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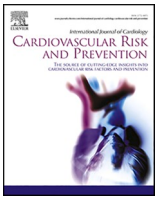

Associations of renal sinus fat with blood pressure and ectopic fat in a diverse cohort of adults

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ABSTRACT

Background: Renal sinus fat (RSF) is an ectopic fat depot shown to be associated with visceral adiposity and hypertension in predominantly white populations. The purpose of this analysis is to investigate RSF and associations between RSF and blood pressure in a cohort of African American (AA) and European American (EA) adults. A secondary purpose was to explore risk factors associated with RSF.

Methods: Participants were 116 A A and EA adult men and women. Ectopic fat depots were assessed with MRI: RSF, intraabdominal adipose tissue (IAAT), intermuscular adipose tissue (IMAT), perimuscular adipose tissue (PMAT), and liver fat. Cardiovascular measures included diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure, mean arterial pressure, and flow mediated dilation. Matsuda index was calculated for insulin sensitivity. Pearson correlations were used to investigate associations of RSF with cardiovascular measures. Multiple linear regression was used to evaluate contributions of RSF on SBP and DBP and to explore factors associated with RSF.

Results: No difference was observed in RSF between AA and EA participants. RSF was positively associated with DBP in AA participants, but this was not independent of age and sex. Age, male sex, and total body fat were positively associated with RSF in AA participants. Insulin sensitivity was inversely and IAAT and PMAT were positively associated with RSF in EA participants.

Conclusions: Differential associations of RSF with age, insulin sensitivity, and adipose depots among AA and EA adults suggest unique pathophysiological mechanisms influence RSF deposition, which may contribute to chronic disease etiology and progression.

1. Introduction

Ectopic fat, defined as the accumulation of triglycerides in non-adipose tissues (e.g., liver, skeletal muscle, heart, kidney), is strongly associated with insulin resistance and increased cardiometabolic disease risk through its interference with normal cellular and organ function [1]. One ectopic fat depot in particular, renal sinus fat (RSF), has been shown to be associated with hypertension, poor kidney function, type 2 diabetes, and other ectopic fat depots [2–4]. It remains unknown how these relationships translate to diverse populations, especially African American (AA) adults, who as a group, are disproportionately burdened by chronic disease [5].

The renal sinus is a perirenal compartment bounded from the hilum of the kidney to the renal parenchyma [6]. Fat accumulation in the renal sinus can result in compression of renal structures, including the renal vein, renal artery, and renal lymphatic vessels [7,8]. This compression leads to increases in renal interstitial pressure, renal volume, and activation of the renin-angiotensin-aldosterone system (RAAS), contributing to increased sodium reabsorption [8–11]. RSF has been shown to be positively associated with renal size, number of prescribed anti-hypertensive medications, mean arterial pressure, and stage II hypertension [2,10]. Findings from the Framingham Heart Study also revealed independent associations of RSF with renal function and blood pressure after adjustment for visceral fat [3]. However, several of these relationships were found in predominantly white samples, and therefore it remains unclear how they translate to diverse populations, specifically to groups who are disproportionately burdened by chronic disease, such as AA adults.

Ectopic fat deposition is influenced by numerous factors, including sex, race/ethnicity, age, lifestyle, and genetics [12]. Compared to EA adults, AA adults tend to have less visceral and ectopic fat (pancreatic, hepatic) [13–17]. This is despite the higher prevalence of chronic

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diseases (i.e.: type 2 diabetes, hypertension) among AA individuals [5]. Previous research has suggested that not only is ectopic fat accumulation a marker of cardiometabolic disease but is likely involved in its pathogenesis [18]. However, many of these studies have been done in predominantly white populations [19–22], and findings from the few studies that have included AA populations are mixed [13,17,23–25]. It is possible that the direction of the relationship between ectopic fat and cardiometabolic risk factors (i.e.: insulin resistance, hyperlipidemia) differs between AA and EA adults.

The primary purpose of this analysis was to determine if RSF, or its association with blood pressure, differ with race. We tested the specific hypothesis that RSF would be higher in AA adults and would explain higher blood pressure in AA adults. A secondary aim was to explore risk factors associated with RSF in AA and EA adults.

2. Materials and methods

2.1. Subjects and study design

This was a secondary analysis of a cross-sectional, observational study conducted at the University of Alabama at Birmingham (UAB), between 2013 and 2018. Details of the original study can be found elsewhere [24]. Participants were AA and EA men and women aged 19–45 years who were recruited by public advertisement (flyers and newspaper ads). Race/ancestry was determined by self-report, and by genetic admixture analysis as described below. Recruited individuals were screened for glucose tolerance status with a 2-h 75 g oral glucose tolerance test (OGTT), and those with 2-h glucose ≥200 mg/dL were excluded from participation. Other exclusion criteria were absence of regular menstrual cycle; pregnant, lactating, or postmenopausal; smoking; not weight stable (change in weight >2.5 kg in the previous 6 months); taking oral contraceptives; use of any medication known to affect carbohydrate or lipid metabolism, or energy expenditure; and use of anti-hypertensive agents that affect glucose tolerance (e.g.: thiazide diuretics at doses >25 mg/d, angiotensin-converting-enzyme inhibitors). Participants were instructed to maintain their usual activity level, avoid strenuous physical activity the day prior to testing, and avoid all physical activity on the morning of testing. Women were tested 3–7 days after cessation of menstruation, while in the follicular phase of the menstrual cycle. All study assessments were conducted at the core facilities of the Center for Clinical and Translational Science (CCTS), Nutrition Obesity Research Center (NORC), and Diabetes Research Center (DRC). The UAB Institutional Review Board approved the study.

2.2. Anthropometrics

Each participant underwent standard anthropometric measurements (weight and height), wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

2.3. Body composition

Total body fat mass was measured by DXA (iDXA instrument, GE Healthcare). Participants were scanned in light clothing while laying supine with arms at their sides. Magnetic resonance imagining (MRI) was used to measure subcutaneous abdominal adipose tissue (SAAT), intraabdominal adipose tissue (IAAT), thigh intermuscular adipose tissue (IMAT), thigh perimuscular adipose tissue (PMAT), and RSF (Ingenia 1.5T wide bore MRI system; Phillips). Liver fat was assessed using the fast spin echo 2-point Dixon technique [26]. Volumes of SAAT, IAAT, and RSF were assessed via transverse abdominal images obtained via 3D volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE). The echo time, repetition time, and pulse flip angles were selected to optimize the signal-intensity contrast between the adipose and non-adipose tissue compartments. A series of 10 mm slices spaced at 5 mm intervals from the L1-L4/L5 vertebrae was performed for each participant. Scans were later analyzed for volume (cm^3) of adipose tissue using Slice-*O*-Matic image analysis software (version 4.3: Tomovision, Montreal, Canada). RSF was measured from a single slice of the right and left kidneys where the fat was most visible. Because the right kidney is often positioned slightly lower in the abdomen than the left kidney, a different slice was analyzed for each kidney and volume from each slice was added together for the RSF value. Thigh muscle and adipose tissue volume were analyzed using three images from the mid-thigh (mid-point between the anterior iliac crest and the patella). IMAT was partitioned from PMAT by manually drawing a line around the muscle itself to capture adipose tissue located directly between and within muscle groups. Scans were not available for all participants.

2.4. Cardiovascular measures

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained nurses in the UAB Clinical Research Unit after 10 min of seated rest. Mean arterial pressure (MAP) was calculated as: $MAP = DBP + {}^1\!/\!_3\,(SBP - DBP)$. Pulse pressure (PP) was calculated as: $PP = SBP - DBP$ [27]. Endothelial function was assessed by percent change in flow-mediated brachial artery dilation (FMD) via high-resolution ultrasound. Briefly, ultrasound evaluation is performed with a 7.5 MHz linear-array ultrasound probe, and arterial flow determined with a pulsed-Doppler signal. Ischemia is induced by a 5-min blood pressure cuff inflation followed by rapid cuff deflation to induce reactive hyperemia. Arterial diameter measurements are obtained every 5 cardiac cycles at the end-diastolic cardiac phase, which is confirmed by the incident R wave on a synchronized ECG. The 5 largest diameters measured during reactive hyperemia are averaged, and FMD is defined as the percentage increase in diameter from baseline.

2.5. Oral glucose tolerance test and insulin sensitivity

A 2-h 75 g OGTT was completed. Participants arrived in the fasting state and venous access was obtained. Blood was obtained at −10 min and −5 min relative to glucose load ingestion. These fasting values were later averaged to create the fasting measures used for calculations. The oral glucose load was administered, and participants had 5 min to consume it. Blood samples were taken at 10, 20, 30, 60, 90, and 120 min after glucose ingestion. Samples were processed for serum and stored at −85 °C until assayed for glucose, insulin, and *C*-peptide. Matsuda index was calculated as a measure of insulin sensitivity: $\text{Matsuda} = 10,000/\sqrt{[(G_{fasting} \times I_{fasting}) \times (G_{OGTTmean} \times I_{OGTTmean})]}$, where fasting glucose and insulin are taken from time 0 of the OGTT and mean data represent the average glucose and insulin obtained during the entire OGTT [28].

2.6. Assays

Samples obtained before and during the 2-h 75 g OGTT were used to measure serum glucose, total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglycerides using a Stanbio SIRRUS analyzer (Boerne, TX). Insulin was assayed in duplicate using immunofluorescence technology (TOSOH A1A-900 immunoassay analyzer, TOSOH Corp., South San Francisco, CA); assay sensitivity was 0.5 uU/ml; inter-assay CV was 3.95% and intra-assay CV was 1.49%. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula [29,30]. Aldosterone was measured using ALPCO Aldosterone ELISA kits (Salem, NH); minimum assay sensitivity was 15 pg/ml; intra-assay CV was 8% and inter-assay CV was 6.26%.

2.7. Determination of genetic admixture

Admixture analysis was performed on study participants with available DNA samples ($n = 107$). Filtering, quality control, and merging of genetic data were performed using PLINK (version 1.9) and the gaston package in R [31–33]. Study participants were genotyped with the Infinium Global Screening Array v3.0 (Illumina Inc., San Diego, CA, USA) at the Genomics Center at the University of Minnesota. CEU and YRI reference samples from 1000 Genomes Project Phase 3 were used to estimate European and African ancestry (respectively), while Colombian, Pima, Maya, Surui, and Karitiana reference samples from the Human Genome Diversity Project were used to estimate Native American ancestry [34,35]. Prior to analysis, quality control was performed both separately for the reference and study datasets and on the merged datasets. Any individuals and variants meeting the following criteria were removed: 1) non-autosomal SNPs; 2) SNPs or samples with call rate ≤90%; 3) SNPs deviating from Hardy-Weinberg equilibrium ($P < 10^{-7}$); 4) SNPs with minor allele frequency ≤0.01; and 5) 1st degree relatives. Supervised admixture analysis was performed with ADMIXTURE version 1.3.0 [36]. The analysis was conducted with K = 3 clusters to infer ancestry fractions for individuals in the study dataset via comparison with African, European, and Native American reference populations. Since DNA data were missing for 9 individuals, models were adjusted for self-reported race rather than admixture to maximize sample size. In those participants with genetic admixture data, it was confirmed that results were similar regardless of whether self-reported race or admixture was used as a covariate.

2.8. Statistical analyses

Differences in descriptive characteristics by self-reported race were assessed by Chi-square tests for categorical variables and independent samples t-tests for continuous variables. Differences in fat depots by race were evaluated by analysis of covariance (ANCOVA), with 1) RSF, liver fat, SAAT, and IAAT adjusted for total fat mass; and 2) IMAT and PMAT adjusted for total fat mass and thigh skeletal muscle mass. Summary data for fat depots were reported as adjusted means and determined from the ANCOVA models. Pearson correlations were used to investigate relationships of RSF with cardiovascular measures and aldosterone and partial correlations were used to further assess these relationships after adjustment for total fat mass. Multiple linear regression analysis was used to determine if RSF contributes to differences in SBP and DBP between AA and EA participants and to explore factors associated with RSF in AA and EA participants. For models investigating blood pressure, SBP and DBP were each evaluated as outcomes, while age, sex, race, total fat, and RSF were evaluated as independent variables. We also tested for interactions between RSF and race to determine if effect modification was present. For all linear regression models, linear relationships between the outcomes and continuous variables were confirmed with scatterplots. Residual normality was verified with histograms and QQ plots, while residual plots were examined to confirm homoscedasticity. No evidence of multicollinearity was observed in any of the models (all variance inflation factors <5). Assumptions for all other statistical tests (data normality and equal variances) were verified prior to analysis. Any non-normally distributed variables were transformed to achieve a normal distribution. Analyses were conducted with RStudio Statistical Software (R Core Team, 2022, v4.1.3). Statistical tests were two-tailed with significance set at $p < 0.05$.

3. Results

A total of $N = 116$ individuals were included in this secondary analysis. Descriptive characteristics for the entire sample and stratified by self-reported race are presented in Table 1. Briefly, the mean ± SD age of the study sample was 29 ± 7.89 years, 47.41% were males, and 50% identified as AA race. SBP and PP were higher in AA participants; however, no differences by race were observed for DBP, MAP, or FMD. AA participants had lower aldosterone, insulin sensitivity, and triglycerides. Cholesterol, HDL-C, and calculated LDL-C were similar between AA and EA participants.

Table 1
Descriptive characteristics.

	All Participants $N = 116$	African American $n =$ 58	European American $n =$ 58	p*
Age, years	29.2 ± 7.9	29.9 ± 8	28.5 ± 7.8	0.33
Male/Female, n	55/61	25/33	30/28	0.35
BMI, kg/m^2	27.4 ± 5.7	29.3 ± 6.1	25.5 ± 4.7	**0.0002**
Total fat mass, kg†	25.5 (22.5, 26.8)	26.2 (23.1, 29.7)	22.2 (19.8, 24.8)	**0.05**
SBP, mm Hg	117.2 ± 11.51	120.4 ± 11.7	114.1 ± 10.6	**0.003**
DBP, mm Hg	68.1 ± 8.6	68.8 ± 9.3	67.5 ± 7.9	0.43
MAP	84.4 ± 8.3	86 ± 8.9	83 ± 7.5	0.06
PP	49.1 ± 10.4	51.6 ± 10.3	46.7 ± 10.1	**0.01**
FMD, %	10.4 ± 5.4	10.8 ± 5.8	9.9 ± 5.1	0.4
Aldosterone, pg/mL	130.5 (114, 154)	106.5 (90.5, 125.2)	146.4 (130.8, 163.8)	**0.002**
Insulin Sensitivity	5.6 (5.18, 6.5)	4.9 (4.3, 5.6)	6.3 (5.3, 7.4)	**0.022**
Cholesterol, mg/dL	167 (162, 173)	169.1 (160, 178)	164.8 (156, 173)	0.56
Triglycerides, mg/dL	69 (61, 75)	66.4 (58, 76)	81.17 (71.4, 92.3)	**0.03**
HDL-C, mg/dL	58.8 ± 11.5	56.9 ± 10.7	60.6 ± 11.9	0.09
Calculated LDL-C, mg/dL	89.3 (85, 96.8)	96.8 (87.4, 111)	85 (77.6, 91.6)	0.07

All values are means ± SD or median (95% CI).
* p-value for difference between African American and European American.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; FMD, flow mediated dilation; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

RSF volume (mean ± SD) for the entire sample was 1.05 ± 0.82 cm^3 (results not shown). Adjusted means of fat depots by race are shown in Fig. 1A–F. There was no difference in RSF volume between AA and EA participants (0.97 vs. 0.82 cm^3, respectively; $p = 0.25$). Additionally, no differences by race were observed for liver fat or SAAT. EA participants had significantly higher IAAT, whereas AA participants had significantly higher IMAT and PMAT.

Correlations for RSF with cardiovascular measures and aldosterone are presented in Table 2. DBP was positively associated with RSF only in AA participants and remained significant upon adjustment for total fat. MAP was also positively associated with RSF in AA participants; however, this association only approached significance after controlling for total fat. Associations of RSF with SBP, PP, FMD, and aldosterone were not significant in AA or EA participants before or after adjustment for total fat.

Results for the SBP and DBP regression models are presented in Table 3. AA race was associated with SBP in Models 1 and 2 and remained significant after inclusion of RSF and total fat (Model 3). In contrast, race was not associated with DBP. RSF was not observed to be associated with either SBP or DBP. The interaction between race and RSF was not significant for SBP or DBP ($p_{int} = 0.8$ and $p_{int} = 0.39$, respectively; results not shown). Finally, the addition of total fat and RSF to the models explained a small amount of additional variance in SBP and DBP (as seen in the 3% points increase and 12.5% change in R^2 from Model 2 to Model 3 for SBP and the 2% points increase and 22% change in R^2 from Model 2 to Model 3 for DBP).

A secondary aim was to explore risk factors associated with RSF in AA and EA adults (Table 4). In unadjusted models, older age, greater total fat, greater SAAT, greater IAAT, and greater IMAT were associated with greater RSF in both AA and EA participants. Only in EA participants were lower insulin sensitivity and greater PMAT associated with greater

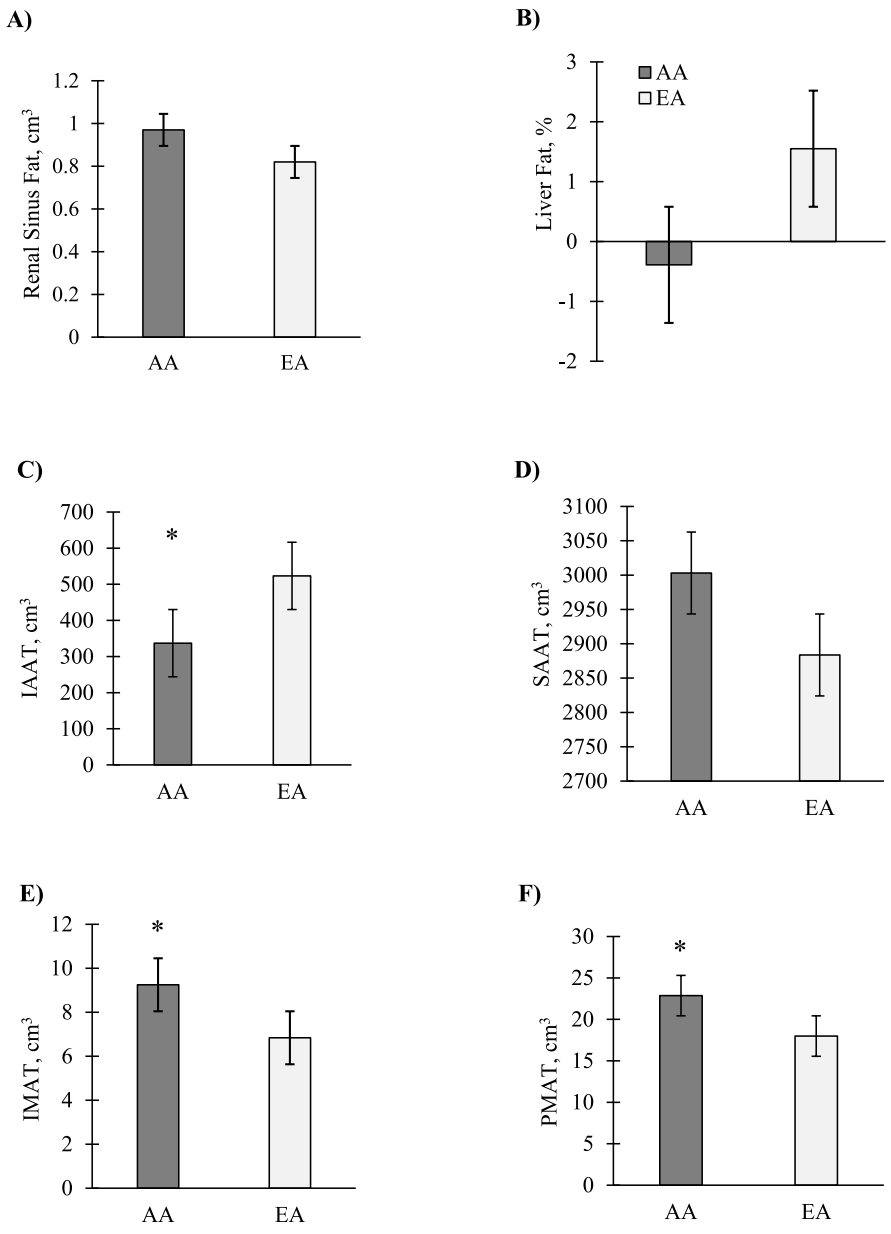

Fig. 1. A–FFat depots by self-reported race. A-B) RSF and liver fat: AA, $n = 58$; EA, $n = 58$. *C*-D) IAAT and SAAT: AA, $n = 57$; EA, $n = 58$. E-F) IMAT and PMAT: AA, $n = 55$; EA, $n = 58$. Data are expressed as adjusted means ± SE. Values for RSF, liver fat, IAAT, and SAAT are adjusted for total fat and values for IMAT and PMAT are adjusted for total fat and thigh skeletal muscle. *$p < 0.01$ for main effect of race. RSF, renal sinus fat; SAAT, subcutaneous abdominal adipose tissue; IAAT, intraabdominal adipose tissue; IMAT, intermuscular adipose tissue; PMAT, perimuscular adipose tissue; AA, African American; EA, European American.

RSF. Upon adjustment for additional covariates, older age, male sex, and greater total fat were associated with greater RSF in AA participants. Among these, the magnitude of the association with greater RSF was highest for age. Lower insulin sensitivity, greater IAAT, and greater PMAT were associated with greater RSF in EA participants, with IAAT having the greatest magnitude of association with greater RSF.

4. Discussion

The present study investigated RSF volume and associations between RSF, blood pressure, and other ectopic fat depots in a cohort of AA and EA adults. To our knowledge, this is the first study to investigate RSF in AA and EA adult men and women. The main findings of the study were that RSF does not differ by race, and that RSF is positively associated with DBP in AA adults, but this is not independent of age and sex. Secondary findings indicated age, male sex, and total fat to be associated with RSF in AA adults and insulin sensitivity, IAAT, and PMAT to be associated with RSF in EA adults.

Race has been shown to influence ectopic fat deposition, with AA individuals often having lower levels of visceral adipose tissue and ectopic fat (pancreatic, hepatic) compared to EA [13–17,37,38]. To our knowledge, RSF has not been compared in AA and EA adults. While we did not find any differences in RSF between AA and EA participants, it is possible that it could be due to a small sample size, and our relatively young and healthy sample (mean age 29 years, 42% of participants with a normal BMI, and no type 2 diabetes) compared to other studies [2,3]. Race differences may be more apparent in older individuals with metabolic disease and/or high levels of ectopic fat. With respect to other fat depots, we found AA participants to have lower IAAT and tended to have lower liver fat compared to EA participants. In contrast, AA participants had significantly greater IMAT and PMAT than EA participants. Prior studies have shown that AA adults have higher levels of IMAT compared to EA adults [39,40]. These observations suggest that the regulation of ectopic fat deposition and distribution may vary with race.

RSF has been shown to be associated with hypertension, number of prescribed anti-hypertensive medications, and renal size [2,3]. RSF has also been shown to be associated with SBP, DBP, and mean arterial pressure independent of BMI and visceral adiposity [3,10]. It is thought

Table 2
Full and partial correlations for renal sinus fat and cardiovascular measures and aldosterone.

	African American *r* (*p*-value)	European American *r* (*p*-value)
SBP		
Unadjusted	0.13 (0.33)	0.008 (0.96)
Total fat	0.07 (0.62)	−0.02 (0.86)
DBP		
Unadjusted	**0.32 (0.02)**	0.17 (0.21)
Total fat	**0.33 (0.02)**	0.1 (0.46)
MAP		
Unadjusted	0.28 (0.03)	0.12 (0.36)
Total fat	0.26 (0.06)	0.06 (0.66)
PP		
Unadjusted	−0.14 (0.31)	−0.12 (0.36)
Total fat	−0.22 (0.1)	−0.1 (0.46)
FMD		
Unadjusted	−0.08 (0.56)	0.03 (0.81)
Total fat	−0.1 (0.5)	−0.04 (0.78)
Aldosterone		
Unadjusted	−0.22 (0.11)	0.019 (0.88)
Total Fat	−0.19 (0.18)	0.07 (0.59)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; FMD, flow mediated dilation.

Table 3
Linear regression models for systolic and diastolic blood pressure.

	R^2	Age	Sex	Race	Total Fat	RSF
SBP						
Model 1	0.15	0.13 (0.13)	−0.36 (2)‡	–	–	–
Model 2	0.24	0.1 (0.12)	−0.38 (1.93)‡	−0.29 (1.93)‡	–	–
Model 3	0.27	0.06 (0.14)	−0.43 (1.95)‡	−0.26 (1.93)†	0.23 (0.0001)*	−0.07 (1.33)
DBP						
Model 1	0.09	0.28 (0.1)†	−0.09 (1.55)	–	–	–
Model 2	0.09	0.27 (0.1)†	−0.11 (1.56)	−0.06 (1.56)	–	–
Model 3	0.11	0.2 (0.11)	−0.09 (1.6)	−0.03 (1.59)	0.05 (0.0001)	0.13 (1.1)

‡$p < 0.001$, †$p < 0.01$, *$p < 0.05$. Standardized β coefficients (SE) shown. Male is reference group for sex. AA is reference group for race. Abbreviations: AA, African American; EA, European American; RSF, renal sinus fat.

that this is due to a compression of renal structures leading to increases in renal interstitial pressure, activation of the RAAS, and sodium retention [8,9]. We found RSF to be positively associated with DBP only in AA participants, however, this was not independent of age and sex. These results are different from those of other studies investigating RSF and blood pressure. Findings from the Framingham Heart Study indicated RSF to be positively associated with hypertension, SBP, and DBP [3]. However, findings from Chughtai et al. did not find an association of RSF with either SBP or DBP. Rather, RSF was found to be associated with number of prescribed anti-hypertensive medications and stage II hypertension [2]. It is possible that our association of RSF with DBP in AA individuals was attenuated upon the inclusion of age and sex as covariates due to our relatively young and healthy sample (mean age 29 years, no type 2 diabetes, no hypertension) compared to other studies. However, it is interesting that neither age nor sex differed by race group. Additionally, we found that the addition of total fat and RSF to linear regression models explained a small amount of additional variance in SBP and DBP. While we did not find RSF to be associated with SBP or DBP, it is possible that a larger sample size would have resulted in different results. Nonetheless, these findings should be explored in a larger and older population.

Like other investigative groups, we found AA participants to have lower aldosterone levels compared to EA participants [41–43]. It remains unclear why some studies have reported lower aldosterone concentrations in AA individuals, but it has been postulated to be related to lower plasma renin activity and likely differences in aldosterone synthetic and stimulatory pathways [44]. Aldosterone levels have been shown to be positively associated with blood pressure in AA individuals [41,45,46], but it remains unknown if aldosterone is associated with RSF. While we did not observe an association between aldosterone and RSF, additional studies are warranted to determine potential mechanisms by which RSF and aldosterone, or other components of the RAAS, could influence blood pressure and subsequent cardiovascular risk in older adults and AA populations.

Ectopic fat accumulation occurs due to an inability of subcutaneous adipose tissue to expand or when subcutaneous adipose tissue stores are saturated and unable to further expand in the presence of energy surplus [12,47]. It is well known that ectopic fat accumulation is influenced by numerous factors, including age, sex, race/ethnicity, genetics, insulin resistance, and lifestyle, but it remains unclear how these factors may differentially influence RSF accumulation in various populations [12,47,48]. We observed unique risk factors to be associated with RSF in AA and EA participants. In AA participants, older age, male sex, and greater total

Table 4
Results from linear regression models investigating risk factors associated with renal sinus fat.

	Unadjusted				Adjusted			
	AA		EA		AA		EA	
	R^2	β ± SE (*p-value*)	R^2	β ± SE (*p-value*)	R^2	β ± SE (*p-value*)	R^2	β ± SE (*p-value*)
Age*	**0.37**	**0.61 ± 0.01 (<0.0001)**	**0.07**	**0.27 ± 0.01 (<0.05)**	**0.45**	**0.53 ± 0.01 (<0.0001)**	0.13	0.21 ± 0.01 (0.13)
Sex†	0.03	−0.17 ± 0.1 (0.2)	0.001	−0.2 ± 0.11 (0.87)	**0.45**	**−0.22 ± 0.1 (<0.05)**	0.13	−0.03 ± 0.14 (0.85)
Insulin Sensitivity	0.001	0.04 ± 0.11 (0.8)	**0.15**	**−0.39 ± 0.08 (<0.01)**	0.47	0.13 ± 0.09 (0.25)	**0.22**	**−0.36 ± 0.1 (<0.05)**
Total Fat‡	**0.14**	**0.38 ± 0.0001 (<0.01)**	**0.09**	**0.3 ± 0.0001 (<0.05)**	**0.45**	**0.23 ± 0.0001 (<0.05)**	0.13	0.26 ± 0.0001 (0.06)
SAAT	**0.11**	**0.33 ± 0.003 (0.01)**	**0.13**	**0.36 ± 0.003 (<0.01)**	0.43	0.1 ± 0.01 (0.7)	0.18	0.47 ± 0.007 (0.09)
IAAT	**0.23**	**0.48 ± 0.04 (<0.001)**	**0.23**	**0.48 ± 0.04 (<0.001)**	0.43	−0.13 ± 0.1 (0.56)	**0.27**	**0.65 ± 0.07 (<0.01)**
Liver Fat	0.008	0.09 ± 0.07 (0.5)	0.02	0.13 ± 0.07 (0.32)	0.45	0.04 ± 0.06 (0.71)	0.13	0.05 ± 0.07 (0.69)
IMAT	**0.15**	**0.38 ± 0.07 (<0.01)**	**0.13**	**0.35 ± 0.07 (<0.01)**	0.45	0.18 ± 0.1 (0.29)	0.16	0.24 ± 0.09 (0.17)
PMAT	0.04	0.19 ± 0.09 (0.16)	**0.14**	**0.36 ± 0.09 (<0.01)**	0.44	0.05 ± 0.12 (0.8)	**0.19**	**0.4 ± 0.15 (0.05)**

Standardized β coefficients shown. Male is reference group for sex.
Adjusted models adjust for age, sex, and total fat unless otherwise noted.
*Adjusted model adjusted for sex and total fat.
†Adjusted model adjusted for age and total fat.
‡Adjusted model adjusted for age and sex.
IMAT and PMAT adjusted for thigh skeletal muscle in all models (unadjusted and adjusted).
Abbreviations: AA, African American; EA, European American; SAAT, subcutaneous abdominal adipose tissue; IAAT, intraabdominal adipose tissue; IMAT, intermuscular adipose tissue; PMAT, perimuscular adipose tissue.

body fat were associated with greater RSF whereas in EA participants, lower insulin sensitivity, greater IAAT, and greater PMAT were associated with greater RSF. Similarly, insulin sensitivity has been shown to be inversely associated with visceral adipose tissue, intrahepatic lipid, intrapancreatic lipid, and intramyocellular lipids in healthy white European men but not black west African men [13]. The reason why insulin sensitivity clusters more strongly with ectopic fat accumulation in White individuals than in Black individuals is not known. Insulin resistance has been shown to have a genetic basis that relates to the inability to expand subcutaneous adipose depots [48] and thereby predisposes to the accumulation of ectopic adipose in the context of positive energy balance. This genetic insulin resistance may explain our observation here of an inverse association between RSF and insulin sensitivity in EA participants. In contrast, insulin resistance in AA participants may occur predominantly due to low mitochondrial oxidative capacity [49] rather than ectopic lipid accumulation, explaining the absence of an association between insulin sensitivity and ectopic lipid. Population heterogeneity in the extent to which insulin resistance is attributed to genetic vs acquired factors, and in the nature of both, undoubtedly exists. However, it is possible that the frequency within a given population (e.g., AA and EA) of genetic variation in specific loci that affect insulin sensitivity exists [50]. Future research is necessary to clarify the unique pathophysiological mechanisms underlying accumulation of ectopic fat in AA and EA populations, and ultimately how these differences influence chronic disease risk.

Strengths of the present study include MRI imaging for assessment of adipose tissue depots, the diverse sample, genetic admixture, and measures of insulin sensitivity. Limitations must also be considered. As a secondary analysis, we were limited to the individuals recruited in the parent study which was a small cohort with a younger age range (mean age 29 years), no type 2 diabetes, and no hypertension. As such, this limited our ability to investigate how older age and chronic disease may impact these associations. However, it may also be considered a strength that we observed such associations in a young cohort, underscoring the need for additional research in a diverse cohort of older adults. Blood pressure was not the main outcome of the parent study, and therefore was only measured once. As a main outcome of the present analysis, a higher standardization is needed, and this could have impacted our results. Further, we had limited lifestyle factors available to investigate associations with RSF (i.e.: physical activity, alcohol consumption, socioeconomic factors). The parent study also utilized a convenience sample, as it recruited adults who responded to school and local newspaper flyers and therefore this could have biased our results. Finally, as a cross-sectional study, causality cannot be inferred.

In conclusion, RSF volume did not differ between AA and EA participants and RSF was positively associated with DBP in AA participants. Although this association was attenuated after adjusting for age and sex, follow-up studies in a sample of older individuals at higher risk for metabolic disease is warranted. Finally, different risk factors were associated with RSF according to race; age, male sex, and total fat were associated with RSF in AA participants while insulin sensitivity, IAAT, and PMAT were associated with RSF in EA participants. Such findings suggest differential pathophysiological mechanisms influence ectopic fat deposition in AA and EA individuals. Future research will be needed to investigate these underlying mechanisms and how they may uniquely contribute to the etiology and progression of chronic disease, particularly over the life course.

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Credit statement

C.A.C.: conceptualization, formal analysis, writing- original draft; B.A.G.: conceptualization, methodology, writing- original draft, funding acquisition; L.A.F: formal analysis, genetic admixture analysis, writing-review & editing; A.M.G: MRI image analysis. All authors reviewed and edited the manuscript and approved the final version. C.A.C. and B.A.G. are the guarantors of this work and, as such, had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of competing interest

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

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