FTO Genotype Is Associated with Body Mass Index after the Age of Seven Years But Not with Energy Intake or Leisure-Time Physical Activity

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Context: A common variant in the FTO gene, rs9939609, associates with body mass index (BMI) in adults and in children aged 7 yr or older.

Objective: Our aim was to examine the associations of the FTO genotype with BMI, cardiovascular risk factors, energy intake, and leisure-time physical activity in children followed up since infancy.

Methods: Healthy participants of the STRIP Study, genotyped for rs9939609, were followed from age 7 months (n = 640) to 15 yr (n = 438). The children were randomly assigned to lifestyle intervention and control groups. Height, weight, blood pressure, and serum lipids were measured annually. Food records and physical activity index were obtained at age 15 yr.

Results: The FTO genotype did not associate with BMI in children younger than 7 yr of age. From age 7 yr onward, the children homozygous for the A allele had progressively higher BMI than the children with one or two T alleles ($P = 0.029$ for FTO by age interaction). Furthermore, in longitudinal, BMI Z-score-adjusted analysis, the AA genotype associated with higher systolic and diastolic blood pressure and with elevated serum total and low-density lipoprotein-cholesterol ($P = 0.01$, $P < 0.001$, $P = 0.05$, and $P = 0.04$ for main effect, respectively). The FTO genotype did not associate with energy intake or physical activity index at age 15. The FTO*Study group interactions were not significant.

Conclusions: Our results suggest that the effect of the FTO genotype on BMI becomes evident only after age 7 yr. These results further suggest that the FTO gene is not directly associated with energy intake or physical activity. **(*J Clin Endocrinol Metab* 94: 1281–1287, 2009)**

The increasing prevalence of childhood obesity is a serious international health problem because obesity sets the stage for several common diseases (1). The environmental risk factors of obesity have been widely studied. However, the genetic factors predisposing to obesity are still poorly understood although the heritability of the body mass index (BMI) is as high as 77% even in children born during the pediatric obesity epidemic (2).

Recently, a genome-wide search for type 2 diabetes-susceptibility genes identified a common variant in the FTO gene, rs9939609, which predisposes to diabetes through an effect on BMI (3). The association of the FTO gene variant with BMI was confirmed in almost 30,000 white European adults and in 10,000 white European children (3). Furthermore, the association of the FTO gene variant with BMI and risk of obesity has been confirmed in some populations (4–8) but not in all (9, 10). Some other FTO gene variants (rs1121980, rs1421085, rs17817449, and rs9930506) have also been shown to associate with increase in BMI and obesity (4, 11–14).

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Abbreviations: BMI, Body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI, physical activity index; SNP, single nucleotide polymorphism.

The findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) and from the Northern Finland Birth Cohort of 1966 (NFBC1966) suggest that the FTO genotype is not associated with fetal growth because the children with different FTO genotypes did not differ from each other in birth weights in these studies (3). The ALSPAC data further revealed that the effect of the FTO genotype on BMI was evident already at the age of 7 yr (3). In a study on obese children, the boys homozygous for T allele in rs9939609 had a significantly lower increase in BMI SD score than the A allele carriers already between the ages of 1 and 3 yr (5). In a recent study, an association was found between the FTO gene polymorphism and adipose tissue accumulation already during the neonatal period (15). To our knowledge, there are no longitudinal studies examining the effect of the FTO genotype on BMI in healthy children younger than 7 yr of age. Because adiposity rebound, which begins between the ages of 3 and 7, has been hypothesized to be one of the critical periods for development of obesity in childhood, we decided to study the effect of the FTO genotype on weight development during this time period (16).

The function of the FTO gene and the effect of the FTO genotype on obesity-related metabolic traits remain poorly described. Two recent studies suggest that the polymorphisms of the FTO gene are associated with energy intake rather than with energy expenditure (17, 18). A Danish study showed that the FTO genotype was associated with insulin sensitivity (19). Freathy *et al.* (20) further suggested that the FTO genotype associated with higher fasting insulin, glucose, and triglycerides and with lower high-density lipoprotein (HDL) cholesterol, but these associations disappeared after adjustment for BMI. To clarify these associations and the mechanisms involved, we examined the associations of the FTO genotype with BMI, cardiovascular risk factors (blood pressure, serum lipids), energy intake, and leisure-time physical activity level in the participants of the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) who were followed up since infancy. We also assessed the interactions between the genotype and the effect of individualized dietary and lifestyle counseling given to half of our study children because previous studies have not been able to show any associations between the genotype and the effect of the lifestyle intervention programs aiming at weight loss (21, 22).

Subjects and Methods

Study design and subjects

A total of 1062 children were recruited to the STRIP study at the well-baby clinics in Turku, Finland, between February 1990 and June 1992 as described (23). At the age of 7 months, the children were randomly assigned either to receive individualized lifestyle counseling aimed at controlling environmental atherosclerosis risk factors (n = 540) or to a control group (n = 522). The study protocol and the intervention were described in detail previously (24). At age 5 yr, 766 children came to the follow-up visit. A blood sample for DNA analysis was obtained from 665 of them. The few children with chromosomal diseases (n = 3) were excluded. The genotype of 22 children could not be determined due to technical problems. The genotyping of the rs9939609 in the FTO gene was successfully carried out in 640 healthy children (299 girls; 324 children belonged to the intervention group). The five children who later developed type 1 diabetes were excluded from the analyses. Between 5 and 15 yr, 196 children (approximately 30% of the children in each FTO genotype group) discontinued participation. They were included in the longitudinal analyses until discontinuation. A survival analysis of the dropouts, using Cox regression model with discrete time distribution, showed that neither the FTO genotype nor the BMI of the child was associated with the premature discontinuation of the study. Although adjusted with STRIP study group and sex, the odds ratios (95% confidence interval) of discontinuation for FTO group (AA *vs.* AT/TT) and for BMI unit (kilogram/meter^2) were 0.87 (0.58–1.32; $P = 0.52$) and 1.04 (0.99–1.11; $P = 0.15$), respectively.

The STRIP study was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital. At the beginning of the study, parents of the children signed informed consent for the study itself and later another informed consent was obtained for gene analysis.

Anthropometric and blood pressure measurements

The birth weights and relative birth weights (SD, the birth weight adjusted for gestational age) were collected from the delivery hospital and well-baby clinic records. The anthropometric measurements were performed at ages 7 months, 13 months, 2 yr, and annually thereafter until age 15 yr. Heights and weights were measured as previously described (24). The BMI was calculated as weight in kilograms divided by the square of height in meters, and furthermore, age- and gender-specific BMI Z-scores were calculated. The beginning of the adiposity rebound was determined as the age at which the child's BMI started to increase again after an initial decrease. From age 2 to 15 yr, the children were classified as overweight according to the international age- and gender-specific BMI cutoff points (25). Waist circumferences were measured with a flexible tape at the midpoint between the lower costal border and the iliac crest. Blood pressure was measured twice at each visit on the right arm with an automatic device (Dinamap Compact T, Criticon, Tampa, FL) while the subject was seated. The mean value of the measurements was used for analysis. The pubertal status was recorded according to Tanner staging (26).

Biochemical analyses

A venous blood sample was drawn annually, except at ages 6 and 8 yr. Until age 4 yr, the blood samples were nonfasting, and thereafter the samples were obtained after a 12-h, overnight fast. After clotting at room temperature for 30 to 60 min and centrifugation at 3400 × *g* for 12 min, serum was separated and stored at −25 C for up to a few weeks. Serum lipid and apolipoprotein concentrations were measured as previously described (27, 28). All serum analyses were done at the laboratory of the National Public Health Institute (formerly the Research and Development Unit of the Social Insurance Institution) in Turku, Finland. Non-HDL cholesterol was calculated, and from age 5 yr onward, the Friedewald formula was used to calculate the low-density lipoprotein (LDL)-cholesterol concentration (29).

Assessment of energy intake and leisure-time physical activity

Before the follow-up visit at age 15, the families completed a 4-d food record on the child's food consumption. A nutritionist reviewed the food records for completeness and accuracy, and thereafter the nutrient composition of diet was analyzed using the Micro-Nutrica PC Program (Research and Development Unit of the Social Insurance Institution) (30).

Leisure-time physical activity habits were assessed at the 15-yr visit with a self-administered questionnaire in which the frequency, duration, and intensity of habitual leisure-time physical activity were reported (31). A leisure-time physical activity index (PAI) was calculated as a multiple of the resting metabolic rate (hours per week) by multiplying the frequency, mean duration in minutes, and mean intensity of weekly leisure-time physical activity, as described (32).

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FTO genotyping

Genomic DNA was extracted from whole blood samples dried on filter paper using a commercially available kit (Gentra Systems, Minneapolis, MN) according to the manufacturer's instructions. FTO polymorphism (rs9939609) was genotyped using TaqMan Genotyping Assay (ID: C_30090620_10) with the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The PCRs containing genomic DNA, 1 × TaqMan Genotyping Master Mix, 900 nM of each primer, and 200 nM of each probe were performed in 384-well plates using the standard protocol in a total volume of 5 μl. As quality control, we used known control samples that were run in parallel with unknown DNA samples and random blind duplicates. The genotype frequencies were 211 (33%), 325 (51%), and 104 (16%) for TT, TA, and AA, respectively. The genotype frequencies in our study population were in Hardy-Weinberg equilibrium. Genotyping was done in the Department of Clinical Chemistry at Tampere University Hospital and University of Tampere.

Statistical analyses

The SAS for Windows 9.1 software (SAS Institute, Cary, NC) was used to carry out statistical analyses. Logarithmic transformation was used for triglycerides because of the skewed distribution. The genotype distributions in boys and girls as well as in the intervention and control groups were compared with Cochran-Mantel-Haenszel statistics for row mean score differences, which were also applied in comparing the pubertal statuses of the 15-yr-old children with different genotypes. Both additive and recessive models for the FTO genotype were fitted, and therefore, the *P* values were multiplied by two. Gender and STRIP study group (intervention and control) together with their interactions to FTO genotype were included in the models. Longitudinal data were analyzed using general linear models with age as a repeated measurement factor. First order autoregressive covariance structure and backward selection were used. The analyses of blood pressure values were adjusted for BMI Z-score and height, and the analyses of serum lipid values were adjusted for BMI Z-score. Logistic regression with age, gender, study group, and their interactions with the FTO genotype as covariates was used to analyze the effect of the FTO genotype on the proportion of overweight children. The birth weights, adiposity rebound, and different phenotypes at the age of 15 yr were analyzed using linear models with backward selection. The statistical significance was set at $P < 0.05$.

Results

A total of 640 healthy children were genotyped for rs9939609 in the FTO gene. The genotype distribution was similar in boys and girls as well as in the intervention and control groups of the STRIP trial ($P = 0.40$ and $P = 0.73$ for gender and study group, respectively). The BMIs and BMI Z-scores of the children with TT and TA genotype were closely similar during the follow-up (Fig. 1), not fulfilling the assumptions of an additive model. Therefore a recessive model was applied in further analyses.

Birth weight or relative birth weight was not associated with the FTO genotype (Table 1). The children were followed up from the age of 7 months to the age of 15 yr. The effect of the FTO genotype on BMI changed over time ($P = 0.004$ for FTO by age interaction) (Fig. 2). Gender and study group had neither an interaction with the FTO genotype nor a main effect on BMI, and consequently, they were dropped out of the model by backward selection. Seventy-five percent of the children with AA and TA/TT genotype had reached the adiposity rebound by the ages of 6.3 and 6.5 yr, respectively. Because the mean age of the children at the beginning of the adiposity rebound was not associated with the FTO genotype (Table 1), we subsequently analyzed the effect of the FTO genotype on BMI before/during the adiposity rebound and after the adiposity rebound. The FTO genotype did not associate with BMI in children aged 7 months to 6 yr (FTO by age interaction was dropped out of the model by backward selection and $P > 0.99$ for the main effect of the FTO). In children aged 7 to 15 yr, the effect of the FTO genotype on BMI changed over time because the children homozygous for the A allele had progressively higher BMI than the children with one or two T alleles ($P = 0.029$ for FTO by age interaction). In children aged 2 to 6 yr, the risk of overweight was not associated with the FTO genotype ($P > 0.99$ for the main effect of the FTO genotype) (Fig. 3). In children aged 7 to 15 yr, the odds ratio of overweight was 1.67 (95% confidence interval, 1.36–2.04) in the children with AA genotype compared with the children with TA/TT genotype ($P < 0.001$). Gender and study group did not modify the effect of the FTO genotype on the risk of overweight.

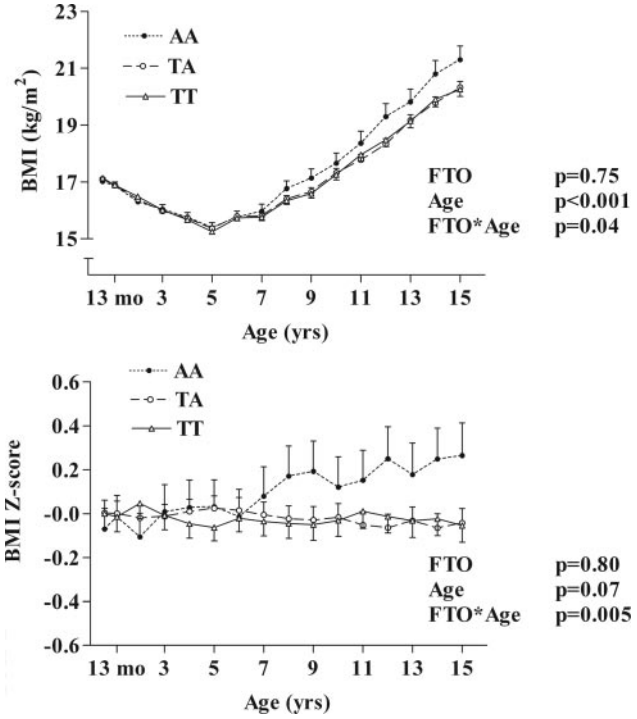

FIG. 1. Mean BMI and BMI Z-score (SE) of the children with AA, TA, and TT genotypes in rs9939609 of the FTO gene. The *P* values are for the additive model.

In the longitudinal BMI Z-score- and height-adjusted analysis, the AA genotype associated with higher systolic and diastolic blood pressure ($P = 0.01$ and $P < 0.001$ for systolic and diastolic blood pressure, respectively) (Fig. 4). Gender and study group did not have an interaction with the FTO genotype on blood pressure values, but they had a main effect on systolic blood pressure ($P = 0.02$ and $P < 0.001$ for gender and study group, respectively). Study group also had a main effect on diastolic blood pressure ($P < 0.001$). Furthermore, after adjustment for BMI Z-score, the AA genotype associated with elevated serum total and LDL-cholesterol concentrations ($P = 0.05$ and $P = 0.04$ for the main effect of the FTO genotype on total cholesterol and LDL-cholesterol, respectively) (Fig. 5). Gender and study group had a main effect on serum total cholesterol and LDL-

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TABLE 1. Associations of rs9939609 variants in the FTO gene with phenotype characteristics at birth and at the beginning of the adiposity rebound

	Mean (SE) by FTO genotype			
	TT	TA	AA	*P* for the recessive model[a]
n (% boys)	211 (58%)	325 (50%)	104 (53%)	
Birth weight (g)	3598.2 (34.2)	3524.8 (30.8)	3537.3 (55.5)	>0.99
Relative birth weight (SD)[b]	0.13 (0.07)	0.06 (0.06)	0.07 (0.11)	>0.99
Age at the beginning of the adiposity rebound (yr) [c,d,e]	5.4 (0.13)	5.4 (0.10)	5.2 (0.19)	>0.99

[a] The *P values were multiplied by two because both the additive and recessive models were fitted.*

[b] Birth weight adjusted for gestational age.

[c] The beginning of the adiposity rebound was determined as the age at which the child's BMI started to increase again after an initial decrease.

[d] The data on the age at the beginning of the adiposity rebound were available from 166, 255, and 72 children with TT, TA and AA genotype, respectively.

[e] Seventy-five percent of the children with TT, TA, and AA genotypes had reached the adiposity rebound by the ages of 6.1, 6.5, and 6.3 yr, respectively.

cholesterol concentrations, but they did not modify the effect of the FTO genotype ($P < 0.001$ for all main effects). The FTO genotype did not associate with HDL-cholesterol, non-HDL-cholesterol, triglycerides, apolipoprotein A-1 or B after adjustment for BMI Z-score (data not shown).

A total of 148, 220, and 71 children with TT, TA, and AA genotypes, respectively, came to the follow-up visit at age 15 yr. The phenotypes of the 15-yr-old children are shown in Table 2. In the 15-yr-old children, there was no significant difference in height between the children with AA genotype and the children with TA or TT genotype, but the children with AA genotype tended to weigh more and had, thus, 1.0 U higher BMI than the children with TA or TT genotype ($P > 0.99$, $P = 0.13$, and $P = 0.04$ for height, weight, and BMI, respectively) (Table 2). The children homozygous for the A allele had a mean waist circumference of 75.2 cm compared with 72.5 cm in the children with at least one T allele ($P = 0.05$). No interactions were found between the gender or study group and the FTO genotype on the anthropometric variables.

At age 15 yr, the FTO genotype did not associate with the mean daily energy intake analyzed from the 4-d food records. Furthermore, the daily energy intake per kilogram of weight or fat, protein, and carbohydrate intakes (as percentage of daily energy intake) were not associated with FTO genotype (Table 2). We also analyzed the leisure-time PAI of the 15-yr-old study children as a measure of physical activity. The leisure-time physical activity was, however, not associated with the FTO genotype (Table 2). No interactions were found between the gender or study group and the FTO genotype on the dietary or physical activity variables.

At age 15 yr, 58.8 and 29.5% of our study subjects were in Tanner stage M/G4 or M/G5 of the pubertal development, respectively. The pubertal development was not associated with FTO genotype ($P > 0.99$ and $P > 0.99$ for M/G and P, respectively).

Discussion

We showed in this longitudinal study starting at age 7 months that the FTO genotype associates with BMI and the risk of overweight in children. Our results confirm the findings of previous studies (3, 5) and demonstrate further that these associations start to develop after the age of 7 yr. Similar to the findings from the ALSPAC and NFBC1966 studies, our study children with different FTO genotypes did not differ from each other in birth weights or relative birth weights, which suggests that the studied variant in the FTO gene is not associated with fetal growth (3). One recent study suggests that the FTO gene polymorphism might associate with adipose tissue accumulation, at least temporarily, already during the neonatal period (15). However, in our study, the FTO genotype was not associated with the timing of

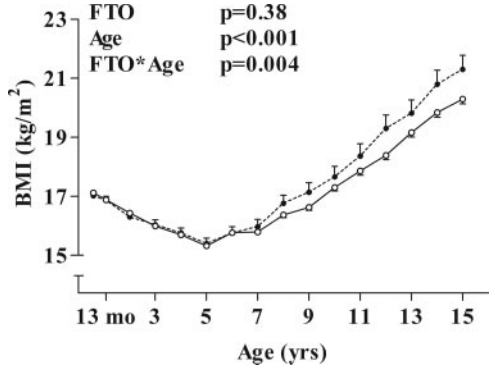

FIG. 2. Mean (SE) BMI of the children with AA genotype (*black circle with broken line*) and the children with TT or TA genotype (*open circle with solid line*) in rs9939609 of the FTO gene. FTO*Gender- and FTO*Study group-interactions were not significant.

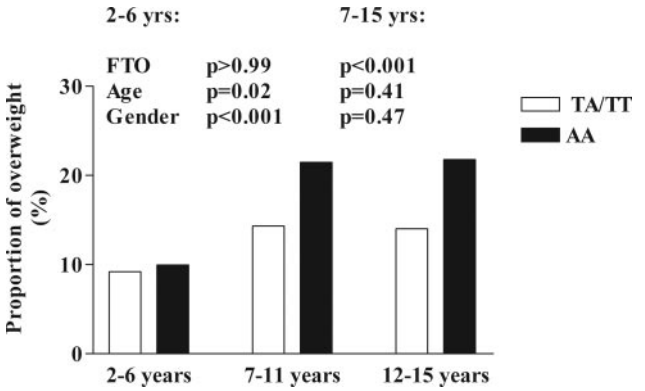

FIG. 3. The proportion of overweight [according to the international age- and gender-specific cutoff points (Ref. 25)] children with AA or AT/TT genotype. FTO*Gender- and FTO*Study group-interactions were not significant.

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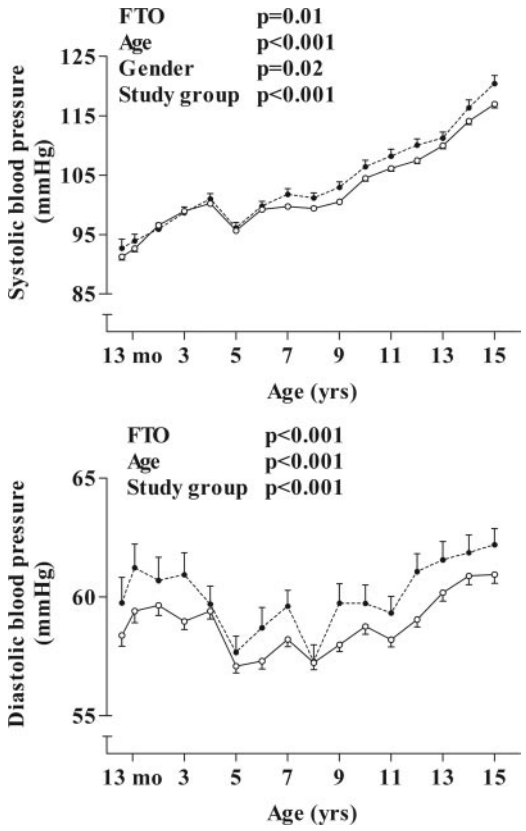

FIG. 4. Mean (SE) systolic and diastolic blood pressure of the children with AA genotype (*black circle with broken line*) and the children with TT or TA genotype (*open circle with solid line*) in rs9939609 of the FTO gene. The *P* values are for the analysis adjusted for BMI Z-score and height. FTO*Gender- and FTO*Study group-interactions were not significant.

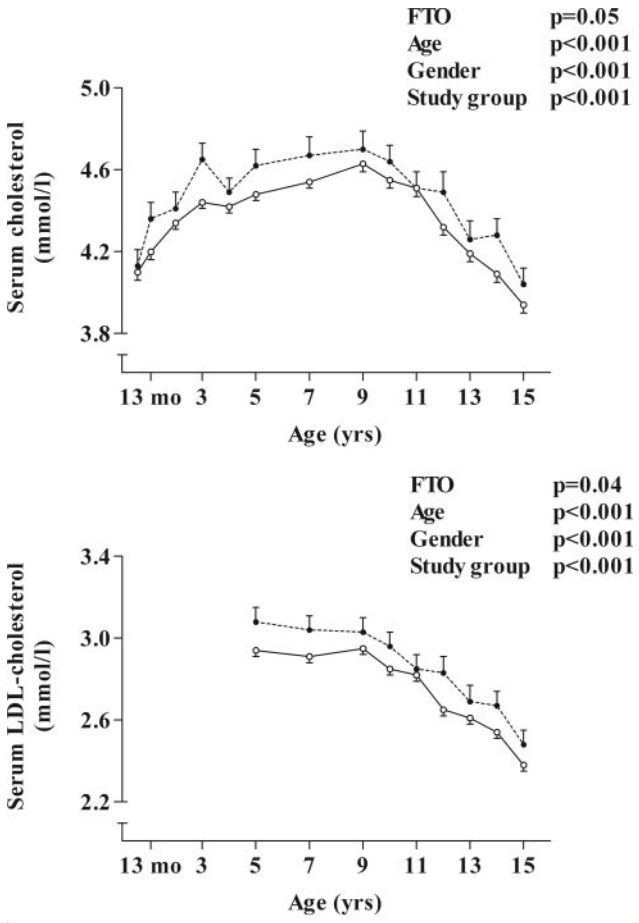

FIG. 5. Mean (SE) serum cholesterol and LDL-cholesterol concentrations of the children with AA genotype (*black circle with broken line*) and the children with TT or TA genotype (*open circle with solid line*) in rs9939609 of the FTO gene. The *P* values are for the analysis adjusted for BMI Z-score. FTO*Gender- and FTO*Study group-interactions were not significant.

adiposity rebound, and the association between the FTO genotype and BMI was found only in children older than 7 yr of age. It remains unknown why the association between the FTO genotype and BMI becomes evident only after the age of 7 yr. One explanation might be that the degree of expression of the FTO gene changes during the adiposity rebound. At the age of 15 yr, our study children who were homozygous for the A allele had 1.0 U higher BMI than those children who had at least one T allele. This difference in BMI is more pronounced than the difference reported in 14-yr-old children in the NFBC1966 (3).

In a previous study, the two copies of the rs9939609 A allele were each associated with a BMI increase of approximately 0.4 kg/m^2 (3). In our study population, the increase in BMI was more marked in those individuals who were homozygous for the A allele, whereas the carriers of one or two T alleles did not differ from each other. Therefore, the recessive model was applied in our study instead of the additive model. Because both additive and recessive models were fitted, all *P* values were multiplied by two to correct for multiple testing. In a Swedish population, the higher BMI and risk of obesity also associated with homozygous AA genotype (5).

Recent studies suggest that FTO is a member of the nonheme dioxygenase superfamily (33, 34). The FTO gene is expressed in many tissues, including several feeding-related sites of the central nervous system and the adipose tissue (35, 36). The function of the FTO gene is under vigorous investigation, and it has been suggested that the gene may be involved in lipolysis (37). Evidence has gathered suggesting that the FTO gene polymorphisms are associated with energy intake rather than with energy expenditure (17, 18). In a very recent study, an association was found between the FTO genotype and energy and fat intake (38). In our study, neither the daily energy intake nor the leisure-time physical activity associated with the FTO genotype. However, both the energy intake data obtained from the food records and the leisure-time physical activity data obtained from self-administered questionnaires are imprecise (39), and therefore, studies with more objective measures of energy homeostasis are needed, *e.g.* to compare the resting energy expenditure in subjects with various FTO genotypes.

Half of our study children belonged to the intervention group of the STRIP trial, and the families of these children had repeatedly received nutritional and lifestyle counseling since the children were 8 months old. The aim of the counseling was to reduce the exposure of these children to the known environmental risk factors of coronary heart disease. It was previously shown that the intake of fat and saturated fat is lower in the intervention children than in the control children (40). Furthermore, the serum cholesterol and LDL cholesterol values are lower in the intervention boys compared with the control boys (28). In the present study, the

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TABLE 2. Associations of rs9939609 variants in the FTO gene with phenotype characteristics at the age of 15 yr

	Mean (SE) by FTO genotype			
	TT	TA	AA	*P* for the recessive model[a]
No. at the age of 15 yr (% of boys)	148 (57%)	220 (48%)	71 (58%)	
Height (cm)	170.1 (0.6)	170.1 (0.6)	170.3 (1.0)	>0.99
Weight (kg)	58.8 (0.9)	59.1 (0.7)	61.9 (1.6)	0.13
BMI (kg/m^2)	20.3 (0.3)	20.3 (0.2)	21.3 (0.5)	0.04
Waist (cm)	72.3 (0.7)	72.7 (0.6)	75.2 (1.2)	0.05
Energy intake (kcal)[b]	2028.3 (47.9)	1989.0 (40.3)	2010.0 (64.3)	>0.99
Energy/weight (kcal/kg)	35.5 (0.9)	34.6 (0.8)	34.0 (1.4)	0.69
Fat intake (E%)	31.1 (0.5)	31.7 (0.4)	30.6 (0.7)	0.27
Protein intake (E%)	17.7 (0.3)	17.4 (0.2)	17.9 (0.4)	0.81
Carbohydrate intake (E%)	51.3 (0.5)	50.9 (0.4)	51.5 (0.7)	0.97
PAI (metabolic equivalent, h/wk)[c]	31.9 (2.1)	26.4 (1.6)	28.5 (2.9)	>0.99

FTO*Study group- and FTO*Gender interactions were not significant. E%, Percentage of daily energy intake.

[a] The *P* values were multiplied by two because both the additive and recessive models were fitted.

[b] Food record was available from 127, 190, and 65 children with TT, TA, and AA genotype, respectively.

[c] PAI was available from 129, 193, and 61 children with TT, TA, and AA genotype, respectively.

study group did not modify the effect of the FTO genotype on BMI or risk of overweight, suggesting that the intervention was not intense enough to abolish the effect of the FTO polymorphism. However, this is not surprising because weight management and treatment of overweight have not been the main goals of the intervention. Similar results were reported in two intervention programs aiming at weight loss (21, 22), although other studies have shown an interaction between FTO genotype and physical activity (19, 41). Furthermore, the study group did not modify the effect of the FTO genotype on blood pressure or serum lipid values. In contrast to previous findings, the associations with the metabolic traits remained significant after adjustment for BMI Z-score (5, 20). These results suggest that not all the effects of the FTO genotype are mediated by weight, but instead, other metabolic pathways might be involved as well.

Interestingly, when the Swedish group analyzed girls and boys separately, they observed the effect of the FTO genotype on BMI and risk of obesity only in girls (5). The gender did not modify the effect of the FTO genotype on BMI or risk of overweight in our analysis, and therefore we concluded that the effect of the FTO genotype was not different in girls and boys. A reason for this difference in the findings may be that the study populations were quite different in these two studies. The Swedish population consisted of 450 severely obese children and 512 normal-weight controls, whereas the children in our study were mainly of normal weight with few modestly overweight children. In adult populations, the FTO genotype associates with BMI in both genders like in our study (3).

We measured only one single nucleotide polymorphism (SNP) in the FTO gene due to the small amount of DNA extracted from dried blood spots. Because there are several other SNPs in the FTO gene shown to be associated with BMI and the risk of obesity (3, 4, 11, 12), it is important to compare the relative impact of all known important SNPs in the FTO gene in a single large study with long-term follow-up extending from the post breast feeding period to adolescence.

In conclusion, this longitudinal study shows that rs9939609 in the FTO gene associates with BMI and risk of overweight already in children, but this association becomes evident only after the age of 7 yr. Our results further suggest that the FTO genotype does not associate with daily energy intake or physical activity.

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Clinical trial registration: NCT00223600 (www.clinicaltrials.gov).

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