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High Dietary Saturated Fat Intake Accentuates Obesity Risk Associated with the Fat Mass and Obesity–Associated Gene in Adults[1–3]

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Abstract

Fat mass and obesity-associated (*FTO*) is the strongest genetic determinant of obesity identified to date. Dietary fat is a key environmental factor that may interact with genotype to affect risk of obesity and metabolic syndrome (MetS). This study investigated associations among *FTO* rs9939609, obesity measures, and MetS phenotypes in adults and determined potential modulation by dietary fat intake at baseline and after a 7.5-y follow-up when MetS cases and controls were selected. *FTO* rs9939609 genotype, biochemical, dietary, and lifestyle measurements were determined in the LIPGENE-SU.VI.MAX study (n = 1754). *FTO rs9939609 A* allele carriers had a higher risk of being overweight or obese [OR = 1.66 (95% CI: 1.07, 2.57); P = 0.02] and of having a larger abdominal circumference [OR = 1.42 (95% CI: 1.01, 1.99); P = 0.04] compared with the *TT* homozygotes. These associations were independent of physical activity and energy intake and were maintained over the follow-up period, particularly in the MetS individuals. High dietary SFA intake (≥15.5% energy) and a low dietary PUFA:SFA intake ratio (<0.38) further accentuated the risk of having a BMI ≥25 kg/m^2 and being abdominally obese. Non-risk allele carriers appeared to be unresponsive to dietary SFA intake or to the dietary PUFA:SFA intake ratio with respect to obesity measures. In conclusion, *FTO* rs9939609 was associated with obesity measures, especially in those with the MetS, which was further exacerbated by high dietary SFA intake at baseline and 7.5 y later. These data indicate important novel modulation of genetic risk by dietary fat exposure in individuals with increased cardiometabolic risk. J. Nutr. 142: 824–831, 2012.

Introduction

Obesity is the primary causal factor in the development of insulin resistance, the hallmark of metabolic syndrome (MetS)[10], a common condition characterized by abdominal obesity, dyslipidemia, and hypertension that is associated with increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (1). The global epidemic of the incidences of obesity, MetS, and T2DM is a clear demonstration of the interaction between environmental and genetic factors in these diet-related polygenic disorders. Genome-wide association studies represent a powerful approach to the identification of genes involved in common polygenic diseases such as obesity and T2DM. Following the identification of the T2DM susceptibility gene *TCF7L2* (2,3), previously unknown genetic variants in the *FTO* gene on chromosome 16 were also linked to T2DM risk through an effect on BMI (4). In that study, the 16% of adults homozygous for the rs9939609 risk A allele were 3 kg heavier and had a 1.7-fold higher risk of obesity relative to the homozygous non-risk allele carriers. Importantly, in a separate analysis, the authors demonstrated increased obesity risk associated with this polymorphism from childhood to old age (4). Several large studies subsequently replicated and confirmed the association with obesity risk in European populations (5–7) and the *FTO* rs9939609 single nucleotide polymorphism has emerged as one of the most important obesity susceptibility gene variants known to date. It has been suggested that the impaired satiety, greater food intake, and more frequent loss of eating control reported by individuals with at least one

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[3] Supplemental Table 1 and Figure 1 are 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.
[10] Abbreviations used: MetS, metabolic syndrome; QUICKI, quantitative insulin-sensitivity check index; T2DM, type 2 diabetes mellitus.
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risk allele may account for the observed increased obesity risk (8–10).

Data on *FTO* rs9939609 and MetS risk in Caucasians are limited, with most investigations to date pertaining to Asian populations (11–14). However, a large meta-analysis of 7 studies involving white Europeans reported that the *FTO* rs9939609 genotype was associated with a modestly higher MetS risk (OR = 1.17). The prevalence of MetS, however, varied widely between studies (6.6–45%), perhaps reflective of differences in cohort demographics (15). To our knowledge, there have not been any reports of the effect of *FTO* rs9939609 on risk of obesity or MetS derived from a MetS case-control–designed study. Interaction between genetic and dietary factors, particularly dietary fat, contribute to susceptibility to obesity and MetS (16–19). Limited cross-sectional analysis of the influence of dietary factors on BMI according to *FTO* rs9939609 genotype indicates that high-fat diets increase obesity risk (20,21). However, these studies did not investigate specific effects of dietary fat type or fatty acid composition. Recent data from a study of 354 children identified an interaction between dietary SFA and the PUFA:SFA intake ratio and obesity associated with *FTO* rs9939609 (22), but no similar data for adult populations exist. The aim of this study was to examine the relationship among *FTO* rs9939609 genotype, obesity measures, and MetS phenotypes in an adult population. An additional novel objective was to investigate whether dietary fat quantity and composition modulated these associations over time by examining the LIPGENE-SU.VI.MAX MetS case-control participants over a 7.5-y period.

Participants and Methods

Participants, MetS classification, and study design. This study is part of a prospective case-control candidate gene study of LIPGENE, an EU Sixth Framework Program Integrated Project entitled "Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis." Participants were selected from an existing national French SU.VI.MAX cohort including 13,000 individuals who were followed for 7.5 y (from 1994 to 2002) (23). The LIPGENE-SU.VI.MAX study is a nested case-control study of MetS consisting of women (35–60 y) and men (45–60 y) recruited from SU.VI.MAX. Additional approval from the Ethical Committee, CCPPRB, of Paris-Cochin Hospital included an additional clause (no. Am 2840–12–706) to perform the biochemical and genetic analysis required for the LIPGENE study. LIPGENE participants were informed of the study objectives and provided signed informed consent using protocol approved by this Ethical Committee. Participants were invited to provide a 24-h dietary record every 2 mo, for a total of 6 records/y. Information was collected with the use of computerized questionnaires that were transmitted during a brief telephone connection via the Minitel Telematic Network (France Télécom). Participants were guided by the software's interactive facilities and by a previously validated instruction manual for coding food portions that included >250 foods presented in 3 different portion sizes. Two intermediate and extreme portions could also be chosen, yielding a total of 7 choices for estimating the quantities consumed (24). Daily dietary intake data were estimated by using food composition tables validated for the French population (25).

Baseline and 7.5-y follow-up data including full clinical examination records were made available to LIPGENE. These data were used to identify cases, individuals who developed ≥3 elements of MetS, during the 7.5-y follow-up period and control participants. MetS cases were selected based on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria for MetS, with some modifications (26). MetS cases were required to fulfill at least 3 of the following 5 criteria: increased waist circumference (>94 cm for men or >80 cm for women), increased fasting blood glucose (≥5.5 mmol/L or treatment for diabetes), increased TG (≥1.5 mmol/L or treatment for dyslipidemia), decreased HDL cholesterol (<1.04 mmol/L for men or <1.29 mmol/L for women) and increased systolic/diastolic blood pressure (≥130/85 mm Hg or antihypertensive treatment). Cases were defined as both men and women with ≥3 abnormalities and controls were defined as men and women with no abnormalities or men with ≤1 abnormality. Cases and controls (n = 1754) were matched according to age (±5 y), gender, and number of dietary records available. For the purpose of the work detailed herein, we report data from both the start of the study and at follow-up 7.5 y later.

Biochemical analysis. Fasting plasma glucose, TG, and HDL and total cholesterol were measured as previously described (23). Plasma insulin and C-peptide were determined by electrochemiluminescence immunoassays (Roche Diagnostics). Plasma LDL cholesterol was measured by enzymatic colorimetric methods (Randox Laboratories and Roche Diagnostics). HOMA-IR, a measure of insulin resistance, was calculated as: [(fasting plasma glucose × fasting plasma insulin)/22.5] (27). The quantitative insulin-sensitivity check index (QUICKI), a measure of insulin sensitivity, was calculated as: [1/(log fasting plasma insulin + log fasting plasma glucose + log fasting FFA)] (28).

DNA extraction and genotyping. DNA extraction from buffy coats and whole genome amplification of low-yielding samples (<10 ng) was performed as previously described (29). Genotyping for *FTO* rs9939609 was conducted by KBiosciences using a competitive allele-specific PCR system (KASPar). A genotype success rate of 99% and a call rate of 99% were achieved.

Statistical analysis. Statistical analysis was performed using SAS for Windows, version 9.0 (SAS Institute). Data are expressed as means ± SEM. After checking for skewness and kurtosis, glucose, insulin, waist, FFA, TG, QUICKI, and HOMA-IR were normalized by logarithmic transformation. Logistic regression determined associations among the *FTO* rs9939609 genotype, obesity measures, and MetS phenotypes (BMI ≥25 kg/m^2, abdominal obesity, high TG and low HDL cholesterol concentrations, fasting hyperglycemia, insulin resistance, impaired insulin sensitivity, and hypertension). Cutoff points for the MetS phenotypes were determined by the MetS criteria. Analyzes were performed on the whole study population and then stratified by gender and MetS status to ascertain the homogeneity of genetic effects. To determine modulation by dietary fat consumption, logistic analyzes were repeated using the median of control individuals to dichotomize intakes and to examine associations in low and high consumers (i.e., below and above dietary fat medians). Generalized estimating equation linear regression (30) investigated interactions among continuous MetS phenotypes, genotype, and SFA intake. Potential confounding factors used in the adjusted multivariate analysis included age, gender, energy intake, smoking status, physical activity, and use of medications. t-Tests and ANOVA models were used to test for associations between phenotypic characteristics and and combined genetic models and 3 genotypes, respectively. Significant ANOVA results were further examined using the Bonferroni post hoc test. Distributions of frequencies for some characteristics were compared using chi-square tests. For all analyses, $P < 0.05$ was considered significant.

Results

Associations between FTO rs9939609 and obesity measures among all participants. Genotype distributions did not deviate from Hardy-Weinberg equilibrium ($P > 0.05$) and are in keeping with previously reported European samples (4,5). At baseline, 29.6% of the population were overweight (BMI 25–29.99 kg/m^2) and 9.8% were obese (BMI ≥30 kg/m^2). Carriers of the risk allele (*A*), who represent 66% of this population, had a 0.76-unit higher BMI (P = 0.001) and 2.34-cm larger waist circumference (P = 0.001) compared with the *TT* homozygotes (**Table 1**). Logistic regression analyses confirmed the deleterious

TABLE 1 Obesity measures, plasma analytes, clinical characteristics, and dietary and lifestyle factors according to the *FTO* rs9939609 genotype among all participants at baseline[1,2]

	TT	*TA*	*AA*	*AA + TA*
n	596	850	307	1157
Male/female, *%*	58/42	62/38	60/40	59/39
MetS cases, *%*	11.5	13.8	16.9	14.7
Age, *y*	51.3 ± 0.2	51.9 ± 0.2	51.6 ± 0.3	51.8 ± 0.2
BMI, *kg/m²*	24.8 ± 0.2*	25.5 ± 0.2‡	25.8 ± 0.3†	25.6 ± 0.1§
Waist, *cm*	85.4 ± 0.5*	87.6 ± 0.5†	88.0 ± 0.8‡	87.7 ± 0.4§
Systolic blood pressure, *mm Hg*	125 ± 0.7	126 ± 0.6	125 ± 0.9	126 ± 0.5
Diastolic blood pressure, *mm Hg*	81 ± 0.4	81 ± 0.4	80 ± 0.6	81 ± 0.3
Glucose, *mmol/L*	5.82 ± 0.03	5.89 ± 0.03	5.90 ± 0.06	5.90 ± 0.03
Total cholesterol, *mmol/L*	6.18 ± 0.04	6.13 ± 0.04	6.13 ± 0.06	6.13 ± 0.03
TG, *mmol/L*	1.25 ± 0.04	1.28 ± 0.03	1.32 ± 0.05	1.29 ± 0.03
Dietary fat intake				
Energy, *kJ/d*	9420 ± 147	9590 ± 222	9470 ± 205	9560 ± 105
Fat, *% energy*	37.5 ± 0.3	37.6 ± 0.3	37.2 ± 0.5	37.5 ± 0.2
SFA, *% energy*	14.6 ± 0.3	14.6 ± 0.2	14.6 ± 0.4	14.6 ± 0.2
MUFA, *% energy*	13.3 ± 0.3	13.7 ± 0.3	13.1 ± 0.3	13.5 ± 0.2
PUFA, *% energy*	5.1 ± 0.1	5.5 ± 0.2	5.1 ± 0.2	5.3 ± 0.1
Physical activity, *%*				
Irregularly active	21.2	23.3	20.3	22.6
<1 h/d	29.7	29.0	33.2	30.2
≥1 h/d	49.2	47.7	46.5	47.2
Smoking status, *%*				
Never	46.2	45.0	40.9	43.9
Former	39.3	44.1	44.9	44.3
Current	14.6	11.0	14.1	11.8

[1] Values are means ± SEM unless otherwise indicated. Symbols indicate different from TT, *$P < 0.005$ [ANOVA comparing the 3 genotype groups (TT, TA, AA)]; †$P < 0.005$, and ‡$P < 0.01$ [compared to *TT* homozygotes (post hoc tests)]; §$P < 0.01$ (*t* tests). MetS, metabolic syndrome.
[2] Distribution of frequencies for physical activity levels and smoking status across genotypes were compared using chi-square tests.

influence of being a risk allele carrier. In the adjusted multivariate models, the *FTO rs9939609 A* allele carriers had an increased risk of abdominal obesity [OR = 1.42 (95% CI: 1.01, 1.99); $P = 0.04$] and of being overweight or obese according to BMI [OR = 1.66 (95% CI: 1.07, 2.5); $P = 0.02$], independent of physical activity levels and total energy intake, compared with the *TT* homozygotes. Homogeneity of the genetic effects on obesity measures were assessed by stratifying according to gender. Gender-specific associations with waist circumference (92.47 vs. 90.18 cm; $P = 0.001$) and BMI (25.95 vs. 25.12; $P = 0.001$) were observed in the male risk allele carriers compared with the non-risk allele carriers and although the effects were in the same direction in the female participants, they were not significant ($P = 0.09$ and $P = 0.08$, respectively).

FTO rs9939609 genotype and obesity among MetS cases and control participants. Given the lack of effect of the *FTO* rs9939609 genotype on the classic MetS phenotypes at baseline, with the exception of abdominal obesity, it was not surprising that there were no genotypic differences with respect to MetS status at follow-up (Table 1). However, it is interesting to note that when MetS cases and controls were analyzed separately at follow-up, the deleterious effect of being a risk allele carrier on BMI and waist circumference was evident in only the MetS cases (**Table 2**). In addition, insulin sensitivity, as assessed by QUICKI, was further impaired in the *A* allele-carrying MetS individuals compared with the non-risk allele carriers ($P = 0.04$). Total cholesterol concentrations were lower in the *A* allele carriers relative to the *TT* homozygotes ($P = 0.04$).

FTO rs9939609 and obesity measures during the follow-up period. The significant trends for associations across *FTO* genotypes for BMI and waist circumference observed at the start of the study were maintained during the follow-up period [OR for abdominal obesity = 1.43 (95% CI: 1.04, 1.96); $P = 0.02$] and [OR for BMI ≥25 kg/m^2 = 1.26 (95% CI: 1.05, 1.87); $P = 0.04$] compared with the *TT* homozygotes). *A* allele carriers had a 0.6-unit higher BMI ($P = 0.003$) and 1.97-cm larger waist circumference ($P = 0.003$) relative to the *TT* homozygotes 7.5 y later (**Fig. 1**). The proportion of overweight and obese men and women increased over the study period (38.9% overweight and 16.1% obese). However, no genotypic differences were observed when weight-stable participants (i.e., 79.7% of the cohort who remained in the same BMI category during the follow-up period) were compared with normal or overweight individuals at the start of the study who progressed into the next BMI category (17.1% of the cohort) ($P = 0.001$). In accordance, we found no differences in the change in BMI or waist circumference over time according to genotype. Similarly, an examination of the change in blood pressure and glucose, TG, and cholesterol concentrations from baseline showed no genotypic differences (**Supplemental Table 1**).

Dietary SFA intake modulates genetic predisposition to obesity. Dietary SFA consumption modulated the relationship between *FTO* rs9939609 and waist circumference. The larger abdominal girth conferred by the *A* allele was further accentuated among high-SFA consumers (greater than median SFA intake) at baseline [OR = 3.05 (95% CI: 1.42, 6.58); $P = 0.004$]

TABLE 2 Obesity measures, plasma measurements, clinical characteristics, and dietary profiles at follow-up according to the *FTO* rs9939609 genotype in MetS cases and control individuals[1,2]

	MetS cases		Controls	
	TT	*AA + TA*	*TT*	*AA + TA*
n	284	593	312	564
Male/female, *%*	59/41	61/39	60/40	58/42
Age, *y*	58 ± 0.3	58 ± 0.2	58 ± 0.3	58 ± 0.2
BMI, *kg/m²*	28.2 ± 0.2	29.1 ± 0.2*	23.1 ± 0.1	23.2 ± 0.1
Waist, *cm*	94.4 ± 0.6	97.4 ± 0.4*	80.1 ± 0.5	80 ± 0.4
Glucose, *mmol/L*	5.58 ± 0.07	5.66 ± 0.05	4.86 ± 0.02	4.88 ± 0.02
Insulin, *pmol/L*	70.2 ± 2.94	75.3 ± 2.08	32.6 ± 1.00	32.4 ± 0.72
QUICKI	0.27 ± 0.00	0.26 ± 0.00‡	0.35 ± 0.00	0.35 ± 0.00
HOMA-IR	2.54 ± 0.15	2.71 ± 0.09	0.99 ± 0.03	0.99 ± 0.02
Total cholesterol, *mmol/L*	5.86 ± 0.06	5.71 ± 0.04‡	5.70 ± 0.05	5.65 ± 0.04
HDL cholesterol, *mmol/L*	1.30 ± 0.02	1.26 ± 0.01	1.67 ± 0.02	1.67 ± 0.01
LDL cholesterol, *mmol/L*	3.65 ± 0.07	3.55 ± 0.05	3.55 ± 0.05	3.49 ± 0.04
TG, *mmol/L*	1.66 ± 0.05	1.65 ± 0.03	0.86 ± 0.02	0.86 ± 0.01
Systolic blood pressure, *mm Hg*	140 ± 0.9	140 ± 0.6	122 ± 0.6	122 ± 0.5
Diastolic blood pressure, *mm Hg*	87 ± 0.6	87 ± 0.4	77 ± 0.4	77 ± 0.3
Physical activity, *%*				
Irregularly active	24.1	28.1	18.4	16.7
<1 h/d	33.3	30.2	26.2	30.3
≥1 h/d	42.5	41.6	55.3	53.1
Dietary intake				
Energy, *kJ/d*	8230 ± 276	8660 ± 196	8800 ± 247	8550 ± 201
Fat, *% energy*	33.5 ± 0.6	33.8 ± 0.5	32.9 ± 0.7	33.5 ± 0.5
SFA, *% energy*	13.9 ± 0.4	14.4 ± 0.2	13.7 ± 0.3	14.1 ± 0.3
MUFA, *% energy*	12.3 ± 0.3	12.4 ± 0.2	12.3 ± 0.3	12.4 ± 0.2
PUFA, *% energy*	5.2 ± 0.2	4.8 ± 0.1	4.8 ± 0.2	4.8 ± 0.1
Protein, *% energy*	16.7 ± 0.3	16.3 ± 0.3	16.9 ± 0.3	16.9 ± 0.3
Carbohydrate, *% energy*	43.4 ± 0.8	42.1 ± 0.6	41.5 ± 0.7	43.2 ± 0.6
Total fiber, *g/d*	21.3 ± 0.9	19.9 ± 0.6	20.1 ± 0.6	20.1 ± 0.6
Soluble fiber, *g/d*	4.2 ± 0.2	3.8 ± 0.1	3.9 ± 0.1	3.9 ± 0.1
Alcohol, *% energy*	5.7 ± 0.6	6.8 ± 0.5	6.7 ± 0.7	5.3 ± 0.4

[1] Values are means ± SEM unless otherwise indicated. Symbols indicate different from TT: *$P < 0.005$, ‡$P < 0.05$ (*t* tests). MetS, metabolic syndrome; QUICKI, quantitative insulin-sensitivity check index.
[2] Distribution of frequencies for physical activity levels and smoking status across genotypes were compared using chi-square tests.

and also at the follow-up period [OR = 2.51 (95% CI: 1.01, 6.23); $P = 0.04$] (**Table 3**). A graphical presentation of these data (**Supplemental Fig. 1**) demonstrates larger waist circumference among the high SFA-consuming risk allele carriers compared with their *TT* homozygote counterparts both at baseline and at follow-up. No significant differences between genotypes were observed at either time point among the low SFA consumers. Examination of SFA intake, as a continuous variable, supports the logistic regression analyses. As dietary SFA intake increases, waist circumference was predicted to increase in the *A* allele carriers but not in the *TT* homozygotes at baseline ($P_{\text{interaction}} = 0.03$) (**Fig. 2***A*) and at the end of the 7.5-y follow-up (*P*-interaction = 0.04) (Fig. 2*B*). The *TT* homozygotes appeared nonresponsive to dietary SFA intake with relatively no change in waist circumference with increasing SFA consumption. There were no significant interactions found when dietary PUFA and MUFA intakes were analyzed (data not shown). However, when we examined the risk of these obesity measures according to the dietary PUFA:SFA intake ratio, risk was further accentuated in individuals with a dietary PUFA:SFA intake ratio in the bottom 50th percentile, suggesting that these gene-diet interactions are dietary SFA specific (Table 3). In keeping with these findings, BMI was also subject to effect modification by dietary SFA. Among the risk allele carriers, those with a high intake of dietary SFA had a greater risk of being overweight and obese at baseline [OR = 3.40 (95% CI: 1.18, 9.78); $P = 0.02$] relative to their low SFA-consuming counterparts. When dietary SFA intake was low (less than median), the associations between *FTO* rs9939609 and obesity measures were no longer significant. Supplemental Figure 1 demonstrates greater BMI among the high SFA-consuming risk allele carriers compared with their *TT* homozygote counterparts both at baseline and follow-up. No significant differences between genotypes were observed among the low SFA consumers. Similar results were found when the dietary PUFA:SFA intake ratio was analyzed. No differences in total energy intake or dietary fat consumption were observed between genotypes at baseline or follow-up.

Discussion

In this study, we demonstrated that a common genetic variant at the *FTO* locus, rs9939609, was associated with increased risk of having a BMI in the overweight or obese category and of being abdominally obese. Increased obesity risk was maintained during the 7.5-y follow-up period and although rs9939609 was not associated with MetS risk, the risk of these obesity-related measures was higher in the risk allele-carrying MetS

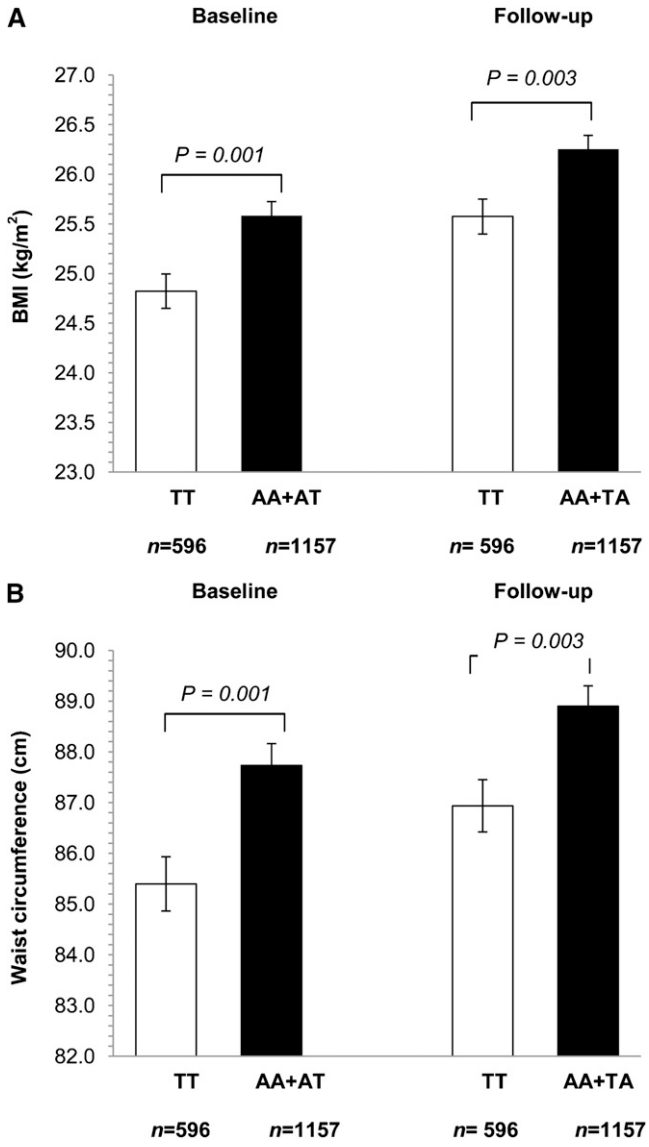

FIGURE 1 BMI (*A*) and waist circumference (*B*) for all participants stratified by *FTO* rs9939609 genotype at baseline and after 7.5 y. Values are mean ± SEM.

cases relative to their non-risk allele-carrying counterparts. A novel finding in this study was that high habitual dietary SFA consumption (≥15.5% of energy) and a low dietary PUFA:SFA intake ratio accentuated obesity risk in the *A* allele carriers but not in the *TT* homozygotes in this adult population, suggesting that genetic predisposition to obesity may be modulated by dietary SFA intake. This may be particularly relevant to individuals with diet-related metabolic disease who are at increased cardiometabolic risk.

Obesity is one of the key causal factors in the development of insulin resistance and MetS. Ideally, obesity prevention would reduce the risk of these conditions; however, current approaches are largely ineffective, probably due in part to genetic heterogeneity and differences in dietary responsiveness between individuals. An imbalance between energy intake and energy consumption contributes to obesity. Interestingly, the *FTO* rs9939609 genotype does not seem to influence obesity risk through energy expenditure, but rather it has been suggested that it plays a role in food choice, with increased energy intake in the risk allele carriers arising from increased preference for energy-dense, high-fat food rather than an increased quantity of food consumed (31). However, the current work does not support this hypothesis, wherein no genotypic differences with respect to total energy or dietary SFA, PUFA, and MUFA intake at baseline were observed, nor were any differences noted for individual macronutrients (dietary fat, protein, carbohydrate, fiber) or alcohol when MetS cases and controls were compared at follow-up. Physical activity levels were also similar across genotypes. A recent large meta-analysis found no change in BMI over time according to the *FTO* rs9939609 genotype (32). In keeping with this finding, we did not observe any differences in change in BMI or waist circumference over time according to genotype, indicating that genotype was not responsible for any further weight gain.

Genetic and environmental factors contribute to susceptibility to diet-related polygenic disorders. Dietary fat is an important environmental factor, wherein excessive exposure plays a key role in the development of MetS (33–38). Recently, we reported novel modulation of MetS risk conferred by the *TCF7L2* genotype by dietary SFA (39). A cross-sectional analysis of the influence of dietary factors and physical activity on BMI according to the *FTO* rs9939609 genotype indicated that high-fat diets increase obesity risk (20,21). Unfortunately, these studies did not investigate specific effects of dietary fat composition. High-fat diets, in particular high-SFA diets, have been shown to exert detrimental effects on adiposity, inflammation, and insulin sensitivity, promoting the development of cardiometabolic disease (36,40–43). Recent data from a study of 354 children and adolescents (aged 6–18 y) identified an interaction between dietary SFA and the dietary PUFA:SFA intake ratio and obesity associated with *FTO* rs9939609, whereby risk allele carriers in the top 50th percentile for SFA consumption and the bottom 50th percentile for the dietary PUFA:SFA intake ratio had increased obesity risk compared with

TABLE 3 OR and 95% CI for risk of obesity measures associated with the *FTO* rs9939609 genotype according to dietary SFA and the dietary PUFA:SFA intake ratio at baseline and follow-up[1]

	<Median	*P*	≥Median	*P*	<Median	*P*	≥Median	*P*
	Dietary SFA intake at baseline				Dietary SFA intake at follow-up			
Abdominal obesity	0.93 (0.60, 1.45)	0.76	3.05 (1.42, 6.58)	0.004	0.95 (0.53, 1.71)	0.87	2.51 (1.01, 6.23)	0.04
BMI ≥25 kg/m^2	1.46 (0.62, 3.47)	0.38	3.40 (1.18, 9.78)	0.02	1.01 (0.43, 2.37)	0.90	1.85 (1.05, 5.01)	0.03
	Dietary PUFA:SFA intake ratio intake at baseline				Dietary PUFA:SFA intake ratio at follow-up			
Abdominal obesity	1.91 (1.06, 3.47)	0.03	1.22 (0.58, 2.56)	0.59	1.13 (0.79, 1.88)	0.09	0.94 (0.49, 1.81)	0.85
BMI ≥25 kg/m^2	2.04 (1.08, 4.89)	0.04	1.33 (0.72, 1.80)	0.45	2.24 (1.37, 3.66)	0.01	0.69 (0.40, 1.87)	0.55

[1] OR and 95% CI for the association between the *FTO* rs9939609 genotype and obesity measures were determined by logistic regression analyses according to dietary SFA and dietary PUFA:SFA intake ratio median levels. Potential confounding factors included in the analyses were age, gender, smoking status, physical activity, and medication use.

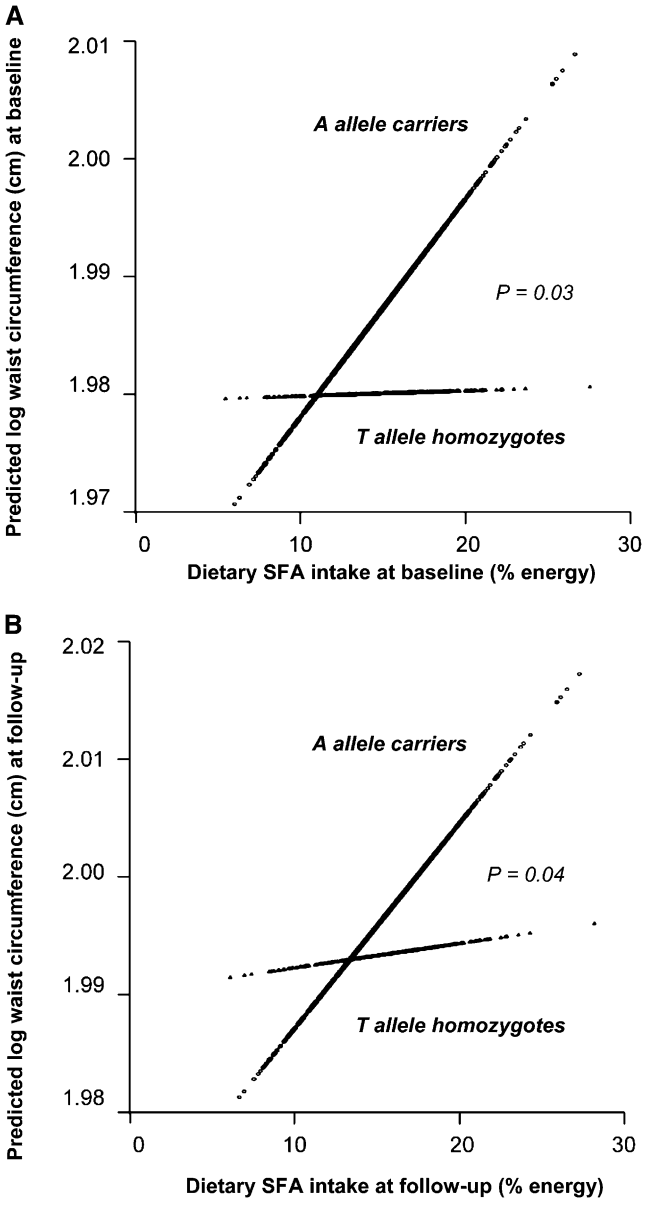

FIGURE 2 Predicted log values of waist circumference by *FTO* rs9939609 plotted against dietary SFA intake in the *A* allele carriers and the *TT* homozygotes at baseline (*A*) (*P*-interaction = 0.03) and at the end of the 7.5-y follow-up (*B*) (*P*-interaction = 0.04). Predicted values were calculated from the regression models containing dietary SFA, genotypes, their interaction term, and potential confounders, including age, gender, case-control status, physical activity, and energy intake. The open circles represent the *A* allele carriers (n = 1157) and the triangles represent the *TT* homozygotes (n = 596).

the *TT* homozygotes (22). Consistent with these findings, we demonstrated in adults that *FTO* rs9939609 risk allele carriers who are high dietary SFA consumers or have a low dietary PUFA:SFA intake ratio have further increased risk of being centrally obese and having a BMI $\geq$25 kg/m^2 compared non-risk allele carriers. Furthermore, the associations between *FTO* rs9939609 and obesity measures were abolished among individuals with a low SFA intake and a high dietary PUFA:SFA intake ratio. In summary, dietary SFA intake, recorded 7.5 y prior to MetS case selection and also after the follow-up, modulated the genetic influence on obesity risk. These results suggest that gene-nutrient interactions are maintained throughout adulthood and that *FTO* rs9939609 risk allele carriers are also most sensitive to saturated fat such that high intake of dietary SFA further accentuates their risk. Conflicting data exist regarding dietary responsiveness according to the *FTO* rs9939609 genotype. In a study designed to examine the effect of a weight loss intervention among obese adults, non-risk allele carriers displayed greater reductions in measures of insulin resistance (44), whereas a 3-y follow-up of individuals adhering to a Mediterranean-style diet had lower weight gain in the risk allele carriers, despite a lack of a significant genotype-nutrient interaction (45). The examination of obesity measures according to SFA intake and genotype in the current work demonstrates larger BMI among the high SFA-consuming risk allele carriers relative to the *TT* homozygotes both at baseline and at follow-up, with no genotypic differences among the low SFA consumers. Collectively, our findings suggest that the long-term effect of dietary fatty acid composition and consumption may have the potential to modify the genetic susceptibility of becoming obese. In particular, *FTO* rs9939609 risk allele carriers could derive the most benefit from current dietary guidelines to reduce SFA intake. Whether a SFA-lowering intervention would result in reduced adiposity measures in *FTO* rs9939609 risk allele carriers would be worthwhile to investigate.

We additionally examined whether other macronutrients modulated genetic risk of obesity phenotypes associated with *FTO* rs9939609. Although higher OR for abdominal obesity and BMI in the overweight or obese category were observed in the low-carbohydrate and low-protein consumers comparing the *A* allele carriers to the *TT* homozygotes, these associations did not reach significance ($P < 0.1$). It is interesting to note that in the study by Sonestedt et al. (21), the gene-nutrient interaction data suggest that the increase in BMI across FTO genotypes was restricted to individuals who consumed high-fat and low-carbohydrate diets. These findings may not be surprising given that some low-carbohydrate diets are also high-fat diets. However, it would appear from our data that high dietary SFA intake is the main nutritional driver of the observed gene-nutrient interactions.

In terms of potential functionality of *FTO* rs9939609, because this single nucleotide polymorphism lies in the first intron of the *FTO* gene, it is thought that the *A* allele might exert its functional effect through altered *FTO* mRNA expression. Interestingly, skeletal muscle *FTO* mRNA levels are greater in males than in females, which may help to explain some of the gender differences observed in the current study, and adipose tissue levels correlate positively with BMI (46). Examination of the potential functional role of *FTO* demonstrated that *FTO* overexpression leads to increased food intake and obesity in mice regardless of whether they are fed a standard or high-fat diet (47). Tung et al. (48) demonstrated a 2.5-fold increase in hypothalamic *FTO* expression in rats following high-fat feeding. Contrary to these findings, a more recent transcriptomic profiling of genome-wide association studies loci associated with obesity demonstrated that *FTO* is downregulated in the hypothalamus of high-fat–fed obese rats, whereas adipose tissue and muscle did not differ relative to the unpurified diet-fed rats (49). The mechanisms allowing dietary SFA to interact with *FTO* are unknown and require further investigation. Interestingly, hypothalamic *FTO* overexpression resulted in a 4-fold increase in expression of signal transducer and activator of transcription 3 (*STAT3*) (49). We previously demonstrated that *STAT3* gene polymorphisms influence the risk of abdominal obesity, which is modulated by dietary SFA intake (19). Given

the importance of *STAT3* in the leptin-signaling pathway, these data suggest a potential mechanism for mediating FTO's actions and potential modulation by SFA.

Several features of this study (comprehensive phenotypic characterization, baseline and follow-up data, large number of male and female cases, and matched controls from all socio-economical categories and areas in the country) make this study particularly robust. Nevertheless, some limitations can be identified. Because dietary consumption was self-reported by using a FFQ, some misclassification of exposure, due to deficiencies in nutrient databases, accuracy of memory, or willingness to divulge these details, was inevitable. The number of dietary records used was minimal (3 in a small number of individuals) but was necessitated to maximize the number of matched cases and controls.

In conclusion, this study provides new data on modulation of obesity risk conferred by *FTO* rs9939609 by dietary SFA intake in adults. Functional characterization and replication of these novel and potentially important findings should be valuable regarding their validation. Obesity is predicted to affect more than 1 billion people by the year 2020 (50); thus, there is a clear need to develop new preventative strategies and evidence-based public health measures to attenuate disease development and reduce dependence on medical care. Understanding the molecular mechanisms underlying these findings may help to improve the therapeutic efficacy of dietary recommendations with a personalized nutrition approach, wherein an individual's genetic profile may determine the choice of dietary therapy/intervention to improve responsiveness and reduce obesity-related cardiometabolic risk.

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