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ORIGINAL RESEARCH

Regional Adiposity and Risk of Heart Failure and Mortality: The Jackson Heart Study

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BACKGROUND: Visceral adipose tissue (VAT) is associated with incident heart failure (HF) and HF with preserved ejection fraction, yet it is unknown how pericardial and abdominal adiposity affect HF and mortality risks in Black individuals. We examined the associations of pericardial adipose tissue (PAT), VAT, and subcutaneous adipose tissue (SAT) with incident HF hospitalization and all-cause mortality in a large community cohort of Black participants.

METHODS AND RESULTS: Among the 2882 Jackson Heart Study Exam 2 participants without prevalent HF who underwent body computed tomography, we used Cox proportional hazards models to examine associations between computed tomography–derived regional adiposity and incident HF hospitalization and all-cause mortality. Fully adjusted models included demographics and cardiovascular disease risk factors. Median follow-up was 10.6 years among participants with available VAT (n=2844), SAT (n=2843), and PAT (n=1386). Fully adjusted hazard ratios (95% CIs) of distinct computed tomography–derived adiposity measures (PAT per 10 cm^3, VAT or SAT per 100 cm^3) were as follows: for incident HF, PAT 1.08 (95% CI, 1.02–1.14) and VAT 1.04 (95% CI, 1.01–1.08); for HF with preserved ejection fraction, PAT 1.13 (95% CI, 1.04–1.21) and VAT 1.07 (95% CI, 1.01–1.13); for mortality, PAT 1.07 (95% CI, 1.03–1.12) and VAT 1.01 (95% CI, 0.98–1.04). SAT was not associated with either outcome.

CONCLUSIONS: High PAT and VAT, but not SAT, were associated with incident HF and HF with preserved ejection fraction, and only PAT was associated with mortality in the fully adjusted models in a longitudinal community cohort of Black participants. Future studies may help understand whether changes in regional adiposity improves HF, particularly HF with preserved ejection fraction, risk predictions.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00005485.

Key Words: Black participants ■ heart failure ■ Jackson Heart Study ■ mortality ■ obesity ■ regional adiposity

Obesity is a major risk factor for heart failure (HF),[1] often represents excess total body adiposity, and has increased in prevalence worldwide during recent decades.[2] An adverse relationship exists between obesity and particularly incident HF despite potentially biased evidence of an inverse relationship between obesity and mortality once HF is established.[3] Although obesity is most commonly defined by the anthropometrics as body mass index (BMI), waist circumference, and waist-to-hip ratio, the deleterious cardiovascular effects of obesity may be attributed to the specific distribution rather than total accumulation of excess fat alone.[4] Regional fat accumulation occurs in the pericardium, visceral, and subcutaneous compartments. Visceral adipose tissue (VAT) refers to the intra-abdominal adipose accumulation of omental and mesenteric adipose tissue, excluding subcutaneous adipose tissue (SAT) and intramuscular fat.[5] SAT refers to the accumulation of adipose tissue outside of the abdominal cavity, and pericardial adipose tissue (PAT) refers to regional fat surrounding the heart. Regional adiposity can be quantified by computed tomography

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CLINICAL PERSPECTIVE

What Is New?

- We newly demonstrate that among Black participants without prevalent heart failure, computed tomography–derived pericardial, visceral, and subcutaneous adiposity have varying risk on incident hospitalized heart failure and all-cause mortality.
- Pericardial and visceral fat volumes were associated with incident heart failure, particularly heart failure with preserved ejection fraction in fully adjusted models including demographics, education, and cardiovascular disease risk factors.
- Pericardial fat volumes were associated with all-cause mortality in the fully adjusted model.

What Are the Clinical Implications?

- This observational study provides insight into the varying relationships between different computed tomography–derived regional adiposity measures, including pericardial, visceral, and subcutaneous adiposity, and incident heart failure and mortality.
- These results will be helpful in understanding how regional fat depots contribute to cardiovascular risk and potentially inform future studies to identify high-risk groups who would benefit from targeted preventive strategies beyond routine screening by anthropometric measures alone.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
PAT	pericardial adipose tissue
SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue

(CT) scans within the abdomen for VAT and SAT[6] and within the thorax for PAT.[7]

Abdominal VAT is proinflammatory and increases cardiovascular disease (CVD) risk by promoting diseases such as diabetes mellitus, dyslipidemia, and hypertension.[8] Waist circumference and waist-to-hip ratio, although intended to indirectly represent the burden of visceral adiposity, in fact do not accurately quantify VAT or SAT.[5] VAT independently predicts HF beyond anthropometrics alone[1] and is more strongly and specifically associated with higher mortality than BMI.[9] PAT trends directly with higher BMIs[10]; is associated with accelerated CVD, insulin resistance, and hypertension in both obese and nonobese individuals[11]; and may be central to the pathogenesis for patients with HF with preserved ejection fraction (HFpEF).[12] SAT, on the other hand, also tracks with BMI but does not appear to be independently associated with subclinical or clinical CVD.[13]

Although the predictive values of VAT and SAT on incident HF have been reported,[1,14] the associations of adiposity measures derived from both thoracic and abdominal CTs and incident HF and mortality is not presently known.[15] Moreover, the associations of regional adiposity with clinical outcomes has not been well characterized in a large population of Black individuals. In this analysis, we aimed to describe the associations of PAT, VAT, and SAT with incident HF hospitalization and all-cause mortality and explored differences in associations between regional adiposity and HFpEF and HF with reduced ejection fraction (HFrEF).

METHODS

Design and Study Participants

The authors will not make their data, analytic methods, and study materials available to other researchers. Requests to access the data set from qualified researchers may be sent to the Jackson Heart Study data coordinating center. The Jackson Heart Study recruited 5300 Black participants who did not have heart disease from the Jackson, MS, metropolitan area between September 2000 and March 2004. Exam 2 measurements were collected between 2005 and 2008, and 2882 participants underwent multidetector CT scans of the thorax and abdomen. Although these participants had abdominal fat quantified,[16] a random subset had pericardial fat quantified in an ancillary study.[17] For the present analysis, we excluded participants with prevalent HF (defined as clinically diagnosed HF in any setting) before Exam 2 (n=34) and those missing measures for BMI, waist, or hip circumference (n=38). Among 4205 Exam 2 participants, the present study population included 2844 participants with measured VAT, 2843 participants with measured SAT, and 1386 participants with measured PAT (Figure S1). The Institutional Review Board of Duke University Health System approved this study, and all participants provided informed consent.

Measure of Adiposity

Anthropometrics

Baseline anthropometric measurements collected during Exam 2 included weight (kilograms), height (inches), and waist and hip circumferences (inches). BMI was

calculated by dividing measured weight in kilograms by height in meters squared (kg/m^2).

Multidetector CT Volumetric Measures of Adiposity

Measures of adiposity depots within the thorax and abdomen were performed using a 16-channel multidetector CT scanner (Lightspeed 16 Pro; GE Healthcare, Milwaukee, WI). Image analysis and quality control were performed at a core imaging laboratory (Wake Forest University School of Medicine, Winston-Salem, NC). Fat tissue attenuation threshold ranged from of –190 to –30 Hounsfield units. Volumetric VAT and SAT were measured either in 60 or 10 mm total blocked slices centered at the L4–L5 spine levels.[16] VAT designated fat within the abdominal cavity excluding intramuscular fat, and SAT designated fat outside the abdominal cavity. Volumetric PAT was measured in 45 mm total blocked slices.[17] PAT designated thoracic volumetric measurements of both epicardial fat (within the pericardium) and paracardial fat (superficial to the pericardium) because the 2 are difficult to distinguish on CT.[17] The correlation coefficient between 2 different readers was 0.95 for VAT and SAT and 0.96 for PAT among randomly selected participants.[17] We scaled the adiposity measures for ease of model interpretation as follows: PAT per 10 cm^3 and VAT or SAT per 100 cm^3.

Covariates

Using baseline data at the time of CT scan (Exam 2), we described demographics, socioeconomic, and clinical factors including age, sex, systolic blood pressure, total cholesterol (mg/dL), hypertension, diabetes mellitus, education, current smoker status, and BMI. Diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL, self-reported history of a physician diagnosis of diabetes mellitus, or the use of diabetes mellitus medications. Similarly, hypertension was defined as blood pressure >140/90 mm Hg or use of blood pressure–lowering medications. Education and current smoking status were carried forward from Exam 1 because they were not collected at Exam 2.

Outcomes

The primary outcomes were incident worsening HF requiring hospitalization and all-cause mortality. All-cause mortality was selected over cause-specific mortality to allow for sufficient analytic power. The index date was the Exam 2 visit date or CT scan date (whichever came later) for each cohort. Outcomes were collected during follow-up, including HF hospitalizations between 2005 and 2015 and all-cause mortality between 2005 and 2018. The protocol for CVD event adjudication has been previously described.[18] Clinically adjudicated HF required a discharge diagnosis of *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 428 and/or underlying cause of death I50 and either (1) radiographic findings consistent with congestive HF or increased venous pressure or (2) autopsy finding of pulmonary edema/congestive HF. Secondary outcomes included hospitalization by HF subtypes, including HFpEF and HFrEF. HFpEF was defined as having an ejection fraction of ≥50% and without a previously reduced EF. HFrEF was defined as having an ejection fraction of <50%.

Statistical Analysis

A total of 3 cohorts included available distinct adiposity measures (PAT, VAT, and SAT) among overlapping participants with available thoracic and abdominal CT scans. We summarized baseline characteristics and tested for differences by quartiles of each adiposity measure using chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. For descriptive purposes, we calculated Kaplan–Meier estimates of HF hospitalization and all-cause mortality by quartiles of each adiposity measure and tested for differences using log-rank tests. Cumulative incidence of the primary outcomes was stratified by quartiles of each adiposity measure. We also examined the association between each adiposity measure and end points via Cox proportional hazards models using a stepped model approach. The first model was unadjusted for each adiposity measure and outcome. The second model adjusted for age, sex, education, and smoking status. Our fully adjusted model, model 3, additionally included other CVD and HF risk factors, including systolic blood pressure, total cholesterol, hypertension, and diabetes mellitus. Model 2 was considered our primary model because cardiovascular risk factors, including hypertension, diabetes mellitus, and hyperlipidemia, likely serve as mediators between adiposity measures and cardiovascular outcomes.[16,17] A separate model explored whether the addition of BMI to the prior fully adjusted model would demonstrate if CT-derived adiposity measures provided additional predictive value over BMI. We tested for the presence of effect modification of BMI via an interaction term and estimated the risk for each outcome and adiposity measure among participants with BMI specific values of 25, 30, and 35 kg/m^2, as they correspond to BMI severity. We used likelihood ratio tests to compare the model with BMI and the interaction term to the fully adjusted model. Where variance inflation factor >3, we considered these models as exploratory to examine whether

the effect of each adiposity measure was dependent on BMI. Study participants were censored at the time of either (1) declining participation or (2) end of study follow-up (December 31, 2015, for HF or May 31, 2018, for mortality). Participants were additionally censored at the time of death for HF hospitalization and in sensitivity analyses of HF subtypes.

Most variables had very low missing rates (<5%). For variables with few missing data (<5%), we imputed continuous variables to the overall median value, dichotomous variables to "no," and multichotomous variables to the most frequent categorical value. We used a prespecified α of 0.05 to establish statistical significance and report 95% CIs. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Among the overall cohort of 2844 participants within the Jackson Heart Study who had CT imaging to measure abdominal adiposity, the mean age was 59.4 years, 35% were men, 54% were obese, 69% had hypertension, 31% had diabetes mellitus, and 30% were current smokers at the time of enrollment. Figure S2 displays the distribution of distinctly measured CT-derived adiposity among the included cohort.

Table 1 describes the baseline characteristics by quartiles of CT-derived adiposity measures. The highest quartile compared with the lowest quartile for both the PAT and VAT groups had participants who were older, men, current smokers, and obese and had higher blood pressure, hypertension, and diabetes mellitus and increased anthropometric and CT-derived adiposity measures. The highest quartile PAT group had lower total cholesterol compared with the lowest quartile group, whereas the total cholesterol was slightly higher with increasing VAT quartiles. As for SAT, the highest quartile compared with the lowest quartile had participants who were younger and women, had fewer smokers, and had more obesity, hypertension, diabetes mellitus, and higher anthropometric and CT-derived adiposity measures.

Measures of Adiposity and Incident HF and All-Cause Mortality

There were a total of 168 incident HF hospitalizations and 329 deaths for each of the VAT and SAT groups and 77 incident HF hospitalizations and 153 deaths in the PAT group during a median follow-up of 10.6 years. The cumulative incidence of HF and all-cause mortality by quartiles of CT-derived adiposity measures are shown in Table 2. There was a trend toward higher incident HF and mortality quartiles of PAT and VAT that met statistical significance; the highest quartiles of each measure had the highest cumulative incidence for each outcome (Figure). In addition, there was a trend toward lower cumulative mortality with increasing quartiles of SAT (16.4% [95% CI, 13.7–19.5] in quartile 1 versus 10.4% [95% CI, 8.3–13.0] in quartile 4) that met statistical significance; however, this trend was not present between quartiles of SAT and HF (P=0.07).

Incident HF Hospitalization

In the unadjusted model, the hazard ratios (HRs) and 95% CIs for incident HF of the adiposity measures were PAT per 10 cm^3 HR, 1.12 (95% CI, 1.08–1.18; P<0.001); VAT per 100 cm^3 HR, 1.10 (95% CI, 1.06–1.14; P<0.001); and SAT per 100 cm^3 HR, 1.00 (0.99–1.02; P=0.94). After adjusting for age, sex, education, and smoking status (primary model), the HRs and 95% CIs for incident HF of the adiposity measures were PAT per 10 cm^3 HR, 1.10 (95% CI, 1.04–1.15; P<0.001); VAT per 100 cm^3 HR, 1.07 (95% CI, 1.03–1.11; P<0.001); and SAT per 100 cm^3 HR, 1.02 (1.00–1.04; P=0.02). In the fully adjusted model including CVD risk factors, the associations of PAT and VAT with incident HF remained statistically significant (Table 3). HR estimates from additional exploratory analyses including model 3 covariates, BMI, and the interaction between BMI and the adiposity measure and incident HF among participants with BMI values of 25, 30, and 35 kg/m^2 are shown in Table S1; there was no statistically significant interaction on adiposity measures and BMI on incident HF (interaction term P values for PAT, VAT, and SAT were 0.40, 0.78, and 0.34, respectively).

There was a total incidence of 73 HFpEF and 74 HFrEF among the group with measured VAT and 36 HFpEF and 28 HFrEF among the group with measured PAT. In a sensitivity analysis on outcomes of HFpEF and HFrEF, both VAT and PAT were associated with incident HFpEF after adjusting for age, sex, education, and smoking: PAT HR, 1.13 (95% CI, 1.06–1.21; P<0.001); VAT HR, 1.10 (95% CI, 1.04–1.15; P<0.001). These associations remained statistically significant in the fully adjusted model 3: PAT HR, 1.13 (95% CI, 1.04–1.21; P=0.002); VAT HR, 1.07 (95% CI, 1.01–1.13; P=0.01). Only VAT was significantly associated with HFrEF in model 2 (HR, 1.07; 95% CI, 1.01–1.13; P=0.02]), but was not associated with HFrEF in model 3 (Table 4).

All-Cause Mortality

The HRs (95% CI) for risk of all-cause mortality by adiposity measures are presented in Table 3. In the

Table 1. Characteristics by Quartiles of Computed Tomography–Measured Adiposity in 2844 Participants of the Jackson Heart Study

	Pericardial Adipose Tissue, N=1386					Visceral Adipose Tissue, N=2844					Subcutaneous Adipose Tissue, N=2843				
	Q1	Q2	Q3	Q4	*P* Value	Q1	Q2	Q3	Q4	*P* Value	Q1	Q2	Q3	Q4	*P* Value
No.*	347	347	346	346		711	711	711	711		711	710	712	710	
Demographics															
Age, y	55.4±10.7	58.7±11.1	60.4±10.4	62.2±10.1	<0.001	56.7±11.0	58.9±11.3	59.7±10.9	62.5±9.7	<0.001	60.6±11.5	60.4±11.1	59.7±10.7	57.1±10.0	<0.001
Male sex	88 (25.4)	102 (29.4)	117 (33.8)	163 (47.1)	<0.001	226 (31.8)	207 (29.1)	269 (37.8)	300 (42.2)	<0.001	491 (69.1)	273 (38.5)	158 (22.2)	80 (11.3)	<0.001
Anthropometric adiposity measures															
BMI, kg/m^2	28.0±5.2	31.1±5.8	32.8±6.3	34.9±6.6	<0.001	27.3±4.9	30.6±5.2	33.0±5.7	35.7±6.7	<0.001	25.7±3.2	29.0±3.2	32.6±3.5	39.3±5.5	<0.001
Weight, kg	78.8±15.8	87.9±17.1	92.3±17.4	101.3±18.8	<0.001	77.0±15.2	86.3±15.4	94.2±16.9	102.6±18.3	<0.001	77.0±13.5	83.3±14.8	91.4±14.7	108.4±16.6	<0.001
Waist circumference, cm	90.9±11.8	100.0±11.8	103.6±13.0	111.8±13.7	<0.001	89.3±11.7	97.7±10.7	105.0±11.7	113.4±13.3	<0.001	90.5±9.8	96.3±10.9	103.2±11.0	115.4±14.1	<0.001
Hip circumference, cm	107.9±11.3	113.4±12.7	115.9±13.3	119.1±13.6	<0.001	106.0±11.1	112.0±11.5	115.8±12.3	120.7±14.7	<0.001	101.2±6.9	107.8±6.5	115.3±6.8	130.2±11.7	<0.001
Waist-to-hip ratio	0.8±0.1	0.9±0.1	0.9±0.1	0.9±0.1	<0.001	0.8±0.1	0.9±0.1	0.9±0.1	0.9 0.1	<0.001	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.049
Computed tomography–measured volumetric adiposity															
Subcutaneous adipose tissue, cm^3	1914.2±927.1	2337.8±960.7	2451.8±972.2	2609.7±984.7	<0.001	1788.5± 909.2	2288.1± 934.0	2540.8± 973.5	2682.1±1000.5	<0.001	1138.3± 317.3	1875.4± 175.2	2565.1± 224.8	3721.2±555.6	N/A
Visceral adipose tissue, cm^3	508.7±228.9	716.5±234.3	854.5±281.6	1181.5±395.5	<0.001	403.8±117.1	663.4±61.3	900.4±78.1	1344.5±286.9	N/A	660.7±351.6	801.6±358.2	878.1±382.1	971.1±368.5	<0.001
Pericardial adipose tissue volume, cm^3	37.4±7.8	57.5±4.8	75.1±5.9	116.1±27.7	N/A	47.5±19.4	62.2±18.5	76.6±24.1	102.5±36.4	<0.001	61.4±30.7	69.6±34.3	75.9±32.1	78.7±30.1	<0.001
Comorbidities															
Systolic blood pressure, mm Hg	124.9±17.7	127.8±19.5	126.1±17.1	128.2±17.4	0.01	126.2±18.8	128.1±18.6	127.3±18.4	129.1±17.2	<0.001	128.2±18.2	128.9±19.0	127.4±17.7	126.2±18.2	0.06
Fasting total cholesterol, mg/dL	198.5±35.9	198.6±39.0	198.9±35.4	192.2±35.5	0.02	195.1±32.5	200.8±35.4	194.9±34.1	195.9±36.0	0.02	194.9±32.3	198.6±35.8	196.9±34.5	196.3±35.6	0.16
Healthy or overweight, BMI <30 kg/m^2	250 (72.0)	175 (50.4)	139 (40.2)	83 (24.0)	<0.001	545 (76.7)	369 (51.9)	239 (33.6)	153 (21.5)	<0.001	658 (92.5)	469 (66.1)	164 (23.0)	15 (2.1)	<0.001
Obese, BMI ≥30 kg/m^2	97 (28.0)	172 (49.6)	207 (59.8)	263 (76.0)	<0.001	166 (23.3)	342 (48.1)	472 (66.4)	558 (78.5)	<0.001	53 (7.5)	241 (33.9)	548 (77.0)	695 (97.9)	<0.001
Hypertension	193 (55.6)	220 (63.4)	245 (70.8)	276 (79.8)	<0.001	413 (58.1)	462 (65.0)	520 (73.1)	569 (80.0)	<0.001	455 (64.0)	480 (67.6)	501 (70.4)	527 (74.2)	<0.001
Diabetes mellitus	44 (12.7)	78 (23.1)	97 (28.5)	145 (42.4)	<0.001	92 (14.7)	153 (25.2)	210 (33.9)	306 (50.1)	<0.001	125 (21.0)	171 (27.6)	223 (35.3)	241 (38.9)	<0.001
Current smokers	63 (18.2)	91 (26.2)	108 (31.2)	138 (39.9)	<0.001	189 (26.6)	188 (26.4)	215 (30.2)	273 (38.4)	<0.001	267 (37.6)	207 (29.2)	220 (30.9)	170 (23.9)	<0.001

(*Continued*)

Table 1. Continued

	Pericardial Adipose Tissue, N=1386					Visceral Adipose Tissue, N=2844					Subcutaneous Adipose Tissue, N=2843				
	Q1	Q2	Q3	Q4	*P* Value	Q1	Q2	Q3	Q4	*P* Value	Q1	Q2	Q3	Q4	*P* Value
Education															
Less than high school	16 (4.6)	46 (13.3)	48 (13.9)	56 (16.2)	<0.001	64 (9.0)	98 (13.8)	91 (12.8)	133 (18.7)	<0.001	121 (17.0)	100 (14.1)	86 (12.1)	79 (11.1)	0.006
High school/ GED	79 (22.8)	75 (21.6)	76 (22.0)	98 (28.3)	0.13	167 (23.5)	178 (25.0)	182 (25.6)	174 (24.5)	0.82	156 (21.9)	184 (25.9)	175 (24.6)	185 (26.1)	0.24
Some college	84 (24.2)	85 (24.5)	89 (25.7)	73 (21.1)	0.53	167 (23.5)	157 (22.1)	171 (24.1)	167 (23.5)	0.84	150 (21.1)	166 (23.4)	172 (24.2)	174 (24.5)	0.42
At least a bachelor's degree	88 (25.4)	60 (17.3)	61 (17.6)	57 (16.5)	0.009	166 (23.3)	125 (17.6)	118 (16.6)	103 (14.5)	<0.001	137 (19.3)	112 (15.8)	143 (20.1)	120 (16.9)	0.12
Postgraduate/ professional	80 (23.1)	81 (23.3)	72 (20.8)	62 (17.9)	0.27	147 (20.7)	153 (21.5)	149 (21.0)	134 (18.8)	0.63	147 (20.7)	148 (20.8)	136 (19.1)	152 (21.4)	0.73

Categorical variables are presented as number (percentages), and continuous variables are presented as mean±SD. BMI indicates body mass index; GED, General Educational Development; N/A, not applicable; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; and Q4, quartile 4.

*Pericardial adipose tissue quartiles: Q1, ≤48.64 cm^3; Q2, 48.65–65.80 cm^3; Q3, 65.81–86.36 cm^3; Q4, >86.36 cm^3. Visceral adipose tissue quartiles: Q1, ≤556.23 cm^3; Q2, 556.24–769.11 cm^3; Q3, 769.12–1039.81 cm^3; Q4, >1039.81 cm^3. Subcutaneous adipose tissue quartiles: Q1, ≤1563.02 cm^3; Q2, 1563.03–2181.32 cm^3; Q3, 2181.33–2975.49 cm^3; Q4, >2975.49 cm^3.

unadjusted model, the HRs and 95% CIs for all-cause mortality of the adiposity measures were PAT per 10 cm^3 HR, 1.12 (95% CI, 1.08–1.16; *P*<0.001); VAT per 100 cm^3 HR, 1.07 (95% CI, 1.04–1.09; *P*<0.001); and SAT per 100 cm^3 HR, 0.98 (95% CI, 0.97–1.00; *P*=0.005). After adjusting for age, sex, education, and smoking status (primary model), the HRs and 95% CIs for all-cause mortality of the adiposity measures were PAT per 10 cm^3 HR, 1.08 (95% CI, 1.04–1.12; *P*<0.001); VAT per 100 cm^3 HR, 1.03 (95% CI, 1.00–1.06; *P*=0.046); and SAT per 100 cm^3 HR, 1.00 (95% CI, 0.99–1.02; *P*=0.78). In the fully adjusted model including CVD risk factors, only the association between PAT and all-cause mortality remained statistically significant (HR, 1.07; 95% CI, 1.03–1.12; *P*=0.002). HR estimates from additional exploratory analyses including model 3 covariates, BMI, and the interaction between BMI and the adiposity measure and all-cause mortality among participants with BMI values of 25, 30, and 35 kg/m^2 are shown in (Table S1); there were stronger positive associations of PAT with all-cause mortality with higher BMI (at BMI 35 kg/m^2 HR, 1.07; 95% CI, 1.02–1.12; *P*=0.09), and weaker negative associations of VAT (at BMI 25 kg/m^2 HR, 0.96; 95% CI, 0.917–0.999; *P*=0.046) and SAT (at BMI 30 kg/m^2 HR, 0.97; 95% CI, 0.95–1.00; *P*=0.04) with all-cause mortality with higher BMI (interaction term *P* values for PAT, VAT, and SAT were 0.09, <0.0001, and 0.0001, respectively).

Interactions of BMI on Associations of CT-Derived Adiposity and Outcomes

Variance inflation factor was >3 with BMI when modeling the relationship between SAT and all-cause mortality and HF hospitalizations. Results from the likelihood ratio tests comparing model 3 to the exploratory models with BMI and the interaction between BMI and each adiposity measure indicated the exploratory model was better for modeling all-cause mortality and VAT (χ^2=15.31, *df*=2, *P*=0.0005), all-cause mortality and SAT (χ^2=16.26, *df*=2, *P*=0.0003) and incident HF hospitalization and SAT (χ^2=6.96, *df*=2, *P*=0.03). HR estimates from exploratory analyses including model 3 covariates, BMI, and the interaction between BMI and the adiposity measure and all-cause mortality at the first quartile, median, and third quartile of PAT, VAT, and SAT are shown in Table S2; there were strong positive associations between PAT and mortality across quartiles with each unit increase in BMI, yet no association of VAT with incident HF and mortality with each unit increase in BMI. SAT was associated with incident HF in the highest SAT quartile and with mortality in the median SAT quartile with each unit increase in BMI.

Table 2. Cumulative Incidence of Heart Failure Hospitalization and All-Cause Mortality by Quartiles of Adiposity Measures in the Jackson Heart Study

	Total Events*	Q1†	Q2	Q3	Q4	*P* Value‡
Pericardial adipose tissue						
Heart failure hospitalization, No. (cumulative incidence) (95% CI)	77	9 (2.7) (1.4–5.1)	16 (4.9) (3.0–7.9)	22 (6.7) (4.5–10.1)	30 (9.2) (6.5–12.9)	0.003
Mortality, No. (cumulative incidence) (95% CI)	153	24 (7.0) (4.7–10.3)	33 (9.8) (7.1–13.5)	36 (10.5) (7.7–14.3)	60 (17.5) (13.9–22.1)	<0.001
Visceral adipose tissue						
Heart failure hospitalization, No. (cumulative incidence) (95% CI)	168	29 (4.3) (3.0–6.1)	22 (3.2) (2.1–4.9)	53 (8.8) (6.6–11.6)	64 (10.3) (8.1–13.1)	<0.001
Mortality, No. (cumulative incidence) (95% CI)	329	71 (10.9) (8.7–13.6)	75 (11.5) (9.3–14.3)	65 (9.6) (7.6–12.2)	118 (17.7) (15.0–21.0)	<0.001
Subcutaneous adipose tissue						
Heart failure hospitalization, No. (cumulative incidence) (95% CI)	168	47 (7.6) (5.7–10.2)	28 (4.4) (3.0–6.5)	48 (7.6) (5.7–10.1)	45 (6.9) (5.1–9.3)	0.07
Mortality, No. (cumulative incidence) (95% CI)	329	107 (16.4) (13.7–19.5)	75 (11.3) (9.1–14.0)	77 (11.8) (9.6–14.7)	70 (10.4) (8.3–13.0)	0.009

Q1 indicates quartile 1; Q2, quartile 2; Q3, quartile 3; and Q4, quartile 4.

*There were totals of 1386, 2844, and 2843 participants in the pericardial adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue groups, respectively.

†Pericardial adipose tissue quartiles: Q1, ≤48.64 cm^3; Q2, 48.65–65.80 cm^3; Q3, 65.81–86.36 cm^3; Q4, >86.36 cm^3. Visceral adipose tissue quartiles: Q1, ≤556.23 cm^3; Q2, 556.24–769.11 cm^3; Q3, 769.12–1039.81 cm^3; Q4, >1039.81 cm^3. Subcutaneous adipose tissue quartiles: Q1, ≤1563.02 cm^3; Q2, 1563.03–2181.32 cm^3; Q3, 2181.33–2975.49 cm^3; Q4, >2975.49 cm^3.

‡*P* values to trend.

DISCUSSION

We report the association of CT-derived pericardial, visceral, and subcutaneous adiposity with incident HF hospitalization and all-cause mortality in the Jackson Heart Study, a longitudinal community cohort study of Black participants (Figure S3). Both higher PAT and VAT were associated with incident HF, including its subtype HFpEF, and all-cause mortality in the primary model adjusting for age, sex, education, and smoking. These associations remained statistically significant after adjustment for CVD risk factors except for VAT and all-cause mortality. There was a consistent, but not statistically significant, decrease in risk of incident HF at increasing levels of BMI for PAT and VAT.

The observed distributions in this study are similar to the previously described variability in CVD risk profiles seen across regional adiposity groups.[1,13,14] Consistent with our hypothesis, having higher PAT or VAT was associated with increased risk for incident HF, HFpEF, and mortality, a finding not seen with higher SAT. Our interaction analyses also demonstrated an association between VAT and mortality dependent on BMI at low BMI, yet similar to other studies, these interactions were not present at BMI values in the range of obesity.[9] Furthermore, CVD risk factors, such as diabetes mellitus, hypertension, and hyperlipidemia, likely serve as mediators between the pathophysiologic mechanisms of regional adiposity and incident HF and its subtypes,[15,19] which may explain the attenuated, nonsignificant association between VAT and mortality. This may additionally explain the smaller, but still statistically significant, associations between PAT or VAT on incident HF hospitalization and PAT and mortality in the fully adjusted models compared with our primary models. In contrast, SAT was inversely associated with mortality in the unadjusted model but not associated with mortality after full adjustment. SAT was associated with incident HF in the unadjusted model, and an association seen between SAT and incident HF in the adjusted primary model was small and likely attributed to statistical chance and possible nonlinearity.

Regarding HF risk, VAT is associated with incident HF among Black individuals,[14] and particularly incident HFpEF but not HFrEF across a multiethnic community cohort.[1] VAT has also been shown to demonstrate a trend toward increased risk of HFpEF among people with healthy BMI (ie, BMI<25 kg/m^2), lending to a "silent obesity phenotype."[1] No prior studies have investigated the effect of PAT in HF incidence. SAT, on the other hand, does not display an independent association with increased cardiovascular risk[20] or incident HF and its subtypes HFpEF and HFrEF.[1]

There are some key similarities and differences between our results and prior reports. Pandey et

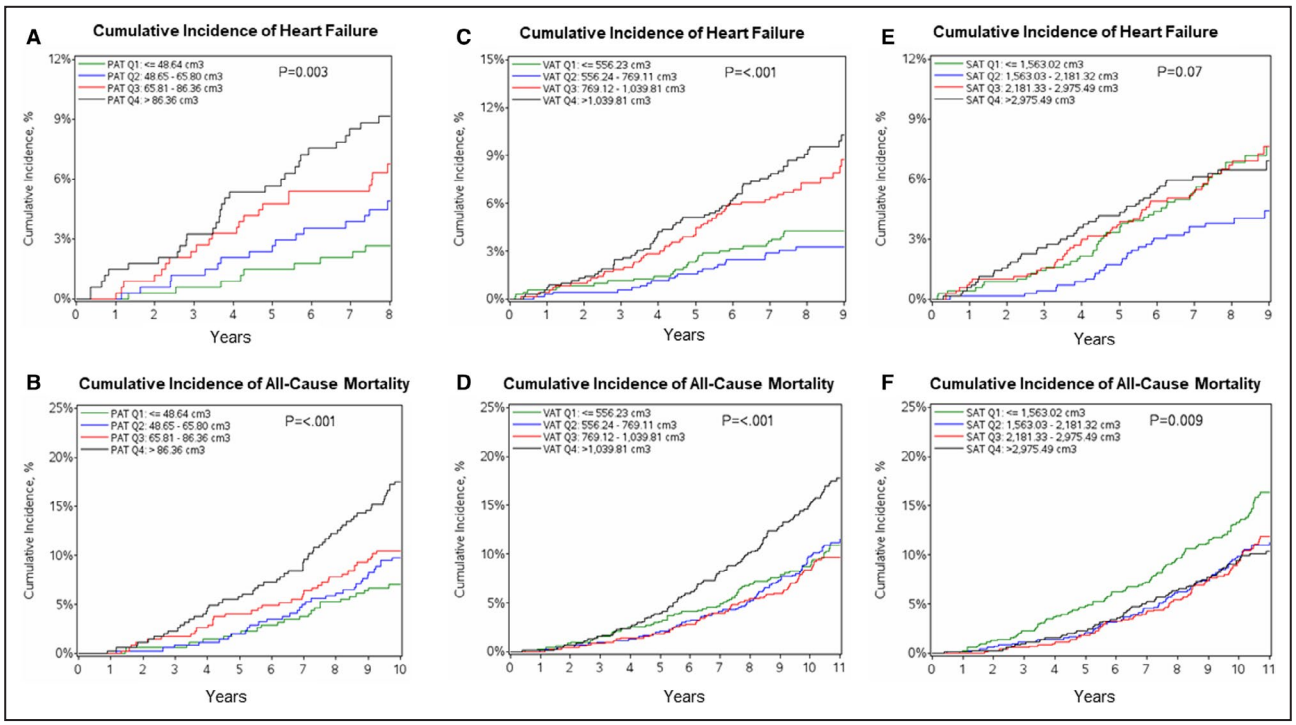

Figure. Cumulative incidence of heart failure and all-cause mortality by regional adiposity quartiles in the Jackson Heart Study.

Incident heart failure and all-cause mortality increased in the highest PAT (**A** and **B**) and VAT (**C** and **D**) quartiles when compared with the lowest quartile. There was no association between the SAT quartiles and incident heart failure (**E**). All-cause mortality decreased with the higher SAT quartiles (**F**). PAT indicates pericardial adipose tissue volume; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue volume.

al reported that VAT was associated with risk of incident any HF in the Jackson Heart Study.[14] In the MESA (Multi-Ethnic Study of Atherosclerosis), VAT was independently associated with incident HF, particularly HFpEF but not HFrEF, even after adjusting for CVD and HF risk factors.[1] The present study was consistent with those findings and additionally demonstrated the novel finding that not only VAT but also PAT were associated with incident HF, including HFpEF, in both our primary and fully adjusted models. Unlike the MESA analysis,[1] we newly demonstrate that VAT is also associated with HFrEF among Black participants in our primary model, and this relationship was attenuated after full adjustment with CVD risk factors. These findings are of clinical importance after acknowledging key observed differences in both cohorts and their population characteristics and risk profiles. The techniques in CT-derived adiposity measurements were similar for both cohorts.[16,17] The average BMI in the Jackson Heart Study, however, was 31.6 (SD 6) kg/m^2, with a mean of 27.3 kg/m^2 in the lowest VAT quartile, compared with a mean of 27.8 (SD 5) kg/m^2 in the total MESA cohort at the index time of CT scan.[1] Because VAT correlates with BMI, there may likely be different obesity profiles between these 2 populations. Compared with MESA, the Jackson Heart Study also had a greater overall risk profile based on baseline higher BMI, prevalence of obesity, VAT, and comorbidities (such as diabetes mellitus, hypertension, and hyperlipidemia). Therefore, the observed relationship between adiposity measures and outcomes in the Jackson Heart Study further emphasizes the critical importance that pericardial and abdominal regional adiposity contribute toward incident HF and mortality despite the elevated cardiovascular risk profile at baseline. Although elevated VAT appears to be associated with metabolic derangements and a prevalence of cardiometabolic diseases in individuals with a healthy weight or those who are overweight (ie BMI <30 kg/m^2),[21] we did not find a significant interaction by BMI between CT-derived adiposity measures and incident HF. This is likely attributed to the higher baseline BMI, VAT, and comorbidities in the Jackson Heart Study population limiting our ability to identify any differential risk that regional adiposity poses on incident HF across BMI subgroups by interaction analyses.

VAT may also have varying predictive risks on outcomes by race/ethnicity beyond traditional HF risk factors alone.[21] MESA comprised relatively fewer Black participants (21.2%).[1] Although the incidence of

Table 3. HRs and 95% CIs for the Association Between Adiposity Measures and Incident Heart Failure Hospitalization and All-Cause Mortality in the Jackson Heart Study

Model*	All-Cause Mortality		Heart Failure Hospitalization	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Pericardial adipose tissue, per 10 cm^3				
1	1.12 (1.08–1.16)	<0.001	1.12 (1.08–1.18)	<0.001
2	1.08 (1.04–1.12)	<0.001	1.10 (1.04–1.15)	<0.001
3	1.07 (1.03–1.12)	0.002	1.08 (1.02–1.14)	0.008
Visceral adipose tissue, per 100 cm^3				
1	1.07 (1.04–1.09)	<0.001	1.10 (1.06–1.14)	<0.001
2	1.03 (1.00–1.06)	0.046	1.07 (1.03–1.11)	<0.001
3	1.01 (0.98–1.04)	0.38	1.04 (1.01–1.08)	0.02
Subcutaneous adipose tissue, per 100 cm^3				
1	0.98 (0.97–1.00)	0.005	1.00 (0.99–1.02)	0.94
2	1.00 (0.99–1.02)	0.78	1.02 (1.00–1.04)	0.02
3	1.00 (0.98–1.01)	0.72	1.01 (1.00–1.03)	0.12

Model 1: computed tomography–derived adiposity only. Model 2: model 1+age, sex, education, and smoking status. Model 3: model 2+hypertension, diabetes mellitus, total cholesterol, and systolic blood pressure. HR indicates hazard ratio.

*There were totals of 1386, 2844, and 2843 participants in the pericardial adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue groups, respectively, and 17 participants with prevalent heart failure among the cohort with pericardial adipose tissue measures and 34 participants with prevalent heart failure among the cohorts with visceral adipose tissue and subcutaneous adipose tissue measures were excluded.

HF and HFpEF in MESA did not differ across ethnicity,[22] MESA was underpowered to explore these differences because of the few HF events over 10 years among Black participants. The present study provides support to prior findings in MESA by investigating the associations between VAT and HF among a cohort of Black participants. Yet larger studies are warranted to explore risk of regional adiposity on incident HF by race/ethnicity.

PAT is associated with accelerated coronary atherosclerosis, insulin resistance, and hypertension both in obese and nonobese individuals[11,23–25] and higher PAT trends with increasing BMI.[10] The detrimental mechanical properties of PAT in HF correlate with increased ventricular wall thickness, worsened left ventricular relaxation, and diastolic dysfunction.[10,26–28] Increased intramuscular cardiac fat is also observed in people with HFpEF compared with those without HF,[29] and removal of pericardial fat has been associated with improved cardiac function.[26,27] The present study confirms the association between PAT with incident HF and HFpEF, and these associations remained significant after adjusting for CVD risk factors. The observed associations of PAT and VAT, but not SAT, with incident HFpEF lend support to a distinct obese–HFpEF phenotype.[30] PAT might play a critical role in the pathogenesis of HF, particularly HFpEF, but future studies are needed to further understand the relationship of PAT and HF.

Study Strengths and Limitations

To our knowledge, this study is first to describe multiple CT-derived pericardial and abdominal adiposity depots and their individual effects on cardiovascular outcomes, namely, incident HF, HFpEF, and mortality, among a longitudinal cohort of Black participants without baseline prevalent HF. Our study provides further insight into the relationship between regional elevation in adiposity on HF and mortality, particularly in relation to other cohorts with fewer participants who were obese at baseline.

We identify several limitations in the present study. First, adjudicated HF events only included incident hospitalized HF, so HF identified in the outpatient setting may have been missed in the present analysis. Second, the number of HF events were few (168 HF events in the VAT and SAT cohorts and 77 HF events in the PAT cohort), and we were underpowered to assess

Table 4. Incidence of Heart Failure Subtype Hospitalizations by Computed Tomography–Derived Adiposity Measures in the Jackson Heart Study

Adiposity Measure	Model*	HFpEF Heart Failure Hospitalization		HFrEF Heart Failure Hospitalization	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PAT	1	1.15 (1.08–1.22)	<0.001	1.10 (1.01–1.20)	0.02
	2	1.13 (1.06–1.21)	<0.001	1.06 (0.96–1.17)	0.23
	3	1.13 (1.04–1.21)	0.002	1.03 (0.94–1.14)	0.51
VAT	1	1.12 (1.06–1.18)	<0.001	1.10 (1.05–1.16)	<0.001
	2	1.10 (1.04–1.15)	<0.001	1.08 (1.01–1.13)	0.02
	3	1.07 (1.01–1.13)	0.01	1.04 (0.99–1.10)	0.15

Model 1: computed tomography–derived adiposity (PAT per 10 cm^3 or VAT per 100 cm^3) only. Model 2: model 1+age, sex, education, and smoking status. Model 3: model 2+hypertension, diabetes mellitus, systolic blood pressure, and total cholesterol. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PAT, pericardial adipose tissue volume; and VAT, visceral adipose tissue volume.

*There were total incidences of 73 HFpEF and 74 HFrEF among the group with measured VAT and 36 HFpEF and 28 HFrEF among the group with measured PAT.

for multiple covariates and interactions by CVD risk factors on adiposity measures and outcomes. We were similarly underpowered to evaluated additional HF subgroups, such as HF with mid-range ejection fraction, who were classified as either HFpEF and HFrEF. We were also limited by power for direct comparison of regional adiposity to each other. Third, this was a retrospective analysis from an observational cohort study, and despite covariate adjustment, there was potential bias for other measured and unmeasured factors to influence the findings. Similarly, the covariate smoking was carried forward from Exam 1 to Exam 2; there is potential for misclassification error because smoking status can change before study start. Fourth, we assessed distinct regional fat compartments and did not adjust for the other fat measures primarily because our aim was to compare and describe each of these associations separately. Finally, we excluded participants with baseline prevalent known HF before Exam 2 at the time of CT scan; however, some people with prevalent HF not yet identified may have been included in the analysis.

CONCLUSIONS

In a large community cohort of Black participants in the United States without baseline HF, these findings show that both higher PAT and VAT are associated with incident HF hospitalization, including the subtype HFpEF, and mortality after adjustment for age, sex, education, and smoking status during a median 10.6 years. These findings remained significant after adjustment for CVD risk factors, except for VAT with all-cause mortality, which was attenuated. Higher SAT was not associated with HF or death. Future prospective studies on dedicated exercise or medical weight loss programs based on regional fat profiles are needed to better understand how changes in regional adiposity affects the development of HF and other cardiovascular outcomes.

COMPETENCIES IN MEDICAL KNOWLEDGE

Among Black participants without prevalent HF, CT-derived pericardial, visceral, and subcutaneous adiposity have varying risk on incident hospitalized HF and all-cause mortality. PAT and VAT were associated with incident HF, HFpEF, and all-cause mortality in models adjusting for age, sex, education, and smoking status (primary models) as well as fully adjusted models including CVD risk factors. PAT and VAT were associated with all-cause mortality in our primary models, and PAT remained significantly associated with all-cause mortality adjusting for CVD risk factors. SAT was not significantly associated with incident HF or mortality. Only VAT was associated with HFrEF in our primary model, and this association was attenuated in the fully adjusted model. Among Black individuals, the extent by which variations in regional adiposity are associated with risk of HF and mortality may be influenced by higher BMI and comorbidities.

TRANSLATIONAL OUTLOOK

This observational study provides insight into the relationship between different CT-derived regional adiposity measures, including pericardial, visceral, and subcutaneous adiposity, showing varying relationships between these measures and incident HF and mortality. These results will be helpful in understanding how regional fat depots contribute to cardiovascular risk and potentially inform future studies to identify high-risk groups who would benefit from targeted preventive strategies beyond routine screening by anthropometric measures alone.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Hazard Ratios and 95% CI for the Association between each adiposity measure and All-Cause Mortality and Incident Heart Failure Hospitalization at levels of BMI.

BMI	All-cause mortality		Heart failure hospitalization	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
	Pericardial Adipose Tissue (per 10 cm^3)			
25	1.014 (0.944, 1.089)	0.71	1.100 (0.982, 1.231)	0.10
30	1.041 (0.989, 1.096)	0.13	1.075 (0.996, 1.160)	0.06
35	**1.069 (1.021, 1.119)**	**0.004**	1.051 (0.983, 1.124)	0.14
	Visceral Adipose Tissue (per 100 cm^3)			
25	**0.957 (0.917, 0.999)**	**0.046**	1.031 (0.968, 1.099)	0.34
30	0.992 (0.958, 1.027)	0.65	1.027 (0.980, 1.077)	0.26
35	1.028 (0.993, 1.064)	0.12	1.023 (0.979, 1.070)	0.31
	Subcutaneous Adipose Tissue (per 100 cm^3)			
25	**0.963 (0.939, 0.988)**	**0.004**	0.975 (0.942, 1.009)	0.15
30	**0.975 (0.953, 0.999)**	**0.04**	0.979 (0.948, 1.011)	0.19
35	0.988 (0.964, 1.012)	0.31	0.984 (0.953, 1.015)	0.30

∗ Model: CT-derived adiposity measure, age, sex, education and smoking status, hypertension, diabetes, cholesterol, blood pressure, BMI, and the interaction between the adiposity measure and BMI.

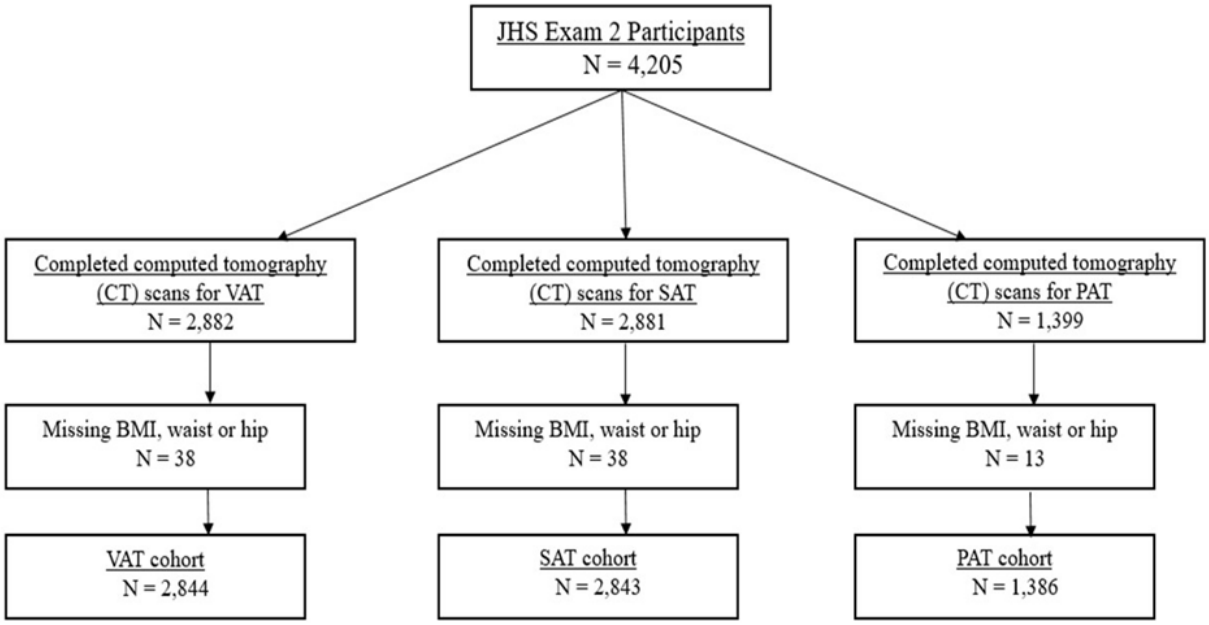
Table S2. Hazard Ratios and 95% CI for the Association between a 1-unit increase in BMI and All-Cause Mortality and Incident Heart Failure Hospitalization for Q1, Median, and Q3 of each scaled adiposity measure.

Scaled adiposity measure	All-cause mortality		Heart failure hospitalization	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Pericardial Adipose Tissue (per 10 cm^3)	BMI			
Q1 (4.86)	0.997 (0.960, 1.036)	0.88	1.059 (1.002, 1.120)	0.04
Median (6.58)	1.006 (0.974, 1.039)	0.71	1.051 (1.005, 1.099)	0.03
Q3 (8.63)	1.017 (0.987, 1.048)	0.26	1.042 (1.001, 1.084)	0.04
Visceral Adipose Tissue (per 100 cm^3)	BMI			
Q1 (5.57)	0.973 (0.947, 1.000)	0.05	1.030 (0.991, 1.071)	0.14
Median (7.69)	0.988 (0.964, 1.013)	0.34	1.028 (0.995, 1.063)	0.10
Q3 (10.40)	1.007 (0.984, 1.031)	0.54	1.026 (0.995, 1.058)	0.10
Subcutaneous Adipose Tissue (per 100 cm^3)	BMI			
Q1 (15.64)	1.003 (0.966, 1.042)	0.88	1.048 (0.995, 1.103)	0.08
Median (21.83)	1.019 (0.983, 1.055)	0.30	1.053 (1.005, 1.104)	0.03
Q3 (29.75)	1.039 (1.004, 1.075)	0.03	1.061 (1.014, 1.110)	0.01

∗ Model: Adiposity measure, age, sex, education, smoking status, hypertension, diabetes, cholesterol, blood pressure, BMI, and the interaction between the adiposity measure and BMI.

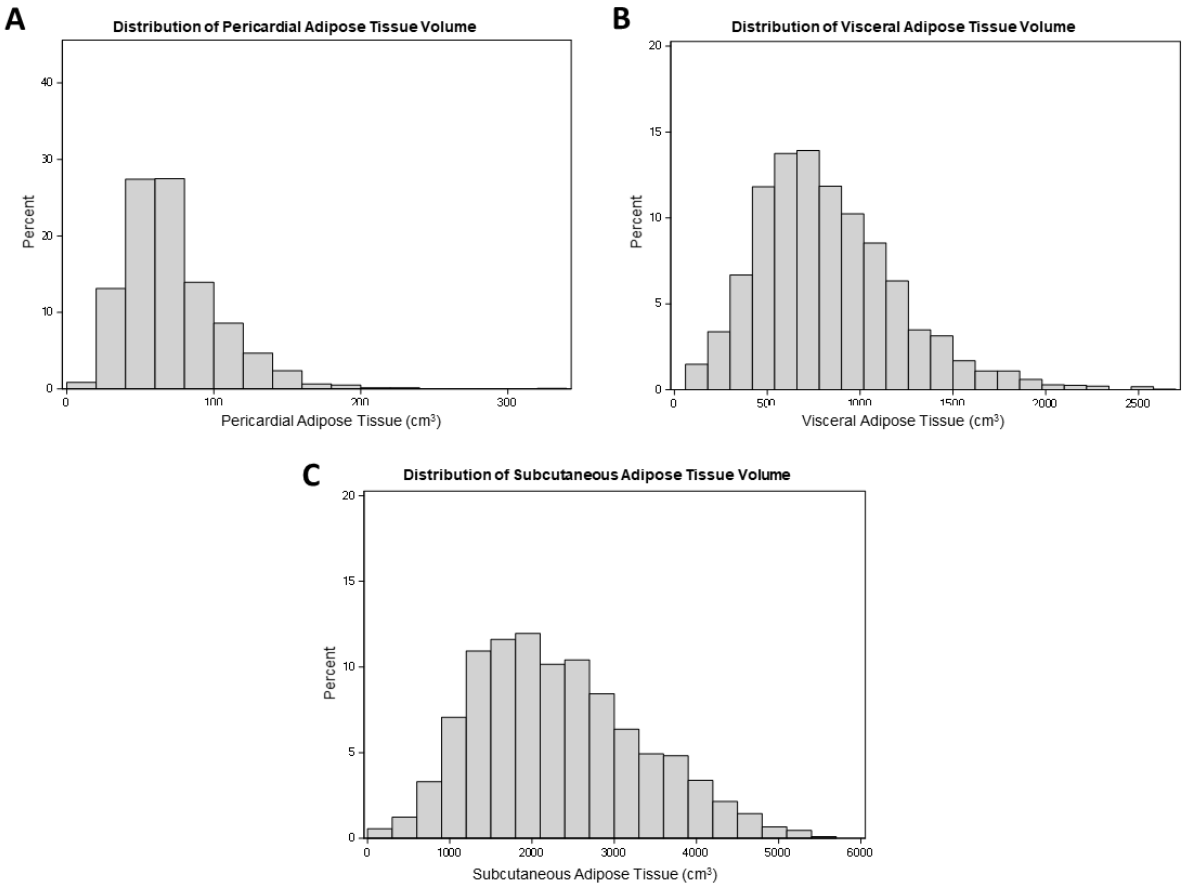
† Variance inflation factors (VIF) as follows: For models with PAT and BMI, VIF for PAT = 1.45, VIF for BMI = 1.45; for models with VAT and BMI, VIF for VAT = 1.64, VIF for BMI = 1.67; for models with SAT and BMI, VIF for SAT = 4.61, VIF for BMI = 4.04.

Figure S1. Adiposity Cohorts within the Jackson Heart Study.



Consort diagram by adiposity measures in the Jackson Heart Study at Exam 2. VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; PAT, pericardial adipose tissue.

Figure S2. Distribution of Regional Adiposity in the Jackson Heart Study.



Adiposity distribution by individual adiposity depots. (A) describes pericardial adipose tissue within a random subgroup of Exam 2 participants (N of 1,386), and (B) and (C) describe visceral adipose tissue (N of 2,844) and subcutaneous adipose tissue distributions (N of 2,843), respectively.

Figure S3. Computed Tomography-derived Measures of Volumetric Pericardial, Visceral, and Subcutaneous Adiposity and Incident Heart Failure in the Jackson Heart Study.