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ORIGINAL ARTICLE

Epidemiology/Genetics

Predictability of genetic risk score for insulin resistance is influenced by both BMI and race

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Abstract

Objective: The study objective was to determine whether associations between a genetic risk score (GRS) for insulin resistance (IR) and measures of insulin sensitivity differ by race and/or BMI status in African American (AA) and European American (EA) adults without diabetes.

Methods: Fifty-three AA and 54 EA participants were classified into "high" or "low" BMI groups using the sample median (25.9 kg/m^2) as the cut point. The GRS was derived from 52 previously identified genetic variants. Skeletal muscle insulin sensitivity was measured with the hyperinsulinemic-euglycemic clamp. The homeostasis model assessment of insulin resistance (HOMA-IR) and the Matsuda index of insulin sensitivity were calculated from oral glucose tolerance test values to determine hepatic and whole-body insulin sensitivity, respectively. Linear regression models, stratified by race, assessed interactions between BMI status and GRS on measures of insulin sensitivity.

Results: In EA participants, associations of GRS with HOMA-IR and the Matsuda index differed by BMI status, where the GRS was associated with IR in the high-BMI group only. In AA participants, associations from the clamp differed by BMI status, but an association was observed only in the low-BMI group.

Conclusions: These results highlight the heterogeneity of IR and support the hypothesis that the relationship between genetic predisposition for IR and obesity is race- and tissue-specific.

INTRODUCTION

In the United States, African Americans (AA) are at greater risk for type 2 diabetes (T2D) compared to European Americans (EAs). The reason for this disparity is not completely clear but is believed to have a strong genetic component [1], possibly relating to insulin resistance (IR), a major pathophysiological contributor to the development of T2D [2]. Multiple studies have identified that AA populations have lower whole-body insulin sensitivity relative to EA populations [3–7], predominantly due to lower skeletal muscle insulin sensitivity [6].

A previous genome-wide association study in a European cohort was used to generate a genetic risk score (GRS) for IR [2]. This earlier study used genetic data from 188,577 individuals to identify genomic regions that were associated with fasting insulin adjusted for BMI and circulating concentrations of high-density lipoprotein cholesterol and triglycerides. Fasting insulin was adjusted for BMI in order to

establish the genetic variants contributing to IR independent of adiposity. The resulting 53 single-nucleotide polymorphisms (SNPs) were individually weighted using an inverse-variance method and then combined into a polygenic risk score, where a greater GRS was indicative of higher genetic risk for IR. The GRS was then validated against values from both the euglycemic clamp and the oral glucose tolerance test (OGTT), and then analyzed to identify associations between the 53 loci and phenotypic metabolic traits. Individuals with higher risk scores were phenotypically characterized by a lower BMI and percentage body fat, specifically in the leg area, and had an elevated risk of incident T2D. Although this risk score might provide insight into the greater prevalence of T2D in the AA population in the United States, the utility of the risk score has not been tested in populations outside of Europe.

Therefore, the purpose of this study was to examine the association of the 53-SNP GRS with direct and surrogate measures of insulin sensitivity/resistance in a population of AA and EA adults in the United States. We tested the hypothesis that the risk score would be associated with direct and surrogate measures of insulin sensitivity/resistance in a U.S. population, particularly in AA populations, who as a group are at elevated risk of T2D. Because obesity affects insulin sensitivity, we stratified the analyses by high versus low BMI status as well as by race.

Study Importance

What is already known?

- African Americans are at higher risk of developing type 2 diabetes compared to European Americans for reasons that are not clear, but genetic contributions have been identified.
- A previously published genome-wide association study in a European cohort derived a genetic risk score from 53 variants associated with insulin resistance, where greater genetic risk was associated with lower adiposity.

What does this study add?

- Genetic risk for insulin resistance may manifest in lean African Americans and in European Americans with overweight/obesity.
- BMI status may differentially impact the link between genetic risk for insulin resistance and measured insulin sensitivity within and between races.

How might these results change the direction of research or the focus of clinical practice?

- Results from this study might be used to improve screening criteria and potentially reduce the racial disparity in type 2 diabetes risk.

METHODS

Participants and data collection

Participants were 53 AA and 54 EA men and women aged 19 to 45 years without T2D who were part of a cross-sectional study investigating the roles of obesity and body fat distribution in the etiology of IR [3]. Race was self-reported; genetic admixture analysis was also conducted. For the cross-sectional study, individuals who were sedentary to moderately active (<2 h/week of moderate exercise) and weight stable over the past 6 months (no changes in body weight >2.67 kg [5 lb]) were recruited by public advertisement. Recruited individuals were screened for diabetes with a 2-h OGTT, and those with a 2-h glucose level ≥200 mg/dL were excluded from participation. Additional exclusion criteria were as follows: (1) current tobacco use; (2) participation in unusual dietary practices (e.g., low-carbohydrate diets); (3) oral contraceptive use; (4) use of medications affecting glucose or lipid metabolism or energy expenditure; (5) use of antihypertensive agents impacting glucose tolerance (e.g., thiazide diuretics at doses >25 mg/day, angiotensin-converting enzyme inhibitors); and (6) women with an irregular menstrual cycle or who were pregnant, lactating, or postmenopausal. The analytic sample for the current study included only participants with genotypic, body composition, and insulin sensitivity data.

Data were collected from 2013 to 2018 at the core facilities of the Center for Clinical and Translational Science, Nutrition Obesity Research Center, and Diabetes Research Center at the University of Alabama at Birmingham. Female participants were tested during the follicular phase of the menstrual cycle. This study was approved by the University of Alabama at Birmingham Institutional Review Board, and all participants provided written and informed consent.

Genotyping and polygenic risk score

DNA was extracted from whole blood samples. Genotyping was performed with the Infinium Global Screening Array version 3.0 (Illumina Inc., San Diego, CA) at the Genomics Center at the University of Minnesota. Genotypes were called using Illumina GenomeStudio software. Imputation was performed with the University of Michigan Imputation Server and TOPMED panel. All SNPs were imputed with high quality (r^2 values >0.95). Filtering, quality control, and GRS calculations were performed in PLINK (version 1.9) [8]. Participants with a call rate of <90% were excluded from all analyses.

The weighted GRS was derived from 52 of the 53 single SNPs previously identified by Lotta et al. [2] as associated with IR (Table S1) and weighted for clamp-measured insulin sensitivity. These 52 SNPs included variants from all five original putative effector genes (*IRS1*, *L3MBTL3*, *FAM13A*, *DNAH10*, and *CCDC92*) that have been suggested to heavily contribute to the predictability of the risk score. SNP weights were obtained from published summary-level data [9]

accessed via the Type 2 Diabetes Knowledge Portal [10]. The GRS was calculated by multiplying each SNP's genotype dosage by its weight and standardized per allele.

Assessment of insulin sensitivity/resistance

Assessments for insulin sensitivity/resistance were administered following a ≥10-h overnight fast. Serum glucose and insulin concentrations were determined with a SIRRUS analyzer (Stanbio Laboratories, Boerne, TX) and a TOSOH AIA-II immunoassay analyzer (TOSCH Corp., San Francisco, CA), respectively, unless otherwise indicated.

A 75-g OGTT was administered to all participants following an overnight fast. Glucose and insulin were measured from blood samples drawn at −15, −5, 10, 20, 30, 60, 90, and 120 min relative to glucose ingestion (0 min). Fasting values for glucose and insulin were determined from the average of the −15 and −5 time points. Surrogate indices were calculated with the following equations [11, 12]:

$$\text{Matsuda index} = \frac{10{,}000}{\sqrt{\left[\text{Fasting plasma glucose}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{Fasting insulin level}\left(\frac{\mu\text{U}}{\text{mL}}\right)\right] \times [\text{Mean OGTT glucose} \times \text{Mean OGTT insulin}]}}$$

$$\text{Homeostasis model assessment of insulin resistance (HOMA}-\text{IR)} = \frac{\text{fasting glucose}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{fasting insulin}\left(\frac{\mu\text{U}}{\text{mL}}\right)}{405}$$

Skeletal muscle insulin sensitivity was directly measured with the hyperinsulinemic-euglycemic clamp [13]. An intravenous catheter was placed in the antecubital vein of one arm for infusion of insulin and glucose, and a second catheter was placed in the contralateral arm to collect blood samples. Insulin was infused for 3 h at a rate of 120 mU/m^2 body surface area per minute. A variable-rate infusion of 20% dextrose solution was used to maintain plasma glucose at the participant's fasting glucose level and was adjusted in response to plasma glucose levels monitored at 5-min intervals with a glucose analyzer (YSI 2300 STAT Plus; YSI, Inc., Yellow Springs, OH). Additional blood samples for determination of glucose and insulin concentrations were collected at 10-min intervals throughout the procedure. The steady-state period was defined as a ≥30-min period occurring at least 1 h after starting the insulin infusion, during which time the coefficients of variation for serum glucose and insulin, and the glucose infusion rate, were <5%. Clamp-derived insulin sensitivity (SI-clamp) was expressed as M/(G × ΔI), where M is the steady-state glucose infusion rate (calculated as milligrams of glucose per kilogram of lean body mass per minute), G is the mean steady-state glucose concentration (milligrams per deciliter), and ΔI is the difference between basal and steady-state serum insulin concentrations (microunits per milliliter).

Assessment of body composition

Body composition measures, including total lean mass, total fat mass, and total percentage body fat mass, were obtained with dual-energy x-ray absorptiometry (iDXA instrument; GE Healthcare, Chicago, IL). Participants wore light clothing and were scanned in a supine position with arms at their sides.

Statistical methods

All analyses and graphs were produced in R version 4.1.0 (R Core Team, 2021). All analyses were two-tailed. Statistical significance was set at $p < 0.10$ for interactions and $p < 0.05$ for all other analyses. Subgroup analyses with self-reported race and BMI status were performed to investigate the influence of these factors on associations between GRS and clinical phenotypes. To model BMI status as a two-category variable, the sample median value for BMI (25.9 kg/m^2) was used as a cut point to divide participants into "low" and "high" BMI groups. Any variables with a non-normal distribution were log-transformed for analysis. Figures were produced with the *visreg* [14], *ggplot2* [15], and *ggpubr* [16] packages in R.

Descriptive characteristics were computed by race and BMI status, and they are expressed as mean (SD), median (interquartile range [IQR]), or *N* (%) for categorical variables. Group differences were assessed with a Student *t* test, Wilcoxon rank sum test, or Pearson χ^2 test as appropriate. Associations between GRS (predictor) and measures of insulin sensitivity/resistance were evaluated with multiple linear regression analysis and were adjusted for sex, age, and total percentage body fat. All models were stratified by race. Interaction terms between GRS and BMI status were tested to determine whether BMI status influenced associations between GRS and the dependent variable. Models were further stratified by BMI status to evaluate these associations separately. Continuous predictors were centered and scaled in all models. Assumptions for normality and homoscedasticity of residuals were confirmed for all models with histograms and scale-location plots, respectively. To measure collinearity, the variance inflation factor was computed, and all models yielded a variance inflation factor of <5.

RESULTS

A total of 107 individuals were included in the analysis. Characteristics of the overall sample and by self-reported race are displayed in

TABLE 1 Descriptive characteristics in all participants and by race.

	Overall	European American	African American	p[a]
N	107	54	53	
Age (y)	28.0 [22.0–26.0]	26.0 [21.0–32.8]	29.0 [23.0–38.0]	0.206
Sex, male	47 (44%)	25 (46%)	25 (47%)	0.618
Genetic ancestry[b]				
African (%)	36.6 [0.100–84.6]	0.100 [0.00–0.600]	84.6 [81.5–88.6]	**<0.001**
European (%)	62.0 [14.0–99.2]	99.2 [98.8–99.8]	13.9 [10.7–17.8]	**<0.001**
American Indian (%)	0.600 [0.00–1.20]	0.200 [0.00–0.900]	0.800 [0.400–1.500]	**0.001**
BMI (kg/m^2)	25.9 [23.1–30.1]	24.3 [22.5–27.1]	29.0 [23.9–32.9]	**<0.001**
Low BMI status	54 (50%)	36 (67%)	18 (34%)	**<0.001**
Total lean mass (kg)	47.94 [42.09–56.47]	46.03 [40.66–54.18]	49.63 [42.94–61.30]	**0.013**
Total fat mass (kg)	24.98 [18.46–30.73]	23.26 [16.53–26.89]	26.79 [18.85–35.68]	0.053
Adiposity (%)[c]	32.1 [25.2–38.8]	32.5 [24.1–38.1]	31.1 [26.6–41.0]	0.564
Fasting glucose (mg/dL)	87 [83–92]	86 [81–93]	87 [83–91.8]	0.98
SI-clamp (M/(G × ΔI)[d])	5.94 [4.3–8.51]	7.8 [5.89–10.4]	4.44 [3.76–6.01]	**<0.001**
HOMA-IR	1.25 [0.882–2]	1.14 [0.78–1.69]	1.37 [1.05–2.31]	0.065
Matsuda index	5.62 [3.87–8.28]	6.41 [4.36–9.33]	5.08 [3.62–6.96]	0.052
Genetic risk score	0.014 [0.014–0.016]	0.014 [0.013–0.015]	0.015 [0.014–0.016]	**0.007**

Note: Data are median [IQR] or *N* (%).
Abbreviations: HOMA-IR, homoeostasis model assessment of insulin resistance; SI-clamp, insulin sensitivity measured by the euglycemic clamp and calculated for lean body mass.
[a]Group differences were assessed using Student *t* test or Pearson χ^2 test as appropriate. Significant differences ($p < 0.05$) are in bold.
[b]Obtained from supervised admixture analysis.
[c]Reflects percentage total body fat.
[d]Measured as the steady-state glucose infusion rate (M) divided by the product of the mean steady-state glucose concentration (G) and the difference between basal and steady-state insulin concentration (ΔI).

Table 1. The study sample was evenly distributed by sex and race, BMI ranged from 17.13 to 43.58 kg/m^2, and participants generally exhibited normal glucose tolerance. Self-reported race was highly congruent with genetically defined ancestry, indicating that race was an appropriate representation of ancestral background for our analyses. AA participants were more likely to have overweight and be in the high-BMI group, whereas insulin sensitivity was higher in EA participants. No differences were observed in body fat percentage and surrogate insulin sensitivity/resistance measures (Matsuda index and HOMA-IR) between EA and AA participants. The GRS ranged from 0.0104 to 0.0173 for the entire sample and were higher in AA participants.

Results indicated that the effect of BMI status on associations between GRS and insulin sensitivity/resistance measures varied by race. Associations with GRS varied as a function of race/BMI depending on whether insulin sensitivity was assessed by SI-clamp or when surrogate measures were employed. The association with SI-clamp was stronger in AA participants with low BMI, whereas associations with surrogate measures were stronger in EA participants with high BMI (Figure 1). No effect of BMI status was observed for associations either with surrogate index in AA participants or with SI-clamp in EA participants. We then stratified these associations by BMI status to further characterize race-specific differences between individuals with low and high BMI status (Table 2). In AA individuals, the GRS was significantly and inversely associated with SI-clamp values in the low-BMI group. Conversely, among EA individuals, the GRS was significantly associated with higher HOMA-IR values and lower Matsuda index values in the high-BMI group. Although the association between GRS and Matsuda index did not differ by BMI status in AA participants, a positive association was observed only in the low-BMI group. No significant associations were observed in EA participants with low BMI or AA participants with high BMI.

DISCUSSION

To our knowledge, this is the first study to test whether the GRS of Lotta et al. [2] is associated with measured and surrogate indices of insulin sensitivity/resistance in a population of healthy adults in the United States. In our study, the associations between GRS and insulin sensitivity/resistance were dependent on BMI status and were race-specific. Our results indicated that genetic risk for IR was associated with surrogate indices in high-BMI EA individuals but was associated with SI-clamp in low-BMI AA individuals. These observations can be explained by reported differences in tissue-specific insulin sensitivity and the ability of insulin sensitivity to promote weight gain in a population-specific manner.

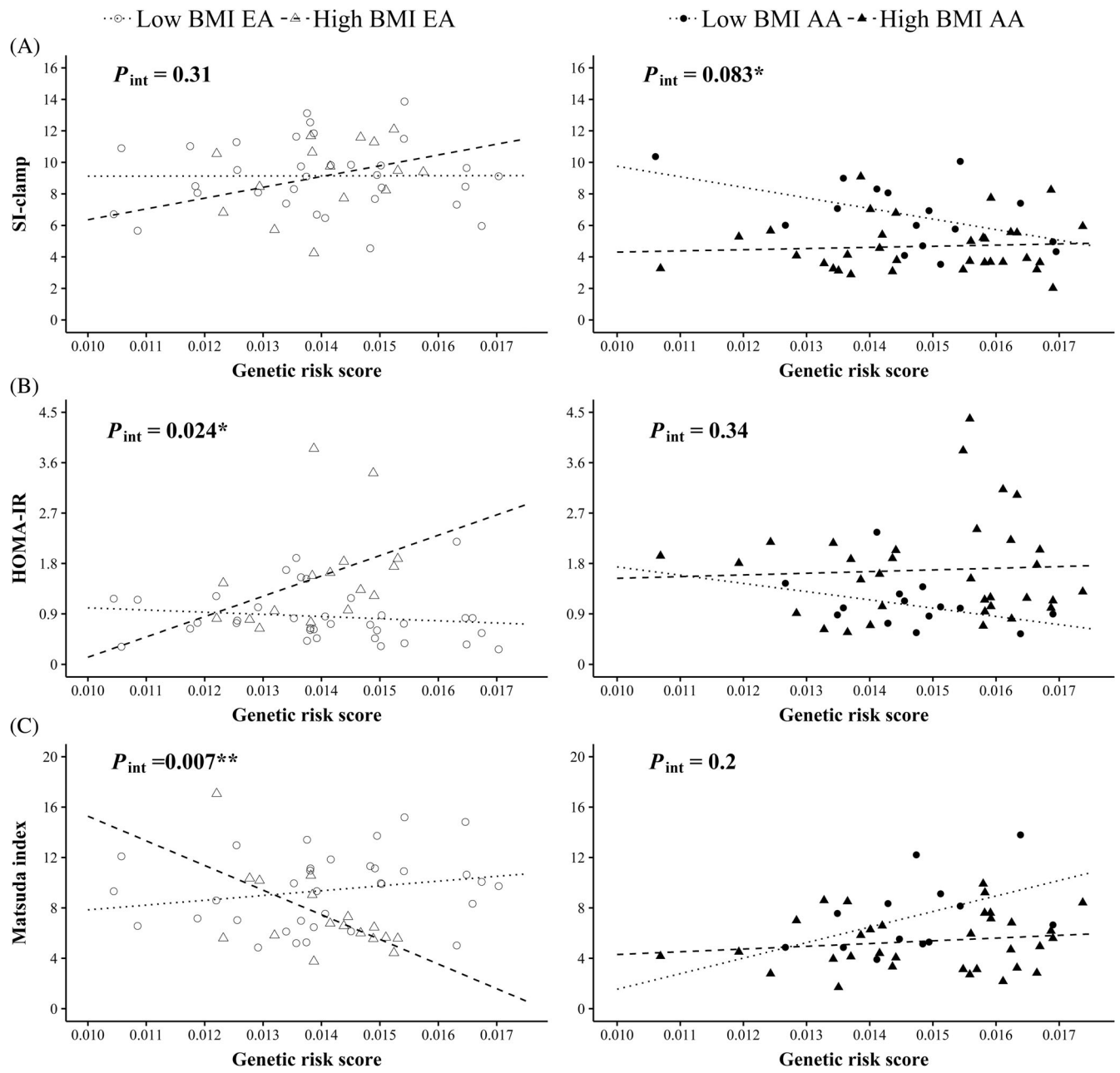

FIGURE 1 Associations of genetic risk score (GRS) with (A) SI-clamp; (B) HOMA-IR; and (C) Matsuda index, stratified by race and then BMI status. *p < 0.1, **p < 0.01 for the interaction term between BMI status and GRS on outcome variables. AA, African American; EA, European American; HOMA-IR, homeostasis model assessment of insulin resistance; SI-clamp, clamp-derived insulin sensitivity expressed as M/(G × ΔI).

In this study, we identified racial differences in the associations between genetic risk for IR and measures of relative insulin sensitivity/resistance. Within the EA group, the GRS was only associated with surrogate indices (HOMA-IR and Matsuda index). This observation may be explained by the predominance of liver-derived IR in EA individuals, which is reflected to a greater extent in HOMA-IR measurement and accounted for in the Matsuda index [17]. Conversely, in the AA group, genetic risk for IR was associated with SI-clamp but not with the surrogate indices. This observation may be explained by the previous report that greater IR in AA individuals occurs predominantly at the level of skeletal muscle [6], which is captured by the clamp but not specifically by HOMA-IR, and more weakly by the Matsuda index. Our results agree with previous research indicating that surrogate measures of insulin sensitivity/resistance are poor predictors of SI-clamp in AA individuals [17]. The euglycemic clamp, particularly at the relatively high dose of insulin used in this study, suppresses hepatic glucose production and thereby reflects skeletal muscle-derived insulin sensitivity [18]. These findings suggest that surrogate measures of insulin sensitivity/resistance, based on glucose and insulin levels, should not be used to compare insulin sensitivity/resistance between AA and EA individuals, or across populations for whom differences exist in the relative contribution of liver and skeletal muscle to insulin sensitivity.

TABLE 2 Independent associations[a] between genetic risk score and measures of insulin sensitivity/resistance, stratified by race and BMI status.

	European American ($n = 54$)		African American ($n = 53$)	
	β (SE)	*p*	β (SE)	*p*
Outcome 1: SI-clamp				
Low BMI	−0.005 (0.012)	0.694	−0.140 (0.065)	**0.035**
High BMI	0.120 (0.023)	0.611	0.015 (0.459)	0.747
Outcome 2: HOMA-IR				
Low BMI	−0.029 (0.053)	0.595	−0.148 (0.075)	0.075
High BMI	0.296 (0.129)	**0.027**	0.029 (0.060)	0.627
Outcome 3: Matsuda index				
Low BMI	0.026 (0.029)	0.372	0.120 (0.030)	**0.004**
High BMI	−0.183 (0.068)	**0.010**	0.018 (0.024)	0.450

Abbreviations: HOMA-IR, homoeostasis model assessment of insulin resistance; SI-clamp, insulin sensitivity measured by the euglycemic clamp and calculated for lean body mass.

[a]Outcomes were assessed with multiple linear regression analysis, stratified by race and BMI status, and were adjusted for age, sex, and percentage total body fat. Significant associations ($p < 0.05$) are in bold.

Our results indicated significant associations between GRS and surrogate measures in EA participants in the high-BMI group only. This may have resulted from the decline in insulin sensitivity that occurred to a variable extent with weight gain, and the subsequent broadening of the range across the sample in the surrogate values. Weight gain is commonly associated with a decrease in insulin sensitivity [19–21]. In EAs as a group, weight gain is reported to result in fat localized to the abdominal region and the liver [22, 23]. Thus, the higher-BMI group displayed not only a wider range of insulin sensitivity/resistance index values but also a greater hepatic IR, which would have manifested in higher HOMA-IR values and lower Matsuda index values. These findings suggest that in EA individuals, being leaner masks the genetic predisposition for IR and that the onset of IR arises from weight gain in at-risk individuals.

This was also the first study, to our knowledge, to investigate the association of the 53-SNP GRS in AA adults. Prior studies have identified subgroups of AA adults with differing predispositions to IR and obesity; one subgroup is insulin sensitive and obesity-prone, and one is insulin resistant and protected against weight gain [24, 25]. These subgroups exist in the AA population in association with differences in elevated postchallenge insulin [4]. Insulin is a lipogenic and antilipolytic hormone, and studies have shown that elevated insulin response to glucose interacts with insulin sensitivity to predict weight gain [26]. In the present study, we can therefore assume that the leaner AA participants were inherently, possibly genetically, insulin resistant. It is possible that the genetic IR seen in this subgroup contributed to the stronger association between the 53-SNP GRS and measured insulin sensitivity/resistance that we observed in the low-BMI subgroup.

The GRS used in this study was developed to gain insight into mechanisms underlying the development of IR. Several loci in the 53-SNP score were tested for functional properties and found to be involved in adipocyte differentiation and adipose tissue expansion. Thus, the genetic basis of IR, at least in part, manifests as the impaired expansion of peripheral adipose tissue, which can be observed as an inverse association between GRS and body fat measures [2]. This association then indicates that genetic IR may yield a protective effect against obesity by limiting body fat gain. This contrasts with the often-reported effect of weight gain to reduce insulin sensitivity. However, it is possible that both genetic IR and a weight-gain–acquired decline in insulin sensitivity result from the same underlying mechanism: metabolic complications resulting from the insufficient storage capacity of peripheral adipose tissue. Nonetheless, metabolic disease ensues only when weight gain is superimposed on a susceptible genetic background [2]; weight gain in nonsusceptible individuals instead results in the "healthy obesity" phenotype [27]. Although weight gain in nonsusceptible individuals results in a mild decline in insulin sensitivity, it does not result in metabolic disease. The reasons for this have not been well defined, but it is possible that decreases in insulin sensitivity may still remain above the threshold that would result in IR-associated pathologies. Alternatively, the lower insulin sensitivity alone may not be sufficient to trigger incident disease in isolation and requires a subsequent physiological component, such as poor β-cell function, to precipitate a loss of homeostatic control of metabolic health.

The original 53-SNP GRS was generated using data from White European adults. This study was the first to test this GRS in a cohort of Americans with European or African ancestry, and therefore our results may differ from those found by Lotta et al. [2]. In our study, the GRS was not associated with the SI-clamp in EA participants. These findings are novel. Although we cannot explain this observation, we have several hypotheses. First, the GRS, which was developed to predict fasting insulin, may not be ideally designed to predict skeletal muscle–derived insulin sensitivity. It is also possible that the EA participants from this U.S. study are more heterogeneous than the European cohort in ways that affect the underlying basis of insulin sensitivity/resistance. Our results also indicated that the 53-SNP GRS was uniquely and unexpectedly associated with measures of insulin sensitivity/resistance in AA participants. For example, the GRS tended to be inversely associated with HOMA-IR values and positively associated with the Matsuda index in low-BMI AA participants. Given that the GRS was inversely associated with the clamp-derived skeletal muscle insulin sensitivity in this group, the positive association seen with the Matsuda whole-body index may reflect the hepatic component, a concept supported by the inverse association of GRS with HOMA-IR values in this group. It is possible that certain SNPs within GRS may reflect pathways beyond peripheral adipose expansion, which may be more relevant to insulin sensitivity/resistance in non-White populations. Because the GRS was developed in a European cohort to predict fasting insulin, the SNPs may not be weighted appropriately for other applications in other populations, perhaps explaining the unexpected associations seen in the AA participants.

Furthermore, SNPs not included in GRS may affect the genetic predisposition for IR in non-White populations. For example, variation in patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) affects hepatic fat accrual in a race-specific manner, with AA individuals having a variant that results in lower accumulation of liver fat [28]. The lower accrual of liver fat in AA individuals may result in lower HOMA-IR values, but this source of variance would not be captured by the 53-SNP GRS. Taken together, our data suggest the provocative hypothesis that in AA individuals, some component of GRS is associated with lower hepatic IR and could be distinct from the components that reflect peripheral adipose expansion. However, given the relatively small sample size of the low-BMI AA group, it is beyond the scope of this study to explore this hypothesis. Thus, our results indicate that future studies in U.S. populations that identify genetic variation predicting tissue-specific insulin sensitivity are warranted, while simultaneously considering the diverse ancestry of the U.S. population.

Strengths of this study include having a sample evenly distributed by sex and race and detailed phenotyping of insulin sensitivity/resistance measures, including the hyperinsulinemic-euglycemic clamp. One limitation of our study was that we used BMI to reflect obesity rather than a direct measure of body fat percentage. However, BMI is widely available at the population level; thus, the present results can be easily applied to future studies. In addition, the original study by Lotta et al. [2] showed that BMI and percentage body fat had the same direction of association with GRS. Other potential concerns were the small sample size and the skewed distribution of BMI groups in each race.

In conclusion, the GRS was significantly associated with surrogate measures of insulin sensitivity/resistance in EA individuals with higher BMI that may reflect insulin action at the liver to a greater degree. In contrast, direct, clamp-derived measures of insulin sensitivity that assess insulin action at the level of skeletal muscle were associated with GRS in AA individuals with a lower BMI. These results support the hypothesis that the relationship between genetic predisposition for IR and BMI status is race- and tissue-specific.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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