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Dietary Fat Modifies the Effects of *FTO* Genotype on Changes in Insulin Sensitivity[1–3]

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Abstract

Background: The common variants in the fat mass and obesity–associated (*FTO*) gene have been associated with obesity and insulin resistance. Recently, studies also linked *FTO* variants with macronutrient intakes.

Objective: We aimed to investigate whether diet interventions varying in macronutrients modified the effects of *FTO* genotypes on changes in insulin resistance.

Methods: We genotyped *FTO* variants rs1558902 and rs9939609 and measured insulin resistance in fasting plasma samples at baseline and at 6-mo and 2-y visits in 743 overweight or obese adults (aged 30–70 y, 60% women) from a randomized weight-loss dietary interventional trial, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. We assessed interactions between *FTO* variants and intakes of dietary fat and protein in relation to change in body weight and insulin resistance using generalized estimating equation models.

Results: We found significant interactions between rs1558902 and dietary fat on changes in homeostasis model assessment of insulin resistance (HOMA-IR) and insulin (P = 0.003 and 0.004, respectively). Each risk allele (*A*) of rs1558902 showed a trend to be related to a 0.05-unit less reduction in both log(insulin) and log(HOMA-IR) among the participants assigned to low-fat diets (both $P = 0.06$), but this was not significantly related to reduction in those assigned to high-fat diets (both $P > 0.1$) during the 2-y period of intervention. Our data showed that the association between rs9939609 and changes in insulin resistance was not modified by diet macronutrient intakes.

Conclusions: Our results show that carriers of the risk alleles of rs1558902 benefit differently in improving insulin sensitivity by consuming high-fat weight-loss diets rather than low-fat diets. Still, given our data, we acknowledge it is difficult to determine whether fat or carbohydrate contributed to the observed associations. This trial was registered at clinicaltrials.gov as NCT00072995. *J Nutr* 2015;145:977–82.

Keywords: FTO, dietary intervention, gene-diet interaction, diabetes, insulin resistance

Introduction

The prevalence of diabetes in the United States has become of epidemic proportions, reaching ~8.3% of the population (1), and type 2 diabetes accounts for up to 95% of diabetes cases (2). Insulin resistance, which is closely related to obesity, plays a determinant role in the development of type 2 diabetes (3) and presents 10–20 y before the onset of the disease (4, 5). Interestingly, the common variants in the fat mass and obesity–associated (*FTO*)[9] gene were also related to insulin resistance and risk of type 2 diabetes (6–8).

Recently, we found that genetic variation in *FTO* was associated with habitual-consumption of macronutrients (9). Similar associations were also found in the Cohorts for Heart and Aging

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[3] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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[9] Abbreviations used: *FTO*, fat mass and obesity–associated; GEE, generalized estimating equation; HOMA-β, homeostasis model assessment of β cell function; POUNDS LOST, Preventing Overweight Using Novel Dietary Strategies.

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Research in Genomic Epidemiology consortium (10). In addition, a previous diet intervention study found that dietary fat intake might modify one *FTO* variant in relation to changes in insulin resistance (11). However, this study only assessed the effects of short-term (10-wk) dietary intervention, and it remains unclear whether the *FTO*-macronutrient interactions persist in long-term interventions.

In the present study, we assessed interactions between 2 common variations in *FTO* and intakes of dietary fat and protein in relation to change in body weight and insulin resistance among participants in a 2-y randomized dietary intervention weight-loss trial, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial.

Methods

Study population. The POUNDS LOST trial is a randomized dietary intervention trial to compare the effects of energy-reduced diets with different compositions of fat, protein, and carbohydrate on weight change over a 2-y period. The study design and methods were previously described in detail (12). In summary, 811 overweight or obese subjects, aged 30–70 y, were randomly assigned to 1 of 4 energy-limited diets. The target percentages of energy derived from fat, protein, and carbohydrate in the 4 diets were 20%, 15%, and 65%; 20%, 25%, and 55%; 40%, 15%, and 45%; and 40%, 25%, and 35%, respectively. Two diets were low in fat (20%) and 2 were high in fat (40%) and 2 were average in protein (15%) and 2 were high in protein (25%) according to a 2-by-2 factorial design. Each participant's caloric prescription represented a deficit of 750 kcal/d from baseline, as calculated from the person's resting energy expenditure and activity level. The main exclusion criteria were as follows: participants who had diabetes treated with medication or unstable cardiovascular disease, those who used medications to influence body weight, and those who expressed insufficient motivation to complete the study. The study was approved by the human subjects committee at the Harvard School of Public Health and Brigham and Women's Hospital, Boston, MA, and the Pennington Biomedical Research Center of the Louisiana State University System, Baton Rouge, LA, and by a data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. All participants provided written informed consent.

Measurements. Body weights were measured in the morning before breakfast at baseline and at the 6-mo and 2-y visits. Height was measured at baseline. BMI was calculated as weight/height^2 (kg/m^2). Race was self-reported and grouped as white, black, and other. Fasting blood samples were collected at baseline and at the 6-mo and 2-y visits. Analyses of glucose and insulin were performed at the Clinical Laboratory at Pennington. Glucose and insulin were measured by using an immunoassay with chemiluminescent detection on the Immulite analyzer (Diagnostic Products). Insulin resistance was estimated by HOMA-IR and calculated from fasting glucose and insulin concentrations (13) as shown in Equation *1*.

$$\frac{\text{fasting blood glucose(mg/dL)} \times \text{fasting blood insulin}(\mu\text{U/mL})}{405} \quad (1)$$

β Cell function was estimated by homeostasis model assessment of β cell function (HOMA-β) (13) and calculated as shown in Equation *2*.

$$\frac{360 \times \text{fasting blood insulin}(\mu\text{U/mL})}{\text{fasting blood glucose(mg/dL)} - 63}\% \quad (2)$$

Genotyping. DNA was extracted from the buffy coat fraction of centrifuged blood by using the QIAmp Blood Kit (Qiagen). The *FTO* variant rs1558902 was genotyped successfully in 743 and the variant rs9939609 in 738 of 811 total participants by using the OpenArray SNP

TABLE 1 Characteristics of study participants according to *FTO* rs1558902 and rs9939609 genotypes[1]

	rs1558902				rs9939609			
Baseline characteristics	*TT* (*n* = 282)	*AT* (*n* = 325)	*AA* (*n* = 136)	*P*	*TT* (*n* = 228)	*AT* (*n* = 360)	*AA* (*n* = 150)	*P*
Age, y	49.8 ± 9.4	51.8 ± 9.3	51.5 ± 8.4	0.04	50.0 ± 9.9	51.5 ± 9.1	51.4 ± 8.5	0.10
Male	93 (33.0)	136 (41.9)	59 (43.4)	0.04	86 (37.7)	145 (40.3)	54 (36.0)	0.62
Race				<0.01				0.05
White	180 (63.8)	285 (87.7)	130 (95.6)		182 (79.7)	284 (78.9)	124 (82.7)	
Black	84 (29.8)	25 (7.7)	3 (2.2)		28 (12.3)	61 (16.9)	23 (15.3)	
Other	18 (6.4)	15 (4.6)	3 (2.2)		18 (7.9)	15 (4.2)	3 (2.0)	
Dietary fat composition				0.48				0.41
High-fat diets (40% of energy)	136 (48.2)	160 (49.2)	74 (54.4)		112 (49.1)	174 (48.3)	82 (54.7)	
Low-fat diets (20% of energy)	146 (51.8)	165 (50.8)	62 (45.6)		116 (50.9)	186 (51.7)	68 (45.3)	
Dietary protein composition				0.69				0.59
High-protein diets (25% of energy)	145 (51.4)	157 (48.3)	65 (47.8)		119 (52.2)	175 (48.6)	71 (47.3)	
Average-protein diets (15% of energy)	137 (48.6)	168 (51.7)	71 (52.2)		109 (47.8)	185 (51.4)	79 (52.7)	
BMI, kg/m^2	33.0 ± 3.7	32.3 ± 4	33.1 ± 3.7	0.61	32.7 ± 3.8	32.5 ± 3.9	33.1 ± 3.8	0.51
Fasting glucose, mg/dL	91.1 ± 11.4	92.6 ± 12.6	91.9 ± 10.5	0.31	91.3 ± 11.8	92.3 ± 12.2	91.8 ± 11	0.58
Fasting insulin,[2] μU/ml	10.4 [9.0]	10.6 [8.0]	10.6 [8.1]	0.80	10.2 [8.3]	10.5 [8.4]	10.7 [8.5]	0.63
HOMA-IR[2]	2.3 [2.1]	2.4 [2.0]	2.5 [2.2]	0.63	2.3 [2.0]	2.4 [2.1]	2.5 [2.3]	0.56
HOMA-β[2]	1.4 [1.1]	1.3 [1.0]	1.3 [1.0]	0.45	1.4 [1.0]	1.3 [1.0]	1.3 [1.0]	0.87
Changes in outcomes at 2 y								
ΔFasting glucose, mg/dL	2.4 [9.4]	2.0 [9.2]	2.4 [8.9]	0.94	1.6 [8.8]	2.3 [8.9]	2.9 [10.5]	0.25
ΔFasting insulin, μU/mL	−1.0 [8.2]	−1.4 [5.7]	−1.5 [4.9]	0.70	−1.1 [8.6]	−1.4 [5.6]	−1.1 [5.2]	0.76
ΔHOMA-IR	−0.1 [2.1]	−0.2 [1.6]	−0.3 [1.4]	0.75	−0.2 [2.2]	−0.2 [1.6]	−0.1 [1.6]	0.63
ΔHOMA-β	−0.3 [1.1]	−0.3 [0.8]	−0.3 [0.6]	0.65	−0.3 [1.3]	−0.3 [0.8]	−0.3 [0.6]	0.88

[1] Values are means ± SDs, *n* (%), or medians [IQRs]. *P* values were calculated by chi-square test for categorical variables and by a general linear model for continuous variables with the assumption of an additive genetic model. *FTO*, fat mass and obesity–associated; HOMA-β, homeostasis model assessment of β cell function; Δ, change in respective outcomes (i.e., the values at 2 y minus baseline values); for ΔFasting insulin, ΔHOMA-IR, and ΔHOMA-β, this means the log-transformed values at 2 y minus the log-transformed baseline values.

[2] *P* values were calculated for the log-transformed values.

TABLE 2 Effects of *FTO* rs1558902 and rs9939609 genotypes on the response of glucose, insulin, and insulin resistance to the dietary fat intervention[1]

	rs1558902							rs9939609						
	Low-fat			High-fat				Low-fat			High-fat			
Outcomes	β	SE	*P*	β	SE	*P*	*P*-interaction	β	SE	*P*	β	SE	*P*	*P*-interaction
Model 1														
ΔFasting glucose, mg/dL	0.29	0.44	0.50	−0.17	0.49	0.50	0.28	0.08	0.46	0.86	0.47	0.56	0.40	0.44
ΔFasting insulin,[2] μU/mL	0.05	0.02	0.06	−0.04	0.03	0.12	0.003	0.04	0.02	0.10	−0.02	0.03	0.37	0.12
ΔHOMA-IR[2]	0.05	0.03	0.06	−0.04	0.03	0.14	0.004	0.04	0.03	0.12	−0.02	0.03	0.52	0.20
ΔHOMA-β[2]	0.04	0.03	0.21	−0.03	0.03	0.18	0.04	0.04	0.03	0.20	−0.03	0.03	0.21	0.08
Model 2														
ΔFasting glucose, mg/dL	0.29	0.43	0.51	−0.13	0.47	0.78	0.30	0.06	0.46	0.90	0.52	0.55	0.34	0.43
ΔFasting insulin,[2] μU/mL	0.05	0.02	0.06	−0.04	0.02	0.12	0.003	0.04	0.02	0.13	−0.02	0.02	0.38	0.15
ΔHOMA-IR[2]	0.05	0.03	0.06	−0.04	0.03	0.14	0.004	0.03	0.03	0.26	−0.02	0.03	0.52	0.24
ΔHOMA-β[2]	0.03	0.03	0.22	−0.03	0.03	0.19	0.05	0.03	0.03	0.24	−0.03	0.02	0.22	0.10

[1] *P* values for model 1 were adjusted for age, sex, race, follow-up time, baseline values for respective outcomes, and concurrent weight change; *P* values for model 2 were further adjusted for baseline BMI. *FTO*, fat mass and obesity–associated; HOMA-β, homeostasis model assessment of β cell function; β, β-coefficient; Δ, change in respective outcomes (i.e., the values at 2 y minus baseline values).
[2] Log-transformed values at 2 y minus log-transformed baseline values.

Genotyping System (BioTrove). The genotype success rate was 99%. Replicate quality control samples (10%) were included and genotyped with >99% concordance. The genotype frequencies for both *FTO* variants in the 2 major races (white and black) were both in Hardy-Weinberg equilibrium ($P > 0.05$).

Statistical analysis. Baseline data are presented as means ± SDs for continuous variables and as numbers and percentages for categorical variables. Baseline characteristics were compared by using chi-square test for categorical variables and by a general linear model with the assumption of an additive genetic model for continuous variables. Insulin concentrations, HOMA-IR, and HOMA-β were log-transformed to improve their imperfect normality. The primary outcomes were changes (i.e., the values at follow-up time minus the baseline values) in fasting insulin, glucose, HOMA-IR, and HOMA-β over the time the participant remained in the trial. The effects of genotype and diet intervention on outcomes at 6 mo and 2 y were correlated and analyzed together by using the generalized estimating equation (GEE) method. Covariate adjustment included age, sex, race, the baseline value for the respective outcome, and concurrent weight loss in model 1 and additionally included baseline BMI in model 2. Additive genetic models were used in the analyses. Gene-diet intervention interactions were tested by including the genotype-by-diet interaction multiplicative terms in the GEE models. As a secondary analysis, linear mixed models were used to test the genotype effect on the trajectory of changes in fasting insulin, glucose, HOMA-IR, and HOMA-β by including a genotype-by-time interaction term. In sensitivity analyses, we analyzed the associations between the white participants only.

All reported *P* values were 2-sided, and 0.05 was considered significant. All data were analyzed with SAS version 9.4 (SAS Institute). This trial was registered at clinicaltrials.gov as NCT00072995.

Results

Characteristics of the study population. Baseline characteristics of participants according to the *FTO* rs1558902 and rs9939609 genotypes are presented in **Table 1**. *FTO* rs1558902 and rs9939609 were in strong linkage disequilibrium ($r^2 = 0.83$). The minor allele frequency for rs1558902 (*A* allele) was 0.402 and for rs9939609 (*A* allele) was 0.447 in the present study population. For variant rs1558902, the genotype frequencies were significantly related to age, sex, and race but not the diet groups. The genotype frequencies for variant rs9939609 were not related to these variables. Insulin, glucose, insulin resistance, and β cell function at baseline were not related to the *FTO* variants.

FTO genotypes and change in insulin resistance. **Table 2** shows the associations of *FTO* genotypes with changes in fasting insulin, glucose, insulin resistance calculated by HOMA-IR and β cell function calculated by HOMA-β according to intake of dietary fat by using repeated measures of changes in these markers at 6 mo and 2 y, with adjustment for age, sex, race, the baseline value for the respective outcome, and concurrent weight loss in model 1 and with additional adjustment for baseline BMI in model 2. In these 2 models, the directions of genetic effects were the same, whereas the magnitudes were similar, and the significance of gene-diet interaction on changes in insulin and HOMA-IR remained after adjusting for baseline BMI. In model 2, each risk allele (*A*) of rs1558902 showed a trend to be

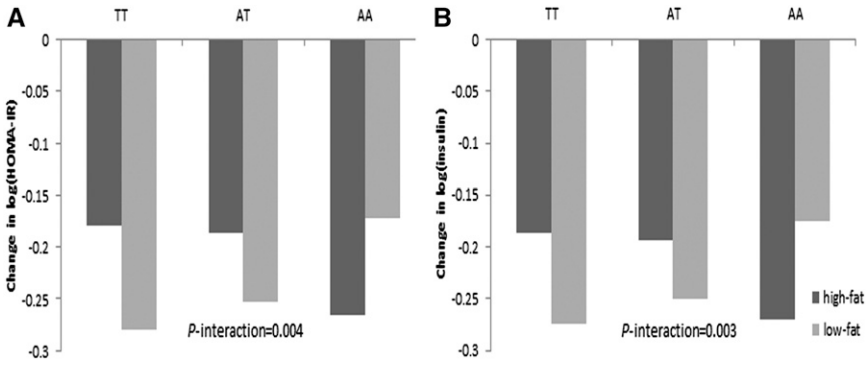

FIGURE 1 Change in insulin resistance measured as HOMA-IR (A) and insulin (B) by *FTO* rs1558902 genotype and dietary fat groups. *P* values were adjusted for age, sex, race, weight change, follow-up time, baseline values for respective outcomes, and baseline BMI. Values are means. *FTO*, fat mass and obesity–associated.

associated with a smaller reduction in both log(insulin) and log (HOMA-IR) among participants assigned to the low-fat diets (both $P = 0.06$), but they were not significantly related with reduction among those assigned to high-fat diets (both $P > 0.1$) during the 2-y period of intervention (P-interaction = 0.003 and 0.004, respectively; Table 2, **Figure 1**). The associations between rs9939609 and changes in glucose, insulin, HOMA-IR, or HOMA-β were not significantly modified by dietary fat intakes. Dietary protein did not significantly modify the genetic effects on these outcomes. The results in white participants only were similar to those observed in the whole study population, although the significance of the interaction between dietary fat and rs1558902 was attenuated (**Supplemental Table 1**). The β-coefficients of the genetic association of rs1558902 with changes in insulin and HOMA-IR were both 0.04 in the low-fat group and were both −0.03 in the high-fat group (both P-interaction = 0.07).

Trajectory of changes in insulin resistance by FTO rs1558902 in response to high-/low-fat weight-loss diets. In a secondary analysis, we used linear mixed models to assess the genotype-by-time interactive effect over the 2-y trial in those assigned to the low- or high-fat diet (**Figure 2**). In both the low- and high-fat diet groups, the genetic associations with changes in fasting insulin and HOMA-IR were more pronounced at the 6-mo visit than at the 2-y visit. However, we did not observe significant genotype-by-time interactions. Similar results were observed when the analyses were restricted to white participants.

Discussion

In the present study, we investigated whether dietary macronutrient composition modified the associations between *FTO* variants and changes in insulin sensitivity in a large, long-term randomized trial with weight-loss dietary interventions, the POUNDS LOST trial. We identified potential gene (*FTO* rs1558902)-by-diet (high- vs. low-fat weight-loss diets) interactions on reduction in fasting insulin and HOMA-IR over the 2-y intervention period. Carriers of the risk alleles (*A*) of rs1558902 might benefit differently by consuming high-fat weight-loss diets but benefit less by consuming low-fat weight-loss diets compared with noncarriers.

Our findings are in line with a previous European short-term dietary intervention trial in which a significant *FTO*–dietary fat interaction was observed in relation to insulin resistance (11), and both studies consistently showed that the risk allele carriers of *FTO* variant may benefit differently from high-fat diets in improving insulin resistance than from low-fat diets. In the European study (Sweden, Denmark, United Kingdom, The Netherlands, Czech Republic, France, and Spain), obese carriers of *FTO* rs9939609 risk alleles showed a greater decrease in insulin resistance with consumption of high-fat diets than did those consuming low-fat diets; however, *FTO* rs1558902 was not genotyped. The single nucleotide polymorphism rs1558902 showed more significant interaction than rs9939609 with dietary fat on insulin resistance. *FTO* rs1558902 and rs9939609 were in strong linkage disequilibrium ($r^2 = 0.83$) in our study. The discrepancy between our study and the European study may be partly due to the heterogeneity in genomic structure among various populations, such as the difference in the minor allele frequency of the specific single nucleotide polymorphisms.

Previous studies suggested that the effects of *FTO* genotype on insulin resistance and diabetes may be not be through adiposity (14, 15). In our study, the interaction between *FTO* variant and dietary fat on improvement in insulin and HOMA-IR remained

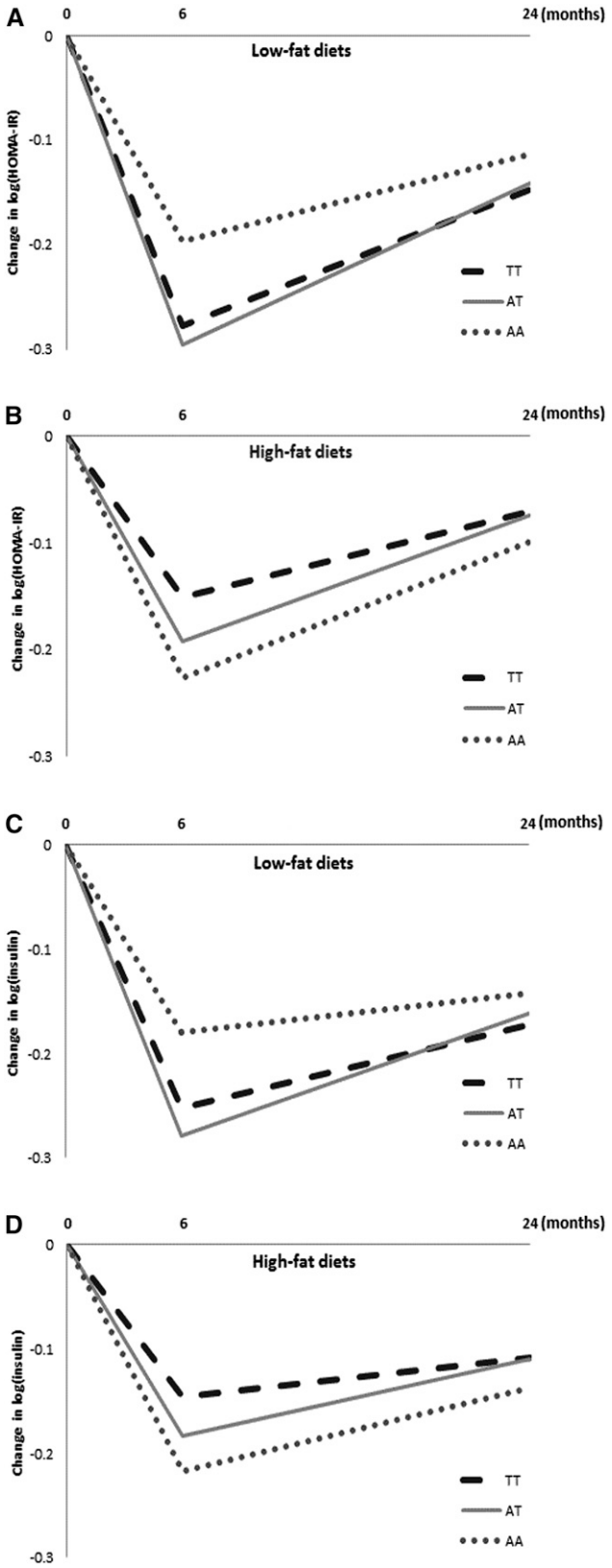

FIGURE 2 Changes from baseline in insulin resistance measured as HOMA-IR (A, B), and insulin (C, D) at the 6-mo and 2-y visits by *FTO* rs1558902 genotype in both the low-fat and high-fat diet groups. No significant genotype-by-time interactions were detected after adjusting for age, sex, race, weight change, baseline values for respective outcomes, and baseline BMI (all $P > 0.05$). Values are means. *FTO*, fat mass and obesity–associated.

significant with adjustment for concurrent weight loss. In this context, our results suggest that the interaction between *FTO* rs1558902 and dietary fat on the changes in insulin resistance might be independent of weight/adiposity change.

The potential mechanism underlying these findings remains unclear. *FTO* expression was found to be increased in skeletal muscle from patients with type 2 diabetes compared with nondiabetic individuals, independent of obesity (16). Several previous studies reported that *FTO* expression could be affected by fasting and feeding status (17–19), suggesting a potential regulatory role of dietary factors. However, evidence directly linking dietary fat and *FTO* gene function is still lacking, and further experimental data are warranted to clarify the potential mechanisms.

The genetic associations with changes in insulin resistance were more pronounced at the 6-mo visit than at the 2-y visit, which is consistent with the trajectory of changes in weight in the POUNDS LOST trial (12). Similar to other weight-loss trials, the diminished adherence to assigned diets that occurred between 6 mo and 2 y may partially explain these decreased genetic associations after 6 mo. The *FTO* variant rs1558902 was reported to have the strongest association with obesity in various populations (20, 21), and variant rs9939609 is the first hit of genome-wide association studies on BMI (22). However, the main effect of these *FTO* variants on weight loss or change in insulin resistance was not significant in the present study. Possible explanations could include the following: that the *FTO* variants primarily influence body fatness early in life, although the effect persists into adulthood; the participants in our study were homogenous regarding BMI and insulin sensitivity; and that the metabolism and biology mechanism of weight loss are different from those of weight gain (11).

The present study is among the first to investigate interactions between *FTO* genetic variation and dietary macronutrients on changes in insulin resistance in a long-term randomized dietary intervention trial. The study design allowed for reliable control of the dietary effects. The large sample size and long intervention period provided a decent chance of detecting moderate gene-diet interactions on change in insulin resistance. We combined repeated measures of outcomes in the analysis by using the GEE method to further increase statistical power. The GEE model is fairly robust to the choices of the correlation structure and flexible for missing data compared with other models (23). Nevertheless, we acknowledge that the current study is exploratory and might be underpowered to detect a small gene-diet interaction effect. There are many possible extensions to this work. The replication of the current finding in an independent trial with similar design is needed. Further research into the underlying mechanism of the identified interaction effect on insulin resistance is warranted. The generalization of this study is limited to whites because 80% of our population was white. High fat usually accompanies low carbohydrate in a diet and vice versa. Therefore, given our data, it is difficult to determine which nutrient (fat or carbohydrate) drove the observed associations.

In conclusion, we report an interactive effect between *FTO* rs1558902 and dietary fat on change in insulin resistance independent of weight loss over a large 2-y dietary intervention trial. Our data suggest that carriers of the risk alleles of rs1558902 might benefit differently in improving insulin sensitivity by consuming high-fat diets than by consuming low-fat diets. However, we also acknowledge that over and above any impact of the dietary intervention on weight loss, there was no significant main effect of the weight-loss diets on changes in insulin sensitivity regardless of *FTO* genotype. Although further investigation is warranted, our findings provide the potential to bring new insights to personalized dietary intervention for diabetes prevention and therapy by using genome-customized approaches.

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YZ and LQ contributed to the study concept and design, data analysis and interpretation, and drafting and critical revision of the manuscript; TH and XZ critically revised the manuscript; GAB and FMS contributed to the study concept, acquisition of data, design and funding of the initial project, and critical revision of the manuscript; JR contributed to the administration, laboratory measurements, and acquisition of data; and LQ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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