

# Race affects the association of obesity measures with insulin sensitivity

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## ABSTRACT

**Background:** Race differences in body composition and fat distribution may in part explain the differences in insulin sensitivity and the disproportionate burden of type 2 diabetes in African Americans.

**Objective:** To determine if differences in body composition and fat distribution explain race differences in insulin sensitivity and identify obesity measures that were independently associated with insulin sensitivity.

**Methods:** Participants were 113 lean, overweight, and obese African-American and Caucasian-American adults without diabetes. Skeletal muscle insulin sensitivity was determined using a hyperinsulinemic-euglycemic clamp ( $SI_{Clamp}$ , insulin rate:120 mU/m<sup>2</sup>/min). Subcutaneous abdominal adipose tissue (SAAT), intra-abdominal adipose tissue (IAAT), and liver fat were measured by MRI; leg fat, total fat, and lean mass were measured by DXA.

**Results:** Race-by-adiposity interactions were significant in cross-sectional analyses utilizing multiple linear regression models for  $SI_{Clamp}$  ( $P < 0.05$ ); higher BMI, fat mass, SAAT, leg fat, and liver fat were associated with lower  $SI_{Clamp}$  in Caucasian Americans but not African Americans. Race-by-IAAT interaction was not significant ( $P = 0.65$ ). A central fat distribution (SAAT adjusted for leg fat) was associated with lower  $SI_{Clamp}$  in African Americans ( $\beta = -0.45$ , SE = 0.11,  $P < 0.001$ ) but not Caucasian Americans ( $\beta = -0.42$ , SE = 0.30,  $P = 0.17$ ). A peripheral fat distribution (leg fat adjusted for IAAT/SAAT) was associated with a higher  $SI_{Clamp}$  in African Americans ( $\beta = 0.11$ , SE = 0.05,  $P = 0.02$ ) but lower  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.28$ , SE = 0.14,  $P = 0.049$ ). Lean mass was inversely associated with  $SI_{Clamp}$  in African Americans ( $\beta = -0.05$ , SE = 0.03,  $P = 0.04$ ) but not Caucasian Americans ( $\beta = 0.08$ , SE = 0.05,  $P = 0.10$ ) in the model for leg fat.

**Conclusions:** Measures of overall adiposity were more strongly associated with  $SI_{Clamp}$  in Caucasian Americans, whereas body fat distribution and lean mass showed stronger correlations with  $SI_{Clamp}$  in African Americans. Insulin sensitivity may have a genetic basis in African Americans that is reflected in the pattern of body fat distribution. These findings suggest a race-specific pathophysiology of insulin resistance, which has implications for the prevention of diabetes and related cardiometabolic diseases. *Am J Clin Nutr* 2020;111:515–525.

**Keywords:** race, adiposity, lean mass, leg fat, insulin sensitivity, hyperinsulinemic-euglycemic clamp

## Introduction

In the USA, African Americans have the highest prevalence of obesity and are disproportionately affected by type 2 diabetes (T2D) (1). The underlying cause for this disparity is not known, but may relate to differences in insulin resistance or decreased insulin sensitivity, which is recognized as an important factor in the etiology of T2D (2). Previous studies using mainly indirect assessment methods report lower insulin sensitivity in African Americans compared with Caucasian Americans (3, 4). However, results have been inconsistent, differing with the method used to assess insulin sensitivity and the obesity status of the study population (3–7).

Furthermore, African Americans have a higher acute insulin response to glucose (3, 8), but lower fasting glucose (9),

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Abbreviations used: HOMA2-IR, homeostasis model of assessment index 2-insulin resistance; IAAT, intra-abdominal adipose tissue; J–N, Johnson–Neyman procedure; SAAT, subcutaneous abdominal adipose tissue;  $SI_{Clamp}$ , skeletal muscle insulin sensitivity assessed by the hyperinsulinemic-euglycemic clamp; T2D, type 2 diabetes.

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postchallenge glucose (5, 10), basal hepatic glucose production (11), and insulin clearance compared with Caucasian Americans (10, 12, 13). These racial differences in insulin-glucose homeostasis highlight the necessity of assessing race differences in insulin sensitivity using direct methods such as the reference standard hyperinsulinemic-euglycemic clamp, in both lean and obese individuals (14).

In addition, while obesity is a leading risk factor for T2D and insulin resistance (15), differences in adipose tissue distribution can influence the association between obesity and insulin resistance. Ectopic fat accumulation in insulin-sensitive tissues such as intrahepatic, intermuscular, or intramyocellular lipid is involved in the etiology of insulin resistance (16, 17). Higher levels of total, visceral, and subcutaneous abdominal adiposity have also been shown to be associated with increased insulin resistance in predominantly Caucasian-American populations (18, 19). Whether these associations extend to African Americans is less clear. Emerging evidence indicates that subcutaneous abdominal adipose tissue (SAAT) is a major determinant of insulin sensitivity in black women, who are more insulin resistant than BMI-matched white women despite having less visceral fat (20, 21). Collectively, these data suggest racial differences in the relation between regional fat distribution and insulin sensitivity.

Therefore, the primary objective of this study was to determine the extent that differences in obesity measures such as BMI, whole-body adiposity, as well as regional and ectopic fat distribution assessed using MRI explain the differences in skeletal muscle insulin sensitivity assessed by the hyperinsulinemic-euglycemic clamp ( $SI_{Clamp}$ ) between African-American and Caucasian-American men and women without diabetes, across a wide range of adiposity. A secondary aim was to identify significant measures of body composition and regional fat distribution that are independently associated with  $SI_{Clamp}$  in lean, overweight, and obese African Americans and Caucasian Americans.

## Methods

### Study design, setting, and participants

This cross-sectional study was conducted at the University of Alabama at Birmingham (UAB), between 2013 and 2018. Lean, overweight, and obese African-American and Caucasian-American men and women, aged 19–45 y, who were sedentary to moderately active (<2 h/wk of moderate, intentional exercise) were recruited by public advertisement. Race was determined by self-report. Individuals with diabetes were excluded from participation following a screening 75 g oral-glucose-tolerance test (2-h glucose  $\geq 200$  mg/dL). Other exclusion criteria included absence of a regular menstrual cycle; pregnant, lactating, or postmenopausal; smoking; not weight stable (change in weight >5 lbs or 2.3 kg) in the previous 6 mo; active engagement in unusual dietary practices (e.g. low-carbohydrate diets); taking oral contraceptives; use of any medication known to affect carbohydrate or lipid metabolism, or energy expenditure; and use of antihypertensive 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, to avoid strenuous physical activity the day prior to testing, and to avoid all physical activity on the morning of testing. Women were tested 3–7 d 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 and all participants provided written informed consent.

### Insulin sensitivity assessed by $SI_{Clamp}$ and the homeostasis model assessment of insulin resistance index 2

Skeletal muscle insulin sensitivity ( $SI_{Clamp}$ ) was assessed using the hyperinsulinemic-euglycemic clamp. All  $SI_{Clamp}$  tests were performed in an outpatient setting in the Clinical Research Unit (CRU) at UAB's CCTS after a  $\geq 10$  h overnight fast. With the participant in a recumbent position, an intravenous catheter was placed in an antecubital vein for insulin and glucose infusion. The insulin solution (regular Humulin, Eli Lilly & Co.) was prepared with normal saline and infused at 120 mU/m<sup>2</sup>/min (individualized to the participant's body surface area) for 3 h using an Alaris point-of-care unit with Guardrails software (Carefusion Corp.). Blood glucose concentrations were measured at the bedside at 5-min intervals using a glucose analyzer (YSI 2300 STAT Plus, YSI, Inc.), and an infusion of 20% dextrose was adjusted to maintain the blood glucose concentration at the individual's fasting level. The steady-state period for each individual was defined as a  $\geq 30$  min period that occurred  $\geq 1$  h after initiation of the insulin infusion, during which the CVs for blood glucose, serum insulin, and glucose infusion rate were <5%. Another catheter was placed in the contralateral arm for sequential blood sampling every 10 min for the determination of glucose (SIRRS analyzer, Stanbio Laboratories) and insulin (TOSOH AIA-II immunoassay analyzer, TOSCH Corp.) concentrations. The intra- and interassay CVs were 1.28% and 2.48% for serum glucose, and 1.49% and 3.95% for insulin, respectively.

$SI_{Clamp}$  ( $10^{-4}$ .dL.kg<sup>-1</sup>.min<sup>-1</sup>/[ $\mu$ U/mL]) was defined as  $M/(G \times \Delta I)$ , where M is the steady-state glucose infusion rate (mg/kg body mass/min), G is the steady-state serum glucose concentration (mg/dL), and  $\Delta I$  is the difference between basal and steady-state serum insulin concentrations ( $\mu$ U/mL).

The homeostasis model of assessment index 2- insulin resistance (HOMA2-IR) was also used to assess insulin resistance (22). HOMA2-IR is computed using fasting insulin and glucose and may primarily reflect hepatic insulin resistance.

### Body composition and regional fat distribution determined by MRI and DXA

Total and regional body composition including total lean mass, fat mass, and leg fat were measured by DXA (iDXA instrument, GE Healthcare). Participants were scanned in light clothing while lying supine with arms at their sides.

SAAT, intra-abdominal adipose tissue (IAAT), and liver fat were determined by MRI (Ingenia 1.5T wide bore MRI system; Philips). Liver fat was assessed using the fast spin echo 2-point Dixon technique (23). Volumes of 2 abdominal adipose tissue compartments, SAAT and IAAT, were assessed via transverse abdominal images obtained using 3D volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE). The echo time, repetition time, and pulse flip angles

**TABLE 1** Participant characteristics by race<sup>1</sup>

	African Americans ( <i>n</i> = 55)	Caucasian Americans ( <i>n</i> = 58)	<i>P</i> <sup>2</sup>
Participant demographics			
Age, y	30 ± 1	28 ± 8	0.20
Gender, males/females	25/30	30/28	0.51
Metabolic measurements			
SI <sub>Clamp</sub> , 10 <sup>-4</sup> .dL.kg <sup>-1</sup> .min <sup>-1</sup> /(μU/mL)	3.0 ± 1.2	5.2 ± 2.4	<0.001
Fasting glucose, mg/dL	91.1 ± 8.4	88.6 ± 9.2	0.13
Fasting insulin, <sup>3</sup> μU/mL	9.6 ± 5.2	7.5 ± 4.5	0.03
HOMA2-IR <sup>3</sup>	1.1 ± 0.6	0.8 ± 0.5	0.03
Body weight and composition			
Weight, kg	85.9 ± 19.1	76.5 ± 15.0	0.005
BMI, kg/m <sup>2</sup>	29.3 ± 5.9	25.8 ± 4.7	0.001
DXA measurements			
Total fat mass, kg	28.8 ± 12.1	24.8 ± 10.5	0.06
Total fat mass, %	32.9 ± 9.5	31.7 ± 8.9	0.49
Total lean mass, kg	53.4 ± 11.7	48.9 ± 9.2	0.02
Leg fat, kg	10.9 ± 5.0	8.8 ± 3.8	0.01
MRI measurements			
Subcutaneous abdominal adipose tissue, <sup>4</sup> L	3.7 ± 2.2	2.9 ± 1.7	0.03
Intra-abdominal adipose tissue, <sup>4</sup> L	0.6 ± 0.5	0.8 ± 0.8	0.18
Liver fat, <sup>5</sup> %	0.4 ± 5.9	1.9 ± 7.6	0.26

Data are unadjusted mean ± SD, unless otherwise stated.

<sup>1</sup>Total analyzed *n* = 113 (African Americans: 55, Caucasian Americans: 58) for all data unless otherwise stated.

<sup>2</sup>*P* value for differences between races by independent samples t-test (continuous variables) or chi-square test (categorical variables).

<sup>3</sup>Total analyzed *n* = 111 (African Americans: 54, Caucasian Americans: 57) for insulin and HOMA2-IR data; 2 outliers (values >3 SD over the group mean due to elevated fasting insulin) were excluded from analyses.

<sup>4</sup>Total analyzed *n* = 112 (African Americans: 55, Caucasian Americans: 57) for SAAT and IAAT data; no abdominal MRI images were available for 1 Caucasian American.

<sup>5</sup>Total analyzed *n* = 112 (African Americans: 54, Caucasian Americans: 58) for liver fat; data from 1 African American was excluded due to severe artifact. HOMA2-IR, homeostasis model of assessment index 2-insulin resistance; IAAT, intra-abdominal adipose tissue; SAAT, subcutaneous abdominal adipose tissue; SI<sub>Clamp</sub>, skeletal muscle insulin sensitivity assessed by the hyperinsulinemic-euglycemic clamp.

were selected to optimize the signal-intensity contrast between adipose and nonadipose tissue. A series of 10 mm slices spaced at 5 mm intervals from the L1-L4/5 vertebrae was performed for each individual. Images were analyzed for IAAT and SAAT using Slice-O-Matic software (version 4.3, Tomovision) for abdominal fat volume.

## Statistical analyses

Race comparisons of descriptive characteristics were made by chi-square tests (categorical variables) and independent samples t-test (continuous variables). Multiple linear regression models were used to assess the interaction between race and various measures of obesity, body composition, and regional fat distribution (e.g., BMI, fat mass, lean mass, SAAT, IAAT, liver fat, and leg fat) on SI<sub>Clamp</sub> and HOMA2-IR. Independent variables were entered into the model by hierarchical regression. Age, sex, and total lean and total fat mass were included as covariates in the models, except when there was significant multicollinearity (e.g., between BMI/SAAT/leg fat and total fat). One outlier for SI<sub>Clamp</sub> (>4 standardized residuals and high standardized DFFit statistic) was excluded from these analyses. Omission of the outlier improved the residuals of the models, and the homoscedasticity assumption was met. As residual values of HOMA2-IR obtained after adjustment for race, age, sex, liver fat, and total lean and total fat mass in multivariate analysis were

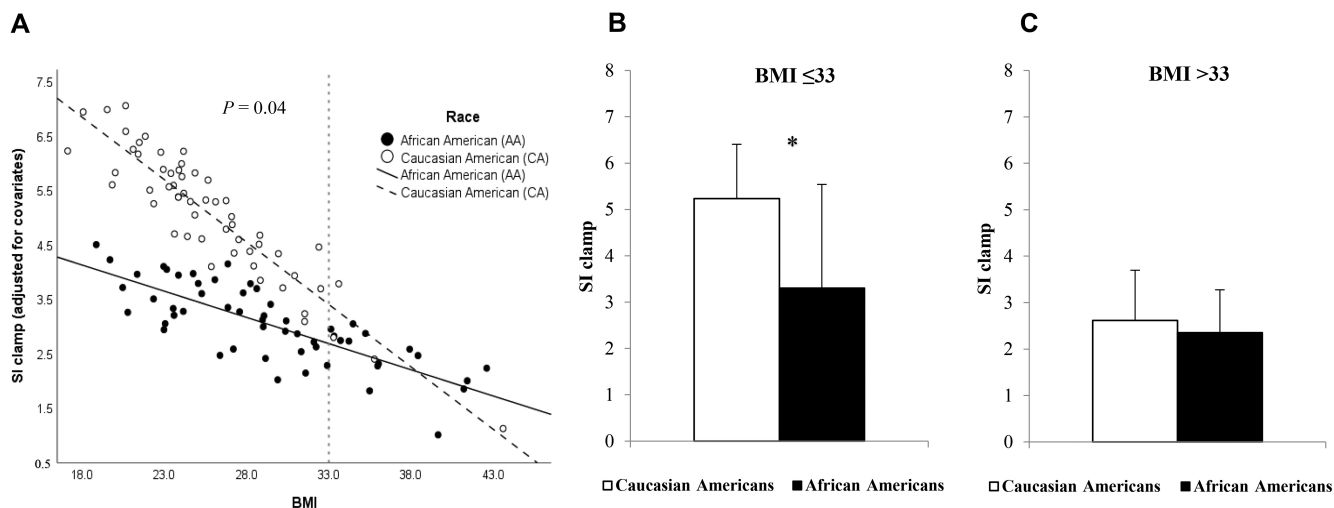
not normally distributed, logarithmically transformed HOMA2-IR was used in these analyses.

ANCOVA was used to investigate whether differences in lean mass, or total and regional adiposity accounted for the racial difference in SI<sub>Clamp</sub>. Comparisons of regression slopes (test of interaction between race and covariates) were conducted to ascertain whether the assumption of homogeneity of regression slopes was met. Where interaction terms were significant, the Johnson–Neyman (J–N) procedure was used to identify the regions of significance along the observed range of the covariate where the race difference in outcome measure occurred (e.g., range of BMI where African Americans and Caucasian Americans differed in SI<sub>Clamp</sub>) (24). A total sample size of 60 individuals would provide >90% power at an  $\alpha$ -level of 0.05 to detect the hypothesized marginal effect of BMI, hypothesized marginal effect of race, and the hypothesized interaction effect assuming an SD of glucose disposal of 40 mg/kg/min. All analyses were performed with SPSS 25.0 for Windows (SPSS Inc.). Statistical tests were 2-tailed with significance set at *P* < 0.05.

## Results

### Anthropometric and metabolic measurements

**Table 1** presents the metabolic, anthropometric, and regional adiposity characteristics of study participants according to race.



**FIGURE 1** (A) Relation between skeletal muscle insulin sensitivity ( $SI_{Clamp}$   $10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} / \{\mu U/mL\}$ ) assessed by the hyperinsulinemic-euglycemic clamp, and BMI, on the basis of a multiple linear regression model ( $n = 112$ ) adjusted for the covariates sex, age, and total lean mass in African Americans ( $n = 55$ ; black dots, bars, and line) and Caucasian Americans ( $n = 57$ ; white dots, bars, and dashed line).  $P = 0.04$  (race  $\times$  BMI),  $P < 0.01$  (overall model),  $R^2 = 46\%$ . Perforated line represents the critical point for the region of significance on BMI  $\leq 33$ ,  $SI_{Clamp}$  significantly lower in African Americans ( $\beta = -0.08$ , SE = 0.03,  $P = 0.01$ ,  $R^2 = 30\%$ ) compared with Caucasian Americans ( $\beta = -0.33$ , SE = 0.06,  $P < 0.001$ ,  $R^2 = 37\%$ ). (B) \* $SI_{Clamp}$  significantly different between African Americans ( $n = 40$ ) and Caucasian Americans ( $n = 53$ ) with BMI  $\leq 33$ . (C)  $SI_{Clamp}$  not significantly different between African Americans ( $n = 15$ ) and Caucasian Americans ( $n = 4$ ) with BMI  $> 33$ . Values are means; error bars in panels (B) and (C) are SD.

In total, 113 adults (49% African American, 49% males, aged  $29 \pm 8$  y and BMI  $27.5 \pm 5.6$  kg/m<sup>2</sup>) without diabetes participated in the study. Race groups were matched for age and gender distribution. Compared with Caucasian Americans, African Americans had a lower  $SI_{Clamp}$ , and higher fasting insulin and HOMA2-IR ( $P \leq 0.03$ ). African Americans had higher total lean mass, leg fat, and SAAT volume, corresponding to higher weight and BMI ( $P < 0.03$ ). Total fat also tended to be higher in African Americans ( $P = 0.06$ ). IAAT and intrahepatic fat volumes were not significantly different between Caucasian Americans and African Americans ( $P \geq 0.18$ ).

#### Race differences in association between $SI_{Clamp}$ and obesity measures

Race was independently associated with  $SI_{Clamp}$  (significantly lower in African Americans than Caucasian Americans,  $P < 0.001$ ) in all multivariate models that examined the association between  $SI_{Clamp}$  and various obesity measures. Except for the model that included IAAT and leg fat, sex was independently associated with  $SI_{Clamp}$  (significantly lower in males than females,  $P < 0.05$ ).

There was a significant race  $\times$  BMI interaction ( $P = 0.04$ ,  $R^2 = 46\%$ ; **Figure 1A**). A higher BMI was more strongly associated with a lower  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.33$ , SE = 0.06,  $P < 0.001$ ,  $R^2 = 37\%$ ) compared with African Americans ( $\beta = -0.08$ , SE = 0.03,  $P = 0.01$ ,  $R^2 = 30\%$ ). The J-N method was used to explore the association between race and  $SI_{Clamp}$  and identify the range of BMI where differences in  $SI_{Clamp}$  between African Americans and Caucasian Americans were statistically significant. The results showed  $SI_{Clamp}$  was lower in African Americans compared with Caucasian Americans for participants with BMI  $\leq 33$  ( $3.3 \pm 1.2$  versus  $5.2 \pm 2.2$  [ $10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} / \{\mu U/mL\}$ ]; **Figure 1B**). However,  $SI_{Clamp}$

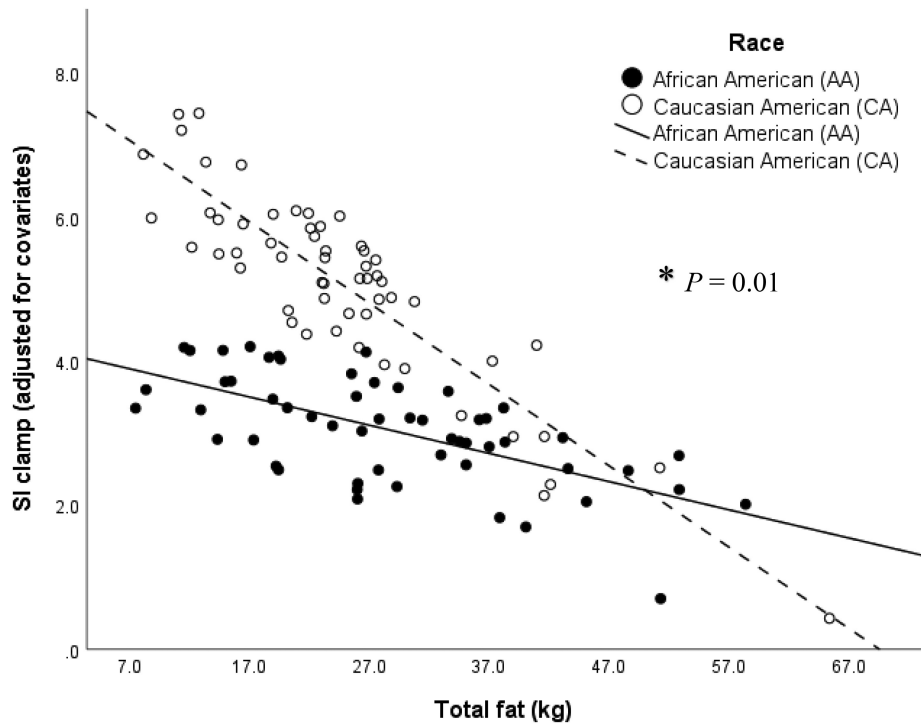
was similar in both races for participants with BMI  $> 33$  ( $2.4 \pm 1.1$  versus  $2.6 \pm 1.0$  [ $10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} / \{\mu U/mL\}$ ]; **Figure 1C**).

Similarly, the race  $\times$  total fat interaction was significant ( $P = 0.01$ ,  $R^2 = 50\%$ ; **Figure 2**). A higher total fat mass was more strongly associated with a lower  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.15$ , SE = 0.03,  $P < 0.001$ ,  $R^2 = 43\%$ ) than in African Americans ( $\beta = -0.04$ , SE = 0.02,  $P = 0.03$ ,  $R^2 = 28\%$ ).

The race  $\times$  SAAT interaction was significant ( $P = 0.046$ ,  $R^2 = 47\%$ ). A higher SAAT volume was more strongly associated with a lower  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.82$ , SE = 0.17,  $P < 0.001$ ,  $R^2 = 33\%$ ) compared with African Americans ( $\beta = -0.27$ , SE = 0.07,  $P < 0.001$ ,  $R^2 = 38\%$ ). In assessing the effect of upper-body relative to lower-body fat distribution on  $SI_{Clamp}$ , leg fat was added as a covariate in the model for SAAT in addition to sex, age, and total lean mass (**Table 2**). The race  $\times$  SAAT interaction remained significant ( $P = 0.047$ ,  $R^2 = 47\%$ ). The inverse association between SAAT and  $SI_{Clamp}$  was strengthened in African Americans ( $\beta = -0.45$ , SE = 0.11,  $P < 0.001$ ;  $R^2 = 44\%$ ), but was no longer significant in Caucasian Americans ( $\beta = -0.42$ , SE = 0.30,  $P = 0.17$ ;  $R^2 = 36\%$ ).

However, the race  $\times$  IAAT interaction was not statistically significant ( $P = 0.65$ ,  $R^2 = 50\%$ ; **Figure 3**), and there was a similar association between IAAT and  $SI_{Clamp}$  in both African Americans ( $\beta = -0.66$ , SE = 0.47,  $P = 0.16$ ,  $R^2 = 31\%$ ) and Caucasian Americans ( $\beta = -0.54$ , SE = 0.53,  $P = 0.32$ ,  $R^2 = 44\%$ ). There was no significant difference between the intercepts ( $P = 0.34$ ). Controlling for leg fat instead of total fat did not alter the results (race  $\times$  IAAT,  $P = 0.68$ ,  $R^2 = 46\%$ ). The inverse association between IAAT and  $SI_{Clamp}$  reached statistical significance in both African Americans ( $\beta = -0.89$ , SE = 0.44,  $P = 0.048$ ,  $R^2 = 29\%$ ) and Caucasian Americans ( $\beta = -1.22$ ,





**FIGURE 2** Relation between skeletal muscle insulin sensitivity ( $SI_{Clamp}$   $10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} / [\mu U/mL]$ ) assessed by the hyperinsulinemic-euglycemic clamp, and total fat mass (kg) measured by DXA, on the basis of a multiple linear regression model ( $n = 112$ ) adjusted for the covariates sex, age, and total lean mass in African Americans ( $n = 55$ ; black dots and line) and Caucasian Americans ( $n = 57$ ; white dots and dashed line). \* $P = 0.01$  significant race  $\times$  total fat interaction,  $P < 0.01$  (overall model),  $R^2 = 50\%$ . A higher total fat mass was more strongly associated with a lower  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.15$ ,  $SE = 0.03$ ,  $P < 0.001$ ,  $R^2 = 43\%$ ) than in African Americans ( $\beta = -0.04$ ,  $SE = 0.02$ ,  $P = 0.03$ ,  $R^2 = 28\%$ ).

$SE = 0.47$ ,  $P = 0.01$ ,  $R^2 = 42\%$ ), and was strengthened in the latter model.

There was also a significant race  $\times$  liver fat interaction ( $P = 0.007$ ,  $R^2 = 52\%$ ; **Figure 4**). Liver fat was inversely associated with  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.08$ ,  $SE = 0.03$ ,  $P = 0.02$ ) but not in African Americans ( $\beta = 0.005$ ,  $SE = 0.03$ ,  $P = 0.87$ ). The race-specific models that included liver fat explained 49% of the variance in

$SI_{Clamp}$  in Caucasian Americans, compared with 28% in African Americans.

The association between HOMA2-IR as a proxy for hepatic insulin resistance and liver fat was also investigated using multiple linear regression. There was a significant race  $\times$  liver fat ( $P = 0.03$ ,  $R^2 = 46\%$ ; **Figure 5**) interaction. Greater liver fat was associated with higher HOMA2-IR in Caucasian Americans ( $\beta = 0.03$ ,  $SE = 0.01$ ,  $P < 0.001$ ) but not in African Americans

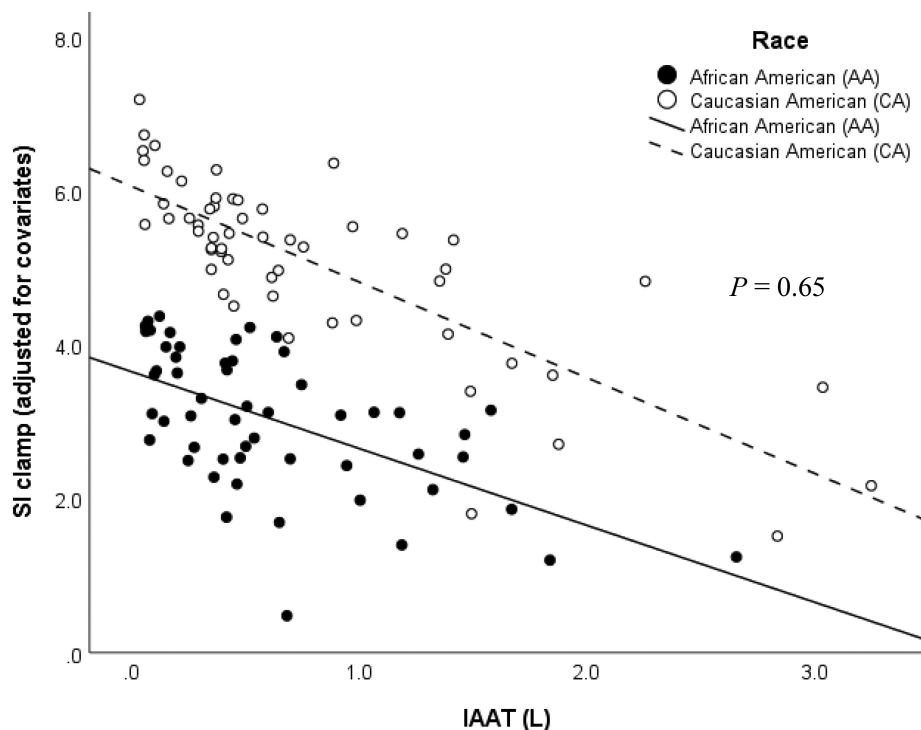
**TABLE 2** Multiple linear regression of subcutaneous abdominal adipose tissue on skeletal muscle insulin sensitivity by race

	$R^2$	$\beta$	SE	$P$ value for $\beta$
Model I: African Americans ( $n = 55$ )	44%			
Sex		-0.009	0.54	0.99
Age, y		0.001	0.02	0.97
Total lean mass, kg		-0.03	0.02	0.22
Leg fat, kg		0.11	0.05	<b>0.03</b>
SAAT, L		-0.45	0.11	<b>&lt;0.001</b>
Model II: Caucasian Americans ( $n = 56$ )	36%			
Sex <sup>1</sup>		3.20	0.93	<b>0.001</b>
Age, y		0.05	0.04	0.18
Total lean mass, kg		0.09	0.05	0.06
Leg fat, kg		-0.23	0.14	0.12
SAAT, L		-0.42	0.30	0.17

Significant race  $\times$  SAAT interaction ( $P = 0.047$ ,  $R^2 = 47\%$ ) in overall model. Boldface type indicates predictors with significant  $P$  values in race-specific models.

<sup>1</sup>Males coded as 0, females coded as 1.

$SI_{Clamp}$ , skeletal muscle insulin sensitivity assessed by the hyperinsulinemic-euglycemic clamp, SAAT, subcutaneous abdominal adipose tissue.



**FIGURE 3** Relation between skeletal muscle insulin sensitivity ( $SI_{Clamp}$   $10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} (\mu U/mL)$ ) assessed by the hyperinsulinemic-euglycemic clamp, and intra-abdominal adipose tissue (IAAT [L]) measured by MRI, on the basis of a multiple linear regression model ( $n = 111$ ) adjusted for the covariates sex, age, and total lean and total fat mass in African Americans ( $n = 55$ ; black dots and line) and Caucasian Americans ( $n = 56$ ; white dots and dashed line).  $P = 0.65$  (race  $\times$  IAAT interaction),  $P < 0.01$  (overall model),  $R^2 = 50\%$ . IAAT, intra-abdominal adipose tissue.

( $\beta = -0.004$ ,  $SE = 0.01$ ,  $P = 0.80$ ). The race  $\times$  leg fat interaction that included liver fat explained 64% of the variance in HOMA2-IR in Caucasian Americans, compared with 25% in African Americans.

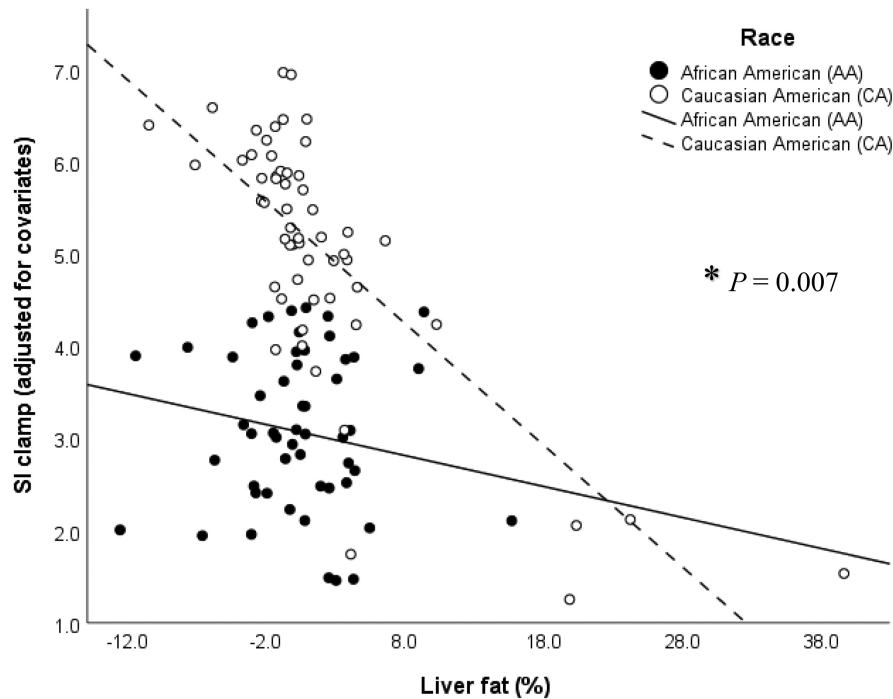
The race  $\times$  leg fat interaction was significant ( $P = 0.009$ ,  $R^2 = 42\%$ ; **Table 3**). Higher leg fat was associated with a lower  $SI_{Clamp}$  ( $\beta = -0.39$ ,  $SE = 0.08$ ,  $P < 0.001$ ,  $R^2 = 34\%$ ) in Caucasian Americans, but not in African Americans ( $\beta = -0.05$ ,  $SE = 0.04$ ,  $P = 0.23$ ,  $R^2 = 23\%$ ). In these race-specific models, a higher total lean mass was associated with a lower  $SI_{Clamp}$  in African Americans ( $\beta = -0.05$ ,  $SE = 0.03$ ,  $P = 0.04$ ) but not in Caucasian Americans ( $\beta = 0.08$ ,  $SE = 0.05$ ,  $P = 0.10$ ). The race  $\times$  leg fat interaction remained significant ( $P = 0.02$ ,  $R^2 = 51\%$ ) when SAAT and IAAT were added as covariates to the model to assess the effect of lower body relative to upper-body fat distribution on  $SI_{Clamp}$  (**Table 4**). In the models with SAAT and IAAT, higher leg fat was associated with a higher  $SI_{Clamp}$  in African Americans ( $\beta = 0.11$ ,  $SE = 0.05$ ,  $P = 0.02$ ,  $R^2 = 46\%$ ), but a lower  $SI_{Clamp}$  ( $\beta = -0.28$ ,  $SE = 0.14$ ,  $P = 0.049$ ,  $R^2 = 42\%$ ) in Caucasian Americans. Further, in these models, IAAT was inversely associated with  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -1.16$ ,  $SE = 0.53$ ,  $P = 0.04$ ), but not African Americans ( $\beta = -0.53$ ,  $SE = 0.40$ ,  $P = 0.19$ ), and SAAT was inversely associated with  $SI_{Clamp}$  in African Americans ( $\beta = -0.41$ ,  $SE = 0.11$ ,  $P < 0.001$ ) but not Caucasian Americans ( $\beta = -0.08$ ,  $SE = 0.33$ ,  $P = 0.81$ ).

The race  $\times$  total lean mass interaction was not significant ( $P = 0.54$ ,  $R^2 = 47\%$ ; **Figure 6**) and the difference between the intercepts was not statistically significant ( $P = 0.91$ ).

## Discussion

The results of this study demonstrate that different metrics of adiposity and regional fat are differentially associated with insulin sensitivity in healthy African Americans and Caucasian Americans. Specifically, measures of overall adiposity were more strongly associated with  $SI_{Clamp}$  in Caucasian Americans, whereas body fat distribution and lean mass showed stronger correlations with  $SI_{Clamp}$  in African Americans. These observations resolve discrepancies in the literature regarding race differences in insulin sensitivity and suggest that development of race-specific preventive and therapeutic strategies may reduce the racial disparity in diabetes prevalence.

A key finding of this study was that higher total adiposity, reflected in total fat mass and BMI, was more strongly associated with a lower  $SI_{Clamp}$  in Caucasian Americans compared with African Americans. Examination of the significant race  $\times$  BMI interaction showed that for participants with  $BMI \leq 33$ ,  $SI_{Clamp}$  was lower in African Americans. However, for participants with  $BMI > 33$ ,  $SI_{Clamp}$  was similar in both races. Although a limited number of Caucasian Americans had  $BMI > 33$ , these results are corroborated by prospective data from a 16-wk controlled, weight loss intervention study that showed insulin sensitivity is similar between races among overweight individuals both before and after weight loss, but lower in African Americans compared with Caucasian Americans among never obese, lean individuals (6, 25). A positive association between adipocyte hypertrophy and insulin resistance has also been reported in insulin-sensitive but not insulin-resistant African American women (26). Collectively,



**FIGURE 4** Relation between skeletal muscle insulin sensitivity ( $SI_{Clamp} 10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} / [\mu U/mL]$ ) assessed by the hyperinsulinemic-euglycemic clamp, and liver fat (%) measured by MRI, on the basis of a multiple linear regression model ( $n = 111$ ) adjusted for the covariates sex, age, and total fat and total lean mass in African Americans ( $n = 54$ ; black dots and line) and Caucasian Americans ( $n = 57$ ; white dots and dashed line). \*  $P = 0.007$  significant race  $\times$  liver fat interaction,  $P < 0.01$  (overall model),  $R^2 = 52\%$ . Liver fat was inversely associated with  $SI_{Clamp}$  in Caucasian Americans ( $\beta = -0.08$ ,  $SE = 0.03$ ,  $P = 0.02$ ,  $R^2 = 49\%$ ) but not in African Americans ( $\beta = 0.005$ ,  $SE = 0.03$ ,  $P = 0.87$ ,  $R^2 = 28\%$ ).

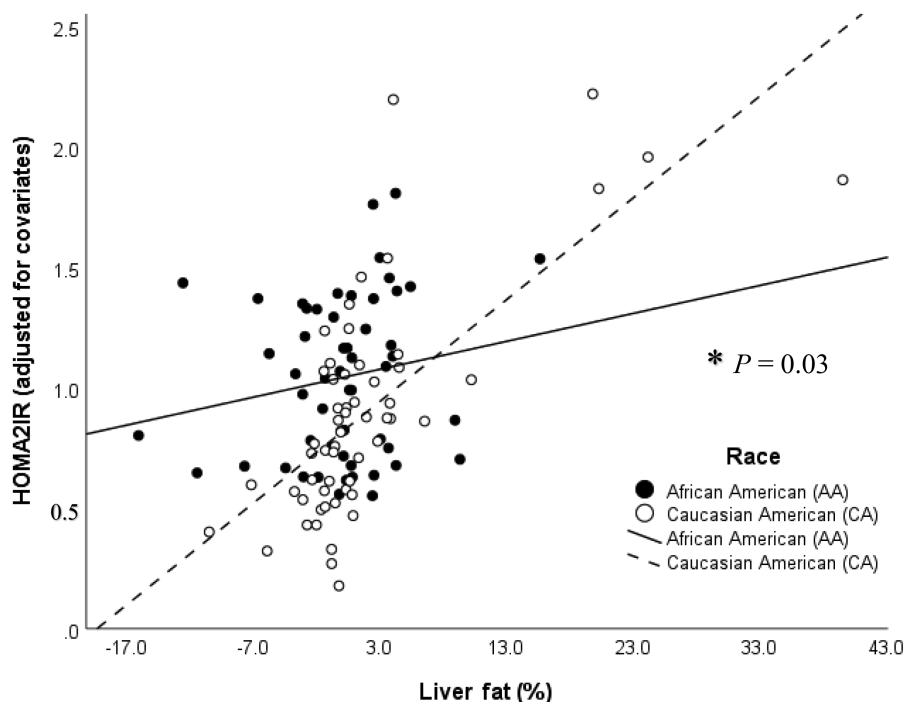
the data imply the existence of a phenotype of insulin resistance in lean African Americans that protects against weight gain, and another of relative insulin sensitivity that predisposes to weight gain (25). Thus, the question of whether insulin sensitivity differs between African Americans and Caucasian Americans depends on the specific phenotype examined and may explain the inconsistent findings from previous research (3–5, 7, 21, 26).

Similar to measures of total adiposity, regional adipose depots explained more of the variance in  $SI_{Clamp}$  in Caucasian Americans than African Americans. A higher SAAT volume was more strongly associated with a lower  $SI_{Clamp}$  in Caucasian Americans compared with African Americans. This is consistent with reports that SAAT (especially deep SAAT) is strongly associated with insulin resistance in predominantly white populations (19, 21). However, controlling for leg fat mitigated the association in Caucasian Americans, suggesting that overall adiposity, whether in central or peripheral depots, is a more significant determinant of  $SI_{Clamp}$  in Caucasian Americans. In contrast, among African Americans, adjustment for leg fat strengthened the inverse association of SAAT with  $SI_{Clamp}$ , indicating that an upper-body fat distribution is a particularly relevant metabolic health measure in this racial group.

Likewise, high leg fat was associated with a lower  $SI_{Clamp}$  in Caucasian Americans but not African Americans. However, when SAAT and IAAT were included, the resulting model explained the most variance in  $SI_{Clamp}$  in African Americans. Leg fat was inversely associated with  $SI_{Clamp}$  in Caucasian Americans but positively associated with  $SI_{Clamp}$  in African Americans suggesting that a peripheral fat distribution is associated with a

higher  $SI_{Clamp}$  in African Americans. In support of this concept, obese black women have lower expression of adipogenic and lipogenic genes in gluteal adipose tissue when compared with obese white women, and this lower gene expression is associated with lower insulin sensitivity (27). Evidence from integrative genetic analyses suggest that insulin resistance occurs as a result of genetically determined defects in adipose differentiation and expansion that manifest as an impaired capacity to store fat in the gluteofemoral region (28). Further, impaired peripheral adipose storage capacity predicts the development of cardiovascular disease and T2D (28). Taken together, these novel findings indicate that African Americans may be particularly sensitive to the development of insulin resistance in response to impaired gluteal adipogenic capacity and the inability to protect against ectopic fat accumulation. Whether this has a genetic basis is unclear and warrants investigation.

Both race groups showed similar inverse associations between IAAT and  $SI_{Clamp}$ , which agrees with the findings of previous studies (4, 26). However, liver fat was inversely associated with  $SI_{Clamp}$  only in Caucasian Americans. African Americans have less liver fat (29) due in part to variations in the PNPLA3 gene (30) and liver fat was not significantly associated with diabetes risk in African Americans (31). Nevertheless, a smaller study showed liver fat was associated with insulin resistance in both races (26). These discrepant findings may be explained by the higher clamp insulin infusion rate in the current study, which is expected to suppress hepatic glucose production (32). In this study, HOMA2-IR was associated with liver fat in Caucasian Americans but not African Americans and liver fat also explained



**FIGURE 5** Relation between homeostasis model of assessment index 2-insulin resistance and liver fat (%) measured by MRI, on the basis of a multiple linear regression model ( $n = 111$ ) adjusted for the covariates sex, age, and total fat and total lean mass in African Americans ( $n = 53$ ; black dots and line) and Caucasian Americans ( $n = 58$ ; white dots and dashed line). \* $P = 0.03$  significant race  $\times$  liver fat interaction,  $P < 0.01$  (overall model),  $R^2 = 46\%$ . Greater liver fat was associated with higher HOMA2-IR in Caucasian Americans ( $\beta = 0.03$ ,  $SE = 0.01$ ,  $P < 0.001$ ,  $R^2 = 64\%$ ) but not in African Americans ( $\beta = -0.004$ ,  $SE = 0.01$ ,  $P = 0.80$ ,  $R^2 = 25\%$ ). HOMA2-IR, homeostasis model of assessment index 2-insulin resistance.

more of the variance in  $SI_{Clamp}$  and HOMA2-IR in Caucasian Americans. Collectively, these findings suggest that liver fat may play a more important role in the development of insulin resistance in Caucasian Americans than African Americans.

Lean mass was inversely associated with  $SI_{Clamp}$  in African Americans but not Caucasian Americans in the model for leg fat. These results extend the findings of previous studies conducted in women that showed greater skeletal muscle volume in African Americans partially accounted for the race difference in insulin resistance (4). This paradoxical finding may be explained by physiological mechanisms intrinsic to skeletal muscle in African Americans. Impaired bioenergetic capacity of skeletal muscle

mitochondria, which is linked to insulin resistance in T2D (33, 34), has been reported in African-American women (35, 36). African Americans have a higher proportion of glycolytic type II myofibers and a lower proportion of oxidative type I myofibers; this fiber composition may affect oxidative capacity and insulin sensitivity (37–42). Taken together, these differences in skeletal muscle physiology may predispose African Americans to the development of insulin resistance and T2D.

Collectively, these results have important implications for the prevention and treatment of insulin resistance and related metabolic conditions amongst individuals of different races. In contrast to measures that merely target overall adiposity,

**TABLE 3** Multiple linear regression of leg fat (kg) on skeletal muscle insulin sensitivity by race

	$R^2$	$\beta$	SE	$P$ value for $\beta$
Model I: African Americans ( $n = 55$ )	23%			
Sex		-0.23	0.62	0.71
Age, y		0.11	0.02	0.59
Total lean mass, kg		-0.05	0.03	<b>0.04</b>
Leg fat, kg		-0.05	0.04	0.23
Model II: Caucasian Americans ( $n = 57$ )	34%			
Sex <sup>1</sup>		3.3	0.93	<b>0.01</b>
Age, y		0.05	0.03	0.19
Total lean mass, kg		0.08	0.05	0.10
Leg fat, kg		-0.39	0.08	<b>&lt;0.001</b>

Significant race  $\times$  leg fat interaction ( $P = 0.009$ ,  $R^2 = 42\%$ ) in overall model. Boldface type indicates predictors with significant  $P$  values in race-specific models.

<sup>1</sup>Males coded as 0, females coded as 1.



**TABLE 4** Multiple linear regression of leg fat (kg) on skeletal muscle insulin sensitivity by race, with subcutaneous abdominal adipose tissue and intra-abdominal adipose tissue as covariates

	$R^2$	$\beta$	SE	$P$ value for $\beta$
Model I: African Americans ( $n = 55$ )	46%			
Sex		-0.19	0.55	0.73
Age, y		0.02	0.02	0.44
Total lean mass, kg		-0.02	0.02	0.34
Leg fat, kg		0.11	0.049	<b>0.02</b>
SAAT, L		-0.41	0.11	<b>&lt;0.001</b>
IAAT, L		-0.53	0.40	0.19
Model II: Caucasian Americans ( $n = 56$ )	42%			
Sex <sup>1</sup>		2.44	0.97	<b>0.02</b>
Age, y		0.08	0.04	<b>0.03</b>
Total lean mass, kg		0.09	0.05	0.05
Leg fat, kg		-0.28	0.14	<b>0.049</b>
SAAT, L		-0.08	0.33	0.81
IAAT, L		-1.16	0.53	<b>0.04</b>

Significant race  $\times$  leg fat interaction ( $P = 0.02$ ,  $R^2 = 51\%$ ) in overall model. Boldface type indicates predictors with significant  $P$  values in race-specific models.

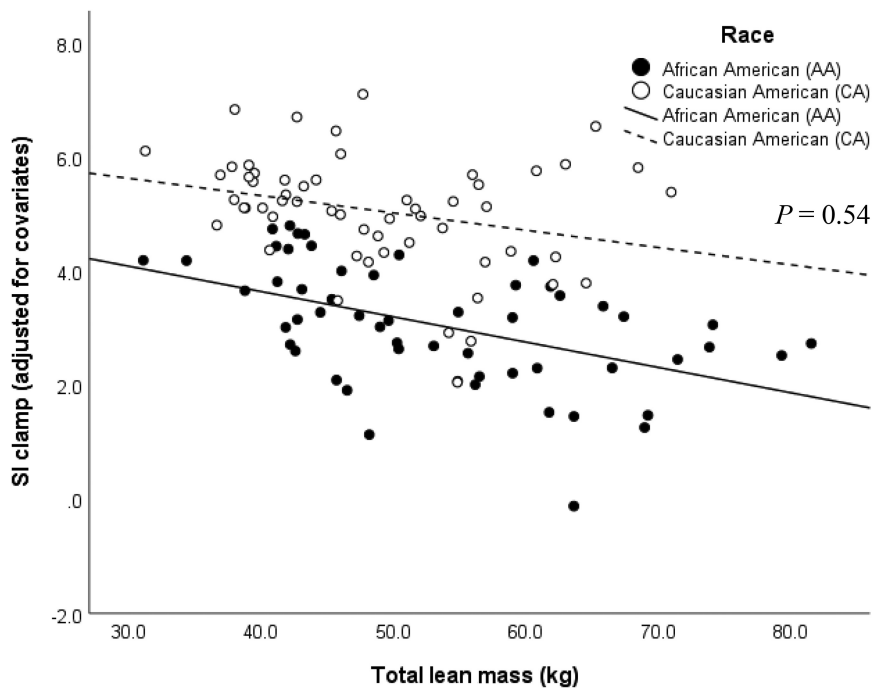
<sup>1</sup>Males coded as 0, females coded as 1.

IAAT, intra-abdominal adipose tissue; SAAT, subcutaneous abdominal adipose tissue.

strategies that promote a redistribution of adipose by reducing ectopic fat and promoting peripheral fat deposition are likely to be more beneficial to African Americans. Emerging evidence shows a carbohydrate-restricted diet produced preferential loss of IAAT and intermuscular adipose tissue compared with a eucaloric low-fat diet in women with polycystic ovary syndrome (43). Future research should examine whether these improvements in body fat distribution occur to a greater extent in African Americans.

Clinical studies should also assess the effects of thiazolidinediones on body fat distribution and insulin sensitivity in African Americans. These insulin-sensitizers affect fat metabolism by activating PPAR $\gamma$ , causing adipose tissue remodeling by promoting adipocyte differentiation and peripheral adipose expansion (44).

Important strengths of this study include the assessment of insulin sensitivity using the hyperinsulinemic-euglycemic clamp and assessment of fat distribution using MRI techniques in



**FIGURE 6** Relation between skeletal muscle insulin sensitivity ( $SI_{Clamp} \cdot 10^{-4} \cdot dL \cdot kg^{-1} \cdot min^{-1} / [\mu U/mL]$ ) assessed by the hyperinsulinemic-euglycemic clamp, and total lean mass (kg) measured by DXA, on the basis of a multiple linear regression model ( $n = 112$ ) adjusted for the covariates sex, age, and total fat mass in African Americans ( $n = 55$ ; black dots and line) and Caucasian Americans ( $n = 57$ ; white dots and dashed line).  $P = 0.54$  (race  $\times$  total lean mass interaction),  $P < 0.01$  (overall model),  $R^2 = 47\%$ .

a biracial cohort of lean, overweight, and obese men and women. However, the cross-sectional nature of the study does not establish causality.

In conclusion, overall adiposity was significantly associated with  $SI_{Clamp}$  in Caucasian Americans, whereas body fat distribution and lean mass showed stronger associations with  $SI_{Clamp}$  in African Americans. Research is needed to determine if specific insulin resistance phenotypes have a genetic basis in both African Americans and Caucasian Americans, and how best to intervene in a phenotype-specific manner to minimize the development of metabolic disease.

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The authors' contributions were as follows—JT and BAG: had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; JT and BAG: analysis and interpretation of data, drafting of the manuscript; all authors: study concept and design, critical revision of the manuscript for intellectual content, read and approved the final manuscript. Obtained funding: AMG, TWG, MEL, MJQ, GF, and BAG. None of the authors reported a conflict of interest related to this study.

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