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In non-obese girls waist circumference predicts insulin resistance is comparably to MRI fat measures and superior to BMI

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Abstract

Objective—To investigate the degree to which waist circumference (WC), BMI, and MRI measured abdominal fat deposition predict insulin resistance (IR) in non-obese girls of diverse racial and ethnic backgrounds.

Methods—Fifty-seven non-obese girls (12 African-American, 16 Hispanic White and 29 non-Hispanic White girls), aged 11–14 years old were assessed for WC, MRI hepatic proton density fat fraction, visceral and subcutaneous adipose tissue volume, BMI Z-score, fasting insulin, HOMA-IR, adiponectin, leptin, sex hormone binding globulin, HDL cholesterol, and triglycerides.

Results—Univariate and multivariate analyses adjusted for race and ethnicity indicated that only WC and visceral adipose tissue volume were independent predictors of fasting insulin and HOMA-IR, while dependent predictors were hepatic proton density fat fraction, BMI Z-score, and subcutaneous adipose tissue volume. Hispanic White girls showed significantly higher mean fasting insulin, HOMA-IR, and lower sex hormone binding globulin than non-Hispanic White girls (p-value <0.01).

Conclusions—In non-obese girls of diverse racial and ethnic backgrounds, WC, particularly when adjusted for race or ethnicity, is an independent predictor of IR comparable to MRI-derived measurements of fat and superior to BMI Z-score.

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Keywords

Ethnicity; Race; Non-obese; HOMA-IR; Waist Circumference; MRI

Introduction

Comorbidity rates related to obesity, most notably type 2 diabetes mellitus, have increased in parallel to rises in pediatric obesity during past decades and are incurring profound health and economic burdens. In the U.S., approximately 3,700 youth are diagnosed with type 2 diabetes mellitus (T2DM) annually (1). Importantly, youth with T2DM exhibit more rapid deterioration of beta cell function than older adults, and often develop significant cardiovascular morbidity and mortality in the 3rd decade of life (2, 3). These findings highlight the need for reliable and cost-effective methods to identify youth at greatest risk for metabolic consequences of obesity. Currently, there is lack of consensus whether body mass index (BMI), waist circumference (WC), or another anthropometric measure provides a superior screening approach (4, 5). Development of consensus is complicated by evidence that the metabolic effects exerted by a given amount of fat vary with race and ethnicity (6, 7), and that WC and BMI fail to directly quantify site-specific fat deposition.

While WC and BMI are easily obtained estimates of adiposity, magnetic resonance imaging (MRI), can evaluate and quantify fat deposition with high accuracy and at specific anatomic sites. In obese adolescents, MRI demonstrates higher levels of visceral adipose tissue (VAT) and hepatic fat in subjects of Hispanic and European descent compared to those of African descent despite similar overall body fat percentage (8, 9). These imaging results suggest that racial and ethnic patterns of fat deposition may contribute to racial and ethnic disparities in rates and pathophysiology of T2DM and other metabolic disease (10). Importantly, these racial or ethnic tendencies for deleterious fat deposition can be detected at lower levels of accrued fat (11). For example, non-obese Hispanic adolescent girls exhibit higher levels of hepatic fat measured by MRI, with tighter correlations between insulin resistance (IR) and hepatic fat than non-obese, non-Hispanic white peers (7).

With its ability to accurately and rapidly quantify fat without the use of ionizing radiation, MRI holds promise for accurately defining pathologic connections between compartmentalization of fat deposition and metabolic health. However, MRI currently remains an impractical clinical screening tool. Instead, prevention and early intervention strategies are better served by clinically available measures that can identify those at risk for adverse metabolic effects of excess fat who should receive further laboratory or imaging. This study, innovative in its focus on non-obese girls of African-American (AA), Hispanic (H), and non-Hispanic white (NHW) ancestry, investigates whether anthropometric measures (i.e. WC and BMI Z-score) provide metabolic risk assessment comparable in value to MRI derived measurements of fat deposition (VAT, subcutaneous adipose tissue [SCAT], and hepatic proton density fat fraction [hepatic PDFF]).

Methods

Study Population

Non-obese female students who attended a local middle school fall registration were invited to participate in this cross-sectional study. Once written consent and assent were obtained for the HIPAA compliant and IRB approved study, personal and family medical history, and self-identified race and ethnicity (per NIH race and ethnicity criteria for subjects in clinical research) were collected at registration. Individuals of Asian descent were not included. Height was measured using a stadiometer and recorded to the nearest 0.5 cm. Waist circumference was measured twice and recorded to the nearest 1mm just above the iliac crests with Graham-Field® cloth woven measuring tape. Weight was measured without shoes in light clothes on a beam balance platform scale to the nearest 0.1 kg. BMI was then calculated. Self-assessment of Tanner staging for breast and pubic hair was performed (12). Study entrance criteria included a non-obese BMI percentile of < 90th percentile per CDC 2000 sex- and age-specific BMI growth charts and age 11–14 years old. Based on family self-identification, subjects were allocated to Hispanic White (H) or non-Hispanic White (NHW) or African American (AA) groups. To ensure recruitment of a non-obese study group, we set the upper limit for BMI percentile at the 90th percentile, rather than 95th. Exclusion criteria included: BMI greater than the 90th percentile for age and gender, Type 1 or Type 2 diabetes mellitus, chronic diseases (including infectious or inflammatory diseases), treatment with glucose metabolism altering (e.g. metformin) or lipid altering (e.g. statin) agents, or pregnancy.

Laboratory

Venipuncture was performed in the early morning after an overnight fast. Blood was processed immediately and analyzed at the University of Wisconsin Hospital and Clinics Laboratory for glucose, insulin, luteinizing hormone, estradiol, sex hormone binding globulin (SHBG), HDL cholesterol, and triglycerides. Glucose was determined by hexokinase method; insulin, luteinizing hormone, and estradiol by chemiluminescent immunoassay; triglycerides by enzymatic assay; HDL with direct homogeneous measures (University of Wisconsin Hospital and Clinics Laboratory, Madison, WI); and SHBG was measured by a quantitative electrochemiluminescent immunoassay (ARUP Laboratories, Salt Lake City, UT). A portion of the sample was analyzed at the University of Wisconsin National Primate Research Center for adiponectin and leptin by radioimmunoassay (Linco-Millipore, St. Charles, MO) both run per kit protocols. Homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated from fasting glucose (mg/dL) and insulin (μ U/ml) values: $(\text{fasting glucose} \times \text{fasting insulin}/405)$. Quantitative magnetic resonance imaging was performed at the Wisconsin Institute for Medical Research (WIMR). The Human Subjects Committee of the University of Wisconsin IRB approved all procedures.

Image Acquisition and Reconstruction

Volumetric 3D quantitative magnetic resonance imaging (MRI) was performed using a clinical 3 Tesla scanner (MR750, GE Healthcare, Waukesha, WI) and a 32-channel phased array body coil (Neocoil, Pewaukee WI), and all image acquisition and reconstruction was performed using established and accepted protocols (13–21). All images were determined

using an investigational version of a confounder-corrected chemical shift encoded water-fat separation method (3D-IDEAL-SPGR) (13, 22). Two acquisitions were performed, including a sagittal 3D volume that covered from the liver dome to the pelvic floor (to quantify VAT and SCAT), and an axial 3D volume covering the liver to quantify hepatic PDFF. Acquisition parameters for the sagittal acquisition included: a single sagittal slab with 6 echoes- first echo time/echo spacing = 0.8/1.2ms, echo train length = 6 (1shot), flip angle/repetition time/bandwidth = $3^\circ/9\text{msc}/\pm 167\text{kHz}$, field of view = $48\times 38\times 47\text{cm}$, matrix size = $148\times 118\times 156$. True spatial resolution = $3.2\times 3.2\times 3\text{mm}^3$, interpolated to $1.9\times 1.9\times 1.5\text{mm}^3$ through zero-filling. Scan time = 26s. The axial acquisition included a single sagittal slab with 6 echoes- first echo time/echo spacing = 1.2/2.0ms, echo train length = 6 (2 shots of 3 echoes), flip angle/repetition time/bandwidth = $3^\circ/8.3\text{msc}/\pm 125\text{kHz}$, field of view = $44\times 40\times 22\text{cm}$, matrix size = $230\times 160\times 14$, Spatial resolution = $1.7\times 1.7\times 8\text{mm}^3$, 2D parallel imaging (ARC) with $R=2.86$. Scan time = 23s. For both acquisitions, separated water-only and fat-only images, as well as quantitative hepatic PDFF maps (23) were calculated using an automated on-line reconstruction algorithm. The acquisition and reconstruction are designed to avoid or correct for all known confounders, including spectral modeling of fat (24), corrects for eddy currents (15), T1 bias (25), T2* decay (16), and noise related bias (25). Because all known confounders have been addressed, the resulting PDFF map provides an accurate and fundamental measure of the fat concentration in tissue (13, 26).

Hepatic PDFF was determined by averaging PDFF value measured from 9 regions of interest placed in each of the 9 Couinaud segments of the liver (22, 27). Hepatic steatosis was defined as PDFF >5.56% (19).

Manual VAT and SCAT quantification was performed from the L3 to L5 vertebral levels. Segmentation was performed in SliceOmatic v5.0 as follows. Intestinal gas and bowel contents, as well as background voxels were masked prior to application a 45% threshold on the fat fraction images (20). Fat signal near the spine and bone marrow were manually erased.

Statistics

Metabolic lab parameters and subjects' characteristics measured on a continuous scale are presented as means $\pm$ standard deviations and were compared for race and ethnicity groups using analysis of variance. Nonparametric Spearman's rank correlation analysis was performed to evaluate bivariate associations between variables. Categorical variables were compared between groups using Fisher's exact test. Tukey's Honestly Significance Difference (HSD) method was used to control the type I error when conducting multiple comparisons between the three groups. Multivariate analyses were conducted to examine whether BMI Z-score, WC, hepatic PDFF, SCAT and VAT measures predict IR, after adjusting for race and ethnicity. These analyses were conducted for each measure separately. Furthermore, multivariate regression analyses were conducted to identify independent predictors for IR. All potential predictors were included in an initial, non-parsimonious model. The backward and forward selection methods with a selection criterion of $p<0.1$ were then used to determine a parsimonious model which included only significant predictors. The identification of independent predictors was validated using the least

absolute shrinkage and selection operator (LASSO) variable selection method. Fasting insulin concentration and HOMA IR values were log-transformed in the regression analyses to meet the assumption of normality. Statistical inference was performed with maximum likelihood estimation. All statistical analyses were performed with SAS software (version 8.2; SAS Institute, Cary, NC). All *P* values were 2-sided, and *P* values $\leq .05$ were considered statistically significant.

Results

A summary of the characteristics of the 57 subjects (12 AA, 16 H, 29 NHW) is presented in Table 1. There were no statistically significant differences in mean age, BMI Z-score, WC, estradiol levels, or occurrence of menarche among the racial and ethnic groups when adjusting for multiple comparisons. For the unadjusted comparisons significant differences were detected when comparing WC between Hispanics vs. Non-Hispanics ($p=0.029$) and between African Americans vs. Non-Hispanics for LH ($p=0.038$). The significant difference in LH may have been attributable to the presence of an outlier in the AA group. With removal of the subject with a LH of 103.5, the difference was non-significant. Using the CDC 2000 sex- and age-specific BMI growth chart, the mean BMI Z-scores were consistent with mean BMI percentiles at the 63rd percentile in AA subjects, the 64th percentile in H subjects, and the 58th percentile in NHW subjects.

Comparison of the metabolic lab parameters by race and ethnicity, indicated that the H subjects had significantly higher mean fasting insulin ($23.3 \pm 11.9 \mu\text{IU/mL}$ vs. $12.6 \pm 6.14 \mu\text{IU/mL}$, $p=0.002$), higher mean HOMA-IR (5.18 ± 3.20 vs. 2.76 ± 1.42 , $p=0.006$), and lower mean SHBG ($44.0 \pm 24.1 \text{ nmol/L}$ vs. $72.3 \pm 28.6 \text{ nmol/L}$ vs. $p=0.004$) than NHW subjects when adjusted for multiple comparisons (table 2). As shown in table 2, there were no statistically significant differences detected between H and NHW groups for any of the 5 other metabolic parameters (adiponectin, leptin, HDL, and triglycerides), and there were no statistically significant differences between AA and H groups or between AA and NHW groups for any of the 8 metabolic parameters (fasting insulin, HOMA-IR, SHBG, adiponectin, leptin, HDL, and triglycerides) when adjusted for multiple comparisons (table 2).

Overall, moderate to strong correlations of WC with metabolic parameters (fasting insulin, HOMA-IR, triglycerides, SHBG, adiponectin, and leptin) were observed, similar to those seen with VAT and SCAT (table 3). BMI Z-score correlations with metabolic parameters were only significant with fasting insulin, HOMA-IR, SHBG, adiponectin, and leptin (table 3). Waist circumference correlated more strongly with all of these metabolic parameters than BMI Z-score, however, the difference in *r*-values did not reach statistical significance. Figure 1 illustrates the correlations of waist circumference and BMI Z-score with HOMA-IR.

In multivariate analyses, WC, BMI Z-score, Hepatic PDFF, VAT, and SCAT remained statistically significant predictors for fasting insulin and HOMA-IR, after adjusting for race and ethnicity. The partial Spearman's rank correlations for predicting fasting insulin levels

increased substantially for SCAT and VAT from 0.34 and 0.29 to 0.63 and 0.69, respectively, after adjusting for race and ethnicity.

In order to identify independent predictors for fasting insulin and HOMA-IR, multivariate regression analyses were conducted. In the initial non-parsimonious model, WC, BMI Z-score, hepatic PDFF, SCAT, VAT, age and race and ethnicity were included as independent variables the model. The backward and forward selection method was used to identify parsimonious models (See methods). In the parsimonious model, WC ($p=0.012$), VAT ($p=0.0031$) and race and ethnicity (AA vs. NHW, $p=0.0092$; H vs. NHW, $p=0.022$) were identified as statistically significant independent predictors for fasting insulin (table 4). The adjusted R square value for this model was 0.54. Analogously, WC ($p=0.013$), VAT ($p=0.0024$) and ethnicity (H vs. NHW, $p=0.0049$) were identified as statistically significant predictors for HOMA-IR with an adjusted R square value of 0.53 (table 4). There was no statistically significant difference in the slope of the correlation between WC and VAT ($p=0.15$ for fasting insulin and $p=0.16$ for HOMA-IR). These results were confirmed using the lasso variable selection method.

Discussion

In this group of non-obese young females of African-American, Hispanic White, and non-Hispanic White background, WC independently predicted IR to a degree comparable to (i.e. not significantly different from) that of MRI derived VAT and stronger than BMI Z-score. While WC has been previously shown to correlate with MRI measured VAT in both obese and non-obese youth (28), this study adds the novel observation that, at non-obese levels of adiposity defined by BMI percentile, WC predict HOMA-IR and fasting insulin better than BMI Z-score and to a similar degree as MRI derived measures of fat (Hepatic PDFF, VAT, and SCAT).

These results suggest that, in non-obese girls, use of WC alone can improve pediatric risk stratification for IR risk over the current BMI-based approach. Evidence from other studies suggests that inclusion of both WC- and BMI-based measurements improves pediatric risk stratification into general categories of “healthy” and “unhealthy” obesity (5, 29, 30). A key finding of this study is the additional utility of WC in identifying non-obese (by BMI criteria) subjects who are already experiencing adverse health consequences from adiposity. Therefore, greater reliance on assessment of WC, easily obtained in clinical practice, could provide valuable information about a child’s fat distribution and risk for IR. Increasing use of electronic medical records may facilitate incorporation of WC and other anthropometric measures into clinically useful predictive equations (31).

Importantly, the predictive value of WC for fasting insulin and HOMA-IR was increased by racial and ethnic adjustments in the non-obese girls. While admittedly based on relatively few subjects, this finding suggests that adjustment of BMI and/or WC thresholds that would trigger concern for underlying IR based on an individual’s race or ethnicity may be appropriate, since it appears that certain ethnic or racial groups manifest adverse health effects at lower degrees of fat deposition (32, 33). In the US, WC percentile curves based on NHANES data for African-American and Mexican-American youth have greater absolute

raw waist circumferences than White children, so a larger percentage of non-White children may be identified as high risk using WC criteria compared to BMI alone (34).

The waist circumference to height ratio has been proposed as an informative marker of abdominal obesity and metabolic risk because relative to WC or BMI it is more independent of patient age, pubertal status, and gender (35). Further, a waist circumference to height ratio of greater than 0.5 was proposed to define central obesity for all races and ethnicities instead of the use of various BMI or WC thresholds to assess habitus and metabolic risk—a threshold that additionally provides patients with a simple message to keep their WC less than $\frac{1}{2}$ their height (36). However, use of the waist circumference to height ratio, rather than waist circumference, did not improve prediction of IR in our non-obese adolescent cohort (data not shown) and further study is needed in pediatric patients.

A fundamental issue is determining the best anatomic cross-section to measure WC. Interestingly, in youth, WC measurement at 4 different abdominal cross-sections (midpoint between iliac crest and lowest rib, top of the iliac crest, minimal abdominal circumference, and level of the umbilicus) does not affect WC correlations with VAT or fasting glucose and lipids (37). However, a standardized approach to WC measurements would minimize variability, improve reproducibility and thereby increase its clinical and research utility (38). This study, following the technique utilized for generation of the previously mentioned NHANES database, used the top of the iliac crests as markers, which provide bilateral bony landmarks to minimize variability of WC measurement.

This study has potential limitations, beginning with categorization of subjects into broad racial and ethnic groups (which include genetic and cultural heterogeneity among subjects) and inclusion of children with one or more parents with African or Hispanic ancestry into the African-American or Hispanic cohort, respectively. Enrollment for subgroup analysis was relatively small, so that observations describing differences based on race and ethnicity are preliminary and require confirmation with studies of greater numbers of subjects. In addition, whether the findings described here are applicable to male subjects, and adolescents of other races and ethnicities, remains uncertain. Further, future inclusion of subjects with BMI percentiles above the 90th percentile in would be expected to allow increase the level and variability of IR and allow analysis of how evolving obesity affects prediction of IR by BMI-, WC-, and MRI-based measures. In addition, although efforts were made to document similar pubertal maturation between groups (based on self-assessment and estradiol levels), variations in pubertal status could remain a potential confounding factor, given important effects of puberty on IR (39). Additionally, although verification of Tanner staging by a medical provider would have confirmed staging assessment, formal evaluation was not performed given the potential for reduced enrollment that mandatory physical examination would have created. Further, while fasting indices used in this study correlate closely with OGTT in assessing IR in obese adolescents (40), oral glucose tolerance testing (OGTT) may yield IR assessments more closely aligned with gold-standard hyperinsulinemic-euglycemic clamp testing. Strengths of this study include analysis of children of different races and ethnicities, and use of advanced quantitative MRI methods to quantify fat deposition and correlate with standard laboratory markers of IR. An additional strength was the unique focus on non-obese subjects from diverse racial and ethnic

backgrounds (mean BMI Z-scores at the 63rd, 64th, and 58th percentiles for the African American, Hispanic, and non-Hispanic white, respectively).

Conclusion

Waist circumference measurement is an informative and inexpensive risk stratification tool for IR in children, even before progression of adiposity into obesity as defined by BMI percentile. Specifically, in a cohort of non-obese girls, waist circumference predicted IR better than BMI Z-score and to a similar extent as quantitative MRI measurements of fat. Additionally, WC and MRI VAT independently predicted IR, and this prediction was further strengthened when racial and ethnic background was taken into account. The fact these findings were evident in a cohort of non-obese adolescent girls strengthens the concept that adverse metabolic changes can occur early in the course of fat deposition, making early detection and promotion of healthy physical activity and nutrition of at-risk but still non-obese children paramount, particularly since obesity prevalence rises sharply during early grade school (41).

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Abbreviations

AA	African American
BMI	body mass index
H	Hispanic
Hepatic PDFF	hepatic proton density fat fraction
HDL	high density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
IR	insulin resistance
MRI	magnetic resonance imaging
NHW	non-Hispanic White
T2DM	type 2 diabetes mellitus
SCAT	subcutaneous adipose tissue
SHBG	sex hormone binding globulin
VAT	visceral adipose tissue
WC	waist circumference

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Figure 1.
Correlations of Waist Circumference and BMI Z-score with HOMA-IR in non-obese girls.

Table 1

Characteristics of Study Participants

	African-American (AA)	Hispanic (H)	Non-Hispanic White (NHW)
Number of Subjects	12	16	29
Age (years)	12.41±0.91	12.40±1.03	12.57±1.17
BMI Z-score	0.34±0.98	0.36 ±0.70	0.21 ±0.67
Waist Circumference (cm)	69.05±6.12	75.50±10.66	65.15±15.66
Estradiol (pg/mL)	77.46±92.82	68.00±86.86	49.76±34.00
Luteinizing Hormone (mIU/mL)	14.85±29.57	6.15±8.08	4.37±4.13
Self-Assessed Breast Tanner Stage	33% (4/12)	25% (4/16)	24% (7/29)
Percent post-menarchal	31% (4/13)	56% (9/16)	52% (14/29)

No significant racial or ethnic differences among groups in above variables, with all p-values >0.05 when comparisons of ethnic and racial groups means were adjusted for multiple comparisons using Tukey's Honestly Significance Difference method.

Table 2

Metabolic Parameters of Study Participants

	African-American (AA)	Hispanic (H)	Non-Hispanic White (NHW)
Fasting Insulin (μIU/mL)	19.15±11.76	23.25±11.90*	12.62±6.14*
HOMA-IR	4.07±3.06	5.18±3.20*	2.76±1.42*
SHBG (nmol/L)	58.00±26.67	44.00±24.10*	72.31±28.64*
Adiponectin (μg/mL)	13.90±2.97	13.23±6.66	14.74±6.53
Leptin (ng/mL)	13.37±5.67	11.68±6.90	9.03±5.04
HDL (mg/dL)	53.15±8.69	52.00±10.25	53.14±13.88
Triglycerides (mg/dL)	67.31±24.44	87.75±39.28	77.66 ±23.42

* Significant difference (p-value < 0.01) in mean fasting insulin, HOMA-IR, and SHBG between H and NHW groups; otherwise, no significant differences among racial and ethnic group means with all p-values >0.05 when adjusted for multiple comparisons using Tukey's Honestly Significant Difference method. SHBG, sex hormone binding globulin.

Table 3

Correlations of Waist Circumference, BMI Z-score, Hepatic PDFF, VAT, and SCAT with Metabolic Parameters for All Study Participants (n=57)

	WC (cm)	BMI Z-score	Hepatic PDFF	VAT	SCAT
Fasting Insulin (μIU/mL)	r=0.49**	r=0.31*	NS	r=0.41**	r=0.54**
HOMA-IR	r=0.49**	r=0.29*	NS	r=0.43**	r=0.54**
SHBG (nmol/L)	r=-0.55**	r=-0.30*	r=-0.54**	r=-0.37**	r=-0.69**
Adiponectin (μg/mL)	r=-0.41**	r=-0.34*	NS	r=-0.36**	r=-0.31**
Leptin (ng/mL)	r=0.66**	r=0.50**	r=0.3*	r=0.28**	r=0.71**
HDL (mg/dL)	r=-0.36**	NS	NS	r=-0.37**	r=-0.38**
Triglycerides (mg/dL)	r=0.35**	NS	NS	r=0.39**	r=0.28*

* p-value 0.05,

** p-value 0.01,

NS = p-value not significant.

WC, waist circumference; PDFF, proton density fat fraction, VAT, visceral adipose tissue; SCAT, subcutaneous adipose tissue; NS, not significant; SHBG, sex hormone binding globulin.

Table 4
 Parsimonious multivariate model for Waist Circumference and VAT (adjusted for race and ethnicity)

	Fasting Insulin			HOMA IR		
	β (SE)	p-value	R ²	β (SE)	p-value	R ²
Waist Circumference	0.013 (0.005)	0.012	0.54	0.013 (0.005)	0.013	0.53
VAT	0.005 (0.002)	0.0031		0.006 (0.002)	0.0024	
Race/Ethnicity						
AA vs. NHW	0.41 (0.15)	0.0092		0.31 (0.16)	0.057	
H vs. NHW	0.39 (0.12)	0.022		0.37 (0.13)	0.0049	
AA vs. H	0.02 (0.16)	0.898		−0.06 (0.17)	0.717	

β slope parameter (non-standardized); SE, standard error; R², coefficient of determination; PDFF, proton density fat fraction, VAT, visceral adipose tissue; SCAT, subcutaneous adipose tissue; AA, African American; NHW, non-Hispanic White; H, Hispanic.