DJ, Manintveld OC, et al. Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail*. 2021;15(3):e009238.
18. Bachar GN, Dicker D, Kornowski R, Atar E. Epicardial adipose tissue as a predictor of coronary artery disease in asymptomatic subjects. *Am J Cardiol*. 2012;110(4):534-538.
19. Nerlekar N, Brown AJ, Muthalaly RG, et al. Association of epicardial adipose tissue and high-risk plaque characteristics: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6(8).
20. Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol*. 2010;56(10):784-788.

21. Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol*. 2011;57(17):1745-1751.

22. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments. *Circulation*. 2007;116(1):39-48.

23. El Khoudary SR, Shields KJ, Janssen I, et al. Cardiovascular fat, menopause, and sex hormones in women: the SWAN cardiovascular fat ancillary study. *J Clin Endocrinol Metab*. 2015;100(9):3304-3312.

24. Kammerlander AA, Lyass A, Mahoney TF, et al. Sex differences in the associations of visceral adipose tissue and cardiometabolic and cardiovascular disease risk: the Framingham Heart Study. *J Am Heart Assoc*. 2021;10(11).

25. Hetemäki N, Savolainen-Peltonen H, Tikkanen MJ, et al. Estrogen metabolism in abdominal subcutaneous and visceral adipose tissue in postmenopausal women. *J Clin Endocrinol Metab*. 2017;102(12):4588-4595.

26. El Khoudary SR, Zhao Q, Venugopal V, et al. Effects of hormone therapy on heart fat and coronary artery calcification progression: secondary analysis from the KEEPS trial. *J Am Heart Assoc*. 2019;8(15):e012763.

27. Chen Y, Chen J, Li J, et al. Impact of epicardial adipose tissue on right cardiac function and prognosis in pulmonary arterial hypertension. *Chest*. 2024;165(5):1211-1223.

28. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest*. 2021;159(1):337-346.

29. Tong Y, Udupa JK, Torigian DA. Optimization of abdominal fat quantification on CT imaging through use of standardized anatomic space: a novel approach. *Med Phys*. 2014;41(6):063501.

30. Kawut SM, Archer-Chicko CL, Demichele A, et al. Anastrozole in pulmonary arterial hypertension. A randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2017;195(3):360-368.

31. Harada K, Amano T, Uetani T, et al. Cardiac 64-multislice computed tomography reveals increased epicardial fat volume in patients with acute coronary syndrome. *Am J Cardiol*. 2011;108(8):1119-1123.

32. Iwasaki K, Matsumoto T, Aono H, et al. Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. *Clin Cardiol*. 2011;34(3):166-171.

33. Nerlekar N, Thakur U, Lin A, et al. The natural history of epicardial adipose tissue volume and attenuation: a long-term prospective cohort follow-up study. *Sci Rep*. 2020;10(1):7109.

34. Guglielmi V, Maresca L, D'Adamo M, et al. Age-related different relationships between ectopic adipose tissues and measures of central obesity in sedentary subjects. *PLoS ONE*. 2014;9(7):e103381.

35. Liu J, Fox CS, Hickson DA, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab*. 2010;95(12):5419-5426.

36. Kim MN, Park SM, Cho DH, et al. The relationship between epicardial adipose tissue and coronary artery stenosis by sex and menopausal status in patients with suspected angina. *Biol Sex Differ*. 2018;9(1):52.

37. Zhu J, Zhou W, Xie Z, Li W, Zhuo K. Impact of sex and menopausal status on the association between epicardial adipose tissue and diastolic function in patients with type 2 diabetes mellitus. *Acad Radiol*. 2023;30(5):823-832.

38. Mair KM, Gaw R, Maclean MR. Obesity, estrogens and adipose tissue dysfunction—implications for pulmonary arterial hypertension. *Pulm Circ*. 2020;10(3):1-21.

39. Dutour A, Abdesselam I, Ancel P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. *Diabetes Obes Metab*. 2016;18(9):882-891.

40. Iacobellis G, Mohseni M, Bianco SD, Banga PK. Liraglutide causes large and rapid epicardial fat reduction. *Obesity (Silver Spring)*. 2017;25(2):311-316.

41. Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol*. 2018;17(1):6.

42. Díaz-Rodríguez E, Agra RM, Fernández ÁL, et al. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res*. 2018;114(2):336-346.

43. Iacobellis G, Villasante Fricke AC. Effects of semaglutide vs dulaglutide on epicardial fat thickness in subjects with type 2 diabetes and obesity. *J Endocr Soc*. 2020;4(4):bvz042.

44. Larsen BA, Laughlin GA, Saad SD, Barrett-Connor E, Allison MA, Wassel CL. Pericardial fat is associated with all-cause mortality but not incident CVD: the Rancho Bernardo Study. *Atherosclerosis*. 2015;239(2):470-475.

45. Tonelli AR, Arelli V, Minai OA, et al. Causes and circumstances of death in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2013;188(3):365-369.