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Dietary Intake, *FTO* Genetic Variants, and Adiposity: A Combined Analysis of Over 16,000 Children and Adolescents

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The *FTO* gene harbors variation with the strongest effect on adiposity and obesity risk. Previous data support a role for *FTO* variation in influencing food intake. We conducted a combined analysis of 16,094 boys and girls aged 1–18 years from 14 studies to examine the following: *1*) the association between the *FTO* rs9939609 variant (or a proxy) and total energy and macronutrient intake; and *2*) the interaction between the *FTO* variant and dietary intake, and the effect on BMI. We found that the BMI-increasing allele (minor allele) of the *FTO* variant was associated with increased total energy intake (effect per allele = 14.3 kcal/day [95% CI 5.9, 22.7 kcal/day], $P = 6.5 \times 10^{-4}$), but not with protein, carbohydrate, or fat intake. We also found that protein intake modified the association between the *FTO* variant and BMI (interactive effect per allele = 0.08 SD [0.03, 0.12 SD], *P* for interaction = 7.2×10^{-4}): the association between *FTO* genotype and BMI was much stronger in individuals with high protein intake (effect per allele = 0.10 SD [0.07, 0.13 SD], $P = 8.2 \times 10^{-10}$) than in those with low intake (effect per allele = 0.04 SD [0.01, 0.07 SD], $P = 0.02$). Our results suggest that the *FTO* variant that confers a predisposition to higher BMI is associated with higher total energy intake, and that lower dietary protein intake attenuates the association between *FTO* genotype and adiposity in children and adolescents.

Common single nucleotide polymorphisms (SNPs) located in the first intron of the gene associated with

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fat mass and obesity (*FTO*) are the first adiposity/BMI-associated variants identified through genome-wide association studies (GWASs) (1–3), and to date this remains the locus with the largest influence on BMI in adults, as well as in children and adolescents (4). The mechanism by which *FTO* variants influence adiposity is unclear. Previous animal studies have suggested a role of Fto in regulating energy homeostasis, but it is unknown whether it influences energy intake (5,6) or energy expenditure (7,8). In addition, it is not clear which gene's function is affected by the functional variants at this locus: *FTO* itself or another gene located downstream or upstream of *FTO*, such as *IRX3* (9) and *RPGRIP1L* (10).

In many human studies (11–20), the BMI-increasing allele of *FTO* variants has been reported to be associated with increased food intake, total energy intake, fat or protein intake, suggesting that diet mediates the association with BMI. However, these associations have not been replicated in a number of other studies (21–35). In addition, there is an increasing interest in examining whether lifestyle factors influence the associations between *FTO* variants and adiposity. While there is evidence that physical activity reduces the effect of *FTO* on BMI, at least in adults (36), the few studies (12,20,26,32,34,35,37,38) that have investigated interaction with dietary factors in relation to BMI/obesity have generated conflicting results regarding potential interactions. Our recent large-scale meta-analysis (39) indicated that *FTO* variants were associated with protein intake in adults and that underreporting of dietary intake in obese participants might be a major issue in the analysis. Studies in children are of particular interest in this regard, since this population is less biased by comorbidities, and their treatment and exposure to environmental contributors is shorter.

The relatively small sample size of individual studies, the modest genetic effect size, and the inevitable measurement errors might be major reasons for these inconsistent observations. Thus, studies with larger sample sizes are needed to clarify interrelations among *FTO* variants, dietary intake, and adiposity. Herein we report the results of a combined analysis of 16,094 children and adolescents from 14 studies to examine the following: *1*) whether the *FTO* rs9939609 variant (or a proxy SNP) is associated with dietary intake of total energy and macronutrients (protein, carbohydrate, and fat); and *2*) whether dietary intake influences the association between the *FTO* variant and BMI.

RESEARCH DESIGN AND METHODS

Study Participants

The current analysis included cross-sectional data on 16,094 children and adolescents (15,352 whites, 478 African Americans, and 267 Asians) aged 1–18 years from 14 studies (Supplementary Table 1). The study design, recruitment of participants, and data collection of individual studies have been described in detail previously (14,23,24,40–50). In each study, informed consent was obtained from subjects' parents or guardians and subjects (if appropriate). Each study was reviewed and approved by the local institutional review board.

Study-specific characteristics for each study are shown in Supplementary Table 2. The ranges of mean values across studies were as follows: age 1.1–16.4 years; BMI 16.2–24.7 kg/m^2; total energy intake 1,017–2,423 kcal/day; total protein intake 12.9–16.8% (percentage of total energy intake); total carbohydrate 43.4–59.0%; and total fat intake 28.1–40.0%.

Assessment of BMI and Dietary Intake

BMI was calculated as body weight (kg)/height (m^2). Body weight and height were measured in all studies except for one study which used self-reported data in a subsample (Supplementary Table 3). For two studies (43,48) with children younger than 2 years of age, length (height) was measured to the nearest millimeter with children in a supine position. Dietary intake (total energy, protein,

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carbohydrate, and fat) was assessed using validated food frequency questionnaires (four studies), multiple-day dietary/food records (three studies), multiple-day 24-h recalls (four studies), both dietary records and 24-h recalls (one study), diet history determined by consulting and information system (one study), or a brief-type self-administered diet history questionnaire (one study) (Supplementary Table 3). Macronutrient intake was expressed as the percentage of total energy intake.

Genotyping

FTO SNP rs9939609 or a proxy (linkage disequilibrium $r^2 = 1$ in the corresponding ethnic group) was genotyped using direct genotyping methods or Illumina genome-wide genotyping arrays, or imputed using MACH (http://csg.sph.umich.edu/abecasis/MACH/) with a high imputation quality ($r^2 = 1$) (Supplementary Table 4). The studies provided summary statistics based on data that met their quality control criteria for genotyping call rate, concordance in duplicate samples, and Hardy-Weinberg equilibrium *P* value.

Statistical Analysis

A standardized analytical plan, which is described below, was sent to study analysts from the 14 studies, and analyses were performed locally. BMI was transformed to age-standardized *z* score by sex in each study before analysis. A linear regression model under additive allelic effects was applied to examine associations of *FTO* variant with BMI, total energy intake, and intake of fat, protein, and carbohydrate (expressed as the percentage of total energy), adjusted for pubertal status (if available), physical activity (if available), and eigenvectors (data from GWASs only). We additionally adjusted for BMI when evaluating the association between *FTO* variant and dietary intake. In addition, the difference in BMI between the low– and high–dietary intake groups (dichotomized at medians in each study) was also examined. Interactions between *FTO* genotype and dietary intake and their effect on BMI were tested by including the respective interaction terms in the models (e.g., interaction term = rs9939609 SNP × total energy intake [dichotomized at the medians in each study]). We examined the association between *FTO* variant and BMI stratified by low– and high–dietary intake groups (dichotomized at medians in each study). All of the analyses were conducted in boys and girls separately, except for one study that combined the data from boys and girls, with sex as a covariate. Analyses were also conducted in each race, and in cases and controls separately if studies included multiple ancestries or had a case-control design.

Detailed summary statistics from each study were subsequently collected, and we pooled β-coefficients and SEs from individual studies using the Mantel-Haenszel fixed-effects method, as well as the DerSimonian and Laird random-effects method implemented in Stata, version 12 (StataCorp LP, College Station, TX). The significant *P* value was 0.005 after Bonferroni adjustment for 10 independent tests: *FTO*-BMI association (1 test); diet-BMI associations (3 tests; we considered total energy, protein, carbohydrate, and fat intake as 3 independent variables); *FTO*-diet associations (3 tests); and *FTO*-diet interactions (3 tests). Between-study heterogeneity was tested by the Cochran *Q* statistic and quantified by the values for the proportion of variance explained by interstudy differences (I^2). Low heterogeneity was defined as an I^2 value of 0–25%, moderate heterogeneity as an I^2 of 25–75%, and high heterogeneity as an I^2 of 75–100%. The *P* value for heterogeneity was derived from a χ^2 test. We also performed stratified meta-analyses in subgroups according to ethnicity (whites, African Americans, or Asians), sex, age group (mean age <10 vs. ≥10 years), geographic region (North America, Europe, or Asia), study sample size ($n < 500$ vs. $n \geq 500$), study design (population based vs. case-control), dietary intake assessment method (dietary records or 24-h recalls vs. food frequency questionnaire or others), and adjustment for physical activity (yes vs. no).

RESULTS

FTO Variants and BMI

We found a significant association between the minor allele (A-allele) of the *FTO* SNP rs9939609 (or its proxies) and a higher BMI in all participants combined (effect per allele =

Table 1—Associations between *FTO* SNP rs9939609, BMI, and dietary intake in a fixed-effects meta-analysis of 16,097 children and adolescents

	Model 1*			Model 2†		
	β (95% CI)	*P*	I^2	β (95% CI)	*P*	I^2
BMI *z* score	0.07 (0.05, 0.09)	4.7×10^{-10}	40%			
Total energy (kcal/day)	14.6 (6.3, 23.1)	6.5×10^{-4}	0%	14.7 (6.3, 23.1)	6.5×10^{-4}	6%
Protein (% of energy)	0.0 (−0.1, 0.0)	0.10	0%	0.0 (−0.1, 0.0)	0.09	0%
Carbohydrate (% of energy)	0.0 (−0.1, 0.1)	0.96	24%	0.0 (−0.1, 0.1)	0.92	15%
Fat (% of energy)	0.1 (−0.1, 0.2)	0.40	34%	0.1 (−0.1, 0.2)	0.35	29%

Data are β-coefficients (95% CI) per minor allele of FTO rs9939609 or a proxy ($r^2 = 1$) are given for each trait. Analyses from individual studies were conducted separately and then combined by meta-analysis of 16,097 children and adolescents (15,352 whites, 478 African Americans, and 267 Asians). I^2 values are also given. *Adjusted for age, pubertal status (if available), physical activity (if available), region (if available), and eigenvectors (GWAS data only). †Further adjusted for BMI based on model 1.

0.07 SD [95% CI 0.05, 0.09 SDs], $P = 4.7 \times 10^{-10}$) (Table 1). The association was significant in 15,352 whites (effect per allele = 0.08 SD [0.05, 0.10 SDs], $P = 2.9 \times 10^{-11}$), but not in 478 African Americans (effect per allele = −0.12 SD [−0.26, 0.02 SDs], $P = 0.08$) or 267 Asians (effect per allele = 0.11 SD [−0.12, 0.09 SDs], $P = 0.87$), separately.

FTO Variants and Dietary Intake

The minor allele of the *FTO* variant was significantly associated with higher total energy intake in all participants combined (effect per allele = 14.6 kcal/day [6.3, 23.1 kcal/day], $P = 6.5 \times 10^{-4}$), with no heterogeneity among studies ($I^2 = 0\%$) (Table 1). This association was unchanged after further adjustment for BMI (effect per allele = 14.7 kcal/day [6.3, 23.1 kcal/day], $P = 6.5 \times 10^{-4}$). The association between *FTO* variant and total energy intake was found in whites ($P = 0.001$) and Asians ($P = 0.01$), but not in African Americans ($P = 0.80$), although directions of associations were consistent across ethnicities (P for heterogeneity = 0.07) (Fig. 1). In stratified meta-analyses according to sex, age group, geographic region, study design, dietary intake assessment

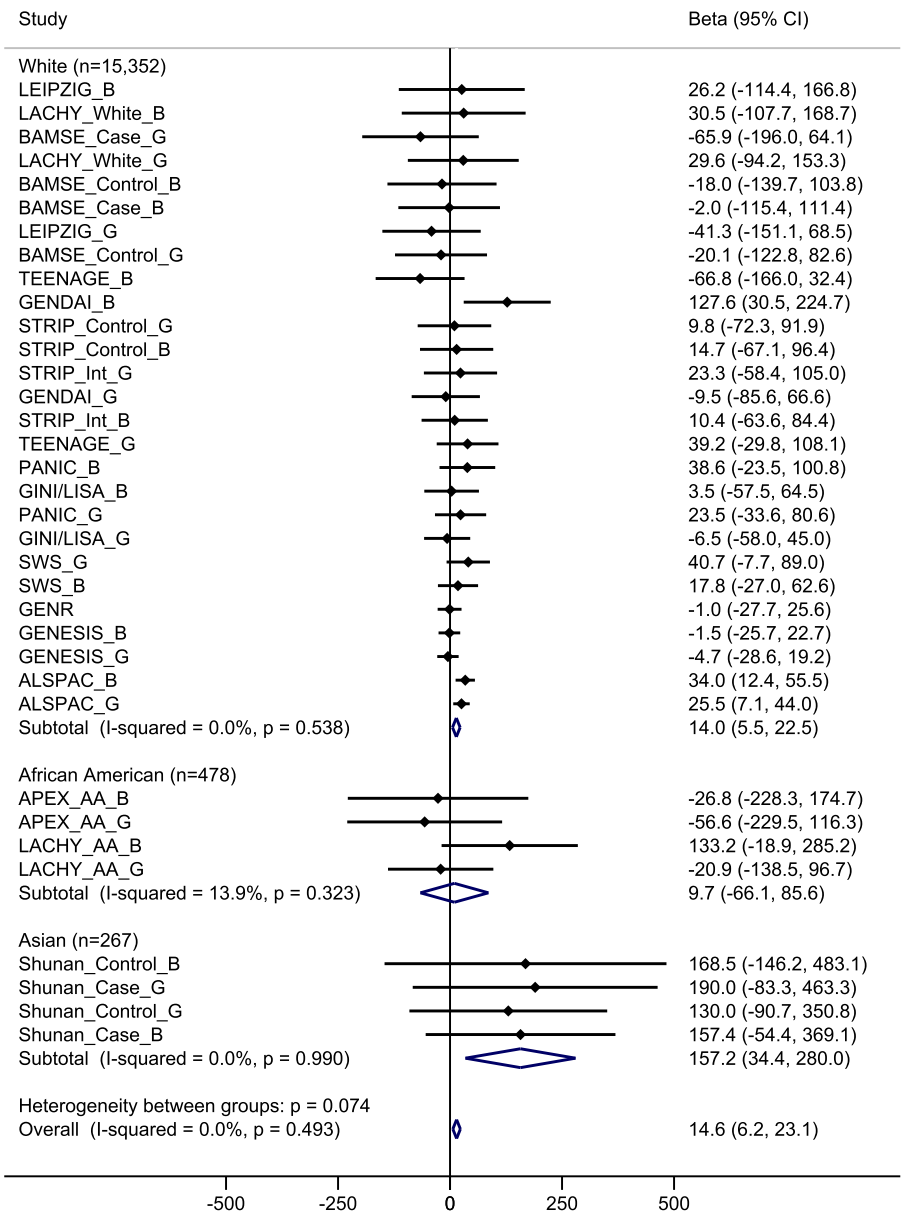

Figure 1—Forest plot of the association between *FTO* SNP rs9939609 and total energy intake in a fixed-effects meta-analysis of 16,097 children and adolescents. The studies are shown in boys (_B), girls (_G), or mixed case patients (_Case) and control subjects (_Control) for case-control studies and whites (_White) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The β represents the difference in total energy intake per minor allele of SNP rs9939609 or a proxy ($r^2 = 1$), adjusted for age, pubertal status (if available), physical activity (if available), region (if available), and eigenvectors (GWAS data only).

method, and adjustment for physical activity (Supplementary Fig. 1), the directions of the associations between *FTO* variant and total energy intake were consistent across subgroups. Of note, the association was stronger in studies with a mean age for participants of ≥10 years than in studies with a mean age of <10 years (effect per allele = 25.3 vs. 4.2 kcal/day, *P* for heterogeneity = 0.014). Since most studies had a mean age for participants of >7.5 years and three studies had a mean age between 1.0 and 3.5 years, we further examined the association between *FTO* variant and total energy intake according to the following three categories of age: studies with a mean age for participants between 1.0 and 3.5 years (effect per allele = 2.4 kcal/day); studies with a mean age for participants between 7.5 and 10 years (effect per allele = 10.6 kcal/day); and studies with a mean age for participants of ≥10 years old (effect per allele = 25.3 kcal/day).

We did not find evidence for associations between *FTO* variant and intake of protein (*P* = 0.10), carbohydrate (*P* = 0.96), or fat (*P* = 0.40), and there was a low or moderate heterogeneity among studies (I^2 = 0%, 24%, and 34%, respectively) (Table 1 and Supplementary Figs. 2, 3, and 4). Further adjustment for BMI did not notably change the results.

We also performed meta-analyses for *FTO* variant and dietary intake using the random-effects method, resulting in similar findings (Supplementary Table 5).

Dietary Intake and BMI

Higher total energy and protein intake were significantly associated with higher BMI (Supplementary Table 6). Difference in BMI between the high and low energy intake groups was 0.04 SD (95% CI 0.01, 0.02 SDs, *P* = 0.004), and difference in BMI between the high–protein intake and low–protein intake groups was 0.09 SD (0.07, 0.12 SDs, $P = 5.0 \times 10^{-10}$). There was no significant difference in BMI between the high–carbohydrate intake and low–carbohydrate intake groups (difference in BMI = −0.02 SD [−0.05, 0.01 SDs], *P* = 0.12), and a nominally significant difference in BMI between the high–fat intake and low–fat intake groups (difference in BMI = −0.03 SD [−0.06, −0.001 SDs], *P* = 0.04).

Interaction Between *FTO* Variants and Dietary Intake on BMI

We observed a significant interaction between *FTO* variant and dietary protein intake on BMI in all participants combined (effect per allele for interaction = 0.08 SD [95% CI 0.03, 0.12 SDs], *P* for interaction = 7.2×10^{-4}), showing that lower protein intake attenuated the association between the *FTO* variant and BMI, with no heterogeneity among studies (I^2 = 0%) (Table 2). In stratified analysis by low–protein intake and high–protein intake groups (dichotomized at medians of protein intake in each study: ranging from 12.9% to 16.8% across studies). The association between *FTO* variant and BMI among participants in the low–protein intake group (effect per allele = 0.04 SD [95% CI 0.01, 0.07 SDs], *P* = 0.02) was significantly weaker than that in the high–protein intake group (effect per allele = 0.10 SD [0.07, 0.13 SDs], $P = 8.2 \times 10^{-10}$) (Table 2). Although the interaction was found in whites (*P* for interaction = 0.001) but not in African Americans (*P* = 0.84) or Asians (*P* = 0.11) separately, there was no significant heterogeneity among these ethnic groups (*P* for heterogeneity = 0.53) (Fig. 2). In stratified meta-analyses (Supplementary Fig. 5), we found similar interaction patterns between *FTO* variant and protein intake on BMI across subgroups divided by sex, age group, geographic

Table 2—Interaction between *FTO* SNP rs9939609 and dietary intake on BMI in a fixed-effects meta-analysis of 16,097 children and adolescents

	Association between FTO variant and BMI			Interaction effect		
	β (95% CI)	*P*	I^2	β (95% CI)	*P*	I^2
Total energy (kcal/day)				−0.03 (−0.07, 0.02)	0.20	0%
Low-intake group	0.08 (0.05, 0.12)	2.9×10^{-7}	25%			
High-intake group	0.05 (0.02, 0.08)	8.0×10^{-4}	25%			
Protein (% of total energy intake)				0.08 (0.03, 0.12)	7.2×10^{-4}	0%
Low-intake group	0.04 (0.01, 0.07)	0.02	0%			
High-intake group	0.10 (0.07, 0.13)	8.2×10^{-10}	34%			
Carbohydrate (% of total energy intake)				0.00 (−0.04, 0.04)	0.98	10%
Low-intake group	0.08 (0.05, 0.11)	1.6×10^{-6}	20%			
High-intake group	0.07 (0.04, 0.10)	9.9×10^{-6}	26%			
Fat (% of total energy intake)				0.00 (−0.05, 0.05)	0.89	0%
Low-intake group	0.08 (0.05, 0.11)	6.7×10^{-7}	24%			
High-intake group	0.07 (0.03, 0.10)	4.1×10^{-5}	34%			

Data are β-coefficients (95% CI) per minor allele of FTO rs9939609 or a proxy (r^2 = 1) for BMI (*z* score), adjusted for age, pubertal status (if available), physical activity (if available), region (if available), and eigenvectors (GWAS data only). Analyses from individual studies were conducted separately and then combined by meta-analysis of 16,097 children and adolescents (15,352 whites, 478 African Americans, and 267 Asians). I^2 values are also given. High- and low-intake groups were defined by medians of each dietary intake in each study. Medians of total energy intake ranged from 1,160 to 2,422 kcal/day, medians of protein intake ranged from 12.9% to 16.8%, medians of carbohydrate intake ranged from 44.2% to 59.0%, and medians of fat intake ranged from 28.0% to 41.0% across studies.

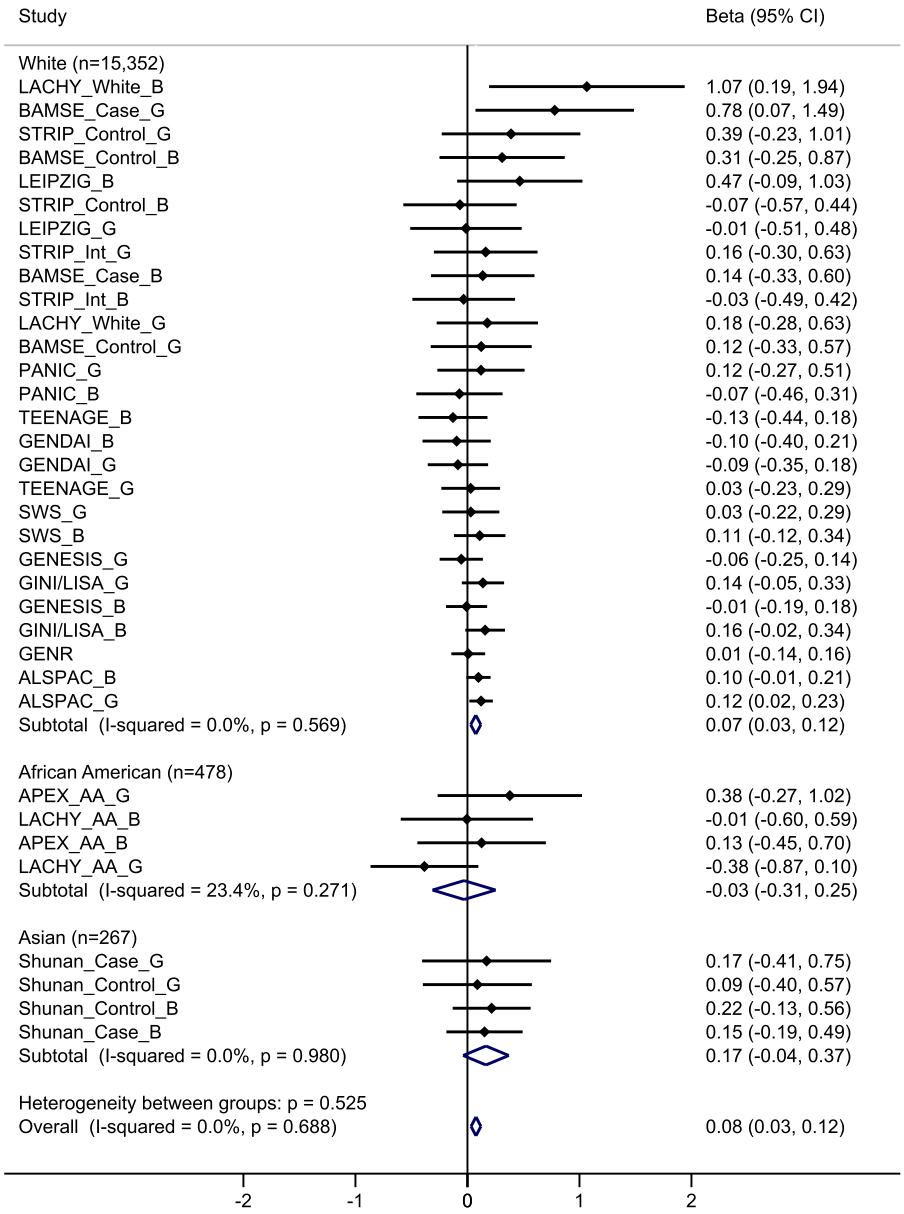

Figure 2—Forest plot of the interaction between *FTO* SNP rs9939609 and dietary protein intake on BMI in a fixed-effects meta-analysis of 16,097 children and adolescents. The studies are shown in boys (_B), girls (_G), or mixed case patients (_Case) and control subjects (_Control) for case-control studies and whites (_White) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The β represents the difference in BMI per minor allele of SNP rs9939609 or a proxy (r^2 = 1) comparing participants in the high–protein intake group to those in the low–protein intake group, adjusted for age, pubertal status (if available), physical activity (if available), region (if available), and eigenvectors (GWAS data only).

region, study design, dietary intake assessment method, and adjustment for physical activity (all *P* for heterogeneity $>$ 0.11).

We did not find substantive evidence for interactions between *FTO* variant and total energy intake (*P* for interaction = 0.20), carbohydrate intake (*P* for interaction = 0.98), or fat intake (*P* for interaction = 0.89) on BMI (Table 2 and Supplementary Figs. 6, 7, and 8). The heterogeneity among studies was low (I^2 = 0%, 15%, and 5%, respectively). In analyses stratified by levels of dietary intake, associations between *FTO* variant and BMI were similar in high- and low-intake groups (Table 2).

In addition, since there was little or no heterogeneity in interactions between *FTO* variant and dietary intake on BMI across studies, the results were similar when we performed meta-analyses using the random-effects method (Supplementary Table 7).

DISCUSSION

We confirmed the association between an index SNP in the *FTO* gene, rs9939609 (or its proxy), and BMI in white

children and adolescents and in all participants combined, but did not detect significant association in African American or Asian children and adolescents. This might be due to the relatively small sample size used by studies of African Americans or Asians included in the current analysis and/or to different linkage disequilibrium patterns across *FTO* intron 1 between different ethnic groups, particularly in populations of African ancestry (4,51). Other index SNPs within *FTO* locus might be needed in future studies of African American children and adolescents.

Although studies of *FTO* association with dietary intake in adults have been more numerous and often better powered with larger sample sizes than similar studies conducted in children and adolescents, the reported results have been inconsistent (16–20,25–34). Our and other studies even observed an inverse association between *FTO* variant and total energy intake in adults, which might be partly due to under-reporting of total energy intake among individuals with a higher BMI (19,20,39). In the current analysis, we demonstrated an association between the BMI-increasing allele of the *FTO* variant and higher total energy intake. However, we did not observe a significant association between *FTO* variants and percentages of energy derived from protein, which has been observed in adults (39), or other macronutrients.

An apparently stronger, and more consistently reported, effect of *FTO* on total energy intake in children and adolescents could have several explanations. The influence of social desirability bias and the under-reporting issues are smaller in children than in adults (52–54). It is possible that the effect of *FTO* variation on appetite may be stronger in children and adolescents than in adults. Consistent with this hypothesis and with the idea that *FTO* genetic effects might vary over the life course, previous studies (49,55–60) have reported an increasing effect of *FTO* variants on BMI from early childhood to adolescence, with a subsequently decreasing effect throughout adulthood. Our result is also consistent with this, as we observed a stronger association between *FTO* variant and total energy intake in studies of older children than in studies of younger children.

Several lines of evidence from animal and in vitro studies are consistent with the observed association between *FTO* variant and total energy intake in humans. It has been reported that overexpression of *Fto* in mice led to increased food intake (5), and *Fto* expression in hypothalamus was regulated by feeding, fasting, and energy restriction (61–67). Further studies showed that glucose and amino acid deprivation decreases *Fto* expression, suggesting a role of FTO in cellular nutrient sensing (68,69), possibly acting via hypothalamic mammalian target of rapamycin pathways known to regulate food intake (70). A recent study (71) suggested a link among FTO, ghrelin (a key mediator of ingestive behavior), and impaired brain food-cue responsivity in both animals and humans. Interestingly, a recent study (9) has challenged the established view of *FTO* as the major gene associated with BMI and risk of obesity, reporting that the region of *FTO* intron 1 harboring the BMI-associated variants are strongly associated with *IRX3* gene (500 kbp downstream of *FTO* intron 1) expression in cerebellar brain samples. However, it has been pointed out that the cerebellum is not primarily involved in food intake or appetite regulation and *FTO* expression may function in a site-dependent manner (72). In addition, another study (10) suggested that *RPGRIP1L,* located >100 bp 5′ in the opposite transcriptional orientation of *FTO*, may be partly or exclusively responsible for the obesity susceptibility signal at the *FTO* locus.

One novel finding of our study is the interaction between the *FTO* variant and dietary protein intake on BMI. The effect size of *FTO* variant on BMI in children with a low–protein intake was much smaller than in children with a high–protein intake, suggesting that low–protein intake may attenuate the influence of *FTO* variation on BMI. A study of 354 Spanish children and adolescents reported a significant interaction between the *FTO*-rs9939609 variant and dietary saturated fat intake on BMI (38), and several adult studies also found interactions between the *FTO* variant and total fat or saturated fat intake on BMI and obesity risk (20,26,34), while no significant interaction between the *FTO* variant and dietary intake was observed in our meta-analysis of adult data (39). In addition, we previously found that dietary protein intake might modify the effects of *FTO* variants on changes in body composition, fat distribution, and appetite in a 2-year weight-loss trial (73,74). A recent mouse study (6) showed that loss of *Fto* gene altered protein utilization and body composition; and consistently, other studies (68,69) also suggest that *FTO* may influence body composition through cellular sensing of amino acids. Given the increasing evidence supporting the role of FTO in protein metabolism and body composition, future investigations on this topic might help to clarify the mechanisms underlying the observed interaction between the *FTO* variant and protein intake, and its effect on BMI.

Major strengths of our study include a large sample size of >16,000 children and adolescents from 14 studies, a wide range of studies with data from early childhood to late adolescence, and the standardized analytical plan across studies. There are some limitations in our study. Our analysis was conducted based on cross-sectional data. Measurement errors in dietary assessment are inevitable since self-reported data on dietary intake are all subject to bias. We only included dietary data on total energy and macronutrient intake, but no data on specific foods or more specific types of fatty acids or micronutrients, which may potentially interact with the FTO variant as suggested previously (26,34,38). We were unable to examine other adiposity proxies, but were limited to the consideration of BMI, which cannot distinguish body composition and does not give any indication about body fat distribution. To the best of our knowledge, this is to date the largest analysis of *FTO* variant and dietary intake in children and adolescents, though more data are needed to further

confirm our results. In particular, most of the children and adolescents included in our analysis are individuals of European ancestry (95% of all samples), and it is unknown whether our results can be generalized to other ethnic groups.

In summary, we demonstrated an association between the BMI-increasing allele of *FTO* variant and total energy intake based on data from 16,094 children and adolescents. Our data also show that dietary protein intake may modify the influence of *FTO* variants on BMI, offering new insight into the interrelationships between *FTO* genetic variants, dietary intake, and obesity.

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