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Heterogeneity in Effects of Genetically Determined Adiposity on Insulin Resistance and Type 2 Diabetes: The Atherosclerosis Risk in Communities Study

Tingting Liu^{*,a}, Changwei Li^{*,b}, Luqi Shen^b, Ye Shen^b, Weibo Mao^{b,c}, and Shengxu Li^a

^aDepartment of Epidemiology Tulane University School of Public Health and Tropical Medicine, New Orleans, LA

^bDepartment of Epidemiology & Biostatistics, University of Georgia College of Public Health, Athens, GA

^cDepartment of Nephrology, Fuling Center Hospital of Chongqing City, Chongqing, China

Abstract

Background—A recent genome-wide association study has identified 12 genetic variants robustly associated with body fat percentage (BF%) with diverse cardiometabolic consequences. We developed three genetic risk scores (GRSs) according to the associations of the 12 individual variants with type 2 diabetes (T2D) and test the GRSs' associations with insulin resistance and T2D in the Atherosclerosis Risk in Communities Study.

Methods—In 6,895 European-American participants, we calculated GRS-I as the number of BF %-increasing alleles from variants associated with increased risk of T2D, GRS-D from variants associated with decreased risk of T2D, and GRS-ALL from all 12 variants. Linear and logistic regression models were used to evaluate associations of the GRSs with insulin resistance and risk of T2D, respectively, adjusted for age, sex, smoking, and drinking, and additionally for body mass index (BMI).

Results—GRS-D was significantly associated with decreased levels of fasting insulin ($P=0.014$) and homeostasis assessment of insulin resistance ($P=0.023$). While GRS-I was not associated with insulin resistance measures, it was with T2D ($P=0.002$). Further adjustment for BMI did not substantially change the above associations. GRS-ALL was inversely associated with insulin resistance after controlling for covariates including BMI; GRS-ALL was not associated with T2D.

Correspond to: Shengxu Li, MD, PhD, MPH, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, 1440 Canal Street, Room 2029, New Orleans, LA 70112, Phone: (504) 988-1048; sli10@tulane.edu; Changwei Li, MD, PhD, MPH, Department of Epidemiology & Biostatistics, University of Georgia College of Public Health; B.S. Miller Hall Room 120, 101 Buck Road, Athens, GA, Phone: (706) 583-0918; changwei.li@uga.edu.

*These authors contributed equally.

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Conclusion—Genetically determined BF% has differential effects on cardiometabolic risk, which may partly explain the heterogeneity in obesity-induced cardiometabolic risk and have implications for developing new strategies mitigating obesity-induced cardiometabolic consequences.

Keywords

body fat; insulin resistance; type 2 diabetes; genetic association studies

Introduction

Obesity, commonly defined as body mass index (BMI) ≥ 30 kg/m², is a major risk factor for cardiometabolic disorders including dyslipidemia, cardiovascular disease, and insulin resistance/type 2 diabetes (T2D)^{1, 2}. As a result, we have witnessed a parallel increase in T2D prevalence as obesity prevalence increases over time³.

Despite the established link between obesity and cardiometabolic risk, accumulating evidence suggests that cardiometabolic consequences of obesity are heterogeneous^{4, 5}. A small proportion of obese individuals do not have obesity-associated cardiometabolic abnormalities⁶. However, it has been argued that BMI does not differentiate fat mass from lean mass and body fat percentage (BF%) may be a more sensitive measure for cardiometabolic risk than BMI. For example, Gómez-Ambrosi et al. found that body fat percentage (BF%) was significantly higher in participants with prediabetes than those with normoglycemia and a comparable normal BMI⁷.

A recent large-scale meta-analysis of genome-wide association studies (GWAS) identified 12 loci robustly associated with BF%⁸. Interestingly, the effects of the BF%-increasing alleles at these loci on T2D and insulin resistance are diverse⁸. These findings provide supporting evidence that heterogeneity in obesity-associated cardiometabolic consequences may be genetically determined.

To further characterize cardiometabolic risk profiles associated with these BF% variants, we developed three genetic risk scores (GRSs) according to the associations of the 12 individual variants with insulin resistance and T2D and tested the associations of the GRSs with insulin resistance and T2D in participants of the Atherosclerosis Risk in Communities (ARIC) Study.

2. Methods

2.1. Study Participants

The ARIC Study is a population-based prospective cohort study of cardiovascular disease and its risk factors⁹. It included a cohort of 15,792 persons randomly selected and recruited from four field centers in the United States: Forsyth County, North Carolina; Jackson County, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. The ARIC participants received comprehensive medical and social examinations at baseline and every three years thereafter. The baseline examination took place during 1987-1989.

Data on genotypes, diabetes related measures, and important covariates were cataloged in the database of Genotype and Phenotype (dbGaP)¹⁰.

Since the genomic loci for BF% were identified in population of predominantly European ancestry, we performed the current analysis among European-American participants of the ARIC Study. Among participants who attended baseline examination, diabetes was measured among 9,093 European-American participants. Of these, genotype data were available for 6,895 participants (75.8%).

Demographic information was obtained from standardized self-report forms. Weight was measured to the nearest 0.1 kilogram and height was measured in centimeters. BMI was calculated as weight in kilogram divided by height in squared meters. Blood pressure was measured twice following a 5-minute rest by trained and certified technicians according to the standardized ARIC study protocol using validated, automated devices¹¹. Physical activity was evaluated by trained interviewers using the Baecke Questionnaire^{12, 13}. Ordinal scores from 1 (low) to 5 (high) were generated for sport, leisure, and work related activities, respectively¹⁴. Dietary intake was assessed by using Willett's 61-item food frequency questionnaire^{15, 16}. Daily total energy intake was calculated assuming that one gram of fat, alcohol, protein, and carbohydrate contained 9, 7, 4, and 4 kilocalories, respectively.

The ARIC study was approved by the Ethical Review Committee of each participating site, and informed consent was obtained from all participants. The current study was approved by the Institute Review Boards (IRBs) at University of Georgia and Tulane University, respectively.

2.2. Cardiometabolic risk factors and T2D

Total serum cholesterol and triglycerides were measured by enzymatic methods. High-density lipoprotein cholesterol (HDL-C) was measured after dextranmagnesium precipitation. For those with triglyceride levels under 400 mg/dL, low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation¹². Information on fasting status, blood glucose, insulin, and diabetes medication use was also collected. This information was used to identify participants with T2D according to the diagnosis guideline of the American Diabetes Association¹³. T2D was defined as use of glucose-lowering medications, fasting blood glucose ≥ 126 mg/dL, or random blood glucose ≥ 200 mg/dL. We calculated homeostatic model assessment of insulin resistance (HOMA-IR) using equations reported by Matthews et al.¹⁴.

2.3. Genotyping and Genotype Imputation

Genome-wide autosome single nucleotide polymorphisms (SNPs) were genotyped using the Affymetrix 6.0 platform for a total of 8,620 unrelated European-American ARIC participants, and are available from the dbGaP. SNPs were removed with Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$, missing rate $> 10\%$, or minor allele frequency (MAF) $< 1\%$. Individuals with missing genotype rate $> 20\%$ were also removed before imputation. After quality control, a total of 703,117 SNPs remained for genotype imputation. Imputation based on the ALL ancestry panel of the 1000 Genome Phase III integrate Release Version 5¹⁵ was

conducted for all European-American participants using MiniMac software¹⁶. After imputation, SNPs with imputation quality score $r^2 < 0.3$ were removed.

Eleven of the 12 reported BF% variants⁸, including rs543874, rs6755502, rs6738627, rs2943652, rs693839, rs4788099, rs1558902, rs9906944, rs6567160, rs4808150, rs6857, and rs3761445, were imputed with high quality. The *CRTC1* variant rs757318 was not imputed. We used rs4808150 that was in complete linkage disequilibrium ($r^2=1.0$) with rs757318 to represent the *CRTC1* locus. The genotypes of the 12 variants with fractional values ranging from 0 to 2 for the 6,895 European-American participants were used for analysis.

2.4. Statistical Analysis

Categorical variables are described in percentage, and continuous variables are presented as mean (standard deviation [SD]). Comparisons in study variables were conducted by Chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

Among the 12 loci associated with BF%, five BF%-increasing alleles were associated with increased risk of T2D, three with reduced risk of T2D, and four were largely metabolically neutral (with no association with T2D)⁸. Therefore, we generated three genetic risk scores (GRSs) for BF% as the sum of BF% increasing alleles: GRS-D, GRS-I, and GRS-ALL. GRS-I was calculated by using the five BF% SNPs (rs1558902, rs6567160, rs6755502, rs6857, and rs9906944 in or near genes *FTO*, *MC4R*, *TMEM18*, *TOMM40/APOE*, and *IGF2BP1*, respectively) that are associated with increased risk of T2D, GRS-D the three BF% SNPs (rs2943652, rs6738627, and rs3761445 in or near genes *IRS1*, *COBLL1/GRB14*, and *PLA2G6/PICK1*, respectively) associated with reduced risk of T2D, and GRS-ALL all 12 SNPs regardless of their individual associations with T2D risk. Multiple linear and logistical regression models were applied to evaluate the associations of the GRSs and insulin resistance and T2D, respectively. We built three multiple logistic regression models to assess associations of each GRS with T2D risk, with adjustment for age, sex, smoking, and drinking in Model 1, additional adjustment for BMI in Model 2 and further adjustment for education, physical activity index score, total calories from dietary and ethanol consumption, HDL-C, LDL-C, and triglycerides in Model 3. Analysis on insulin and HOMA-IR was only limited to those who fasted and did not take antidiabetic or lipids-lowering medications. All the analyses were conducted using the SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3. Results

Among the 6,895 European-American participants, 44.6% were men with an average age of 53.9 (5.7, SD) years and 55.4% were women with an average age of 54.7 (5.7) years (Table 1). The overall prevalence of type 2 diabetes was 3.7%.

Both GRS-I and GRS-ALL were strongly associated with BMI and WHR. On average, one-unit increase in GRS-I was associated with 0.24 kg/m² (standard error [SE]=0.04) increase in BMI ($P=2.67 \times 10^{-8}$) and 0.002 (SE=0.001) units increase in WHR ($P=0.001$). Per unit

increase in GRS-ALL was associated with 0.10 (SE=0.03) units increase in BMI ($P=6.14\times 10^{-5}$) and 0.001 (SE=0.0004) units increase in WHR ($P=0.04$). However, GRS-D was not associated with BMI ($P=0.74$) or WHR ($P=0.68$).

GRS-D was associated with reduced fasting insulin levels and HOMA-IR, with -1.37 (0.56) units and -0.05(0.02) changes per unit increase in GRS-D, respectively. There was no association of GRS-I and GRS-ALL with fasting insulin or HOMA-IR (Table 2). However, with further adjustment for BMI, the GRS-ALL became significantly and inversely associated with both HOMA-IR and fasting insulin. GRS-D was not associated with risk of T2D. On the other hand, GRS-I was significantly associated with increased risk of T2D, with per unit increase in GRS-I associated with 17% (95% CI: 6% -30%) increased odds of T2D ($P=0.001$) after controlling for age, sex, smoking, and drinking (Table 3). In the full model that was adjusted for age, sex, education, BMI, smoking, drinking, physical activity, total calories intake from dietary and ethanol consumption, LDL-C, HDL-C, and TG, odds ratio associated with one standard deviation increase in GRS-I was 1.16 (95% CI: 1.04 – 1.29, $P=0.008$) (Table 3). However, there was no association of GRS-ALL with risk of T2D in all three models. Associations of individual variants with cardiometabolic risk factors are shown in Supplementary Table.

4. Discussion

In this large study from a well-characterized study sample, we revealed that genetically determined BF% had differential effects on insulin resistance and T2D risk. GRS-I was significantly associated with increased T2D risk independent of BMI, while GRS-D was significantly associated with lower levels of insulin and HOMA-IR. Our findings highlight that the effects of BF on cardiometabolic risk are heterogeneous.

As expected, both GRS-I and GRS-ALL were strongly associated with BMI, which is highly correlated with BF%¹⁷. On the other hand, GRS-D was not associated with BMI, suggesting that BF%-increasing genetic variants included in GRS-D may not increase anthropometrically assessed adiposity. It is possible that the genetically determined BF% may not be captured by anthropometric measures because the GRS-D variants explain very limited variance in BF%.

The associations of GRS-I with T2D and insulin resistance are consistent with their effects on adiposity. However, we further demonstrated that the association between GRS-I and T2D was independent of BMI. This may suggest that the association of GRS-I with T2D is driven by mechanisms other than through general adiposity. BMI, a measure of general adiposity, has been criticized for its lacks of differentiating fat mass from fat free mass^{18–20} and of reflecting fat distribution²¹.

The fact that GRS-I significantly increased T2D risk, but was not associated with insulin resistance measures, indicates that GRS-I variants may increase risk of T2D through pathways other than insulin resistance, such as pancreas alpha cell function and glucagon secretion²². A recent study among non-obese T2D men showed that BF measures were

correlated with fasting glucagon levels²³. Future studies on the underlying mechanisms for loci included in GRS-I and their link to glucagon are needed.

The positive association of GRS-ALL with BMI and WHR is consistent with their associations with BF%. Lack of its association with insulin resistance measures may be caused the opposing effects from GRS-I and GRS-D. The inverse association of GRS-ALL with insulin resistance after adjustment for BMI may reflect the fact that GRS-D's association with insulin resistance was independent of BMI, while GRS-I's association was, at least partially, dependent on BMI. Given the well-established association between BF% and insulin resistance, the inverse association of GRS-ALL with insulin resistance after BMI adjustment indicates that loci with BF%-increasing, yet metabolically beneficial, alleles may be overrepresented among the 12 loci identified by GWAS.

The findings from the current study confirm the heterogeneity in cardiometabolic consequences of genetically determined BF%, as previously reported⁸, and suggest that the relationship between adiposity and risk of T2D is complex. The underlying mechanisms for the heterogeneity cannot be addressed by the current observational study. However, we speculate that the following mechanisms may contribute to this heterogeneity. First, GRS-I variants are likely to be associated with a more centrally distributed obesity phenotype, while GRS-D variants are likely to be associated with a more peripherally distributed obesity phenotype. It is known that subcutaneous fat is more metabolically benign than visceral fat^{24–26}. Second, GRS-I variants may be associated with increased adiposity but not increased expandability of adipose tissue; conversely, GRS-D variants are likely to increase adiposity, which may be compensated by increased adipose tissue expandability. Adipose tissue expandability is critical for cardiometabolic health²⁷. Finally, different yet to be recognized pathways may be involved in the differential associations of GRS-I and GRS-D with cardiometabolic health. For example, GRS-I variants may be more pro-inflammation²⁸. Our findings also support that the so called “metabolically healthy obesity” phenotype may be partly genetically determined²⁹.

The current findings also have implications for designing Mendelian randomization studies. Mendelian randomization is an important approach to making causal inference on an association that is easily confounded by hard-to-control confounding factors^{30, 31}. There have been a rapidly increasing number of Mendelian randomization studies in cardiometabolic diseases since the beginning of GWAS³². Our findings clearly raise concerns on using a genetic risk score derived from multiple variants that have diverse, sometimes opposing, effects on a particular phenotype, or from multiple variants that may have pleiotropic effects beyond the primary phenotypic effect³². In the current study, if GRS-ALL was used to make a causal inference on the link between BF% and insulin resistance, an erroneous conclusion might have been drawn.

Major strengths of the present study include a well characterized study cohort and a large sample size, particularly the large number of overweight/obese participants that allowed higher statistical power. A major limitation of the current study is that only non-Hispanic Whites were included. This is due to two reasons: 1) all the BF% loci were identified among participants of predominantly European ancestry⁸ and 2) there were limited numbers of

African American participants in the ARIC Study, and statistical power will be limited. Considering different LD structures between populations of distinct ancestries, the current findings may not be applicable to other ethnic groups. Further understanding of how genetic contribution to BF% may influence T2D risk in populations of other ancestries will be equally important.

In conclusion, our results suggest that genetically determined BF% has different effects on cardiometabolic risk including T2D. Our study support the concept that health consequences of obesity are heterogeneous, which is partly genetically determined. Our study also has implications in designing Mendelian randomization studies and in developing therapeutic drugs for cardiometabolic diseases. Future studies are warranted to delineate the mechanisms for the observed heterogeneity in cardiometabolic consequences of these BF% loci.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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T.L., C.L., and S.L. drafted, reviewed, and edited the manuscript, L.S., Y.S., and W.M. contributed to the study design, data analysis, discussion, and reviewed, and edited the manuscript. All authors were involved in planning the manuscript, its critical review and editing, subsequent revisions, and approval for submission. S.L. and C.L. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1

Characteristics of the ARIC participants at baseline by sex

Variable	Female (n=3,823)	Male (n=3,072)
Age, years	53.9 (5.7)	54.8 (5.7)
Education, %		
Basic or no education	13.5%	15.0%
Intermediate education	51.1%	37.9%
Advanced education	35.4%	47.1%
Drinking status, %		
Current drinker	63.8%	71.0%
Former drinker	13.4%	19.5%
Never drinker	22.9%	9.5%
Physical activity index score	6.9 (1.4)	7.4 (1.4)
Total calorie from dietary and ethanol intake	1499.1 (564.6)	1787.5 (705.8)
BMI, kg/m ²	26.3 (5.3)	27.3 (3.9)
WHR	0.9 (0.1)	1.0 (0.1)
Fasting glucose, mg/dL	100.4 (25.9)	105.2 (27.5)
Insulin, SI	75.2 (132.5)	91.1 (133.3)
HOMA-IR	3.0 (7.4)	3.9 (13.4)
LDLC, mmol/L	3.5 (1)	3.6 (0.9)
HDLC, mg/dL	58.3 (17.4)	43.0 (12.4)
Triglycerides, mg/dL	125.7 (79.7)	145.1 (91.6)
SBP, mmHg	137.6 (16.1)	140.2 (14.7)
DBP, mmHg	90.6 (9.5)	93.6 (9.8)

BMI=body mass index; DBP=diastolic blood pressure; LDLC=low-density lipoprotein cholesterol; HDLC=high-density lipoprotein cholesterol; HOMA-IR=homeostatic model assessment of insulin resistance; SBP=systolic blood pressure; WHR=waist-hip-ratio

Mean (standard deviation) is shown unless otherwise specified.

Table 2

Associations between the genetic risk scores and cardiometabolic risk factors

Variable	GRS-D		GRS-I		GRS-ALL	
	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
BMI	0.02 (0.05)	0.74	0.24 (0.04)	2.67×10^{-8}	0.10 (0.03)	6.14×10^{-5}
WHR	0.0003 (0.001)	0.68	0.002 (0.001)	0.001	0.001 (0.0004)	0.04
Insulin	-1.37 (0.56)	0.01	0.57 (0.51)	0.26	-0.19 (0.30)	0.53
Insulin*	-1.36 (0.48)	0.005	-0.77 (0.44)	0.08	-0.74 (0.26)	0.005
HOMA-IR	-0.05 (0.02)	0.02	0.02 (0.02)	0.26	-0.01 (0.01)	0.60
HOMA-IR*	-0.05 (0.02)	0.01	-0.03 (0.02)	0.08	-0.03 (0.01)	0.009

BMI=body mass index; GRS-ALL=genetic risk score including all 12 variants for body fat percentage; GRS-D=genetic risk score including three body fat percentage variants associated with decreased type 2 diabetes risk; GRS-I=genetic risk score including five body fat percentage variants associated with increased type 2 diabetes risk; HOMA-IR=homeostatic model assessment for of insulin resistance; WHR=waist-hip ratio

P values were adjusted for age, sex, smoking, and drinking.

* additionally adjusted for body mass index.

Table 3

Odds Ratio of type 2 diabetes associated with per SD change in genetic risk scores for body fat percentage.

Models*	GRS-D		GRS-I		GRS-ALL	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Model 1	0.96 (0.86 - 1.07)	0.45	1.17 (1.06 - 1.30)	0.002	1.04 (0.99 - 1.11)	0.14
Model 2	0.95 (0.85 - 1.06)	0.38	1.13 (1.02 - 1.25)	0.02	1.03 (0.97 - 1.09)	0.32
Model 3	0.95 (0.84 - 1.06)	0.35	1.16 (1.04 - 1.29)	0.008	1.04 (0.98 - 1.11)	0.23

GRS-ALL=genetic risk score for all body fat percentage loci; GRS-D=genetic risk score for body fat percentage loci decreasing type 2 diabetes risk; GRS-I= genetic risk score for body fat percentage loci increasing type 2 diabetes risk

* Covariates included in the three models:

Model 1: Age, sex, smoking, and drinking;

Model 2: variables in model 1 plus body mass index;

Model 3: variables in model 2 plus education, physical activity index, energy intake from dietary and ethanol consumption, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides