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Genetic variation near *IRS1* is associated with adiposity and a favorable metabolic profile in US Hispanics/Latinos

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Abstract

Objective—We examined associations of *IRS1* genetic variation with adiposity and metabolic profile in US Hispanic/Latino individuals of diverse backgrounds.

Methods—Previously genome-wide association study identified *IRS1* variants (rs2943650, rs2972146, rs2943641, and rs2943634) as related to body fat percentage (BF%) and multiple metabolic traits were tested among up to 12,730 adults (5232 men; 7515 women) from the Hispanic Community Health Study/Study of Latinos.

Results—The C-allele (frequency=26%) of rs2943650 was significantly associated with higher BF% in overall (β=0.34±0.11% per allele; *P*=0.002) and in women (β=0.41±0.14% per C-allele; *P*=0.003), but not in men (β=0.28±0.18% per C-allele; *P*=0.11), though there was no significant sex-difference. Using the inverse-normal-transformed data to compare effect sizes, we found that the association with BF% was stronger in Hispanic/Latino women than that previously reported in European women (β=0.054±0.018SD vs β=0.008±0.011SD per C-allele; *P*=0.03). We also observed that the BF%-increasing allele of rs2943650 was significantly associated with lower

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Conflict of interest

The authors declare no conflict of interest.

levels of fasting insulin, HOMA-IR, Hemoglobin A1c and triglycerides, and higher HDL-cholesterol ($P<0.05$).

Conclusions—Our study confirmed and extended previous findings of *IRS1* variation associated with increased adiposity but a favorable metabolic profile in US Hispanics/Latinos, with a relatively stronger genetic effect on BF% in Hispanic/Latino women compared to European women.

Keywords

Adiposity; Cardiovascular Risk; Insulin resistance; Genetics; Hispanics

Introduction

Obesity is associated with insulin resistance, dyslipidemia and hypertension, and therefore represents a major risk factor for a number of metabolic diseases (1). However, most interestingly, a large-scale meta-analysis of genome-wide association studies (GWAS) for body fat percentage (BF%) identified a variant of which the adiposity-increasing allele is associated with favorable metabolic outcomes (2), illustrating the complexity of the relationship between obesity and metabolic diseases. Specifically, the C-allele (frequency=36%) of a common single nucleotide polymorphism (SNP), rs2943650, near *IRS1* (insulin receptor substrate 1), was found to be associated with higher BF%, but also with a favorable metabolic profile (2). Other SNPs near *IRS1*, all in high linkage disequilibrium (LD) with rs2943650 according to the HapMap CEU, have also been identified by GWAS for various metabolic traits, including insulin resistance and type 2 diabetes (rs2943641; $r^2_{CEU} = 1.0$ with rs2943650) (3), triglycerides and HDL-cholesterol (rs2972146; $r^2_{CEU} = 0.95$ with rs2943650)(4), and coronary artery disease (rs2943634, $r^2_{CEU} = 0.83$ with rs2943650) (5). These GWAS findings are in line with the biological function of *IRS1*, which plays a key role in the insulin signaling pathway (6, 7), but an understanding of observed associations of *IRS1* variants with both increased adiposity and a favorable metabolic profile remains incomplete. In addition, most previous studies are restricted to populations of European ancestry (2, 3, 4, 5), and only limited information regarding these intriguing findings on *IRS1* variants is available in other ethnic groups. Associations of the *IRS1* variants with insulin resistance and hyperglycemia have been confirmed in a cohort of Puerto Ricans living in Boston (8). However, this study did not report on association with BF%, and the participants did not represent the full diversity of US Hispanics/Latinos.

US Hispanics/Latinos are disproportionately affected by obesity and related metabolic diseases (9, 10). Elevated levels of adiposity traits, including higher BF%, are associated with increased prevalence of diabetes, dyslipidemia and hypertension, as well as unfavorable levels of metabolic biomarkers, in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (11), a population-based cohort of US Hispanics/Latinos. In the current study, we examined whether the previously observed association of SNPs near *IRS1* with adiposity and metabolic traits are also observed in up to 12,747 individuals of diverse Hispanic/Latino backgrounds from the HCHS/SOL.

Methods

Participants

The HCHS/SOL is a population-based study of 16,415 Hispanic/Latino adults living in four U.S. metropolitan areas (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA). To be eligible, individuals had to be 18–74 years old at recruitment; self-identify as Hispanic/Latino; able to travel to the local study field center; and no plans to move out of the study area. Participants were recruited using a two-stage probability sample design, as described previously (12). Of 39,384 individuals who met eligibility criteria, 41.7% enrolled, representing 16,415 persons from 9,872 households. A comprehensive battery of interviews relating to personal and family characteristics, health status and behaviors, and a clinical assessment with blood draw, were conducted at an in-person clinic baseline visit during 2008–2011. In the current study, a total of up to 12,747 participants who consented to participate genetic studies were included. The study was approved by the Institutional Review Boards at all participating institutions, and all participants gave written informed consent.

Measurements

Measurements of weight and BF% were obtained from the Tanita body composition analyzer (model TBF-300A; Tanita Corporation, Arlington Heights, IL). Height and waist and hip circumference were measured to the nearest centimeter based on a standard protocol (www.cscc.unc.edu/hchs). Body weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood samples (fasting and after a 2-hour oral glucose load) were collected and processed according to standardized protocols (www.cscc.unc.edu/hchs). Total serum cholesterol was measured using a cholesterol oxidase enzymatic method and HDL cholesterol with a direct magnesium/dextran sulfate method. LDL cholesterol was calculated using the Friedewald equation (13). Plasma glucose was measured using a hexokinase enzymatic method (Roche Diagnostics). Hemoglobin A1c (HbA1c) was measured using a Tosoh G7 Automated HPLC Analyzer (Tosoh Bioscience). Fasting insulin was measured using two commercial immunoassays (ELISA, Mercodia AB, Uppsala, Sweden; and sandwich immunoassay on a Roche Elecsys 2010 Analyzer, Roche Diagnostics, Indianapolis, IN); early measures conducted with the Mercodia assay were calibrated, and values were equivalent to the Roche method. Homeostatic model assessment of insulin resistance (HOMA-IR) was computed based on the following equation: fasting glucose × fasting insulin/405 (14).

Genotype data

Four SNPs (rs2943650, rs2972146, rs2943641, and rs2943634) near *IRS1*, previously identified in GWAS for BF%, insulin resistance and type 2 diabetes, blood lipids, and coronary artery disease (2, 3, 4, 5), were analyzed in the current study. Genotype data on SNPs rs2943641 and rs2943634 were derived from the HCHS/SOL Custom array (15041502 B3), which consists of the Illumina Omni 2.5M array (HumanOmni2.5-8v1-1) plus ~150k custom SNPs. Genotype and quality control (QC) were performed by Illumina Microarray Service at LA Biomed and the HCHS/SOL Genetic Analysis Center. The QC process and quality filters used at HCHS/SOL Genetic Analysis Center have been previously

described (15, 16). SNPs rs2943650 and rs2972146 were imputed based on the 1000 Genomes Project phase 1 reference panel including Hispanic/Latino populations (i.e., Mexicans, Colombians and Puerto Ricans), using SHAPEIT2 (v2.r644) (17) and IMPUTE2 (v2.3.0) (18), both with almost perfect imputation scores (info= 0.998 and 0.999, respectively). Genetic principal components (PC) and kinship coefficients (KC) were calculated using PC-AiR and PC-Relate to provide PC estimates robust to relatedness and KC estimates robust to population structure, admixture and deviations from Hardy-Weinberg Equilibrium (16).

Identification of Hispanic/Latino background

Individuals were classified into six “genetic analysis subgroups” (Hispanic/Latino background groups: Cuban, Dominican, Puerto Rican, Mexican, Central American, or South American) based on their self-reported background and position in the n-dimensional space defined by the first 5 genetic principal components (PCs) (16). For each group, a 99% tolerance hyper-ellipsoid was defined based on individuals who also self-reported as that background. Individuals within the hyper-ellipsoid for their self-reported background group were assigned to the corresponding genetic analysis group. Individuals who were outside the hyper-ellipsoid for their self-reported background group (or those who self-reported as “Other” or “Mixed") were assigned to the genetic analysis group with the closest hyper-ellipsoid center. The concordance between the six genetic analysis subgroups and the specific Hispanic/Latino background groups reported by participants is very high (range 92–98%, mean 96%).

Statistical analysis

We used a linear mixed model (LMM) to examine associations of *IRS1* variants with BF% and other metabolic traits, adjusted for fixed effect covariates, including age, sex, field center, sampling weights, Hispanic/Latino background (six genetic analysis subgroups), and the first five PCs. Genetic relatedness (a matrix of pairwise kinship coefficients), household membership and census block group membership were also modeled as random effects to account for correlation between trait values of individuals. Variance components for each random effect were estimated under the null model (no genotype main effect) using Average Information Restricted Maximum. For each SNP, the effect size (Beta) and its standard error (SE) were estimated by using generalized least squares with the trait covariance structure estimated from the null model. A Wald test was performed to test for association at each SNP. Because associations between *IRS1* variants and BF% were previously reported to be more pronounced in men than in women (2), all analyses were also performed in men and women separately. In addition, associations with BF% were also stratified by Hispanic/Latino background (6 genetic analysis subgroups).

For individuals using lipid-lowering medications, we added a constant to each of their lipid traits, of which the amount was determined by the class of medication used (19). Associations with glycemic traits (fasting glucose, fasting insulin, HbA1c, 2-hour glucose, and HOMA-IR) were tested in individuals without diabetes. As distributions for BMI, triglycerides, fasting insulin and HOMA-IR were right-skewed, values were natural log-transformed before the analyses. Waist circumference and Waist-to-hip ratio (WHR) were

also adjusted for BMI. All association analyses were repeated after inverse normal transformation of residuals after fitting the null model to an approximate mean of 0 and an approximate SD of 1, allowing comparison of effect sizes across different traits.

Results

Description of genotype and phenotype data

Among the 12,747 US Hispanics/Latinos (5,232 men and 7,515 women) included in the analyses, Hispanic/Latino backgrounds were: 11% Central American, 18% Cuban, 9% Dominican, 37% Mexican, 18% Puerto Rican, and 7% South American. In addition, 20% of participants had diabetes, and 5% of participates had self-reported coronary heart disease. The mean (SD) of BF% is 28.1 (8.2)% in men and 38.9 (7.7)% in women (Table 1).

The previously identified BF%-associated variant, rs2943650, showed moderate-to-strong LD with the other three *IRS1* variants, rs2943634 (r^2=0.65), rs2943641 (r^2=0.75), and rs2972146 (r^2=0.64), in US Hispanics/Latinos (Supplemental Table 1), while these variants showed a high LD pattern in Europeans (r^2>0.8, according to HapMap CEU). The minor allele frequency (MAF) of the variant rs2943650 (C-allele) was 29%, and varied across Hispanic/Latino backgrounds, ranging from 20% in Mexicans to 49% in Dominicans (Supplemental Table 2).

IRS1 variants, body fat percentage and other adiposity traits

In a pooled analysis of all participants, the minor allele (C-allele) of rs2943650 was significantly associated with higher BF% (β=0.34 ± 0.11% per allele; *P*=0.002) (Table 2). The association tended to be more pronounced in women (β=0.41± 0.18%; *P*=0.003) than in men (β=0.28 ± 0.14%; *P*=0.11), but this sex difference was not significant. Using the inverse-normal-transformed data to compare effect sizes, we found that the association with BF% was stronger in Hispanic/Latino women than that previously reported in European women (β=0.054 ± 0.018SD vs β=0.008 ± 0.011SD; *P*=0.03), while there was no significant difference between Hispanic/Latino men and European men (β=0.032 ± 0.022SD vs β=0.035 ± 0.009SD; *P*=0.88) (data in Europeans were reported by Kilpeläinen et al. (2)). In addition, the minor allele (C-allele) of rs2943650 was significantly associated with higher BMI (natural log-transformed) (β=0.007±0.003; *P*=0.013), but not associated with BMI-adjusted waist circumference (*P*=0.77) or WHR (*P*=0.92) (Supplemental Table 3).

Consistent with the modest LD between the four *IRS1* SNPs, the associations of the other three *IRS1* variants with BF% was consistent with those observed for rs2943650 (Table 2). We examined whether either of the four variants was driving the observed associations using conditional analyses, but found no evidence for any one being the lead SNP, suggesting that they all represent the same signal within or near the *IRS1* locus.

We further examined associations between rs2943650 and BF% among individuals with different Hispanic/Latino backgrounds separately. The minor-allele of rs2943650 showed significant associations (Cuban and Dominican) or non-significant associations (Central American, Mexican and Puerto Rican) with higher BF% among five of the six Hispanic/Latino background groups, whereas a non-significant trend toward an inverse association

was observed in South Americans (Figure 1). However, there was no statistically significant heterogeneity between groups (P>0.27; Cochran's Q test). Moreover, we examined associations between rs2943650 and BF% in men and women separately within each Hispanic/Latino background group, and did not find significant sex difference (All P>0.05) (Supplemental Table 4). However, a nominal-significant inverse association between rs2943650 and BF% was observed in men of South American group (P=0.027).

IRS1 variants and metabolic traits

We then examined the associations of the *IRS1* variants with multiple metabolic traits (Supplemental Table 3; Figure 2). The minor allele (BF%-increasing-allele) of rs2943650 was significantly associated with lower HbA1c (P=0.003), higher HDL cholesterol (P=0.002), and lower triglycerides (P=0.03); and these associations remained significant after further adjusting for BF%. Using the inverse-normal-transformed data, the effect size of rs2943650 minor allele on BF% (0.041 ± 0.014 SD per allele) was similar with that on HbA1c (−0.043 ± 0.014 SD per allele), and slightly larger than those on HDL cholesterol (0.033 ± 0.014 SD per allele) and triglycerides (−0.027 ± 0.014 SD per allele) (Figure 2). After adjustment for multiple tests for one genetic variant (4 SNPs are in the moderate-to-strong LD) and 11 independently measured traits (we did not count HOMA-IR which was calculated based on fasting insulin and glucose), associations of rs2943650 with BF%, HbA1c and HDL-c remained significant (P<0.0045).

Generally similar results were observed for the other three *IRS1* variants (Supplemental Table 3). The minor allele of *IRS1* variants were associated with lower fasting insulin (P=0.08 to 0.01) and lower HOMA-IR (P=0.08 to 0.009) after, but not before, adjusting for BF% (Supplemental Table 3). In addition, associations of *IRS1* variants with adiposity measures and lipids did not materiality change in sensitivity analysis after we excluded participants with diabetes and self-reported coronary heart disease (Supplemental Table 5).

Discussion

In the present study, we confirmed and extended previous findings (2, 8) that genetic variation near *IRS1* associates with increased adiposity, but a favorable metabolic profile (low levels of fasting insulin, HOMA-IR, HbA1c and triglyceride, and high HDL cholesterol levels) among individuals of diverse Hispanic/Latino backgrounds. In addition, we also found a relatively stronger genetic effect on BF% in Hispanic/Latino women than that previously reported in European women.

Previous data in Europeans showed that the association between *IRS1* rs2943650 variant and BF% was more pronounced in men than in women (2), while we did not observe such sex-difference in US Hispanics/Latinos. Moreover, our further analysis indicated that the genetic effect on BF% was larger in Hispanic/Latino women than that in European women, but there was no significant difference between Hispanic/Latino men and European men. It has been speculated that the previously observed relatively weaker genetic effect on adiposity in women might be related to more subcutaneous fat in women driven by hormones compared to men (20), which may attenuate the influence of *IRS1* variation on subcutaneous fat (2). However, it is unclear whether the observed ethnic-difference in genetic effect is related to

different fat deposition between Hispanic/Latino women and European women. Hispanic/Latino women have higher prevalence of obesity (9) and higher BF% than non-Hispanic white women (21, 22), but comparison of accurate fat deposition between them need further investigations. In addition, it is should be noted that the previous GWAS in Europeans included multiple cohorts using bioimpedance analysis (BIA) and/or dual-energy X-ray absorptiometry (DEXA) measures (2), while we used Tanita-BIA to estimate BF%. However, our method has been reported to have good agreement with DEXA in Hispanics/Latinos (23), and similar results between using BIA and DEXA measures were reported in the previous GWAS in Europeans (2)..

Genetic heterogeneity in associations with adiposity measures (e.g., BF% and WHR) between men and women (sex-specific effect) has been observed in previous studies. For example, a number of loci (including *IRS1*) have shown significant sex-specific effects on BMI-adjusted WHR and BF% in recent GWAS (2, 24, 25). In addition, a few SNPs exhibited significant evidence for heterogeneity of effect on BMI between ethnic groups, but it remains unclear whether these results may reflect true heterogeneity or are due to (LD) differences across ancestries (25). Nevertheless, recent large GWAS meta-analyses including multiple ethnic groups considering genetic heterogeneity provides insight into the genetic architecture of complex metabolic diseases (25, 26). However, ethnic-specific effects of BF %-associated SNPs have not been well-examined as previous studies included most individuals of European-ancestry but few of non-European-ancestry (2, 24). Thus, the observed ethnic-difference in women needs validation, and future studies using same methods with more accurate adiposity measures across different ethnic groups might help clarify this interesting finding.

One unique element of this study is the diversity of Hispanic/Latino backgrounds in our sample. Previous genetic studies on obesity and related metabolic outcomes conducted in US Hispanics/Latinos have largely examined individuals of single background (mostly Mexicans) or unidentified origins (8, 27, 28, 29, 30). However, the complexity of the biological and cultural diversity within US Hispanics/Latinos has been well-acknowledged. Our genetic analysis identified six genetic groups (Cuban, Dominican, Puerto Rican, Mexican, Central American, or South American), which are highly consistent with the self-reported Hispanic/Latino backgrounds. In our study, associations with higher BF% were generally consistent among these groups, except for the South American group which showed a non-significant inverse association between the rs2943650 and BF%. This discrepancy might be also due to relatively small sample size, different phenotype and/or genotype distributions, since South American group was the smallest group, and had the lowest BF% and MAF of SNPs among 6 Hispanic background groups. Nevertheless, there was no significant heterogeneity across groups.

In addition to the confirmed associations of *IRS1* variants with fasting insulin, HOMA-IR, HDL cholesterol and triglycerides (2, 3, 4), a novel finding of our study is the significant association between *IRS1* variants and HbA1c levels. Given the well-established role of *IRS1* in insulin resistance, it is possible that the observed associations with HbA1c might be through the regulation of blood glucose. A recent study suggested that the *IRS1* G972R missense is associated with uncontrolled diabetes (e.g., HbA1c >8%) through interaction

with oral anti-diabetes drugs among patients with type 2 diabetes (31). However, *IRS1* variants were not associated with HbA1c levels in previous GWAS among Europeans and Asians (32, 33). Moreover, *IRS1* variants were associated with insulin resistance to a lesser extent (only significant after adjusting for BF%) and were not associated with fasting glucose in our study of US Hispanics/Latinos, suggesting other pathways beyond glucose metabolism might be involved (32, 33).

The mechanisms underlying the observed associations of *IRS1* variants with both increased adiposity and a favorable metabolic profile remain unclear. Kilpeläinen et al. (2) found that the BF%-increasing allele of rs2943650 was associated with increased abdominal subcutaneous fat but not visceral fat, which may contribute to a favorable metabolic profile. This association suggests a role of the *IRS1* locus in the distribution and storage of body fat. A number of studies have suggested that increased leg fat (mainly subcutaneous fat) is associated with favorable levels of metabolic traits, especially with low insulin resistance, low triglycerides and high HDL-cholesterol (34, 35, 36, 37), but no data on associations between *IRS1* variants and leg fat have been published. On the other hand, our findings may also reflect the fact that high insulin sensitivity may promote lipid storage in adipocytes and thus results in increased adiposity. In line with this speculation, genetic scores of insulin sensitivity increasing alleles (including the *IRS1* variant) have been associated with increased adiposity (38, 39). Indeed, the SNP rs2943650 is significantly associated with gene expression of *IRS1* in subcutaneous adipose tissue (P=3.5×10^{-7}) (data from the GTEx, http://www.gtexportal.org), suggesting a role of the *IRS1* variant in regulating insulin signaling pathway in adipose tissue. However, we could not exclude the independent pleiotropic effects of *IRS1* variants on adiposity and metabolic traits. A number of obesity-susceptibility loci were found to show pleiotropic associations with various metabolic traits, and half of the significant associations were directionally inconsistent with the phenotypic correlations (40).

Major strengths of this study include a population-representative sample of US Hispanics/Latinos of diverse backgrounds, and multiple adiposity and metabolic biomarkers measured. However, our study lacked data on regional fat deposition measured by DEXA, computed tomography or magnetic resonance imaging, as these approaches require high cost and time investment for large epidemiological studies. Other limitations of the study include the nature of cross-sectional data and hence a lack of data on incident diabetes and cardiovascular disease events. Future studies using longitudinal data may help clarify whether *IRS1* variation first influence adiposity and then affect metabolic diseases, or whether these associations are independent.

In summary, this study generally confirmed the previous GWAS findings of *IRS1* variants associated with increased adiposity and a favorable metabolic profile in US Hispanics/Latinos. We also found a relatively stronger genetic effect on BF% in Hispanic/Latino women compared to European women. These findings further imply the complexity of biological and molecular mechanisms that link obesity with metabolic diseases. Studies with more accurate adiposity measures (e.g., regional fat deposition) are needed to further investigate relationships between *IRS1* genetic variants, adiposity, and metabolic traits in US Hispanics/Latinos.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Emerging Risk Factors C, Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011; 377:1085–1095. [PubMed: 21397319]
2. Kilpelainen TO, Zillikens MC, Stancakova A, Finucane FM, Ried JS, Langenberg C, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nature genetics. 2011; 43:753–760. [PubMed: 21706003]
3. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proenca C, et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nature genetics. 2009; 41:1110–1115. [PubMed: 19734900]
4. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010; 466:707–713. [PubMed: 20686565]
5. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, et al. Genomewide Association Analysis of Coronary Artery Disease. New England Journal of Medicine. 2007; 357:443–453. [PubMed: 17634449]
6. Araki E, Lipes MA, Patti M-E, Bruning JC, Haag Iii B, Johnson RS, et al. Alternative pathway of insulin signalling in mice with targeted disruption of the IRS-1 gene. Nature. 1994; 372:186–190. [PubMed: 7526222]
7. Tamemoto H, Kadowaki T, Tobe K, Yagi T, Sakura H, Hayakawa T, et al. Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1. Nature. 1994; 372:182–186. [PubMed: 7969452]
8. Zheng JS, Arnett DK, Parnell LD, Smith CE, Li D, Borecki IB, et al. Modulation by dietary fat and carbohydrate of IRS1 association with type 2 diabetes traits in two populations of different ancestries. Diabetes care. 2013; 36:2621–2627. [PubMed: 23596181]

9. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA: the journal of the American Medical Association. 2012; 307:491–497. [PubMed: 22253363]
10. Rodriguez CJ, Allison M, Daviglus ML, Isasi CR, Keller C, Leira EC, et al. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. Circulation. 2014; 130:593–625. [PubMed: 25098323]
11. Qi Q, Strizich G, Hanna DB, Giacinto RE, Castaneda SF, Sotres-Alvarez D, et al. Comparing measures of overall and central obesity in relation to cardiometabolic risk factors among US Hispanic/Latino adults. Obesity (Silver Spring). 2015; 23:1920–1928. [PubMed: 26260150]
12. Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol. 2010; 20:642–649. [PubMed: 20609344]
13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical chemistry. 1972; 18:499–502. [PubMed: 4337382]
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28:412–419. [PubMed: 3899825]
15. Laurie CC, Doheny KF, Mirel DB, Pugh EW, Bierut LJ, Bhangale T, et al. Quality control and quality assurance in genotypic data for genome-wide association studies. Genetic epidemiology. 2010; 34:591–602. [PubMed: 20718045]
16. Conomos MP, Laurie CA, Stilp AM, Gogarten SM, McHugh CP, Nelson SC, et al. Genetic Diversity and Association Studies in US Hispanic/Latino Populations: Applications in the Hispanic Community Health Study/Study of Latinos. Am J Hum Genet. 2016; 98:165–184. [PubMed: 26748518]
17. Delaneau O, Zagury JF, Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. Nature methods. 2013; 10:5–6. [PubMed: 23269371]
18. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS genetics. 2009; 5:e1000529. [PubMed: 19543373]
19. National Cholesterol Education Program Expert Panel on Detection E, and Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]
20. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev. 2000; 21:697–738. [PubMed: 11133069]
21. Carpenter CL, Yan E, Chen S, Hong K, Arechiga A, Kim WS, et al. Body fat and body-mass index among a multiethnic sample of college-age men and women. Journal of obesity. 2013; 2013:790654. [PubMed: 23691288]
22. Li C, Ford ES, Zhao G, Balluz LS, Giles WH. Estimates of body composition with dual-energy X-ray absorptiometry in adults. Am J Clin Nutr. 2009; 90:1457–1465. [PubMed: 19812179]
23. Beeson WL, Batech M, Schultz E, Salto L, Firek A, Deleon M, et al. Comparison of body composition by bioelectrical impedance analysis and dual-energy X-ray absorptiometry in Hispanic diabetics. Int J Body Compos Res. 2010; 8:45–50. [PubMed: 21318088]
24. Lu Y, Day FR, Gustafsson S, Buchkovich ML, Na J, Bataille V, et al. New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. Nat Commun. 2016; 7:10495. [PubMed: 26833246]
25. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015; 518:197–206. [PubMed: 25673413]
26. Replication DIG, Meta-analysis C, Asian Genetic Epidemiology Network Type 2 Diabetes C, South Asian Type 2 Diabetes C, Mexican American Type 2 Diabetes C, Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples C. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet. 2014; 46:234–244. [PubMed: 24509480]

27. DeMenna J, Puppala S, Chittoor G, Schneider J, Kim JY, Shaibi GQ, et al. Association of common genetic variants with diabetes and metabolic syndrome related traits in the Arizona Insulin Resistance registry: a focus on Mexican American families in the Southwest. Human heredity. 2014; 78:47–58. [PubMed: 25060389]
28. Consortium STD, Williams AL, Jacobs SB, Moreno-Macias H, Huerta-Chagoya A, Churchhouse C, et al. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. Nature. 2014; 506:97–101. [PubMed: 24390345]
29. Graff M, Fernandez-Rhodes L, Liu S, Carlson C, Wassertheil-Smoller S, Neuhouser M, et al. Generalization of adiposity genetic loci to US Hispanic women. Nutrition & diabetes. 2013; 3:e85. [PubMed: 23978819]
30. Young KA, Fingerlin TE, Langefeld CD, Lorenzo C, Haffner SM, Wagenknecht LE, et al. Exploring differences in adiposity in two U.S. Hispanic populations of Mexican origin using social, behavioral, physiologic and genetic markers: the IRAS Family Study. Ethnicity & disease. 2012; 22:65–71. [PubMed: 22774311]
31. Prudente S, Morini E, Lucchesi D, Lamacchia O, Bailetti D, Mercuri L, et al. IRS1 G972R missense polymorphism is associated with failure to oral antidiabetes drugs in white patients with type 2 diabetes from Italy. Diabetes. 2014; 63:3135–3140. [PubMed: 24947357]
32. Chen P, Takeuchi F, Lee JY, Li H, Wu JY, Liang J, et al. Multiple nonglycemic genomic loci are newly associated with blood level of glycated hemoglobin in East Asians. Diabetes. 2014; 63:2551–2562. [PubMed: 24647736]
33. Soranzo N, Sanna S, Wheeler E, Gieger C, Radke D, Dupuis J, et al. Common variants at 10 genomic loci influence hemoglobin A(1)(C) levels via glycemic and nonglycemic pathways. Diabetes. 2010; 59:3229–3239. [PubMed: 20858683]
34. Boorsma W, Snijder MB, Nijpels G, Guidone C, Favuzzi AM, Mingrone G, et al. Body composition, insulin sensitivity, and cardiovascular disease profile in healthy Europeans. Obesity. 2008; 16:2696–2701. [PubMed: 18927552]
35. Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Yudkin JS, et al. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. Diabetes care. 2004; 27:372–377. [PubMed: 14747216]
36. Wu H, Qi Q, Yu Z, Sun Q, Wang J, Franco OH, et al. Independent and opposite associations of trunk and leg fat depots with adipokines, inflammatory markers, and metabolic syndrome in middle-aged and older Chinese men and women. J Clin Endocrinol Metab. 2010; 95:4389–4398. [PubMed: 20519350]
37. Zhang X, Hu EA, Wu H, Malik V, Sun Q. Associations of leg fat accumulation with adiposity-related biological factors and risk of metabolic syndrome. Obesity (Silver Spring). 2013; 21:824–830. [PubMed: 23404933]
38. Yaghootkar H, Scott RA, White CC, Zhang W, Speliotes E, Munroe PB, et al. Genetic evidence for a normal-weight "metabolically obese" phenotype linking insulin resistance, hypertension, coronary artery disease, and type 2 diabetes. Diabetes. 2014; 63:4369–4377. [PubMed: 25048195]
39. Scott RA, Fall T, Pasko D, Barker A, Sharp SJ, Arriola L, et al. Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independent of obesity. Diabetes. 2014; 63:4378–4387. [PubMed: 24947364]
40. van Vliet-Ostaptchouk JV, den Hoed M, Luan J, Zhao JH, Ong KK, van der Most PJ, et al. Pleiotropic effects of obesity-susceptibility loci on metabolic traits: a meta-analysis of up to 37,874 individuals. Diabetologia. 2013; 56:2134–2146. [PubMed: 23827965]

STUDY IMPORTANCE

What is already known about this subject?

- Adiposity is related to impaired metabolic profiles and adverse cardiovascular health outcomes.
- *IRS1* genetic variation has been associated with elevated body fat percentage but a favorable metabolic profile in non-Hispanic White population.
- U.S. Hispanics/Latinos, especially Hispanic/Latino women, have higher prevalence of obesity and higher body fat percentage, compared to their non-Hispanic White counterparts.

What does this study add?

- We show among a novel, population-based sample of up to 12,730 Hispanics/Latinos that *IRS1* variation is associated with increased adiposity but favorable levels of metabolic biomarkers.
- Genetic effect of *IRS1* variation on BF% is stronger in Hispanic/Latino women than that previously reported in non-Hispanic White women, while there is no significant difference between Hispanic/Latino men and non-Hispanic White men.

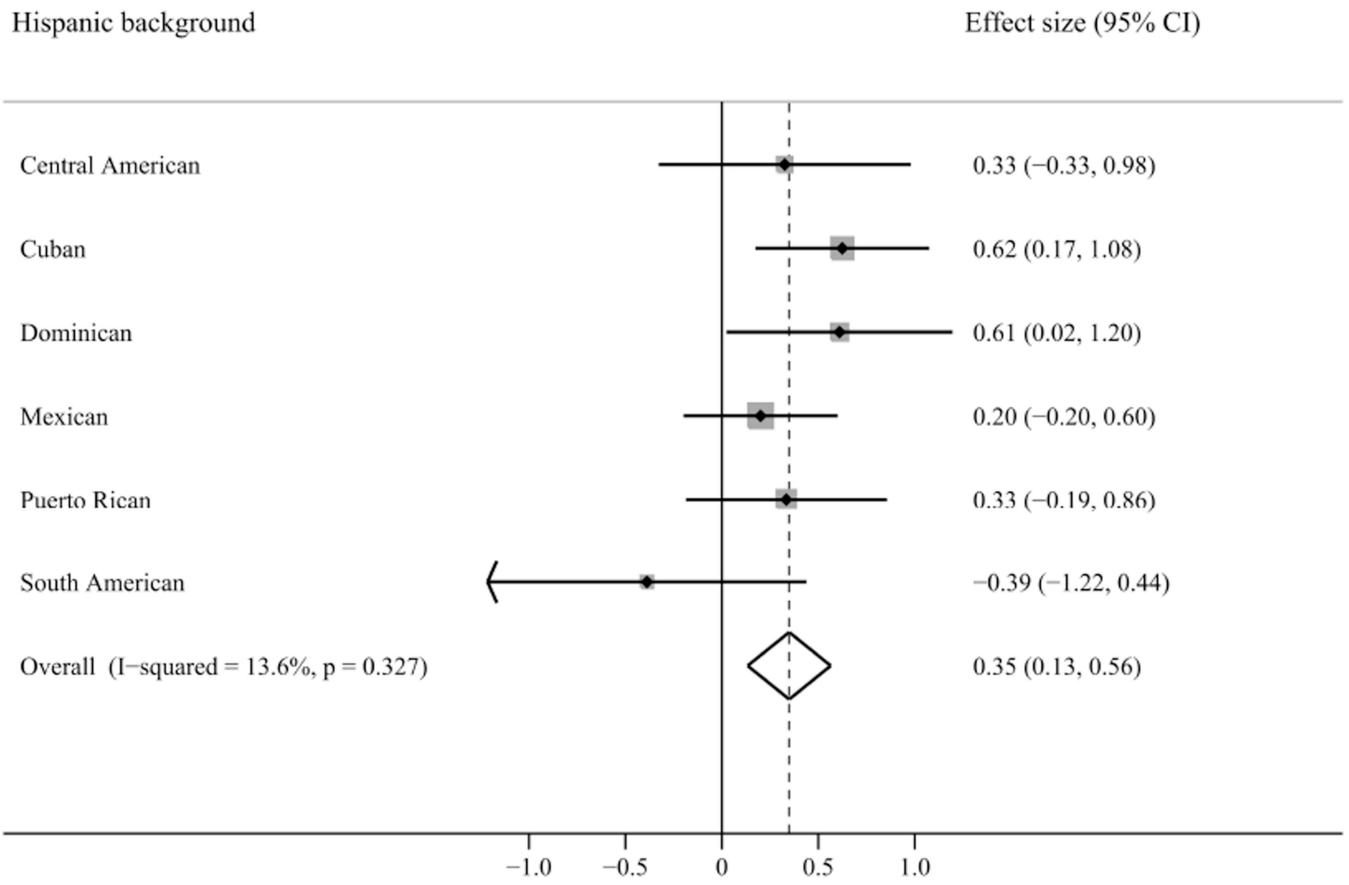

Figure 1.

Association between the SNP rs2943650 near *IRS1* and Body fat percentage across Hispanic/Latino background groups.

*Data are effect size (95% confidence interval) for each minor allele of rs2943650 on body fat percentage (%), adjusted for age, sex, sampling weights, relatedness and population structure (kinship coefficients and eigenvectors). Overall results were pooled by fixed effect meta-analysis.

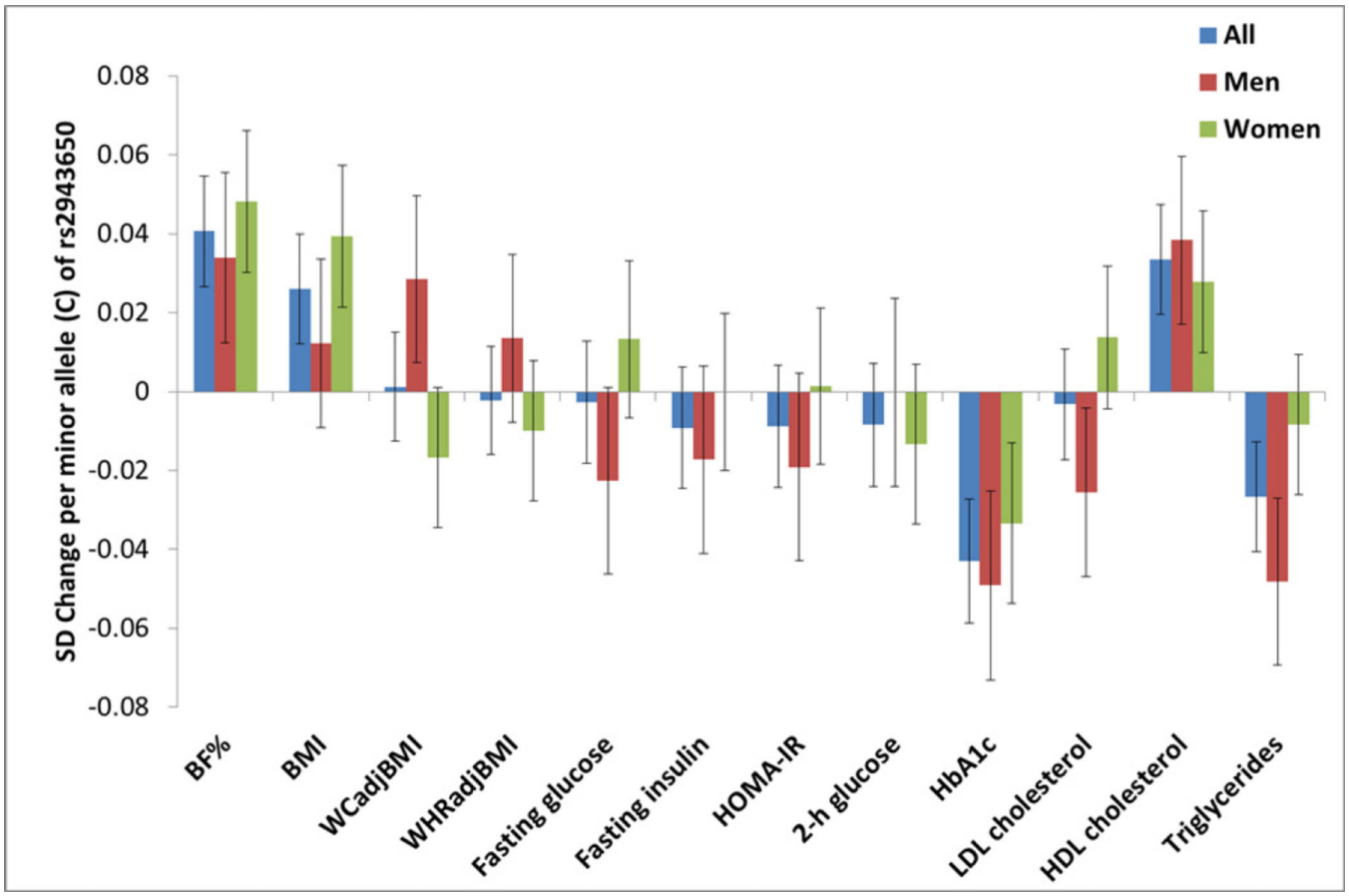

Figure 2.

Associations of the minor (C) allele of rs2943650 near *IRS1* with obesity traits, glycemic traits and blood lipids.

All traits were inverse normally transformed to approximate normality (mean= 0, SD=1) in men and women separately, adjusted for age, sex (if appropriate), sampling weights, Hispanic/Latino background, relatedness and population structure (kinship coefficients and eigenvectors). Data are effect size and standard errors (error bars).

Table 1

Characteristics of participants

	All	Men	Women	P for sex-difference
No. of participants	12747	5232	7515	-
Hispanic/Latino background *				-
Central American	1397 (11)	568 (11)	829 (11)	
Cuban	2257 (18)	1062 (20)	1195 (16)	
Dominican	1180 (9)	410 (8)	770 (10)	
Mexican	4750 (37)	1877 (36)	2873 (38)	
Puerto Rican	2242 (18)	945 (18)	1297 (17)	
South American	921 (7)	370 (7)	551 (7)	
Age, years	46.1 (13.9)	45.3 (14.2)	46.7 (13.6)	<0.001
Diabetes, n (%)	2501 (20)	997 (19)	1504 (20)	0.01
Self-reported coronary artery disease, n (%)	700 (5)	379 (7)	321 (4)	<0.001
Body fat percentage, %	34.5 (9.5)	28.1 (8.2)	38.9 (7.7)	<0.001
BMI, kg/m^2	29.8 (6.1)	29.1 (5.3)	30.3 (6.5)	<0.001
Waist circumference, cm	98.3 (13.9)	99.1 (13.4)	97.8 (14.3)	<0.001
Waist-to-hip ratio	0.92 (0.08)	0.95 (0.07)	0.90 (0.07)	<0.001
Fasting glucose, mg/dl	93.8 (8.3)	95.9 (8.2)	92.3 (8.1)	<0.001
Fasting insulin, mU/L	12. 1(8.4)	12.1 (9.0)	12. 1(8.4)	0.88
HOMA-IR	2.8 (2.2)	2.9 (2.3)	2.8 (2.1)	0.009
2-hour glucose, mg/dl	115.8 (31.2)	110.7 (31.8)	119.3 (30.2)	<0.001
HbA1c, %	5.47 (0.37)	5.45 (0.37)	5.47 (0.36)	0.001
LDL cholesterol, mg/dl †	128.9 (38.1)	128.6 (37.8)	129.1 (38.4)	<0.001
HDL cholesterol, mg/dl †	48.7 (13.2)	44.4 (11.9)	51.8 (13.2)	<0.001
Triglycerides, mg/dl †	142.6 (102.3)	159.5 (122.5)	130.8 (83.5)	<0.001

Data are mean (SD) or n (%).

* Hispanic/Latino background was defined based on their self-reported background and position in the n-dimensional space defined by the first 5 genetic principal components (PCs).

† These variables were adjusted to account for average effects of lipid medication use.

Table 2

Association between SNPs near IRS1 and Body fat percentage

SNP	Position	Minor allele	Minor allele	All			Men		Women		P for sex-differences
				MAF	Beta (SE)*	*P*	Beta (SE)*	*P*	Beta (SE)*	*P*	
rs2943650	Chr2:227105921	C	T	0.29	0.34 (0.11)	0.002	0.28 (0.18)	0.11	0.41 (0.14)	0.003	0.57
rs2943634	Chr2:227068080	A	C	0.27	0.37 (0.11)	0.001	0.26 (0.18)	0.15	0.45 (0.14)	0.002	0.40
rs2943641	Chr2:227093745	T	C	0.24	0.32 (0.12)	0.006	0.28 (0.19)	0.14	0.36 (0.14)	0.013	0.73
rs2972146	Chr2:227100698	G	T	0.22	0.22 (0.12)	0.065	0.19 (0.19)	0.32	0.27 (0.15)	0.069	0.74

*Effect size for each minor allele of SNP on body fat percentage (%), adjusted for age, sex (if appropriate), sampling weights, Hispanic/Latino background, relatedness and population structure (kinship coefficients and eigenvectors).