

Attenuation of the Effect of the *FTO* rs9939609 Polymorphism on Total and Central Body Fat by Physical Activity in Adolescents

The HELENA Study

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Objective: To examine whether physical activity attenuates the effect of the *FTO* rs9939609 polymorphism on body fat estimates in adolescents.

Design: Cross-sectional study.

Setting: Athens, Greece; Dortmund, Germany; Ghent, Belgium; Heraklion, Greece; Lille, France; Pécs, Hungary; Rome, Italy; Stockholm, Sweden; Vienna, Austria; and Zaragoza, Spain, from October 2006 to December 2007.

Participants: Adolescents from the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (n=752).

Main Exposure: Physical activity.

Main Outcome Measures: The *FTO* rs9939609 polymorphism was genotyped. Physical activity was assessed by accelerometry. We measured weight, height, waist circumference, and triceps and subscapular skinfolds; body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) and body fat percentage were calculated.

Results: The A allele of the *FTO* polymorphism was significantly associated with higher BMI (+0.42 per risk allele), higher body fat percentage (+1.03% per risk allele), and higher waist circumference (+0.85 cm per risk allele). We detected significant or borderline gene \times physical activity interactions for the studied body fat estimates (for interaction, $P = .02, .06, \text{ and } .10$ for BMI, body fat percentage, and waist circumference, respectively). Indeed, the effect of the *FTO* rs9939609 polymorphism on these body fat parameters was much lower in adolescents who met the daily physical activity recommendations (ie, ≥ 60 min/d of moderate to vigorous physical activity) compared with those who did not: +0.17 vs +0.65 per risk allele in BMI, respectively; +0.40% vs +1.70% per risk allele in body fat percentage, respectively; and +0.60 vs +1.15 cm per risk allele in waist circumference, respectively.

Conclusion: Adolescents meeting the daily physical activity recommendations may overcome the effect of the *FTO* rs9939609 polymorphism on obesity-related traits.

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THERE IS COMPELLING EVIDENCE that human obesity is a multifactorial disorder where both genes^{1,2} and lifestyle factors, including diet and physical activity,^{3,4} are important contributors. Among the obesity-related genes, polymorphisms in the fat mass- and obesity-associated gene (*FTO*) are strongly associated with body fat estimates in populations of different ethnic backgrounds or ages.⁵⁻¹⁰ It was estimated that each copy of the *FTO* rs9939609 minor allele (ie, A allele) corresponds to approximately 1.5-kg-heavier body weight, and the prevalence of this risk allele in white individuals is around 40%.⁶

Several studies suggested that the deleterious effect of the *FTO* polymorphism could

be attenuated by physical activity,¹¹⁻¹³ whereas others were not able to show such effect.¹⁴⁻¹⁶ These studies were mainly focused on adult populations and all assessed physical activity by means of self-reported questionnaires. One study in 438 adolescents aged 15 years failed to detect an interaction between the *FTO* rs9939609 polymorphism and self-reported physical activity.¹⁶

The US Department of Health and Human Services recently released physical activity guidelines for youth.¹⁷ They suggested that children and adolescents should participate in physical activity for 60 min/d or longer, and most of the activity should be of moderate to vigorous intensity.

The goals of our study were to investigate the interaction between the *FTO* rs9939609 polymorphism and physical

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Group Information: The HELENA Study Group members are listed on page 331.

activity objectively assessed by accelerometry on body mass index (BMI), body fat percentage, and waist circumference and to assess whether meeting the daily physical activity recommendations could abolish the deleterious effect of the *FTO* rs9939609 polymorphism on body fat estimates in a cohort of European adolescents.

METHODS

PARTICIPANTS

Adolescents were part of the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS). The HELENA-CSS was designed to obtain reliable and comparable data on nutrition and health-related parameters of a sample of European adolescents.^{18,19} A total of 3865 adolescents were recruited between October 2006 and December 2007. Adolescents were randomly selected from schools using a proportional cluster sampling taking into account geographical distribution in each city, private/public school ratio, and number of classes by school. One-third of the classes were randomly selected for blood collection, resulting in a total of 1155 blood samples for the subsequent clinical biochemistry assays and genetic analyses. Among these participants, 752 adolescents (413 girls) with data on *FTO* rs9939609, BMI, and physical activity were included in this study (namely, the final sample). The 2 samples (the “blood” sample and the “final” sample) were similar in terms of genotype frequencies (TT: 37.9 vs 36.6, respectively; TA: 45.5 vs 47.1, respectively; and AA: 16.7 vs 16.4, respectively; $P = .87$) and levels of moderate to vigorous physical activity (mean [SD], 45.6 [17.7] vs 40.4 [14.0] min/d, respectively; $P = .41$), whereas the BMIs were different (mean [SD], 22.7 [5.6] vs 21.7 [6.8], respectively; $P < .001$). After receiving complete information about the aims and methods of the study, all adolescents and their parents or guardians were fully informed and signed an informed written consent. All participants met the general HELENA-CSS inclusion criteria.^{18,19} The study was performed following the ethical guidelines of the Declaration of Helsinki 1961 (revision of Edinburgh 2000), Good Clinical Practice, and legislation about clinical research in humans in each of the participating countries. The protocol was approved by the corresponding local human research review committees of the centers involved.²⁰

ASSESSMENT OF BODY FAT

Weight and height were measured following standard procedures,²¹ and BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in triplicate at the midpoint between the superior iliac spine and the costal edge in the midaxillary line with an anthropometric unelastic tape (SECA 200; Seca Deutschland, Hamburg, Germany) and was used as a surrogate measure of central body fat. It was recorded to the nearest 0.1 cm. Skinfold thickness was measured to the nearest 0.2 mm in triplicate on the left side at the biceps, triceps, subscapularis, suprailium, thigh, and medial calf with a Holtain Caliper (Holtain Ltd, Crymmych, Wales).²¹ Body fat percentage was calculated from skinfold thicknesses (triceps and subscapularis) using the equations by Slaughter et al.²²

ASSESSMENT OF PUBERTAL STATUS

Pubertal stage was recorded by a trained researcher of the same sex as the child, according to Tanner and Whitehouse²³ and as described elsewhere.²⁴

Table. Characteristics of the Study Cohort

Characteristic	Boys		Girls	
	No.	Mean (SD)	No.	Mean (SD)
Age, y	339	14.5 (1.4)	413	14.4 (1.3)
BMI	339	20.6 (3.3)	410	21.1 (3.4)
Body fat, %	330	19.3 (10.6)	408	26.0 (7.2)
Waist circumference, cm	313	72.7 (7.9)	378	70.6 (8.0)
Moderate to vigorous PA, min/d	339	68.1 (25.2)	413	51.2 (20.1)
Adolescents achieving the recommended daily PA level, % ^a	200/339	59	111/413	27

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PA, physical activity.

^aAt least 60 min/d of moderate to vigorous PA.^{17,26}

ASSESSMENT OF PHYSICAL ACTIVITY

Physical activity was assessed during 7 consecutive days with a uniaxial accelerometer (GT1M; ActiGraph, Pensacola, Florida) attached to the lower back. Adolescents were instructed to wear the accelerometer during all time awake and to remove it only during water-based activities. At least 3 days of recording with a minimum of 8 hours registered per day was set as an inclusion criterion. The time-sampling interval (epoch) was set at 15 seconds.²⁵ We calculated the time engaged in at least moderate physical activity (≥ 3 metabolic equivalents) based on a standardized cutoff of 2000 counts/min or more. Moderate to vigorous physical activity was dichotomized into less than 60 min/d and 60 min/d or longer.^{17,26}

GENOTYPING

The *FTO* rs9939609 genotyping was done by an Illumina system (Illumina, Inc, San Diego, California) using the GoldenGate technology (GoldenGate Software, Inc, San Francisco, California). The genotyping success rate was 100%. The genotype distribution respected Hardy-Weinberg equilibrium ($P = .56$).

STATISTICAL ANALYSIS

The genotypes were coded as an ordinal variable (ie, 0 = TT, 1 = TA, 2 = AA). We analyzed the differences in body fat estimates (BMI, body fat percentage, and waist circumference) between the 3 *FTO* rs9939609 genotypes with an additive model using a mixed-effects linear regression model with random intercept allowing the center effects to be random and with age and sex as potential confounders (fixed effects). To test for the existence of an interaction between the *FTO* rs9939609 polymorphism and moderate to vigorous physical activity (<60 min/d and ≥ 60 min/d) on body fat estimates (BMI, body fat percentage, and waist circumference), we used the same model but added the cross-product term *FTO* \times physical activity. Finally, we repeated the analyses stratified by moderate to vigorous physical activity categories (<60 min/d and ≥ 60 min/d of moderate to vigorous physical activity).

Analyses were performed using SPSS version 16.0 statistical software for Windows (SPSS Inc, Chicago, Illinois). The level of significance was set to .05 for all but the interaction effect, which was considered to .10.

RESULTS

Characteristics of the study sample are shown in the **Table**. Genotype frequencies were 275 (0.37%), 354

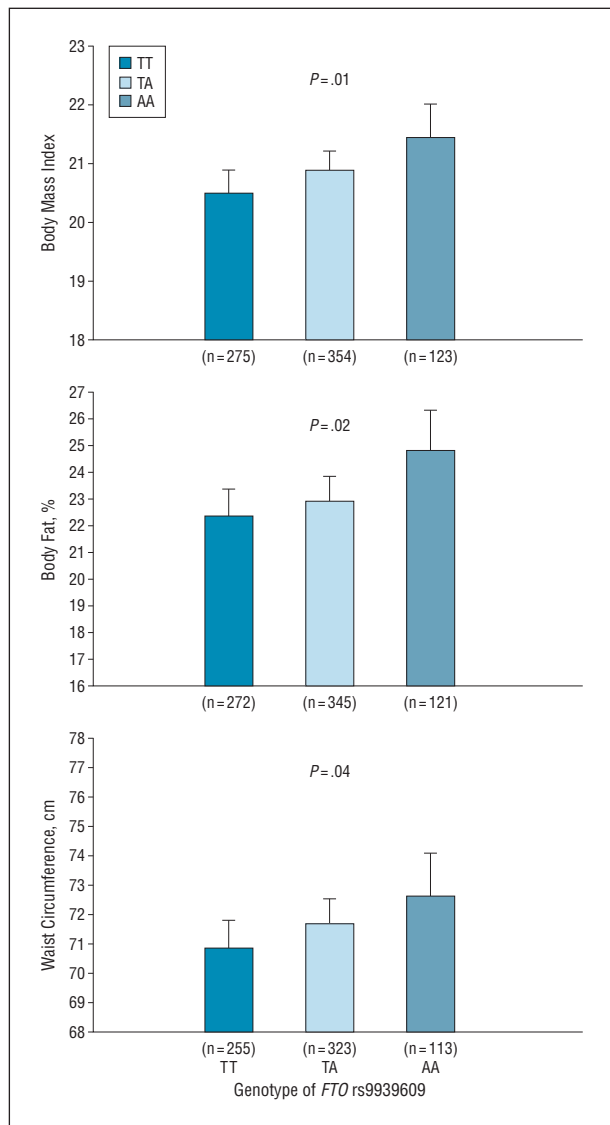


Figure 1. Association between the *FTO* polymorphism rs9939609 and mean body mass index (calculated as weight in kilograms divided by height in meters squared), body fat percentage, and waist circumference. Error bars indicate 95% confidence intervals. Values are adjusted for center, sex, and age.

(0.47%), and 123 (0.16%) for the TT, TA, and AA genotypes, respectively.

ASSOCIATION BETWEEN THE *FTO* rs9939609 POLYMORPHISM AND BODY FAT ESTIMATES

We observed that the minor A allele of the *FTO* polymorphism was significantly associated with higher BMI (+0.42 per risk allele; 95% confidence interval [CI], 0.10 to 0.75; $P=.01$), higher body fat percentage (+1.03% per risk allele; 95% CI, 0.19 to 1.88; $P=.02$), and higher waist circumference (+0.85 cm per risk allele; 95% CI, 0.04 to 1.66; $P=.04$) after adjusting for age, sex, and center (**Figure 1**).

INTERACTION BETWEEN THE *FTO* rs9939609 POLYMORPHISM AND PHYSICAL ACTIVITY

We did not observe significant differences among the *FTO* genotypes in time spent participating in moderate

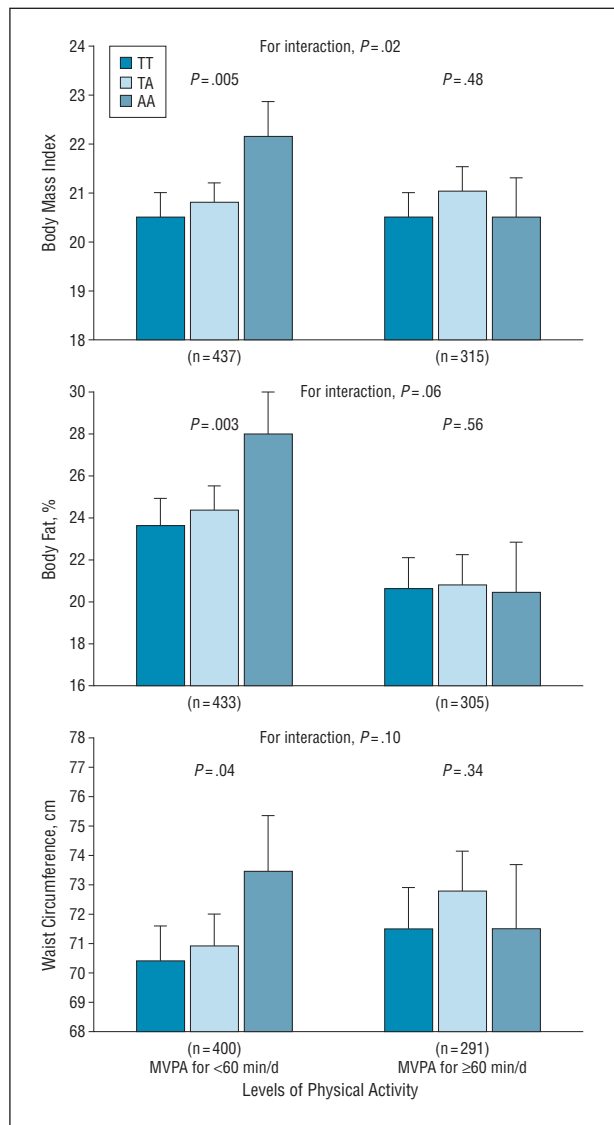


Figure 2. Interaction effect between the *FTO* polymorphism rs9939609 and levels of moderate to vigorous physical activity (MVPA) (<60 min/d vs ≥ 60 min/d) on mean body mass index (calculated as weight in kilograms divided by height in meters squared), body fat percentage, and waist circumference. Error bars indicate 95% confidence intervals. Values are adjusted for center, sex, and age.

to vigorous physical activity (mean [SD], 61.2 [24.1], 57.1 [23.2], and 60.1 [24.3] min/d for the TT, TA, and AA genotypes, respectively; $P=.54$). We observed significant interactions between the *FTO* polymorphism and physical activity (<60 and ≥ 60 min/d of moderate to vigorous physical activity) when considering BMI (for interaction, $P=.02$), body fat percentage (for interaction, $P=.06$), or waist circumference (for interaction, $P=.10$). Indeed, in those adolescents who spent less than 60 min/d participating in moderate to vigorous physical activity ($n=441$ [59%]), the A allele of the *FTO* polymorphism was significantly associated with higher BMI (+0.65 per risk allele; 95% CI, 0.21 to 1.10; $P=.005$), higher body fat percentage (+1.70% per risk allele; 95% CI, 0.58 to 2.81; $P=.003$), and higher waist circumference (+1.15 cm per risk allele; 95% CI, 0.04 to 2.26; $P=.04$) after adjusting for center, sex, and age (**Figure 2**). In contrast, in those adolescents who

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spent at least 60 min/d participating in moderate to vigorous physical activity (n=311), the A allele of the *FTO* polymorphism was not associated with higher BMI (+0.17 per risk allele; 95% CI, -0.31 to 0.66; P=.48), body fat percentage (+0.40% per risk allele; 95% CI, -0.92 to 1.73; P=.56), or waist circumference (+0.60

cm per risk allele; 95% CI, -0.63 to 1.82; P=.34) after adjusting for center, sex, and age (Figure 2).

The results were similar in boys and girls and were similar when we adjusted for pubertal status instead of age (data not shown). Likewise, the results did not change after further adjusting for height squared in those mod-

els where waist circumference was involved (data not shown).

COMMENT

As expected, the minor A allele of rs9939609 was associated with higher levels of BMI, body fat percentage, and waist circumference in our adolescent population. We observed a gene \times physical activity interaction for all of the study's body fat estimates, and the stratified analyses (<60 and ≥ 60 min/d of moderate to vigorous physical activity) revealed that the minor A allele was not associated with BMI, body fat percentage, or waist circumference in those adolescents who spent at least 60 min/d participating in moderate to vigorous physical activity. These findings have important public health implications and indicate that meeting the physical activity recommendations may offset the genetic predisposition to obesity associated with the *FTO* polymorphism in adolescents.

The results of this study are consistent with the findings of previous studies showing an association between *FTO* polymorphisms and obesity-related traits in different ethnic populations in adults, adolescents, or children.⁵⁻¹⁰ Further, we confirm that the association between the *FTO* rs9939609 polymorphism and adiposity estimates was attenuated once we took into account the levels of physical activity assessed by accelerometry.

To our knowledge, our study is the first to report an interaction between the *FTO* rs9939609 polymorphism and physical activity level on adiposity indices using objectively assessed physical activity in adolescents. Indeed, this study replicates previous findings of gene \times physical activity interaction in adults.¹¹⁻¹³ Vimalaswaran et al¹¹ reported an interaction between the *FTO* rs1121980 polymorphism and self-reported physical activity on BMI ($P = .004$) and waist circumference ($P = .02$) in 20 374 adults from the European Prospective Investigation Into Cancer and Nutrition-Norfolk Study. They showed a reduced but still significant ($P < .001$) effect of the *FTO* rs1121980 polymorphism on both BMI (+0.25 per risk allele) and waist circumference (+0.64 cm per risk allele) in physically active individuals compared with the inactive group (BMI, +0.44 per risk allele; waist circumference, +1.04 cm per risk allele). A similar effect size was observed in the Inter99 study composed of 5554 middle-aged Danish individuals.¹² Andreassen et al¹² also found an interaction between the *FTO* rs9939609 polymorphism and self-reported physical activity (for interaction, $P = .007$). Rampersaud et al¹³ observed an interaction between the *FTO* rs1861868 polymorphism and objectively assessed physical activity (for interaction, $P = .01$) in 704 Old Order Amish individuals. They reported that the increase per risk allele in BMI was attenuated in individuals in the upper half of the physical activity distribution (+0.30 per risk allele) compared with individuals within the lower half of the physical activity distribution (+1.12 per risk allele). Despite participants' differences in age and ethnicity, the effect sizes observed in our study are similar to those reported previously.

Our findings do not concur, however, with other studies that failed to observe an interaction between the *FTO* polymorphism and physical activity.¹⁴⁻¹⁶ For example,

Hakanen et al¹⁶ found no interaction between the *FTO* rs9939609 polymorphism and leisure-time physical activity in 438 Finnish adolescents aged 15 years. It is worth noting that most of the earlier-mentioned studies¹¹⁻¹⁶ assessed physical activity by a self-reported questionnaire, whereas we assessed physical activity by an objective method (ie, accelerometry). It is known that the assessment of physical activity by questionnaire may have lower accuracy, especially in young people.^{27,28} In epidemiologic research, self-reported questionnaires are common tools to assess physical activity level because they are easy to use and inexpensive. However, the sporadic nature of youths' physical activity makes these activities difficult to recall, quantify, and categorize. Also, youths have a lesser ability to accurately recall intensity, frequency, and especially duration of the activities.²⁷

Findings from our study should be taken with caution owing to its cross-sectional nature. Lifestyle intervention studies in adolescents are needed to determine to what extent the effect of *FTO* on obesity-related traits can be modified, especially in genetically predisposed individuals. Findings from lifestyle intervention studies in adults are promising. Franks et al²⁹ reported that the genetic (*FTO* rs9939609 polymorphism) effect on subcutaneous adipose tissue gain tended to be attenuated ($P = .05$) after a 1-year program of intensive lifestyle intervention.

In conclusion, our results suggest that physical activity can ameliorate the deleterious effect of the *FTO* rs9939609 polymorphism on body fat estimates in adolescents. Indeed, adolescents meeting the daily physical activity recommendations may overcome the effect of this gene on obesity-related traits.

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