Dietary intake, *FTO* genetic variants and adiposity: a combined analysis of over 16,000 children and adolescents

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ABSTRACT

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: 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 on BMI. We found that the BMI-increasing allele (minor allele) of *FTO* variant was associated with increased total energy intake (effect per allele=14.3[5.9, 22.7] kcal/day, $P=6.5\times10^{-4}$) 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[0.03, 0.12]SDs, *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[0.07, 0.13]SDs, $P=8.2\times10^{-10}$) than in those with low intake (effect per allele=0.04[0.01, 0.07]SDs, *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.

Introduction

Common single nucleotide polymorphisms (SNPs) located in the first intron of the fat mass and obesity associated (*FTO*) gene are the first adiposity/body mass index (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 variant(s) 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, the BMI-increasing allele of *FTO* variants has been reported to be associated with increased food intake, total energy intake, fat or protein intake (11-20), 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 that have investigated interaction with dietary factors in relation to BMI/obesity have generated conflicting results potential interactions(12; 20; 26; 32; 34; 35; 37; 38). Our recent large-scale meta-analysis indicated that *FTO* variants were associated with protein intake in adults and under-reporting of dietary intake in obese participants might be a major issue in the analysis (39). 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.

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

Materials 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 (**Supplemental 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 **Supplemental Table 2**. The ranges of mean values across studies were age 1.1 to 16.4 years, BMI 16.2 to 24.7 kg/m^2, total energy intake1017 to 2423 kcal/day, total protein intake 12.9 to 16.8% (percentage of total energy intake), total carbohydrate 43.4 to 59.0%, and total fat intake 28.1 to 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 (**Supplemental**

Table 3). For two studies with children aged younger than 2 years, length (height) was measured in a supine position to the nearest millimeter (43; 48). Dietary intake (total energy, protein, carbohydrate, and fat) was assessed using validated food frequency questionnaires (FFQs) (four studies), multiple-day dietary/food records (three studies), multiple-day 24-hour recalls (four studies), both dietary records and 24-hour recalls (one study), diet history consulting and information system (one study), or brief-type self-administered diet history questionnaire (one study) (**Supplemental Table 3**). Macronutrient intake was expressed as the percentage of total energy intake.

Genotyping

FTO SNP rs9939609 or a proxy (linkage disequilibrium [LD] 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://www.sph.umich.edu/csg/abecasis/MACH/) with a high imputation quality (r^2=1) (**Supplemental 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, 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 (GWAS data 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 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 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 beta coefficients and standard errors from individual studies using the Mantel and Haenszel fixed effects method as well as the DerSimonian and Laird random effects method implemented in Stata, version 12 (StataCorp LP, College Station, Texas, USA). Significant *P*-value was 0.005 after Bonferroni's 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 Cochran's *Q* statistic and quantified by the I^2 value. 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%. *P* for heterogeneity was derived from a *chi*-squared test. We also performed stratified meta-analyses in subgroups according to ethnicity (whites, African Americans, or Asian), sex, age group (mean age<10 vs. ≥10 years), geographic region (North America, Europe, or Asia), study sample size (n<500 vs. ≥500), study

design (population-based vs. case-control), dietary intake assessment method (dietary records or 24-hour recalls vs. FFQ 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 higher BMI in all participants combined (effect per allele=0.07 [95% CI 0.05, 0.09] SDs, $P=4.7\times10^{-10}$) (**Table 1**). The association was significant in 15,352 whites (effect per allele=0.08 [0.05, 0.10] SDs; $P=2.9\times10^{-11}$), but not in 478 African Americans (effect per allele=-0.12 [-0.26, 0.02] SDs; $P=0.08$) or 267 Asians (effect per allele=0.11 [-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 [6.3, 23.1] kcal/day, $P=6.5\times10^{-4}$), with no heterogeneity among studies ($I^2=0\%$) (**Table 1**). This association was unchanged after further adjustment for BMI (effect per allele =14.7 [6.3, 23.1] kcal/day, $P=6.5\times10^{-4}$). 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) (**Figure 1**). In stratified meta-analyses according to sex, age group, geographic region, study design, dietary intake assessment method, and adjustment for physical activity (**Supplemental Figure 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 ≥10 years old than in studies with a mean

age <10 years old (effect per allele =25.3 vs. 4.2 kcal/day; *P* for heterogeneity=0.014). Since most studies had a mean age >7.5 years and three studies had a mean age between 1.0 to 3.5 years old, we further examined the association between *FTO* variant and total energy intake according to three categories of age: studies with a mean age between 1.0 to 3.5 years old (effect per allele =2.4 kcal/day); studies with a mean age between 7.5 and 10 years old (effect per allele =10.6 kcal/day); and studies with a mean age ≥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, Supplemental Figure 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 (**Supplemental Table 5**).

Dietary intake and BMI

Higher total energy and protein intake were significantly associated with higher BMI (**Supplemental Table 6**). Difference in BMI between the high and low energy intake groups was 0.04 [0.01, 0.02] SDs (*P*=0.004), and difference in BMI between the high and low protein intake groups was 0.09 [0.07, 0.12] SDs ($P=5.0\times10^{-10}$). There was no significant difference in BMI between the high and low carbohydrate intake groups (difference in BMI = -0.02 [-0.05, 0.01] SDs; *P* = 0.12), and a nominally significant difference in BMI between the high and low fat intake groups (difference in BMI = -0.03 [-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 [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 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 [0.01, 0.07] SDs, *P*=0.02) was significantly weaker than that in the high protein intake group (effect per allele = 0.10 [0.07, 0.13] SDs, $P=8.2\times10^{-10}$) (**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) (**Figure 2**). In stratified meta-analyses (**Supplemental Figure 5**), we found similar interaction patterns between *FTO* variant and protein intake on BMI across subgroups divided by sex, age group, geographic 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 Supplemental Figure 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 (**Supplemental 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 a relatively small sample size used by African American or Asian studies included in the current analysis and/or to different LD 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 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 underreporting 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 have reported an increasing effect of *FTO* variants on

BMI from early childhood to adolescence, with a subsequently decreasing effect throughout adulthood (49; 55-60). 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 mTOR pathways known to regulate food intake (70). A recent study suggested a link between FTO, ghrelin (a key mediator of ingestive behavior), and impaired brain food-cue responsivity (71) in both animals and humans. Interestingly, a recent study has challenged the established view of *FTO* as the major gene associated with BMI and risk of obesity (9), reporting that the region of *FTO* intron 1 harboring the BMI-associated variants are strongly associated with *IRX3* gene (500kbp 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 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(10).

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 two-year weight-loss trial (73; 74). A recent mouse study showed that loss of *Fto* gene altered protein utilization and body composition (6); and consistently, other studies also suggest that *FTO* may influence body composition through cellular sensing of amino acids (68; 69). 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 on BMI.

Major strengths of our study include a large sample size of over 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, 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 the largest analysis of *FTO* variant and dietary intake in children and adolescents to date, 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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Q.Q. designed the study, researched data and wrote the manuscript. M.K.D, T.O.K., H.R.T., S.J.B., G.V.D., M.S., V.H., J.C.K., A.K., T.A.L., G.L., J.M., I.N., M.O., O.R., R.R., R.A.S., M.E.S.B., V.B., K.S., J.W.H., H.I., V.W.V.J., J.L., V.L., E.M., Y.P., N.P., H.S., J.H., N.J.T., H.Y., E.Z., and T.W. researched data and edited/reviewed the manuscript. C.R.I., Y.M., R.C.K., J.W., R.J.F.L., and F.B.H. contributed to discussion and edited/reviewed the manuscript. Q.L. designed the study, contributed to discussion and edited/reviewed the manuscript.

Drs. Qibin Qi and Lu Qi are the guarantors of this work and, as such, have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data.

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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‡		
	Beta (95% CI)	*P*	I^2	Beta (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%

*Beta 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). Values for proportion of variance explained by inter-study differences (I^2) 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.

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

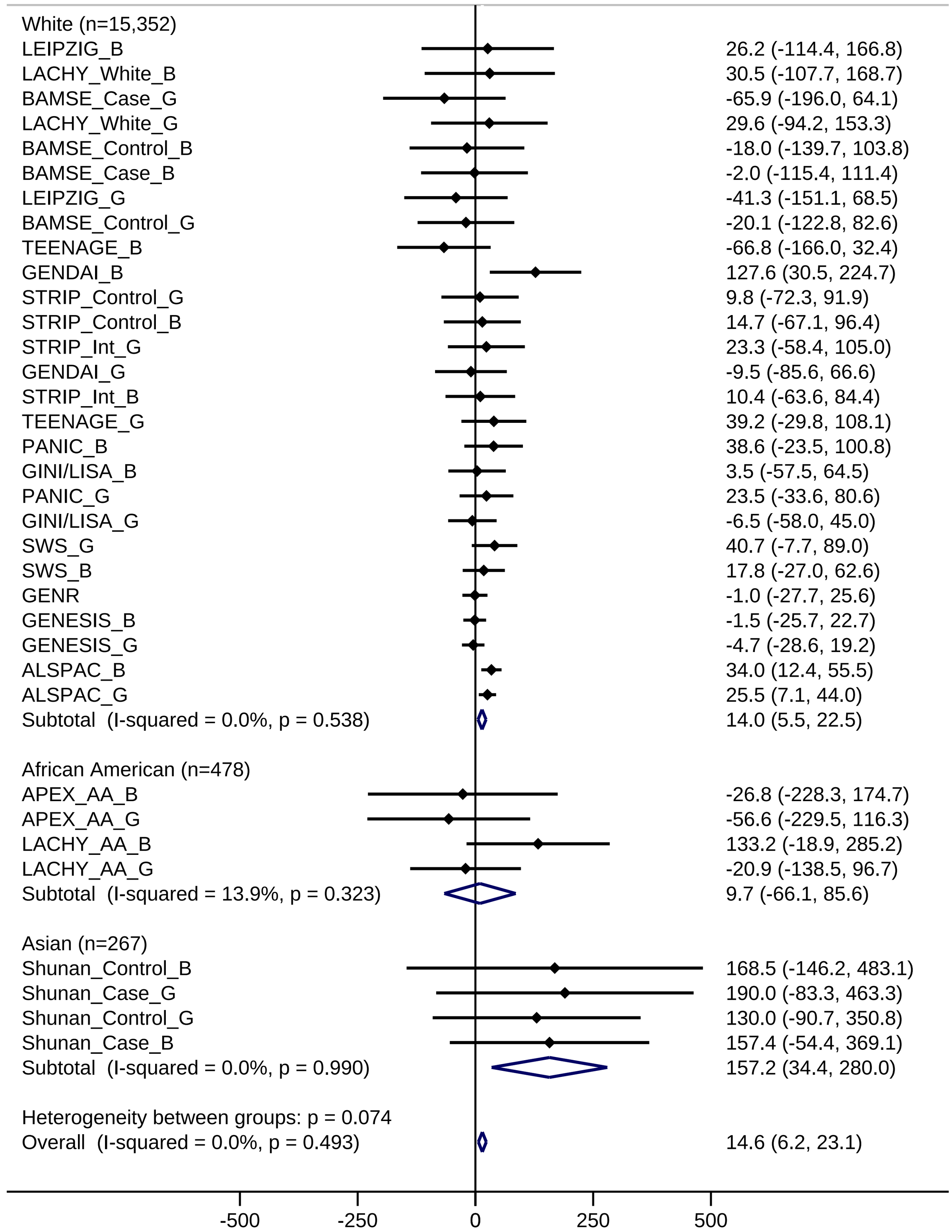
*Data are beta coefficients (95% CI) per minor allele of FTO rs9939609 or a proxy (r^2=1) for BMI (z-score), adjusted for age, pubertal status (if available), physical activity (if available), region (if available) and eigenvectors (GWAS data only). Analyses from individual studies were conducted separately, and then combined by meta-analysis of 16,097 children and adolescents (15,352 Whites, 478 African Americans, and 267 Asians). Values for proportion of variance explained by inter-study differences (I^2) 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 1160 to 2422 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.

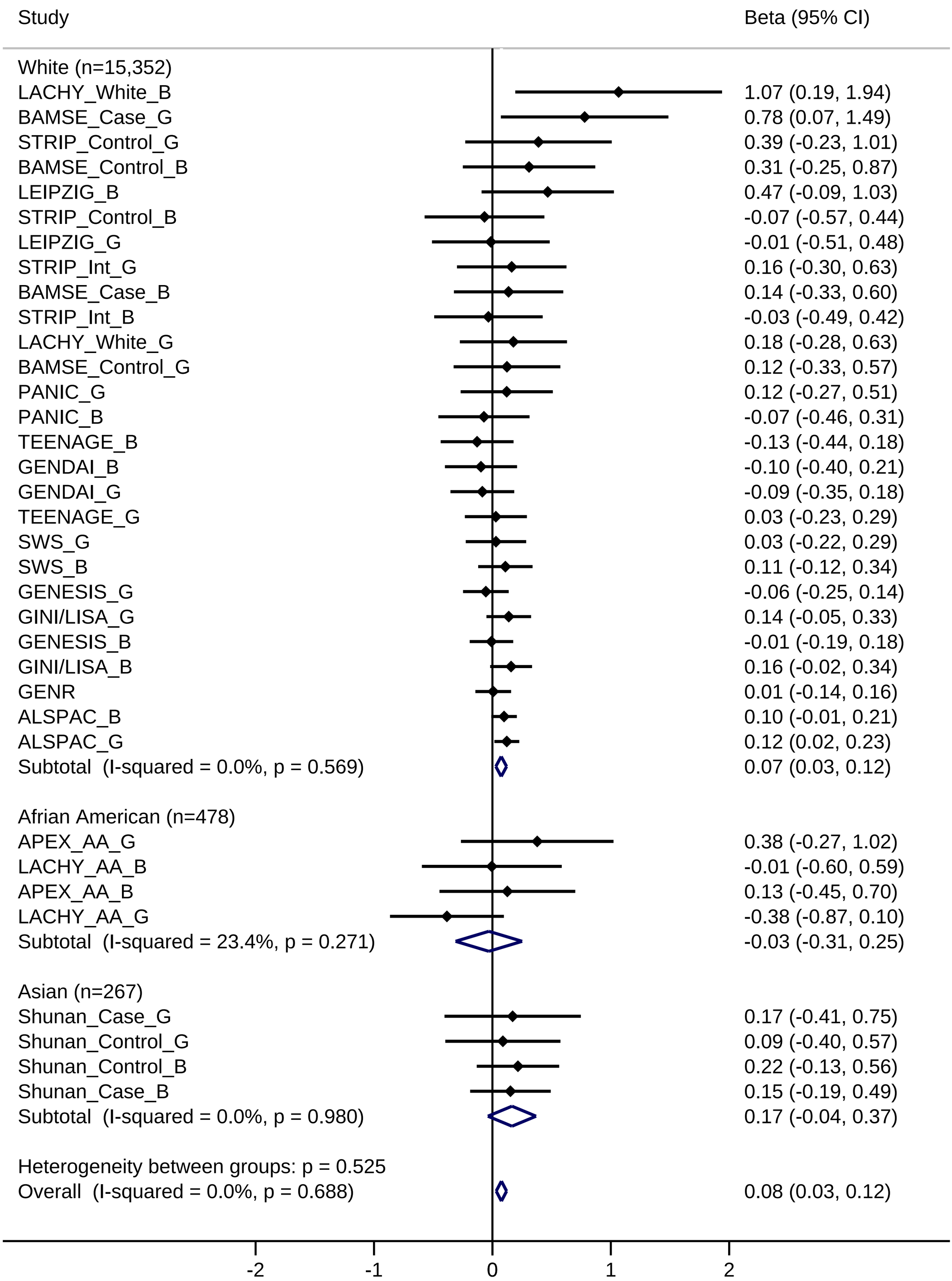
Figure Legend

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, cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta 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).

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, cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta 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).

Study	Beta (95% CI)
White (n=15,352)	
LEIPZIG_B	26.2 (-114.4, 166.8)
LACHY_White_B	30.5 (-107.7, 168.7)
BAMSE_Case_G	-65.9 (-196.0, 64.1)
LACHY_White_G	29.6 (-94.2, 153.3)
BAMSE_Control_B	-18.0 (-139.7, 103.8)
BAMSE_Case_B	-2.0 (-115.4, 111.4)
LEIPZIG_G	-41.3 (-151.1, 68.5)
BAMSE_Control_G	-20.1 (-122.8, 82.6)
TEENAGE_B	-66.8 (-166.0, 32.4)
GENDAI_B	127.6 (30.5, 224.7)
STRIP_Control_G	9.8 (-72.3, 91.9)
STRIP_Control_B	14.7 (-67.1, 96.4)
STRIP_Int_G	23.3 (-58.4, 105.0)
GENDAI_G	-9.5 (-85.6, 66.6)
STRIP_Int_B	10.4 (-63.6, 84.4)
TEENAGE_G	39.2 (-29.8, 108.1)
PANIC_B	38.6 (-23.5, 100.8)
GINI/LISA_B	3.5 (-57.5, 64.5)
PANIC_G	23.5 (-33.6, 80.6)
GINI/LISA_G	-6.5 (-58.0, 45.0)
SWS_G	40.7 (-7.7, 89.0)
SWS_B	17.8 (-27.0, 62.6)
GENR	-1.0 (-27.7, 25.6)
GENESIS_B	-1.5 (-25.7, 22.7)
GENESIS_G	-4.7 (-28.6, 19.2)
ALSPAC_B	34.0 (12.4, 55.5)
ALSPAC_G	25.5 (7.1, 44.0)
Subtotal (I-squared = 0.0%, p = 0.538)	14.0 (5.5, 22.5)
African American (n=478)	
APEX_AA_B	-26.8 (-228.3, 174.7)
APEX_AA_G	-56.6 (-229.5, 116.3)
LACHY_AA_B	133.2 (-18.9, 285.2)
LACHY_AA_G	-20.9 (-138.5, 96.7)
Subtotal (I-squared = 13.9%, p = 0.323)	9.7 (-66.1, 85.6)
Asian (n=267)	
Shunan_Control_B	168.5 (-146.2, 483.1)
Shunan_Case_G	190.0 (-83.3, 463.3)
Shunan_Control_G	130.0 (-90.7, 350.8)
Shunan_Case_B	157.4 (-54.4, 369.1)
Subtotal (I-squared = 0.0%, p = 0.990)	157.2 (34.4, 280.0)
Heterogeneity between groups: p = 0.074	
Overall (I-squared = 0.0%, p = 0.493)	14.6 (6.2, 23.1)




Study
Beta (95% CI)
White (n=15,352)
LACHY_White_B
1.07 (0.19, 1.94)
BAMSE_Case_G
0.78 (0.07, 1.49)
STRIP_Control_G
0.39 (-0.23, 1.01)
BAMSE_Control_B
0.31 (-0.25, 0.87)
LEIPZIG_B
0.47 (-0.09, 1.03)
STRIP_Control_B
-0.07 (-0.57, 0.44)
LEIPZIG_G
-0.01 (-0.51, 0.48)
STRIP_Int_G
0.16 (-0.30, 0.63)
BAMSE_Case_B
0.14 (-0.33, 0.60)
STRIP_Int_B
-0.03 (-0.49, 0.42)
LACHY_White_G
0.18 (-0.28, 0.63)
BAMSE_Control_G
0.12 (-0.33, 0.57)
PANIC_G
0.12 (-0.27, 0.51)
PANIC_B
-0.07 (-0.46, 0.31)
TEENAGE_B
-0.13 (-0.44, 0.18)
GENDAI_B
-0.10 (-0.40, 0.21)
GENDAI_G
-0.09 (-0.35, 0.18)
TEENAGE_G
0.03 (-0.23, 0.29)
SWS_G
0.03 (-0.22, 0.29)
SWS_B
0.11 (-0.12, 0.34)
GENESIS_G
-0.06 (-0.25, 0.14)
GINI/LISA_G
0.14 (-0.05, 0.33)
GENESIS_B
-0.01 (-0.19, 0.18)
GINI/LISA_B
0.16 (-0.02, 0.34)
GENR
0.01 (-0.14, 0.16)
ALSPAC_B
0.10 (-0.01, 0.21)
ALSPAC_G
0.12 (0.02, 0.23)
Subtotal (I-squared = 0.0%, p = 0.569)
0.07 (0.03, 0.12)
Afrian American (n=478)
APEX_AA_G
0.38 (-0.27, 1.02)
LACHY_AA_B
-0.01 (-0.60, 0.59)
APEX_AA_B
0.13 (-0.45, 0.70)
LACHY_AA_G
-0.38 (-0.87, 0.10)
Subtotal (I-squared = 23.4%, p = 0.271)
-0.03 (-0.31, 0.25)
Asian (n=267)
Shunan_Case_G
0.17 (-0.41, 0.75)
Shunan_Control_G
0.09 (-0.40, 0.57)
Shunan_Control_B
0.22 (-0.13, 0.56)
Shunan_Case_B
0.15 (-0.19, 0.49)
Subtotal (I-squared = 0.0%, p = 0.980)
0.17 (-0.04, 0.37)
Heterogeneity between groups: p = 0.525
Overall (I-squared = 0.0%, p = 0.688)
0.08 (0.03, 0.12)
-2
-1
0
1
2

Supplemental Tables and Figures

Supplemental Table 1 Basic information of studies participating in the analysis

Study		Study design	Race/ethnic group	No. of participants			Country and Region	References
Short name	Full name			All	Boys	Girls		
ALSPAC	Avon Longitudinal Study of Parents and Children	Birth cohort	Caucasian	5561	2759	2802	UK, Europe	(1)
APEX	Adiposity Prevention through Exercise study	School-based cross-sectional study	African American	250	117	133	USA, North America	(2)
BAMSE	The Children, Allergy, Milieu, Stockholm, Epidemiology Study	Birth cohort / nested case-control study	Caucasian	477	266	211	Sweden, Europe	(3)
GENDAI	Gene and Diet Attica Investigation on Childhood Obesity	School-based cross-sectional study	Caucasian	825	385	440	Greece, Europe	(4)
GENESIS	Growth, Exercise and Nutrition Epidemiological Study in preSchoolers	Population-based cross-sectional study	Caucasian	1733	902	831	Greece, Europe	(5)
GENR	The Generation R Study	Birth cohort	Caucasian	1404	715	689	Netherlands, Europe	(6)
GINI/LISA	German Infant Study on The Influence of Nutrition Intervention PLUS Environmental and Genetic Influences on Allergy Development/Life-Style Factors on The Development of The Immune System and Allergies in East and West Germany PLUS The Influence of Traffic Emissions and Genetics	Birth cohort	Caucasian	1999	1031	968	Germany, Europe	(7; 8)
LACHY	Lifestyle, Adiposity and Cardiovascular Health in Youths Study	School-based cross-sectional study	Caucasian	257	124	133	USA, North America	(2)
			African American	228	91	137		
LEIPZIG	Leipzig Childhood Cohort	Population-based	Caucasian	280	134	146	Germany, Europe	(9)
PANIC	The Physical Activity and Nutrition in Children	Population-based intervention study	Caucasian	409	209	200	Finland, Europe	(10)
SHUNAN	Shunan Child Cohort Study	Case-control study	Asian	267	140	127	Japan, Asia	(11)
SWS	Southampton Women's Survey	Birth cohort	Caucasian	1112	579	533	UK, Europe	(12)
STRIP	Special Turku Coronary Risk Factor Intervention Project	Intervention study	Caucasian	511	261	250	Finland, Europe	(13)
TEENAGE	TEENs of Attica: Genes and Environment study on Greek Adolescents	School-based cross-sectional study	Caucasian	784	354	430	Greece, Europe	(14)

Supplemental Table 2 Study-specific characteristics for studies participating in the meta-analysis

Study	Gender	N	Age, yr	BMI, kg/m^2	Energy, kcal/d	Protein, g/d	Protein, %	Carbohydrate, g/d	Carbohydrate, %	Fat, g/d	Fat, %
ALSPAC	Boys	2759	10.1 (0.3)	18.1 (3.0)	1944.3 (394.8)	65.5 (16.2)	13.6 (2.5)	260.6 (56.8)	53.7 (5.5)	78.4 (20.8)	36.1 (4.9)
	Girls	2802	10.1 (0.3)	18.3 (3.1)	1770.0 (349.7)	58.3 (14.1)	13.3 (2.5)	235.9 (51.0)	53.4 (5.4)	72.5 (18.4)	36.7 (4.7)
APEX	Boys	117	9.8 (1.0)	20.4 (4.9)	1867.5 (692.7)	69.6 (32.2)	14.9 (4.1)	229.0 (85.5)	49.9 (8.6)	76.3 (33.4)	36.0 (6.5)
	Girls	133	9.4 (0.9)	21.1 (5.3)	1705.0 (584.9)	55.6 (20.2)	13.2 (2.8)	229.5 (85.7)	53.8 (6.3)	64.9 (24.8)	34.1 (5.1)
BAMSE_Case	Boys	148	8.4 (0.5)	17.2 (1.8)	1895.2 (476.5)	74.4 (21.0)	15.7 (2.1)	252.3 (62.5)	53.4 (4.6)	65.2 (19.9)	30.8 (3.9)
	Girls	87	8.3 (0.4)	17.4 (2.2)	1823.9 (415.1)	72.7 (17.9)	16.1 (2.6)	242.1 (62.6)	52.9 (7.2)	62.6 (17.0)	31.0 (5.9)
BAMSE_Control	Boys	118	8.3 (0.5)	17.2 (2.0)	1926.2 (456.4)	75.9 (20.2)	15.7 (1.7)	256.0 (62.5)	53.3 (4.1)	66.4 (18.2)	31.0 (3.7)
	Girls	124	8.2 (0.5)	16.9 (1.7)	1838.6 (409.4)	73.6 (17.8)	16.1 (1.9)	243.7 (58.7)	53.0 (3.9)	63.2 (16.0)	30.9 (3.7)
GENDAI	Boys	385	11.2 (0.7)	20.3 (3.5)	2012.6 (630.7)	75.3 (27.1)	15.0 (3.0)	225.9 (78.0)	45.1 (8.0)	89.1 (30.3)	40.5 (6.8)
	Girls	440	11.2 (0.6)	19.7 (3.4)	1792.8 (554.8)	66.2 (22.8)	15.0 (3.5)	204.3 (69.1)	45.8 (7.4)	78.6 (27.5)	39.8 (6.5)
GENESIS	Boys	902	3.4 (0.9)	16.2 (1.6)	1208.5 (267.0)	50.1 (13.3)	16.6 (2.6)	136.6 (34.4)	45.4 (6.6)	54.1 (15.1)	40.1 (5.5)
	Girls	831	3.4 (0.9)	16.2 (1.6)	1160.4 (249.3)	48.0 (12.5)	16.5 (2.6)	131.4 (32.1)	45.5 (6.6)	52.0 (15.1)	40.1 (5.4)
GENR	All	1404	1.1 (0.1)	17.2 (1.3)	1308.9 (352.9)	41.8 (11.6)	12.9 (2.4)	192.1 (51.2)	59.0 (5.7)	41.3 (15.9)	28.0 (5.3)
	Boys	715	1.1 (0.1)	17.4 (1.3)	1346.9 (357.3)	43.1 (12.1)	12.9 (2.4)	197.6 (51.5)	59.0 (5.8)	42.6 (16.3)	28.0 (5.4)
	Girls	689	1.1 (0.1)	17.1 (1.3)	1269.6 (344.2)	40.5 (11.1)	12.9 (2.4)	186.4 (50.2)	59.0 (5.6)	40.1 (15.4)	28.0 (5.1)
GINI/LISA	Boys	1031	10.8 (0.5)	17.3 (2.5)	2217.8 (677.2)	81.2 (29.9)	14.5 (2.4)	295.8 (84.0)	54.0 (6.5)	75.7 (31.8)	30.2 (5.7)
	Girls	968	10.9 (0.5)	17.3 (2.4)	1883.5 (531.6)	68.3 (23.0)	14.5 (2.4)	256.2 (71.6)	54.8 (6.2)	62.6 (24.2)	29.5 (5.5)
LACHY_White	Boys	124	16.2 (1.2)	22.1 (4.0)	2306.2 (566.4)	81.3 (22.8)	14.3 (2.8)	305.3 (83.2)	53.7 (6.4)	86.2 (26.9)	32.7 (4.9)
	Girls	133	16. 1 (1.1)	22.1 (3.9)	1713.4 (530.7)	56.4 (18.1)	13.5 (2.7)	235.9 (74.9)	55.8 (6.2)	62.9 (23.3)	32.1 (5.0)
LACHY_AA	Boys	91	15.9 (1.1)	22.6 (4.6)	2057.0 (517.2)	71.9 (19.9)	14.0 (2.3)	266.3 (78.3)	52.3 (5.6)	80.1 (21.5)	34.5 (4.2)
	Girls	137	16.4 (1.3)	24.7 (6.0)	1634.4 (511.5)	53.3 (17.1)	13.4 (2.9)	216.8 (72.3)	53.8 (6.6)	63.3 (23.2)	33.9 (4.9)
LEIPZIG	Boys	134	11.9 (3.2)	20.27 (5.3)	2145.5 (502.1)	75.5 (19.1)	14.2 (2.6)	250.2 (66.7)	46.7 (6.5)	90.0 (28.4)	37.7 (6.2)
	Girls	146	11.8 (3.2)	20.6 (5.9)	1952.6 (444.0)	67.5 (18.2)	13.9 (2.4)	230.0 (61.1)	47.2 (7.3)	81.4 (24.9)	37.3 (6.8)
PANIC	Boys	209	7.6 (0.4)	16.1 (1.9)	1728.0 (311.2)	72.3 (15.6)	16.8 (2.6)	223.0 (47.5)	51.6 (5.4)	58.1 (14.6)	30.2 (5.1)
	Girls	200	7.6 (0.4)	16.1 (2.2)	1554.9 (285.7)	64.2 (12.4)	16.7 (2.3)	202.6 (40.3)	52.2 (4.9)	51.8 (15.0)	29.8 (5.1)
SHUNAN_Case	Boys	77	11.9 (1.5)	23.3 (2.6)	2422.5 (644.3)	81.2 (23.6)	13.5 (2.0)	345.3 (105.7)	56.7 (6.0)	75.1 (22.4)	28.1 (4.9)
	Girls	53	11.9 (1.5)	23.6 (2.8)	1017.2 (563.9)	71.4 (23.1)	14.3 (2.4)	272.4 (84.4)	53.9 (6.2)	68.5 (24.2)	30.6 (5.1)
SHUNAN_Control	Boys	63	12.2 (1.5)	17.4 (1.7)	2335.7 (643.0)	82.8 (24.8)	14.2 (1.8)	313.1 (90.0)	53.6 (5.7)	79.8 (26.1)	30.7 (4.8)
	Girls	74	11.9 1.5)	17.8 (2.0)	1976.6 (530.0)	71.7 (19.8)	14.6 (1.9)	261.2 (88.4)	52.5 (5.7)	68.9 (17.3)	31.7 (4.6)
STRIP_Int	Boys	128	9.0 (0.0)	16.5 (1.9)	1730.2 (229.8)	69.4 (14.8)	16.1 (2.4)	227.9 (39.6)	52.9 (5.3)	56.5 (15.6)	29.6 (4.8)
	Girls	118	9.0 (0.0)	16.7 (2.0)	1550.9 (296.6)	62.5 (13.0)	16.3 (2.8)	206.5 (53.1)	53.3 (4.7)	50.4 (13.8)	29.0 (4.6)
STRIP_Control	Boys	133	9.0 (0.0)	16.5 (2.2)	1831.6 (329.7)	72.0 (14.5)	15.8 (2.3)	233.4 (44.5)	51.1 (5.2)	65.0 (18.3)	31.7 (5.1)
	Girls	132	9.0 (0.0)	17.2 (2.8)	1604.3 (302.8)	62.8 (13.6)	15.8 (2.3)	203.4 (40.0)	50.9 (5.1)	57.5 (15.6)	32.0 (5.1)
SWS	Boys	579	3.1 (0.1)	16.4 (1.3)	1642.7 (394.2)	57.7 (15.6)	14.1 (1.9)	225.7 (57.1)	55.0 (5.6)	62.0 (18.2)	33.8 (4.6)
	Girls	533	3.1 (0.1)	16.4 (1.6)	1554.9 (386.8)	55.2 (14.8)	14.3 (2.0)	210.6 (56.9)	54.7 (5.7)	59.7 (17.8)	34.5 (4.6)
TEENAGE	Boys	354	13.4 (0.8)	21.5 (3.7)	2017.3 (625.5)	76.5 (25.8)	15.2 (2.8)	221.3 (78.2)	44.2 (7.7)	91.6 (31.9)	41.0 (6.9)
	Girls	430	13.5 (0.9)	21.1 (3.3)	1590.4 (509.0)	58.5 (21.3)	14.6 (3.2)	183.3 (69.5)	45.4 (8.4)	74.0 (30.5)	40.0 (7.3)

Data are means (SD).
AA: African American.

Supplemental Table 3 Methods used for measuring BMI and dietary intakes for studies participating in the meta-analysis

Study	Anthropometric measurement	Dietary intake measurement		Time interval between anthropometric and dietary intake measurements
		Measurement	Description	
ALSPAC	Height was measured to the last complete mm with the use of a Harpenden stadiometer (Holtain Ltd, Crosswell, UK) while the child was not wearing shoes or socks, and weight was measured with the use of a body fat analyzer and weighing scales (Tanita TBF 305; Tanita UK Ltd, Yiewsley, UK).	Dietary Records	Three-day dietary records were collected from the whole cohort between February 2002 and October 2003 when the child was aged 10-11 years. The diary was checked by a nutritionist and the diet records were coded using Diet in, Diet out (DIDO). The coded data were converted to nutrient intakes by using a databased derived from McCance and Widdowson's Composition of Foods (5th edition), augmented with manufacturers' information and information from the nutrient database used by the National Diet and Nutrition survey.(1)	Dietary data, was collected one week before the anthropometric measurements
APEX	Height and weight were measured by standard methods using a wall-mounted stadiometer and a digital scale, respectively.	24-h recall	Free-living diet was measured with individual, non-consecutive, 24-h recalls that covered the period from midnight to midnight of the previous day. In the APEX study, two 24-h diet recalls were obtained from each participant.	Within two weeks
BAMSE	Weight was measured without shoes and with light indoor clothes to the nearest 0.1 kg, using an electronic scale. Height was measured twice without shoes to the nearest 0.1 cm, using a wall-mounted wooden stadiometer.	FFQ	Parents together with their child answered a food-frequency questionnaire with 98 food items and beverages commonly consumed in Sweden. Children were asked how often, on average, they had consumed each type of food or beverage during the past 12 months. There were ten pre-specified response categories that ranged from never to three or more times per day. The food-frequency questionnaire was transformed into nutrients by multiplying the frequency of consumption of each food item by its nutrient content per serving, using composition values obtained from the Swedish National Food Administration Database, and summarized over foods and beverages.	Anthropometrics and dietary intake were measured concurrently
GENDAI	Physical measurements of body weight and height were obtained in light clothing without shoes.	24-h recall	Dietary information was collected via two non-consecutive 24-h recalls. The second dietary recall was always conducted on a different day of the week from the first interview, 3–10 days after the first recall, to calculate usual nutrient intake. The 24-h recall data were analyzed using Nutritionist Pro software, version 2.2 (Axxya Systems-Nutritionist Pro, Stafford, TX, USA). The Nutritionist Pro food database was expanded by adding analyses of traditional Greek foods and recipes, and nutrient information for local processed food items (mainly snack foods, sweets, and fast foods) as shared by industry.	Anthropometrics and dietary intake were measured concurrently
GENESIS	Body weight was recorded to the nearest 10 gr with the use of a Seca digital scale and with subjects standing without shoes in the minimum clothing possible. Recumbent length was measured for all subjects to the nearest 0.1 cm with a portable measuring wooden board that had a stationary head piece, a sliding vertical foot piece and a horizontal back piece with a measure tape mounted on it. Further to recumbent length, standing height was also measured to the nearest 0.1 cm in children older than two years of age, with the use of a commercial stadiometer (Leicester Height Measure).	Food records + 24-h recall	Intake data were obtained for 3 days (2 consecutive weekdays and 1 weekend day) using a combination of techniques comprising weighed food records (during nursery hours) and 24 h recall or food diaries (outside nurseries and under parental supervision).	Food records: same day; 24-h recall: within one week
GENR	Anthropometrics were measured by well-trained staff in community health centers using standardized procedures at the ages of 2, 3, 4, 6, 11, 14, 18, 24, 30, 36 and 48 month. Length was measured in a supine position to the nearest millimeter until the age of 12 months with a neonatometer, after which height was measured in standing position with a Harpenden stadiometer (Holtain Ltd, Dyfed, United Kingdom). Weight was measured with a mechanical personal scale.	FFQ	The FFQ was developed on the basis of an existing validated food questionnaire described in detail previously,(15) and modified according to foods frequently consumed in the Dutch food consumption survey among infants aged 9-18 months of which foods contributing ≥0.1% of the total consumption of energy, protein, fat, carbohydrates and dietary fibre were incorporated in the FFQ. The final FFQ consisted of 211 food items and included questions on the frequency of consumption of these food items over the last month, the amount and type of the food items, and preparation methods. Portion sizes in grams per day were estimated using standardised household measures. To calculate nutrient intake the Dutch food composition Table 2006 was used. A validation study comparing the FFQ against three-day 24h recalls in a representative sample showed intra-class correlation coefficients for macronutrients between 0.4 and 0.7.(16)	Mean (SD): 0.42 (2.06) months Range: -1.91 to 4.22 months
GINI/LISA	Measured (n=1822): Height was measured with light clothing and no shoes to the nearest 0.1cm; Weight was measured wearing underwear to the nearest 0.1kg. Self-reported (n=177): Parents were asked to report children's height to the nearest 1cm and weight to the nearest 1kg without shoes and wearing light clothing.	FFQ	A food frequency questionnaire (FFQ) was developed to measure children's usual food and nutrient intake over the past year, and more specifically to estimate energy, fatty acid and antioxidant intake at 10 years of age.(17) The FFQ comprised a list of 82 food items accompanied by several questions about the preferred fat and energy content of products, preparation methods, diets and food preferences, buying habits and dietary supplement use. The consumption frequencies and portion size estimates were converted to average	Mean (SD): 31 (26) weeks

			consumption in grams per day and linked to the German Nutrient Data Base (BLS) version II.3.1.	
LACHY	Height and weight were measured by standard methods using a wall-mounted stadiometer and a digital scale, respectively.	24-h recall	Free-living diet was measured with individual, non-consecutive, 24-h recalls that covered the period from midnight to midnight of the previous day. We sought to obtain seven recalls from each participant, one of each day of the week and only those subjects that provided at least four recalls were included in the analysis.(18)	Anthropometrics and dietary intake were measured concurrently
LEIPZIG	Height and weight were measured by standard methods using a wall-mounted stadiometer and a digital scale, respectively.	EBIS pro	Quantitative analyses of food diaries over 4 days applying EBIS pro.	Anthropometrics and dietary intake were measured concurrently
PANIC	Trained research staff measured the body height by a wall-mounted stadiometer in the Frankfurt plane without shoes. Body height was measured three times to an accuracy of 0.1 cm, and the mean of the nearest two values was used for the analyses. Body weight was measured to an accuracy of 0.1 kg using the InBody 720 device (Biospace, Seoul, Korea), after overnight fasting, empty-bladdered and standing in light underwear.	Food Records	Dietary intake was assessed by food records of four consecutive days that consisted of two weekdays and two weekend days (99.5% of children), or three weekdays and one weekend day (0.5% of children). The parents were instructed to record all food and drink consumption of their children and to ask their children about their food consumption outside home. The schools and afterschool clubs were asked about the type and preparation of the served food. When the parents returned the records, clinical nutritionists checked the records and filled in missing information with them. The food records were analyzed using the Micro Nutrica dietary analysis software (version 2.5, The Social Insurance Institution of Finland, Turku, Finland).	Mean (SD): 24 (27) days
SHUNAN	The height and body weight were measured from April through June by school nurses during annual medical checkups, in accordance with the Japanese School Health Law. Height was measured to the nearest 0.1 cm while the students stood barefooted, and body weight was measured to the nearest 0.1 kg while the students wore light clothing and no footwear.	BDHQ	Brief-type self-administered diet history questionnaire (BDHQ) was used for assessment of food intake in a previous month.(19)	Mean (SD): 20.9 (12.3) days Range: -68 to 41days
SWS	Weight was measured with Seca scales and height using a Leicester height measurer.	FFQ	Diet was assessed using an eighty-item FFQ that was administered by trained research nurses.(20) The list of food and beverage items was compiled from a review of dietary intake data collected from a nationally representative sample of children aged 3 years, SWS infants and SWS women and 3-year-olds in the Avon Longitudinal Study of Pregnancy and Childhood. The FFQ asked how often in the last 3 months the child had consumed each of the food and beverage items	Anthropometrics and dietary intake were measured concurrently
STRIP	Weight was measured to the nearest 0.1 kg with an electronic scale (S10; Soehnle, Murrhardt, Germany) at each visit. Height was measured to the nearest millimetre with a wall-mounted Harpenden stadiometer (Holtain, Crymych, UK).	Food records	Families kept food records of the children's food intake for four consecutive days (including at least one weekend day). Food records were reviewed by a nutritionist for comleteness and accuracy. Nutrient intakes were analyzed by using Micro Nutrica® programme developed at the Research and Development Centre of Social Insurance Institution, Turku, Finland.	Dietary data was collected 1-2 weeks prior to measurement of weight and height
TEENAGE	Body weight was measured to the nearest 0·1 kg, with the participants barefoot and dressed in light clothing, by the use of a weighing scale (Seca Alpha, Hamburg, Germany). Height was measured to the nearest 0·1 cm using a portable stadiometer while the participants were barefoot with their shoulders in a relaxed position, their arms hanging freely and their head in a normal position, with the eyes looking straight ahead.	24-hour recall	Dietary information was collected via two non-consecutive 24-h recalls. The second dietary recall was always conducted on a different day of the week from the first interview, 3–10 days after the first recall, to calculate usual nutrient intake. The 24-h recall data were analyzed using Nutritionist Pro software, version 2.2 (Axxya Systems-Nutritionist Pro, Stafford, TX, USA). The Nutritionist Pro food database was expanded by adding analyses of traditional Greek foods and recipes, and nutrient information for local processed food items (mainly snack foods, sweets, and fast foods) as shared by industry.	Within 10 days

Supplemental Table 4 Genotyping methods and quality control for the *FTO* SNPs in all studies participating in the meta-analysis

Study	SNP	r^2	Genotyped or imputed	Imputation quality	Method	Minor allele	Boys				Girls			
							MAF	Call rate	P_{HWE}	Concordance rate	MAF	Call rate	P_{HWE}	Concordance rate
ALSPAC	rs9939609	-	Imputed	1	Illumina 550k Custom Chip; MACH (version 1.0.15)	A	0.39	>0.95	-	>0.80	0.39	>0.95	-	>0.80
APEX*	rs9939609	-	Genotyped	-	Taqman SNP Genotyping Assay	A	0.48	0.99	0.92	1	0.48	0.99	0.92	1
BAMSE*	rs8050136	1	Genotyped	-	Illumina 610 Quad Array	A	0.42	1	0.56	-	0.42	1	0.56	-
GENDAI	rs9939609	-	Genotyped	-	Taqman SNP Genotyping Assay	A	0.43	>0.96	0.01	>0.99	0.42	>0.96	0.84	>0.99
GENESIS	rs17817449	1	Genotyped	-	RFLP method	G	0.43	0.94	0.13	1	0.43	0.94	0.60	1
GENR*	rs9939609	-	Imputed	1	Illumina 610 Quad Array; MACH (version 1.0.15)	A	0.27	1	0.99	-	0.27	1	0.99	-
GINI/LISA*	rs9935401	1	Genotyped	-	iPLEX™ Gold Assay	G	0.4	0.97	0.81	>0.95	0.4	0.97	0.81	>0.95
LACHY*	rs9939609	-	Genotyped	-	Taqman SNP Genotyping Assay	A	0.45	0.99	0.34	1	0.45	0.99	0.34	1
LEIPZIG	rs17817449	1	Genotyped	-	Taqman SNP Genotyping Assay	C	0.46	-	0.25	1	0.52	-	0.99	1
PANIC	rs9939609	-	Genotyped	-	Illumina MetaboChip Array	A	0.37	-	0.81	-	0.40	-	0.81	-
SHUNAN_Case	rs9939609	-	Genotyped	-	Taqman SNP Genotyping Assay	A	0.30	1	0.84	-	0.35	1	0.24	-
SHUNAN_Control	rs9939609	-	Genotyped	-	Taqman SNP Genotyping Assay	A	0.21	1	0.28	-	0.15	1	0.09	-
SWS	rs9939609	-	Genotyped		Kbioscience	A	0.41	0.97	0.59	1	0.42	0.97	0.59	1
STRIP _Int	rs9939609	-	Genotyped	-	Illumina MetaboChip Array	A	0.38	1	0.45	1	0.39	1	0.26	1
STRIP _Control	rs9939609	-	Genotyped	-	Illumina MetaboChip Array	A	0.43	1	0.88	1	0.45	1	0.13	1
TEENAGE	rs9939609	-	Genotyped	-	iPLEX™ Gold Assay	A	0.45	0.96	0.75	-	0.41	0.99	0.02	-

r^2: correlation with rs9939609; MAF: minor allele frequency; P_{HWE}: *P*-values for Hardy–Weinberg equilibrium.

*These studies provided data in boys and girls combined.

Supplemental Table 5 Associations of *FTO* SNP rs9939609 or a proxy with intakes of total energy, protein, carbohydrate and fat in a random effects meta-analysis of 16,097 children and adolescents*

	Total energy (kcal/day)			Protein (% of energy)			Carbohydrate (% of energy)			Fat (% of energy)		
	Beta (95% CI)	*P*	I^2	Beta (95% CI)	*P*	I^2	Beta (95% CI)	*P*	I^2	Beta (95% CI)	*P*	I^2
All	14.6 (6.2, 23.1)	0.001	0%	0.0 (-0.1, 0.0)	0.10	0%	0.0 (-0.2, 0.2)	0.82	24%	0.0 (-0.1, 0.2)	0.71	34%
Whites	14.0 (5.5, 22.5)	0.001	0%	0.0 (-0.1, 0.0)	0.13	0%	0.0 (-0.2, 0.2)	0.90	30%	0.1 (-0.1, 0.2)	0.41	32%
African Americans	9.7 (-66.1, 85.6)	0.80	14%	-0.2 (-0.6, 0.2)	0.36	0%	1.1 (0.2, 2.0)	0.02	0%	-0.8 (-1.5, -0.1)	0.02	0%
Asians	157.2 (34.4, 280.0)	0.01	0%	0.0 (-0.5, 0.4)	0.87	0%	0.0 (-0.5, 0.4)	0.87	0%	0.3 (-1.0, 1.5)	0.65	34%

*Data are beta coefficients (95% CI) per minor allele of rs9939609 or a proxy (r^2>0.8) for each trait, adjusting for age, 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).

Supplemental Table 6 Associations between dietary intake and BMI

	Beta (95% CI)*	*P*	I^2
Total energy (kcal/day)			
All	0.04 (0.01, 0.07)	0.004	57%
Whites	0.05 (0.02, 0.08)	0.001	57%
African Americans	-0.18 (-0.37, 0.02)	0.07	63%
Asians	-0.04 (-0.20 0.12)	0.59	0%
Protein (% of energy)			
All	0.09 (0.07, 0.12)	5.0×10^{-10}	68%
Whites	0.09 (0.06, 0.12)	4.1×10^{-9}	72%
African Americans	0.27 (0.08, 0.46)	0.005	0%
Asians	0.04 (-0.12, 0.20)	0.63	35%
Carbohydrate (% of energy)			
All	-0.02 (-0.05, 0.01)	0.12	54%
Whites	-0.02 (-0.05, 0.01)	0.19	58%
African Americans	-0.21 (-0.41, -0.02)	0.03	0%
Asians	-0.04 (-0.12, 0.20)	0.63	35%
Fat (% of energy)			
All	-0.03 (-0.06, -0.001)	0.04	53%
Whites	-0.03 (-0.06, -0.000)	0.05	56%
African Americans	-0.10 (-0.29, 0.09)	0.32	55%
Asians	0.00 (-0.16, 0.16)	0.97	51%

*Beta represents SD difference in BMI (kg/m^2) comparing the high intake group to the low intake group (dichotomized at median of respective dietary intake variable), adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).

Supplemental Table 7 Interaction between *FTO* SNP rs9939609 or a proxy and dietary intakes on BMI in a random effects meta-analysis of 16,097 children and adolescents*

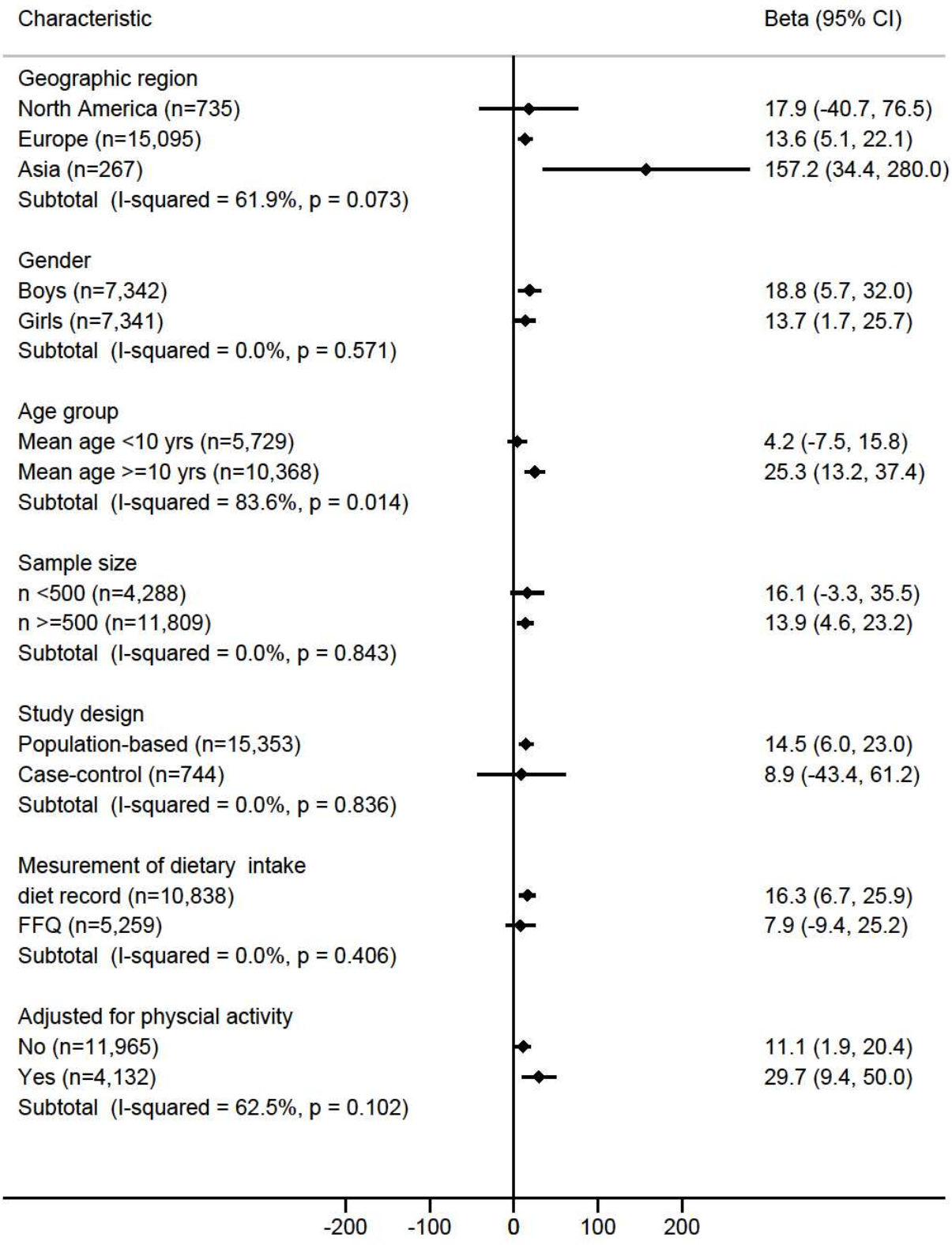
	High dietary intake group†			Low dietary intake group†			Interaction effect		
	Beta (95% CI)	*P*	I^2	Beta (95% CI)	*P*	I^2	Beta (95% CI)	*P*	I^2
Total energy (kcal/day)									
All	0.05 (0.01, 0.09)	0.02	25%	0.07 (0.03, 0.11)	0.001	25%	-0.03 (-0.07, 0.02)	0.20	0%
Whites	0.06 (0.02, 0.10)	0.006	25%	0.08 (0.03, 0.12)	0.002	38%	-0.03 (-0.07, 0.02)	0.30	5%
African Americans	-0.19 (-0.39, 0.01)	0.06	0%	-0.07 (-0.26, 0.13)	0.49	0%	-0.13 (-0.41, 0.15)	0.37	0%
Asians	0.02 (-0.18, 0.22)	0.86	0%	0.01 (-0.18, 0.20)	0.93	0%	0.02 (-0.18, 0.21)	0.84	0%
Protein (%)									
All	0.09 (0.04, 0.13)	3.3×10^{-4}	34%	0.04 (0.01, 0.07)	0.02	0%	0.08 (0.03, 0.12)	0.001	0%
Whites	0.10 (0.06, 0.15)	1.7×10^{-5}	35%	0.04 (0.01, 0.07)	0.02	0%	0.07 (0.03, 0.12)	0.001	0%
African Americans	-0.13 (-0.35, 0.09)	0.26	0%	-0.08 (-0.27, 0.11)	0.39	14%	-0.02 (0.34, 0.31)	0.93	23%
Asians	-0.07 (-0.26, 0.12)	0.48	0%	0.17 (-0.06, 0.39)	0.14	0%	0.17 (-0.04, 0.37)	0.11	0%
Carbohydrate (%)									
All	0.06 (0.02, 0.10)	0.005	26%	0.07 (0.03, 0.11)	0.001	20%	0.00 (-0.05, 0.05)	0.95	15%
Whites	0.07 (0.03, 0.11)	0.001	29	0.08 (0.03, 0.12)	0.001	28%	-0.01 (-0.07, 0.05)	0.72	16%
African Americans	-0.03 (-0.24, 0.19)	0.82	25%	-0.12 (-0.3,3 0.08)	0.24	0%	0.03 (-0.30, 0.36)	0.86	26%
Asians	-0.07 (-0.26, 0.12)	0.48	0%	0.17 (-0.06, 0.39)	0.14	0%	0.17 (-0.04, 0.37)	0.11	0%
Fat (%)									
All	0.06 (0.01, 0.10)	0.01	28%	0.07 (0.03, 0.12)	0.001	26%	0.00 (-0.05, 0.04)	0.89	0%
Whites	0.07 (0.03, 0.11)	0.001	25%	0.08 (0.03, 0.13)	0.002	39%	-0.01 (-0.06, 0.05)	0.86	18%
African Americans	-0.10 (-0.29, 0.09)	0.31	0%	-0.07 (-0.27, 0.13)	0.48	0%	-0.01 (-0.29, 0.27)	0.94	0%
Asians	-0.11 (-0.35, 0.12)	0.35	34%	0.15 (-0.08, 0.38)	0.21	0%	0.12 (-0.08, 0.33)	0.24	0%

*Data are beta (95% CI) per minor allele of rs9939609 or a proxy (r^2>0.8) for BMI (z-score), adjusted for age, 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).

†High and low intake groups were defined by medians for each dietary intake variable.

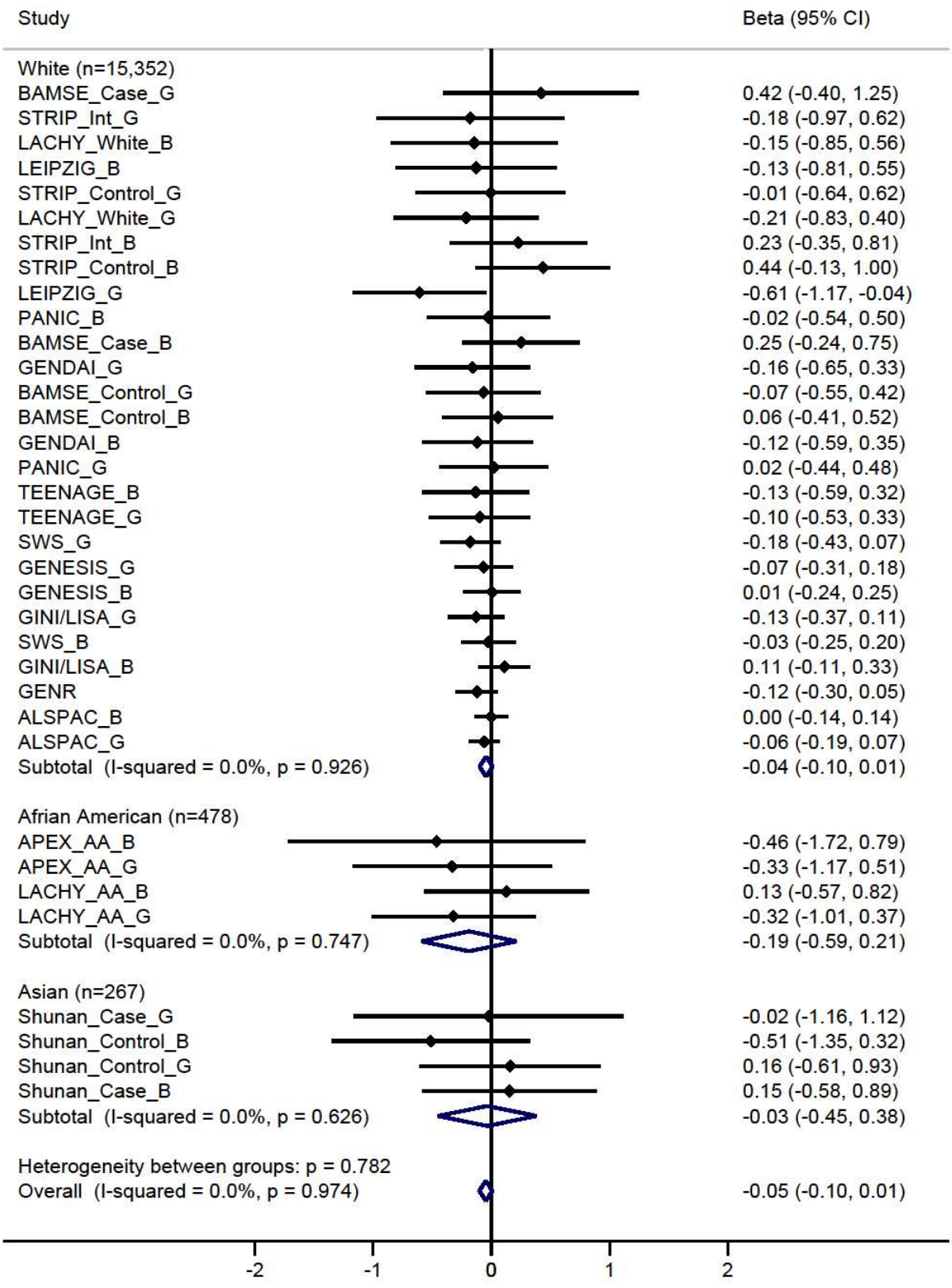
Supplemental Figure 1 Association between *FTO* rs9939609 SNP or a proxy and total energy intake in a fixed effects meta-analysis of 16,097 children and adolescents stratified by study characteristics.

Meta-analyses were stratified by geographic region, gender (one study with mixed data were not included), age group, sample size, study design, measurement of dietary intake, or adjustment for physical activity. The beta represents the difference in total energy intake (kcal/day) per minor allele of SNP rs9939609 or a proxy (r^2=1), adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Characteristic
Beta (95% CI)
Geographic region
North America (n=735)
17.9 (-40.7, 76.5)
Europe (n=15,095)
13.6 (5.1, 22.1)
Asia (n=267)
157.2 (34.4, 280.0)
Subtotal (I-squared = 61.9%, p = 0.073)
Gender
Boys (n=7,342)
18.8 (5.7, 32.0)
Girls (n=7,341)
13.7 (1.7, 25.7)
Subtotal (I-squared = 0.0%, p = 0.571)
Age group
Mean age <10 yrs (n=5,729)
4.2 (-7.5, 15.8)
Mean age >=10 yrs (n=10,368)
25.3 (13.2, 37.4)
Subtotal (I-squared = 83.6%, p = 0.014)
Sample size
n <500 (n=4,288)
16.1 (-3.3, 35.5)
n >=500 (n=11,809)
13.9 (4.6, 23.2)
Subtotal (I-squared = 0.0%, p = 0.843)
Study design
Population-based (n=15,353)
14.5 (6.0, 23.0)
Case-control (n=744)
8.9 (-43.4, 61.2)
Subtotal (I-squared = 0.0%, p = 0.836)
Mesurement of dietary intake
diet record (n=10,838)
16.3 (6.7, 25.9)
FFQ (n=5,259)
7.9 (-9.4, 25.2)
Subtotal (I-squared = 0.0%, p = 0.406)
Adjusted for physcial activity
No (n=11,965)
11.1 (1.9, 20.4)
Yes (n=4,132)
29.7 (9.4, 50.0)
Subtotal (I-squared = 62.5%, p = 0.102)
-200
-100
0
100
200

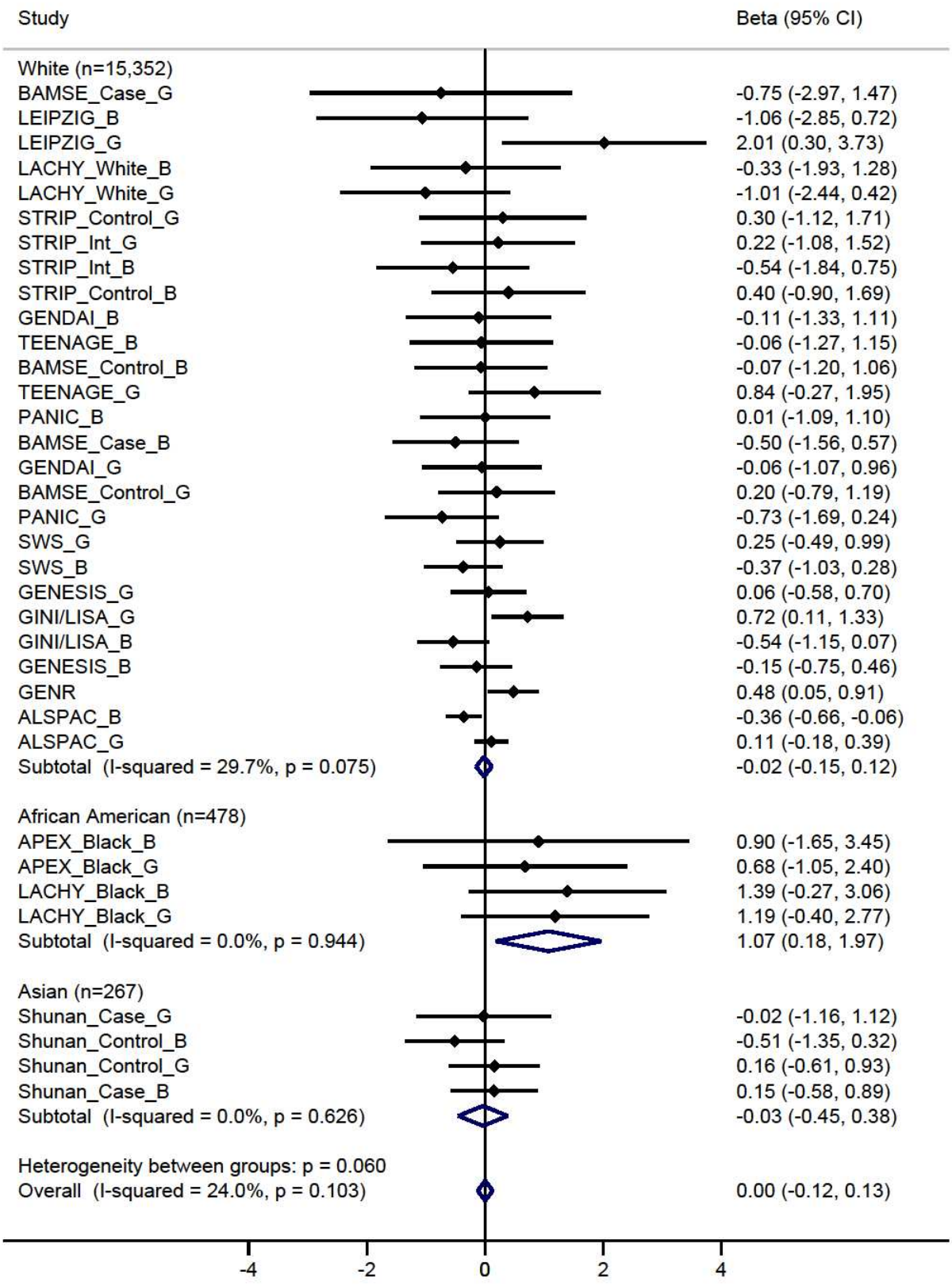
Supplemental Figure 2 Forest plot of the association between *FTO* rs9939609 SNP or a proxy and protein intake in a fixed effects meta-analysis of 16,097 children and adolescents

The studies are shown in boys (_B), girls (_Y) or mixed (GENR study only), cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta represents the difference in protein intake (% of energy) per minor allele of SNP rs9939609 or a proxy (r^2=1), adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Study
Beta (95% CI)
White (n=15,352)
BAMSE_Case_G 0.42 (-0.40, 1.25)
STRIP_Int_G -0.18 (-0.97, 0.62)
LACHY_White_B -0.15 (-0.85, 0.56)
LEIPZIG_B -0.13 (-0.81, 0.55)
STRIP_Control_G -0.01 (-0.64, 0.62)
LACHY_White_G -0.21 (-0.83, 0.40)
STRIP_Int_B 0.23 (-0.35, 0.81)
STRIP_Control_B 0.44 (-0.13, 1.00)
LEIPZIG_G -0.61 (-1.17, -0.04)
PANIC_B -0.02 (-0.54, 0.50)
BAMSE_Case_B 0.25 (-0.24, 0.75)
GENDAI_G -0.16 (-0.65, 0.33)
BAMSE_Control_G -0.07 (-0.55, 0.42)
BAMSE_Control_B 0.06 (-0.41, 0.52)
GENDAI_B -0.12 (-0.59, 0.35)
PANIC_G 0.02 (-0.44, 0.48)
TEENAGE_B -0.13 (-0.59, 0.32)
TEENAGE_G -0.10 (-0.53, 0.33)
SWS_G -0.18 (-0.43, 0.07)
GENESIS_G -0.07 (-0.31, 0.18)
GENESIS_B 0.01 (-0.24, 0.25)
GINI/LISA_G -0.13 (-0.37, 0.11)
SWS_B -0.03 (-0.25, 0.20)
GINI/LISA_B 0.11 (-0.11, 0.33)
GENR -0.12 (-0.30, 0.05)
ALSPAC_B 0.00 (-0.14, 0.14)
ALSPAC_G -0.06 (-0.19, 0.07)
Subtotal (I-squared = 0.0%, p = 0.926) -0.04 (-0.10, 0.01)
Afrian American (n=478)
APEX_AA_B -0.46 (-1.72, 0.79)
APEX_AA_G -0.33 (-1.17, 0.51)
LACHY_AA_B 0.13 (-0.57, 0.82)
LACHY_AA_G -0.32 (-1.01, 0.37)
Subtotal (I-squared = 0.0%, p = 0.747) -0.19 (-0.59, 0.21)
Asian (n=267)
Shunan_Case_G -0.02 (-1.16, 1.12)
Shunan_Control_B -0.51 (-1.35, 0.32)
Shunan_Control_G 0.16 (-0.61, 0.93)
Shunan_Case_B 0.15 (-0.58, 0.89)
Subtotal (I-squared = 0.0%, p = 0.626) -0.03 (-0.45, 0.38)
Heterogeneity between groups: p = 0.782
Overall (I-squared = 0.0%, p = 0.974) -0.05 (-0.10, 0.01)
-2
-1
0
1
2

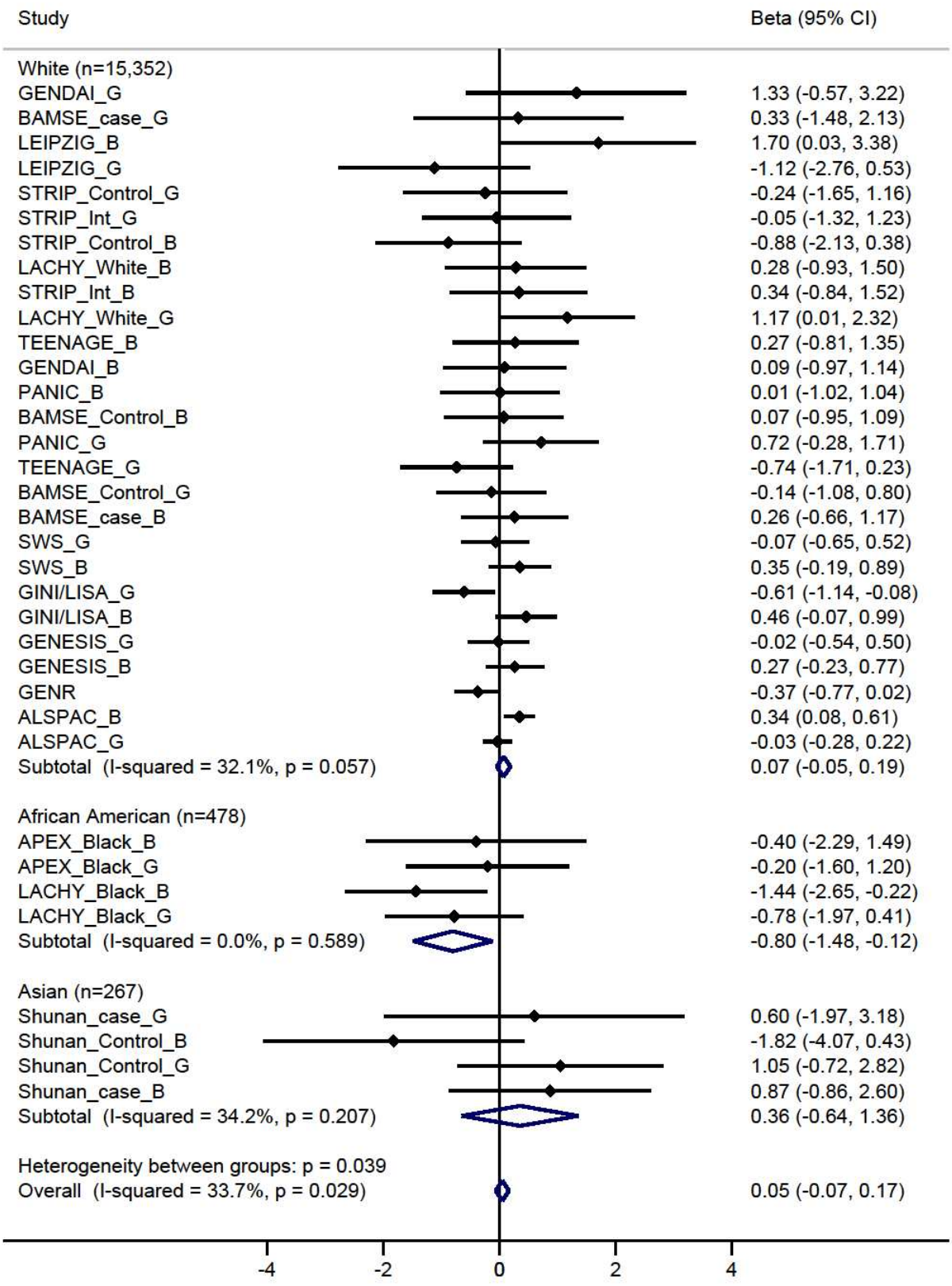
Supplemental Figure 3 Forest plot of the association between *FTO* rs9939609 SNP or a proxy and carbohydrate intake in a fixed effects meta-analysis of 16,097 children and adolescents

The studies are shown in boys (_B), girls (_Y) or mixed (GENR study only), cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta represents the difference in carbohydrate intake (% of energy) per minor allele of SNP rs9939609 or a proxy (r^2=1), adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Study
Beta (95% CI)
White (n=15,352)
BAMSE_Case_G -0.75 (-2.97, 1.47)
LEIPZIG_B -1.06 (-2.85, 0.72)
LEIPZIG_G 2.01 (0.30, 3.73)
LACHY_White_B -0.33 (-1.93, 1.28)
LACHY_White_G -1.01 (-2.44, 0.42)
STRIP_Control_G 0.30 (-1.12, 1.71)
STRIP_Int_G 0.22 (-1.08, 1.52)
STRIP_Int_B -0.54 (-1.84, 0.75)
STRIP_Control_B 0.40 (-0.90, 1.69)
GENDAI_B -0.11 (-1.33, 1.11)
TEENAGE_B -0.06 (-1.27, 1.15)
BAMSE_Control_B -0.07 (-1.20, 1.06)
TEENAGE_G 0.84 (-0.27, 1.95)
PANIC_B 0.01 (-1.09, 1.10)
BAMSE_Case_B -0.50 (-1.56, 0.57)
GENDAI_G -0.06 (-1.07, 0.96)
BAMSE_Control_G 0.20 (-0.79, 1.19)
PANIC_G -0.73 (-1.69, 0.24)
SWS_G 0.25 (-0.49, 0.99)
SWS_B -0.37 (-1.03, 0.28)
GENESIS_G 0.06 (-0.58, 0.70)
GINI/LISA_G 0.72 (0.11, 1.33)
GINI/LISA_B -0.54 (-1.15, 0.07)
GENESIS_B -0.15 (-0.75, 0.46)
GENR 0.48 (0.05, 0.91)
ALSPAC_B -0.36 (-0.66, -0.06)
ALSPAC_G 0.11 (-0.18, 0.39)
Subtotal (I-squared = 29.7%, p = 0.075) -0.02 (-0.15, 0.12)
African American (n=478)
APEX_Black_B 0.90 (-1.65, 3.45)
APEX_Black_G 0.68 (-1.05, 2.40)
LACHY_Black_B 1.39 (-0.27, 3.06)
LACHY_Black_G 1.19 (-0.40, 2.77)
Subtotal (I-squared = 0.0%, p = 0.944) 1.07 (0.18, 1.97)
Asian (n=267)
Shunan_Case_G -0.02 (-1.16, 1.12)
Shunan_Control_B -0.51 (-1.35, 0.32)
Shunan_Control_G 0.16 (-0.61, 0.93)
Shunan_Case_B 0.15 (-0.58, 0.89)
Subtotal (I-squared = 0.0%, p = 0.626) -0.03 (-0.45, 0.38)
Heterogeneity between groups: p = 0.060
Overall (I-squared = 24.0%, p = 0.103) 0.00 (-0.12, 0.13)
-4
-2
0
2
4

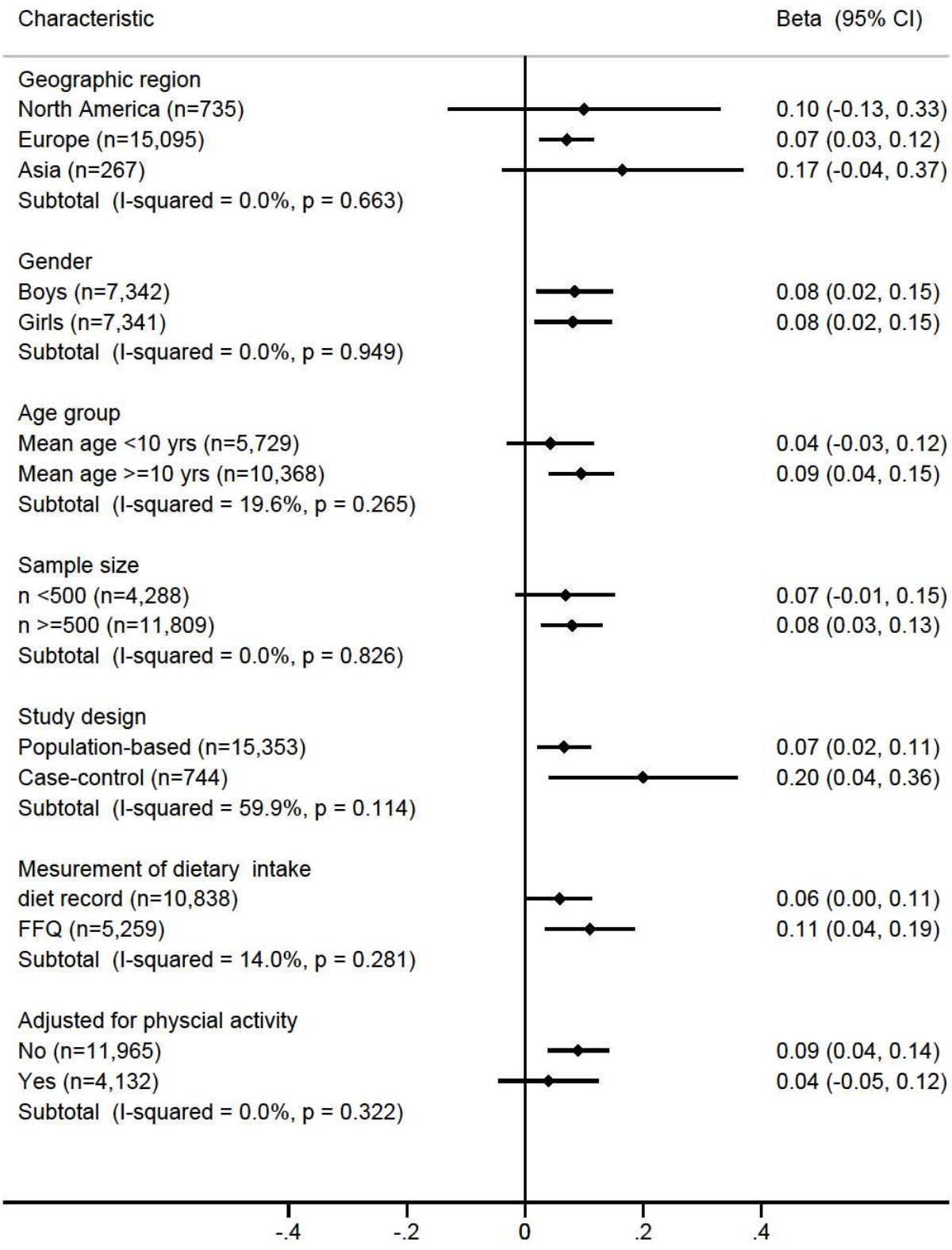
Supplemental Figure 4 Forest plot of the association between *FTO* rs9939609 SNP or a proxy and fat intake in a fixed effects meta-analysis of 16,097 children and adolescents

The studies are shown in boys (_B), girls (_Y) or mixed (GENR study only), cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta represents the difference in fat intake (% of energy) per minor allele of SNP rs9939609 or a proxy (r^2=1), adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Study
Beta (95% CI)
White (n=15,352)
GENDAI_G 1.33 (-0.57, 3.22)
BAMSE_case_G 0.33 (-1.48, 2.13)
LEIPZIG_B 1.70 (0.03, 3.38)
LEIPZIG_G -1.12 (-2.76, 0.53)
STRIP_Control_G -0.24 (-1.65, 1.16)
STRIP_Int_G -0.05 (-1.32, 1.23)
STRIP_Control_B -0.88 (-2.13, 0.38)
LACHY_White_B 0.28 (-0.93, 1.50)
STRIP_Int_B 0.34 (-0.84, 1.52)
LACHY_White_G 1.17 (0.01, 2.32)
TEENAGE_B 0.27 (-0.81, 1.35)
GENDAI_B 0.09 (-0.97, 1.14)
PANIC_B 0.01 (-1.02, 1.04)
BAMSE_Control_B 0.07 (-0.95, 1.09)
PANIC_G 0.72 (-0.28, 1.71)
TEENAGE_G -0.74 (-1.71, 0.23)
BAMSE_Control_G -0.14 (-1.08, 0.80)
BAMSE_case_B 0.26 (-0.66, 1.17)
SWS_G -0.07 (-0.65, 0.52)
SWS_B 0.35 (-0.19, 0.89)
GINI/LISA_G -0.61 (-1.14, -0.08)
GINI/LISA_B 0.46 (-0.07, 0.99)
GENESIS_G -0.02 (-0.54, 0.50)
GENESIS_B 0.27 (-0.23, 0.77)
GENR -0.37 (-0.77, 0.02)
ALSPAC_B 0.34 (0.08, 0.61)
ALSPAC_G -0.03 (-0.28, 0.22)
Subtotal (I-squared = 32.1%, p = 0.057) 0.07 (-0.05, 0.19)
African American (n=478)
APEX_Black_B -0.40 (-2.29, 1.49)
APEX_Black_G -0.20 (-1.60, 1.20)
LACHY_Black_B -1.44 (-2.65, -0.22)
LACHY_Black_G -0.78 (-1.97, 0.41)
Subtotal (I-squared = 0.0%, p = 0.589) -0.80 (-1.48, -0.12)
Asian (n=267)
Shunan_case_G 0.60 (-1.97, 3.18)
Shunan_Control_B -1.82 (-4.07, 0.43)
Shunan_Control_G 1.05 (-0.72, 2.82)
Shunan_case_B 0.87 (-0.86, 2.60)
Subtotal (I-squared = 34.2%, p = 0.207) 0.36 (-0.64, 1.36)
Heterogeneity between groups: p = 0.039
Overall (I-squared = 33.7%, p = 0.029) 0.05 (-0.07, 0.17)
-4
-2
0
2
4

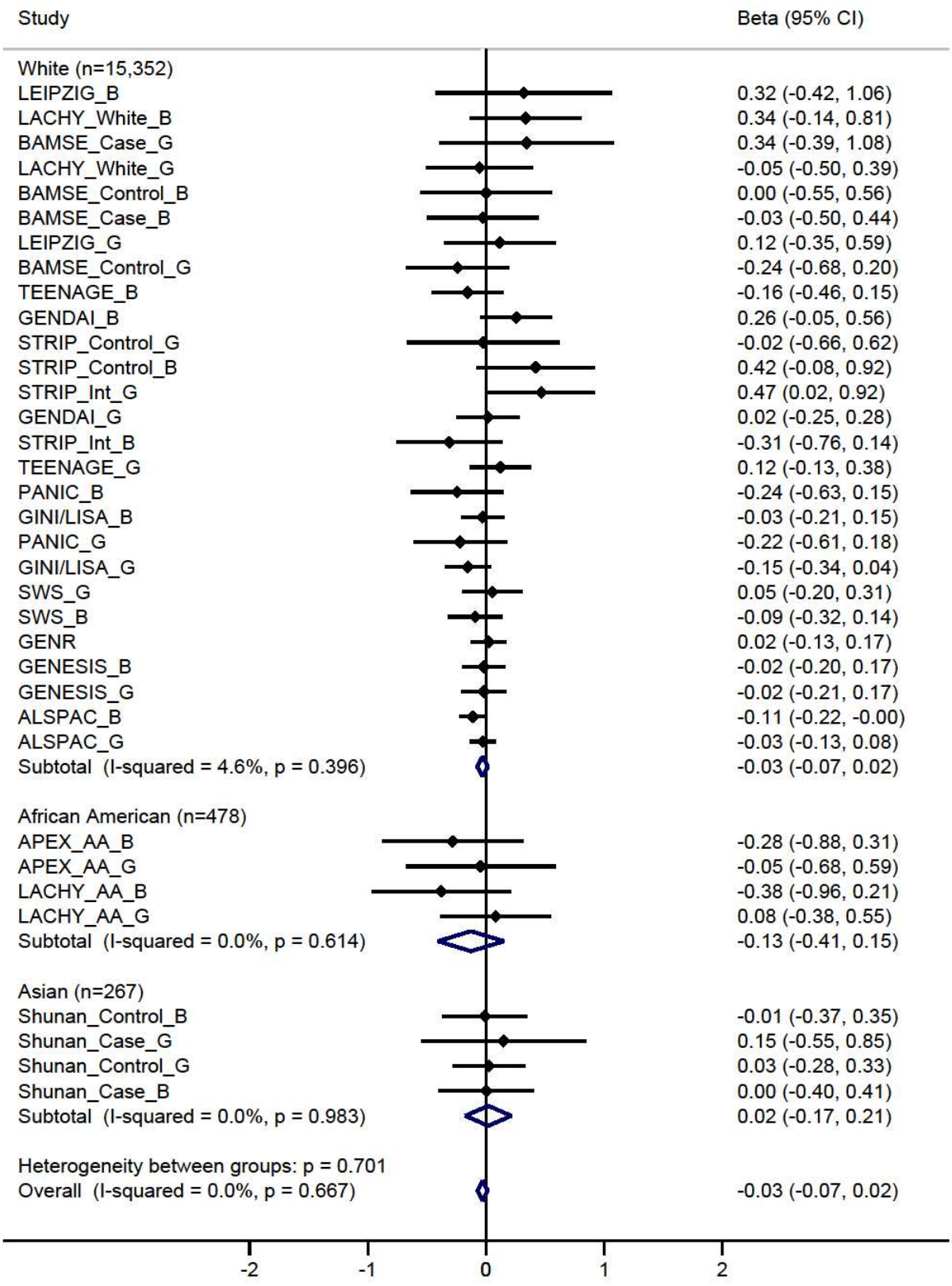
Supplemental Figure 5 Interaction between *FTO* rs9939609 SNP or a proxy and protein intake on BMI in a fixed effects meta-analysis of 16,097 children and adolescents stratified by study characteristics.

Meta-analyses were stratified by geographic region, gender (one study with mixed data were not included), age group, sample size, study design, measurement of dietary intake, or adjustment for physical activity. The beta 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, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Characteristic
Beta (95% CI)
Geographic region
North America (n=735)
0.10 (-0.13, 0.33)
Europe (n=15,095)
0.07 (0.03, 0.12)
Asia (n=267)
0.17 (-0.04, 0.37)
Subtotal (I-squared = 0.0%, p = 0.663)
Gender
Boys (n=7,342)
0.08 (0.02, 0.15)
Girls (n=7,341)
0.08 (0.02, 0.15)
Subtotal (I-squared = 0.0%, p = 0.949)
Age group
Mean age <10 yrs (n=5,729)
0.04 (-0.03, 0.12)
Mean age >=10 yrs (n=10,368)
0.09 (0.04, 0.15)
Subtotal (I-squared = 19.6%, p = 0.265)
Sample size
n <500 (n=4,288)
0.07 (-0.01, 0.15)
n >=500 (n=11,809)
0.08 (0.03, 0.13)
Subtotal (I-squared = 0.0%, p = 0.826)
Study design
Population-based (n=15,353)
0.07 (0.02, 0.11)
Case-control (n=744)
0.20 (0.04, 0.36)
Subtotal (I-squared = 59.9%, p = 0.114)
Mesurement of dietary intake
diet record (n=10,838)
0.06 (0.00, 0.11)
FFQ (n=5,259)
0.11 (0.04, 0.19)
Subtotal (I-squared = 14.0%, p = 0.281)
Adjusted for physcial activity
No (n=11,965)
0.09 (0.04, 0.14)
Yes (n=4,132)
0.04 (-0.05, 0.12)
Subtotal (I-squared = 0.0%, p = 0.322)
-.4
-.2
0
.2
.4

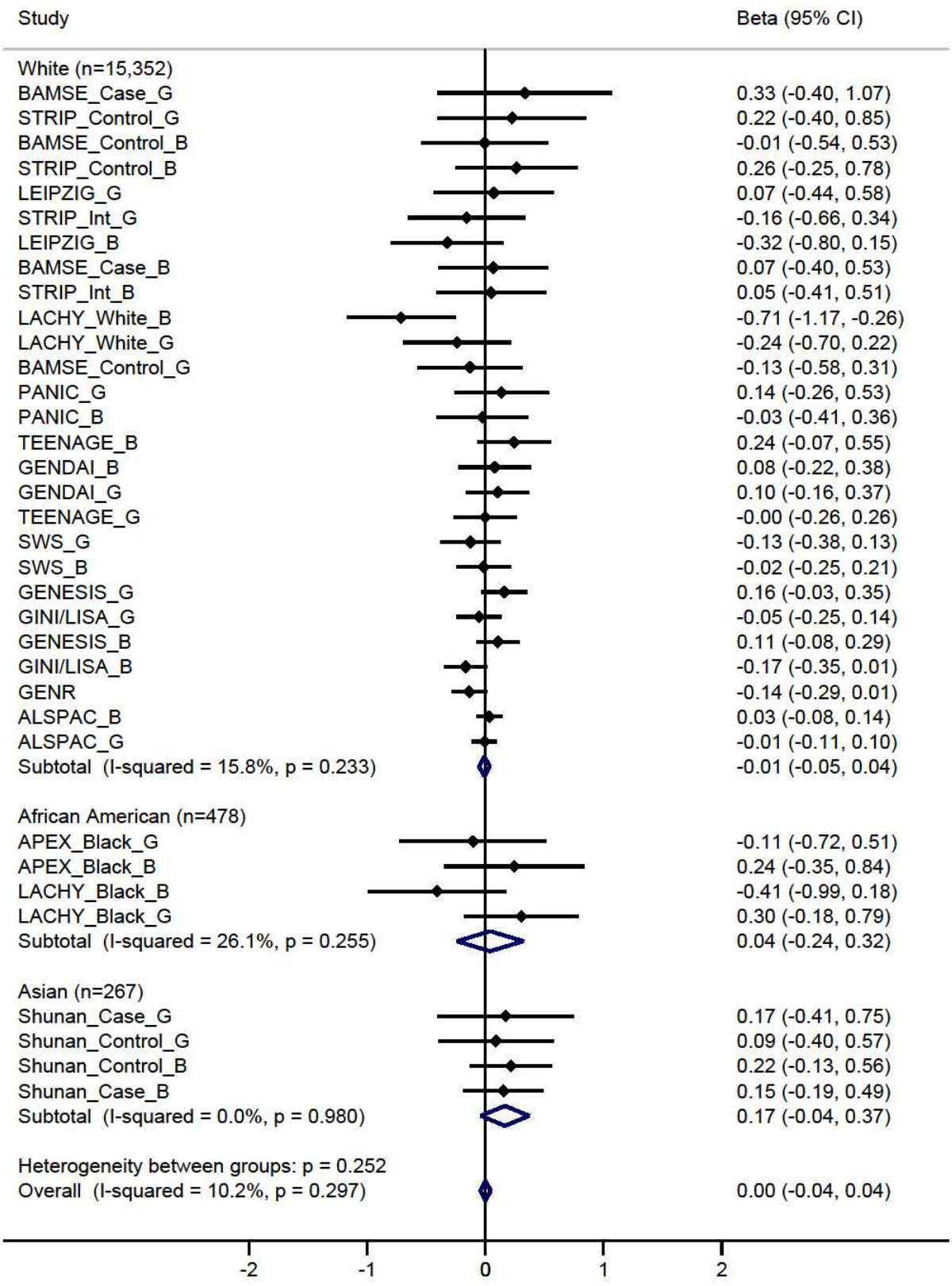
Supplemental Figure 6 Forest plot of the interaction between *FTO* rs9939609 SNP or a proxy and total energy intake on BMI in a fixed effects meta-analysis of 16,097 children and adolescents

The studies are shown in boys (_B), girls (_Y) or mixed (GENR study only), cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta represents the difference in BMI per minor allele of SNP rs9939609 or a proxy (r^2=1) comparing participants in the high energy intake group to those in the low energy intake group, adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Study
Beta (95% CI)
White (n=15,352)
LEIPZIG_B 0.32 (-0.42, 1.06)
LACHY_White_B 0.34 (-0.14, 0.81)
BAMSE_Case_G 0.34 (-0.39, 1.08)
LACHY_White_G -0.05 (-0.50, 0.39)
BAMSE_Control_B 0.00 (-0.55, 0.56)
BAMSE_Case_B -0.03 (-0.50, 0.44)
LEIPZIG_G 0.12 (-0.35, 0.59)
BAMSE_Control_G -0.24 (-0.68, 0.20)
TEENAGE_B -0.16 (-0.46, 0.15)
GENDAI_B 0.26 (-0.05, 0.56)
STRIP_Control_G -0.02 (-0.66, 0.62)
STRIP_Control_B 0.42 (-0.08, 0.92)
STRIP_Int_G 0.47 (0.02, 0.92)
GENDAI_G 0.02 (-0.25, 0.28)
STRIP_Int_B -0.31 (-0.76, 0.14)
TEENAGE_G 0.12 (-0.13, 0.38)
PANIC_B -0.24 (-0.63, 0.15)
GINI/LISA_B -0.03 (-0.21, 0.15)
PANIC_G -0.22 (-0.61, 0.18)
GINI/LISA_G -0.15 (-0.34, 0.04)
SWS_G 0.05 (-0.20, 0.31)
SWS_B -0.09 (-0.32, 0.14)
GENR 0.02 (-0.13, 0.17)
GENESIS_B -0.02 (-0.20, 0.17)
GENESIS_G -0.02 (-0.21, 0.17)
ALSPAC_B -0.11 (-0.22, -0.00)
ALSPAC_G -0.03 (-0.13, 0.08)
Subtotal (I-squared = 4.6%, p = 0.396) -0.03 (-0.07, 0.02)
African American (n=478)
APEX_AA_B -0.28 (-0.88, 0.31)
APEX_AA_G -0.05 (-0.68, 0.59)
LACHY_AA_B -0.38 (-0.96, 0.21)
LACHY_AA_G 0.08 (-0.38, 0.55)
Subtotal (I-squared = 0.0%, p = 0.614) -0.13 (-0.41, 0.15)
Asian (n=267)
Shunan_Control_B -0.01 (-0.37, 0.35)
Shunan_Case_G 0.15 (-0.55, 0.85)
Shunan_Control_G 0.03 (-0.28, 0.33)
Shunan_Case_B 0.00 (-0.40, 0.41)
Subtotal (I-squared = 0.0%, p = 0.983) 0.02 (-0.17, 0.21)
Heterogeneity between groups: p = 0.701
Overall (I-squared = 0.0%, p = 0.667) -0.03 (-0.07, 0.02)
-2
-1
0
1
2

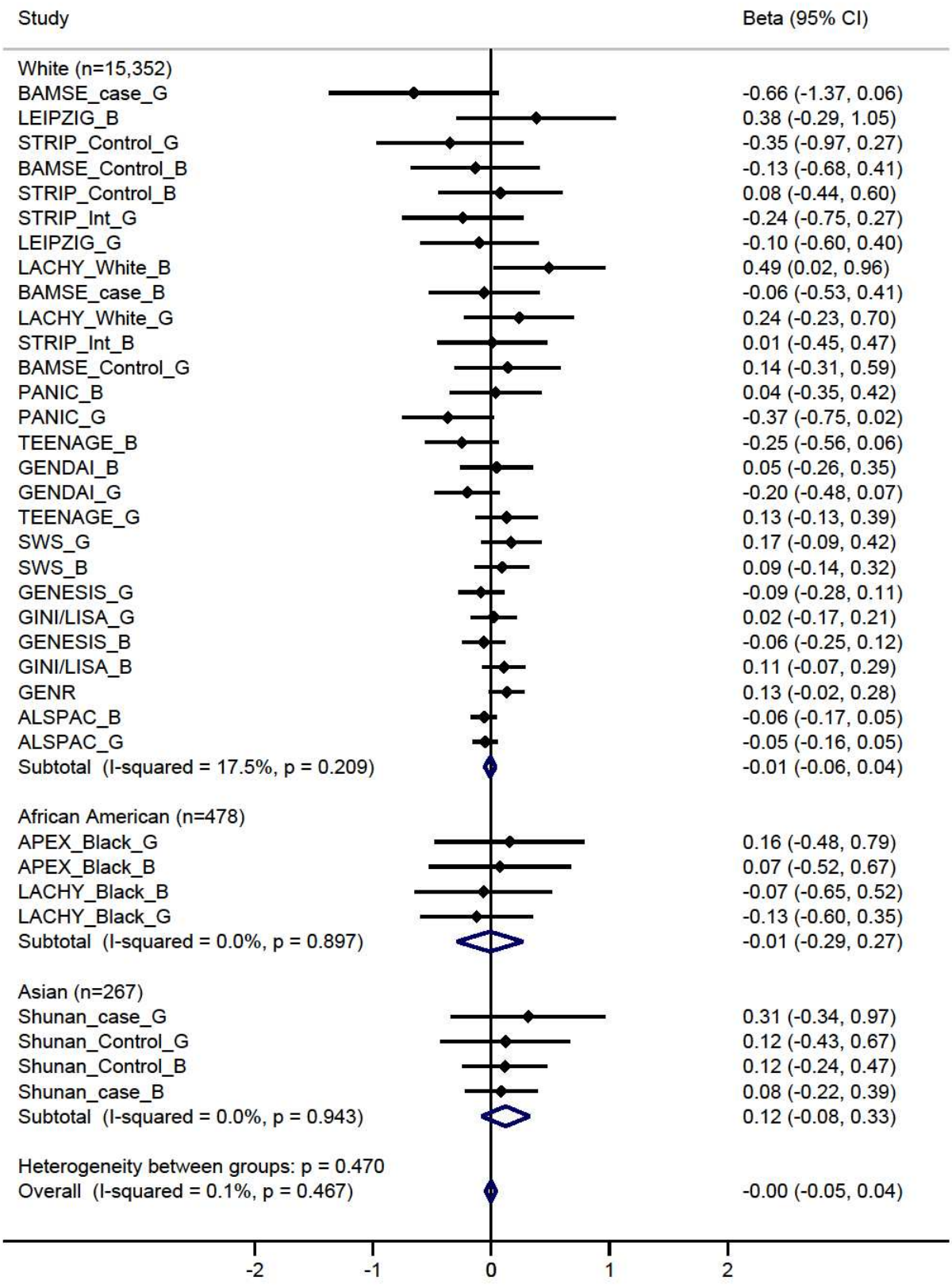
Supplemental Figure 7 Forest plot of the interaction between *FTO* rs9939609 SNP or a proxy and carbohydrate intake on BMI in a fixed effects meta-analysis of 16,097 children and adolescents

The studies are shown in boys (_B), girls (_Y) or mixed (GENR study only), cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta represents the difference in BMI per minor allele of SNP rs9939609 or a proxy (r^2=1) comparing participants in the high carbohydrate intake group to those in the low carbohydrate intake group, adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Study
Beta (95% CI)
White (n=15,352)
BAMSE_Case_G 0.33 (-0.40, 1.07)
STRIP_Control_G 0.22 (-0.40, 0.85)
BAMSE_Control_B -0.01 (-0.54, 0.53)
STRIP_Control_B 0.26 (-0.25, 0.78)
LEIPZIG_G 0.07 (-0.44, 0.58)
STRIP_Int_G -0.16 (-0.66, 0.34)
LEIPZIG_B -0.32 (-0.80, 0.15)
BAMSE_Case_B 0.07 (-0.40, 0.53)
STRIP_Int_B 0.05 (-0.41, 0.51)
LACHY_White_B -0.71 (-1.17, -0.26)
LACHY_White_G -0.24 (-0.70, 0.22)
BAMSE_Control_G -0.13 (-0.58, 0.31)
PANIC_G 0.14 (-0.26, 0.53)
PANIC_B -0.03 (-0.41, 0.36)
TEENAGE_B 0.24 (-0.07, 0.55)
GENDAI_B 0.08 (-0.22, 0.38)
GENDAI_G 0.10 (-0.16, 0.37)
TEENAGE_G -0.00 (-0.26, 0.26)
SWS_G -0.13 (-0.38, 0.13)
SWS_B -0.02 (-0.25, 0.21)
GENESIS_G 0.16 (-0.03, 0.35)
GINI/LISA_G -0.05 (-0.25, 0.14)
GENESIS_B 0.11 (-0.08, 0.29)
GINI/LISA_B -0.17 (-0.35, 0.01)
GENR -0.14 (-0.29, 0.01)
ALSPAC_B 0.03 (-0.08, 0.14)
ALSPAC_G -0.01 (-0.11, 0.10)
Subtotal (I-squared = 15.8%, p = 0.233) -0.01 (-0.05, 0.04)
African American (n=478)
APEX_Black_G -0.11 (-0.72, 0.51)
APEX_Black_B 0.24 (-0.35, 0.84)
LACHY_Black_B -0.41 (-0.99, 0.18)
LACHY_Black_G 0.30 (-0.18, 0.79)
Subtotal (I-squared = 26.1%, p = 0.255) 0.04 (-0.24, 0.32)
Asian (n=267)
Shunan_Case_G 0.17 (-0.41, 0.75)
Shunan_Control_G 0.09 (-0.40, 0.57)
Shunan_Control_B 0.22 (-0.13, 0.56)
Shunan_Case_B 0.15 (-0.19, 0.49)
Subtotal (I-squared = 0.0%, p = 0.980) 0.17 (-0.04, 0.37)
Heterogeneity between groups: p = 0.252
Overall (I-squared = 10.2%, p = 0.297) 0.00 (-0.04, 0.04)
-2
-1
0
1
2

Supplemental Figure 8 Forest plot of the interaction between *FTO* rs9939609 SNP or a proxy and fat intake on BMI in a fixed effects meta-analysis of 16,097 children and adolescents

The studies are shown in boys (_B), girls (_Y) or mixed (GENR study only), cases (_Case) and controls (_Control) for case-control studies, and whites (_W) and African Americans (_AA) for studies with multiple ethnicities separately, sorted by sample size (smallest to largest). The beta represents the difference in BMI per minor allele of SNP rs9939609 or a proxy (r^2=1) comparing participants in the high fat intake group to those in the low fat intake group, adjusted for age, physical activity (if available), region (if available) and eigenvectors (GWAS data only).


Study
Beta (95% CI)
White (n=15,352)
BAMSE_case_G -0.66 (-1.37, 0.06)
LEIPZIG_B 0.38 (-0.29, 1.05)
STRIP_Control_G -0.35 (-0.97, 0.27)
BAMSE_Control_B -0.13 (-0.68, 0.41)
STRIP_Control_B 0.08 (-0.44, 0.60)
STRIP_Int_G -0.24 (-0.75, 0.27)
LEIPZIG_G -0.10 (-0.60, 0.40)
LACHY_White_B 0.49 (0.02, 0.96)
BAMSE_case_B -0.06 (-0.53, 0.41)
LACHY_White_G 0.24 (-0.23, 0.70)
STRIP_Int_B 0.01 (-0.45, 0.47)
BAMSE_Control_G 0.14 (-0.31, 0.59)
PANIC_B 0.04 (-0.35, 0.42)
PANIC_G -0.37 (-0.75, 0.02)
TEENAGE_B -0.25 (-0.56, 0.06)
GENDAI_B 0.05 (-0.26, 0.35)
GENDAI_G -0.20 (-0.48, 0.07)
TEENAGE_G 0.13 (-0.13, 0.39)
SWS_G 0.17 (-0.09, 0.42)
SWS_B 0.09 (-0.14, 0.32)
GENESIS_G -0.09 (-0.28, 0.11)
GINI/LISA_G 0.02 (-0.17, 0.21)
GENESIS_B -0.06 (-0.25, 0.12)
GINI/LISA_B 0.11 (-0.07, 0.29)
GENR 0.13 (-0.02, 0.28)
ALSPAC_B -0.06 (-0.17, 0.05)
ALSPAC_G -0.05 (-0.16, 0.05)
Subtotal (I-squared = 17.5%, p = 0.209) -0.01 (-0.06, 0.04)
African American (n=478)
APEX_Black_G 0.16 (-0.48, 0.79)
APEX_Black_B 0.07 (-0.52, 0.67)
LACHY_Black_B -0.07 (-0.65, 0.52)
LACHY_Black_G -0.13 (-0.60, 0.35)
Subtotal (I-squared = 0.0%, p = 0.897) -0.01 (-0.29, 0.27)
Asian (n=267)
Shunan_case_G 0.31 (-0.34, 0.97)
Shunan_Control_G 0.12 (-0.43, 0.67)
Shunan_Control_B 0.12 (-0.24, 0.47)
Shunan_case_B 0.08 (-0.22, 0.39)
Subtotal (I-squared = 0.0%, p = 0.943) 0.12 (-0.08, 0.33)
Heterogeneity between groups: p = 0.470
Overall (I-squared = 0.1%, p = 0.467) -0.00 (-0.05, 0.04)
-2
-1
0
1
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References

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