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Association of *FTO rs1421085* with obesity, diet, physical activity and socioeconomic status: a longitudinal birth cohort study

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Keywords: *FTO rs1421085*; obesity; diet; cardiorespiratory fitness; physical activity; socioeconomic status

ABSTRACT

Background and aims

FTO variants are among genetic variants frequently associated with obesity. We analyzed the association between *FTO rs1421085* polymorphism and obesity, dietary intake, cardiorespiratory fitness, physical activity and socioeconomic status (SES) from age 9 to 25 years.

Methods and results

The sample included both birth cohorts (originally n = 1176) of the Estonian Children Personality Behaviour and Health Study. The association between *FTO rs1421085* and obesity, dietary intake, cardiorespiratory fitness, physical activity and SES from age 15 to 25 years was assessed using linear mixed-effects regression models. Associations at ages 9 (younger cohort only), 15, 18 and 25 years were assessed by one-way ANOVA.

Male C-allele carriers had significantly ($p < 0.05$) higher body mass index (BMI), sum of 5 skinfolds, body fat percentage and hip circumference from age 15 to 25 years. Findings were similar at age 9 years. In female subjects, waist-to-hip ratio was significantly greater in CC homozygotes. Interestingly, female CC homozygotes had a greater decrease in the rate of change in daily energy intake and lipid intake per year and higher physical activity score at every fixed time point. Moreover, in females, an effect of *FTO* × SES interaction on measures of obesity was observed.

Conclusion

The *FTO rs1421085* polymorphism was associated with obesity and abdominal obesity from childhood to young adulthood in males, and with abdominal obesity from adolescence to young adulthood in females. This association is rather related to differences in adipocyte energy metabolism than lifestyle.

INTRODUCTION

Obesity is a major public health concern, which affected more than 600 million adults in year 2015 [1]. High body mass index (BMI) is a risk factor for several chronic diseases, whereas cardiovascular disease and diabetes are the leading causes of deaths related to high BMI [1]. Obesity is a multifactorial condition with no single linear cause-and-effect, and factors like genetics, biology, individual behaviours, environment and larger societal forces playing a role [2].

The application of genome wide association studies (GWAS) more than 10 years ago enabled to find associations between several genetic variants and different traits [3].

In humans, the gene encoding fat mass and obesity-associated protein (*FTO*) is located in chromosome 16, is over 400 kb in size, and has 9 exons [4]. The *FTO* gene was originally identified in 1999 in a fused-toe mouse model, and called *Fatso* because of its size [5]. In year 2007 a GWAS by Frayling et al. first demonstrated the association between *FTO* *rs9939609* single nucleotide polymorphism (SNP) and obesity [6]. In the same year, these findings were confirmed by two other research groups [7,8]. Subsequently, several GWAS have affirmed the association between different *FTO* SNPs and BMI in children and adults [9–11]. While the studies on *FTO* genotype have addressed different variants and analysed different variables, some of the variants, e.g., *rs1421085*, *rs17817449* and *rs9939609*, are in strong linkage disequilibrium (pairwise r^2 0.85–97) [12,13] and will thus be discussed together.

It is difficult to estimate the contribution of genes to BMI variability as heritability estimates of BMI differ ranging from 0.24 to 0.81 in family studies and 0.47 to 0.90 in twin studies [14]. There is also evidence of a genotype-age and genotype-environment interaction that

contribute to BMI variation [15]. Previous reports about the complex biological mechanism of *FTO* intronic variants have been inconclusive. It is probable that multiple factors associated with both energy consumption and expenditure are involved. Several studies have been conducted to assess the association between *FTO* variants and eating behaviour. Stutzmann et al. (2009) did not find an association between *FTO rs1421085* genotype and snacking or eating large amounts of food in adolescence and adults with European ancestry [16] whereas Wardle et al (2009) found that the common *FTO rs9939609* T-allele is protective of overeating among children aged 4–5 years [17]. *FTO rs1421085* C-allele has been associated with higher perceived hunger score [18], but *FTO rs9939609* was not associated with altered postprandial responses in hunger hormones and metabolic flexibility [19]. Inversely, *FTO rs9939609* (or a proxy) risk allele has been associated with lower energy intake and lower fat and protein intake, when adjusted to body weight [20]. A study by Claussnitzer et al. (2015) demonstrated a role of *FTO rs1421085* C-allele in *IRX3* and *IRX5* expression in preadipocytes, whereas higher expression was associated with reduced white adipocyte browning, resulting in reduced mitochondrial thermogenesis [21]. There is also evidence that the effect of *FTO* may be modified by environment. Importantly, Foraita et al. (2015) observed an interaction between SES and *FTO rs9939609* in childhood obesity [22]. Although evidence for the association between *FTO* intronic variants and obesity is strong, the biological mechanism and the age when the differences occur are still unknown. In previous studies the C-allele of the *FTO rs1421085* gene has been proposed as the risk allele [18], so in the present this study we aimed at clarification of the association between the *FTO rs1421085* C-allele and measures of obesity and abdominal obesity with examining also dietary intake, cardiorespiratory fitness, physical activity and socioeconomic status from childhood to young adulthood in a longitudinal birth cohort study.

METHODS

Study sample

The study sample consisted of both birth cohorts of the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS) (Table 1). The sample was originally formed for the European Youth Heart Study (years 1998/1999) and was subsequently incorporated into ECPBHS. The rationale and procedure for the original sample formation has been described in detail elsewhere [23]. In brief, all schools of Tartu County, Estonia, that agreed to participate (54 of the total of 56) were included into the sampling and 25 schools were selected in order to reach the intended n = 1000. All children from grades 3 (younger birth cohort, aged 9 years) and grades 9 (older birth cohort, aged 15 years) were invited to participate [24]. Follow-up studies for the younger birth cohort took place in age 15 years (n = 483), 18 years (n = 454) and 25 years (n = 441) and for the older birth cohort in age 18 years (n = 417 + additional 62) and 25 years (n = 541). Hence, even while accounting for the attrition the sample still comprises more than 60% of the original sampling target. The cohorts are merged in the analyses because previous studies have revealed no evidence of body composition regulation being related to birth cohort [25,26]. Sample for this analysis excluded pregnant individuals (2 at age 18 and 25 at age 25). Written informed consent was obtained from the subjects and, in case of subjects under the age 18, also from their parents. Data were collected and measurements made during a laboratory visit unless indicated otherwise. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu (license numbers 49/30, 151/11, 197T-14, 235/M-20) and was conducted in accordance with the Declaration of Helsinki.

Anthropometric measurements

Height and body weight were measured using standardized procedures by experienced researchers (mostly by the same person throughout the longitudinal study), and BMI was calculated. A Harpenden caliper (Baty, West Sussex, England) was used to measure skinfold thickness from the left side of the body at the biceps, triceps, subscapular, suprailiac and medial calf areas. Body fat percentage (BF%) was calculated using a formula based on values of skinfold thickness (biceps, triceps, subscapular, suprailiac) [27,28]. Waist circumference was measured between the lower rib margin and the iliac crest, at the end of gentle expiration. Hip circumference was measured over the buttocks, at the level of the great trochanter. Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated. All anthropometrical measurements were taken twice and a mean value was used in the analysis.

Dietary intake

The subjects were asked to complete a 24h (year 1998), 48h (years 2001, 2004, 2007) or 72h (years 2008, 2014) diet record at home during the day(s) before the study day. On the study day a face-to-face interview, using pictures of portion sizes [29], was performed to specify portion sizes that were not recorded in the food diary. Where data on two or three days was available the mean consumption was calculated. To assess dietary intake the Finnish Micro-Nutrica Nutritional Analysis program (Estonian version 2.0, Tallinn University of Technology, Food Processing Institute, Estonia) and the Estonian NutriData food consumption database (versions 4.0–7.0, National Institute for Health Development, Estonia) were used [25].

Cardiorespiratory fitness and physical activity score

Cardiorespiratory fitness (CRF) has been reported as a strong predictor of numerous health outcomes and all-cause mortality [30]. CRF was defined as maximum power output (MPO) per kilogram of body weight (MPO/kg) and determined by a maximum cycle-ergometer test. The protocol for CRF originates from the European Youth Heart Study and has been validated against direct measurement of VO_2max. The correlation between VO_2max measurements and the maximum power output was 0.96 [31]. The procedure of the cycle-ergometer test has been described in detail elsewhere [32]. In short, after a warming up period of 3 minutes, subjects pedaled at a self-selected rate between 60–80 rpm. The initial workload for male subjects was set at 50 W, increasing by 50 W every 3 minutes and the initial workload for female subjects was set at 40 W, increasing by 40 W every 3 minutes until exhaustion. Participants were encouraged by the researcher throughout the cycle-ergometer test and monitored by medical personnel to achieve their maximal performance safely. The following formula was used to calculate MPO: W1 + (W2 × t/180), where W1 is the work rate at the last fully completed stage, W2 is the work rate increment at the final incomplete stage, and t is the time in seconds at the final incomplete stage.

Physical activity levels were evaluated using self-reported and parent-reported questionnaires. At ages 9 and 15 years the questions included participation in training groups and physical activity lessons and self-evaluated physical activity patterns. Questions reflecting participation in training groups and parent-reported physical activity patterns were included at age 18 years. At age 25 years questions including the number of days during the previous week that participants were active for at least 30 minutes and number of days, that participants were involved in work related moderate to vigorous physical activity, were used. For each answer option a numerical value was given, and individual

physical activity scores were computed. The number of questions and thus the possible maximal physical activity score varied in different age points. To account for that physical activity scores were standardized and z-scores were used in longitudinal analysis.

Socioeconomic status score

Self-reported and parent-reported questionnaires were used to assess socioeconomic status (SES). To calculate a SES score, questions about parental education level (ranging from primary and basic education to higher education), total household income (divided into income groups) and self-reported or parent reported SES compared to peers (ranging from poor to among the wealthiest in the country) were used at ages 15 and 18 years. At age 25 years, questions about level of education of the subject, total household income and self-reported SES assessment compared to peers, was used. Individual SES scores were calculated by matching a numerical value for each answer option. SES scores were standardized and z-scores were used in longitudinal analysis.

Genotyping of *FTO rs1421085*

Genomic DNA was extracted from venous blood samples using Qiagen QIAamp® DNA Blood Midi Kit. The real-time polymerase chain reaction (RT-PCR) for genotyping the *FTO rs1421085* polymorphism was performed using a TaqMan Pre-Designed SNP Genotyping Assay (Applied Biosystems; Foster City, CA, USA) C___8917103_10 containing primers and fluorescent probes. Genotyping reactions were performed in a total volume of 10 µl with ~25 ng of template DNA. RT-PCR reaction components and final concentrations were as follows: 1:5 5 x HOT FIREPol® Probe qPCR Mix Plus (ROX) (Solis BioDyne) and 1:20 80 x

TaqMan Primers Probe. Context sequence [VIC/FAM] was as follows: TAGCAGTTCAGGTCCTAAGGCATGA[C/T]ATTGATTAAGTGTCTGATGAGAATT.

Reactions were performed on the Applied Biosystems ViiA™ 7 Real-Time PCR System. The amplification procedure consisted of an initial denaturation step at 95 °C for 12 min and 40 cycles of 95 °C for 15 s and 60 °C for 1 min. Positive and negative controls were added to each reaction plate. No inconsistencies occurred. Genotyping was performed blind to all phenotypic data.

Statistical analysis

Statistical analysis was performed using Stata software, version 14 (StataCorp LP, College Station, Texas, USA). Significance level was set at 0.05. Linear mixed-effects regression models with random intercept and random slope which account for the correlations between repeated measurements within each individual and use all available observations [33], were fitted to estimate the longitudinal association between *FTO rs1421085* genotype and obesity, abdominal obesity, dietary intake and SES score from 15 to 25 years of age. Models with random intercept and slope allow individual variation not only in baseline values, but also in terms of mean response over time, giving the model more flexibility to fit the data [34].

Models for measures of obesity and abdominal obesity were later adjusted to daily energy intake, standardized physical activity score and standardized socioeconomic status (sSES) × *FTO* interaction. Due to non-linearity a mixed-effects regression model with quadratic trends was fitted to estimate the association between *FTO*, CRF and physical activity score. Models with sex × *FTO* and sex × time interactions were fitted to test if the effect of *FTO* genotype is different in male and female subjects.

Measurements of obesity, abdominal obesity, dietary intake, physical activity and SES at baseline (age 15 years) and at follow up points (18 years and 25 years) were defined as the dependent variables. *FTO rs1421085* genotype (TT, TC, CC) was defined as the independent variable. TT-homozygotes were used as the reference group. Time was treated as a continuous variable.

The likelihood-ratio (LR) test was used to assess the goodness of fit of the statistical models. Where interaction with time was not significant and the LR test did not show superiority of the more complicated model, interaction with time was not included in the final model. Unstructured covariance structure and restricted maximum likelihood method was used. Heteroscedasticity was not detected based on graphical examination of standardized residual versus fitted values plot.

Continuous variables are presented as means and standard deviations and grouped by *FTO rs1421085* genotype, age and sex. Differences in anthropometric measurements, dietary intake and physical activity between *FTO rs1421085* genotype at ages 9, 15, 18 and 25 years were assessed by one-way ANOVA. The p values obtained from the pairwise comparisons were corrected by the Bonferroni method.

RESULTS

FTO rs1421085 genotype distribution

All necessary data for analyses was available at different ages as follows: 15 years n = 1074 (male 44.7%), 18 years n = 914 (male 43.8%) and 25 years n = 925 (male 45.2%). The distribution of TT, CT and CC genotypes of the *FTO rs1421085* was 31.2%, 48.3%, 20.5% respectively, the C-allele frequency was 0.45. Allele frequencies agree with National Center for Biotechnology Information database (C-allele frequency 0.45 for Estonia) and published

reports on European ancestry. This is on the higher end of worldwide prevalence. The lowest C-allele frequency in the NCBI database is for Vietnamese (0.15). There was no significant difference in the distribution of genotype frequencies at age 15 years between male (TT = 153, 31.9%; TC = 230, 47.9%; CC = 97, 20.2%) and female (TT = 182, 30.6%; TC = 289, 48.7%; CC = 123, 20.7%) subjects (χ^2 test, p = 0.909). Genotype frequencies were in Hardy–Weinberg equilibrium.

Measurements of obesity

According to the linear mixed-effects regression model male TC heterozygotes had significantly ($p < 0.05$) higher body weight and TC heterozygotes and CC homozygotes had higher BMI, sum of 5 skinfolds and BF%, compared to TT homozygotes at each time point (Figure 1). Similar effect was observed in the adjusted models. The rate of change among male subjects in body weight was 1.92 kg (95% CI 1.83 to 2.01), in BMI 0.46 kg/m^2 (95% CI 0.43 to 0.48), in sum of 5 skinfolds 2.38 mm (95% CI 2.10 to 2.67) and in BF% 0.21 % (95% CI 0.15 to 0.26) per year (Table 2). In female subjects the rate of change in body weight and sum of 5 skinfolds per one unit rise in the SES score differed significantly ($p < 0.05$) between TT homozygotes and CC homozygotes in the adjusted model (Tables 2–3).

Interaction terms for sex × *FTO* were significant ($p < 0.05$) for sum of 5 skinfolds and BF% and a trend ($0.05 \leq p < 0.10$) for BMI was observed. The interaction terms for sex × time were significant ($p < 0.05$) for body weight, BMI, sum of 5 skinfolds and BF%.

One-way ANOVA test at ages 9, 15, 18 and 25 years revealed that male CC homozygotes had significantly higher BMI (by 0.84 kg/m^2, 95% CI 0.02 to 1.65, p = 0.042), compared to TT homozygotes and greater sum of 5 skinfolds compared to TC heterozygotes (by 4.50 mm, 95% CI 0.27 to 8.72, p = 0.033) and TT homozygotes (5.88 mm, 95% CI 0.45 to 11.31, p =

0.029) at age 9 years. Male TC heterozygotes had significantly higher sum of 5 skinfolds (by 6.43 mm, 95% CI 1.63 to 11.23, p = 0.004) and BF% (by 1.65 %, 95% CI 0.46 to 2.84, p = 0.003) at age 15 years compared to TT homozygotes. At age 18 years both CC homozygotes and TC heterozygotes had significantly higher sum of 5 skinfolds (by 11.47 mm, 95% CI 1.24 to 21.70, p = 0.022; 10.87 mm, 95% CI 2.84 to 18.90, p = 0.004) and BF % (by 2.21 %, 95% CI 0.13 to 4.29, p = 0.033; 2.10 %, 95% CI 0.46 to 3.75, p = 0.007) compared to TT homozygotes, respectively. No statistically significant associations were observed by one-way ANOVA between *FTO rs1421085* genotype and measures of obesity in female subjects (Supplementary Tables 1–4).

Measurements of abdominal obesity

Hip circumference measure was significantly ($p < 0.05$) higher in male CC homozygotes and TC heterozygotes, compared to TT homozygotes at each time point. In the adjusted models, similar effect was observed. The rate of change among male subjects in hip circumference was 1.13 cm (95% CI 1.07 to 1.19) per year (Table 2). In female subjects, at each time point, WHR was significantly ($p < 0.05$) greater in CC homozygotes compared to TT homozygotes. The rate of change among female subjects in WHR was 0.003 units (95% CI 0.002 to 0.003) per year (Table 2). In the adjusted model a significant difference ($p < 0.05$) in the rate of change per one unit rise in the SES score between TT homozygotes and CC homozygotes in waist circumference, hip circumference and WHtR in female subjects was observed (Tables 2–3).

Interaction terms for sex × *FTO* were significant ($p < 0.05$) for hip circumference and WHR. The interaction terms for sex × time were significant ($p < 0.05$) for waist circumference, hip circumference, WHR, and WHtR.

One-way ANOVA test at ages 9, 15, 18 and 25 years demonstrated that male CC homozygotes had significantly higher hip circumference (by 2.54 cm, 95% CI 0.26 to 4.81, p = 0.023) at age 9 years and TC heterozygotes had significantly larger hip circumference (by 2.00 cm, 95% CI 0.11 to 3.89, p = 0.034) at age 18 years, compared to TT homozygotes. One-way ANOVA test did not identify any significant associations between measures of abdominal obesity and *FTO rs1421085* genotype in female subjects (Supplementary Tables 1–4).

Dietary intake

Models for male subjects demonstrated that TC heterozygotes had significantly ($p < 0.05$) lower protein and lipid intake in grams per kilogram of body weight (g/kg) and a lower lipid intake as a percentage from daily energy intake (E%), compared to TT homozygotes. The rate of change among male subjects was in protein intake -0.02 g/kg (95% CI -0.02 to -0.01), in lipid intake -0.05 g/kg (95% CI -0.06 to -0.04) and in lipid intake 0.01 E% (95% CI -0.9 to 0.10) per year (Table 4). In female subjects, linear mixed-effects regression models showed a significant difference in the rate of change per year in daily energy intake (kcal) (p = 0.04 for interaction) and lipid intake (g/kg) (p = 0.035 for interaction) between female CC homozygotes and TT homozygotes (Table 4), the former having a larger decrease in the rate of change per year in both daily energy intake (kcal) and lipid intake (g/kg) (Figure 1, Table 5).

One-way ANOVA test at ages 9, 15, 18 and 25 years demonstrated that at age 25 years female CC homozygotes had significantly higher protein intake (E%) (by 1.28 %, 95% CI 0.16 to 2.40, p = 0.019) compared to TT homozygotes. One-way ANOVA did not identify

statistically significant associations between *FTO rs1421085* genotype in male subjects (Supplementary Tables 5–8).

Cardiorespiratory fitness and physical activity score

According to the mixed-effects regression models with quadratic trends a trend ($p \geq 0.05 < 0.1$) in MPO/kg between TC heterozygotes and TT homozygotes was observed, but with opposite direction in male and female subjects. Physical activity score was 0.162 units (95% CI 0.003 to 0.321, p = 0.046) greater in female CC homozygotes compared to TT homozygotes in every fixed timepoint (Figure 1, Table 6).

One-way ANOVA test at ages 9, 15, 18 and 25 years did not demonstrate a statistically significant difference in CRF or physical activity score between *FTO rs1421085* genotypes in male or female subjects (Supplementary Tables 9–12).

Socioeconomic status score

Models for male subjects demonstrated that TC heterozygotes and CC homozygotes had higher standardized SES score at each time point. The rate of change among male subjects in standardized SES was –0.01 units (95% CI –0.02 to 0.01) per year (Table 7). No difference was found among female subjects (Table 7).

One-way ANOVA test at ages 9, 15, 18 and 25 years demonstrated that at age 25 years male CC homozygotes had significantly higher SES score (by 0.86 units, 95% CI 0.06 to 1.67, p = 0.030) and standardized SES score (by 0.34 units, 95% CI 0.02 to 0.65, p = 0.030) compared to TT homozygotes. No statistically significant associations between *FTO rs1421085* genotypes were identified in female subjects by one-way ANOVA (Supplementary Tables 13–15).

DISCUSSION

We observed that male *FTO rs1421085* C-allele carriers had significantly higher body weight, BMI, sum of 5 skinfolds, BF%, and hip circumference from 15 to 25 years of age with no interaction with time; in fact, these associations were present already at age 9 as cross-sectionally analyzed in the single birth cohort studied at that age. In female subjects WHR was significantly higher in CC homozygotes compared to TT homozygotes throughout the study period. A meta-analysis by Hertel et al. (2011) found similar results, when assessing the relationship between *FTO* rs9939609, type 2 diabetes, and BMI across the life span in 41,504 Scandinavians. *FTO* r*s9939609* genotype had a strong effect on BMI (0.28 kg/m^2 per risk allele [$P = 2.0 \times 10^{-26}$] with no *rs9939609* × age interactions on obesity-related traits. They concluded that the effect of *FTO rs9939609* is already present in youth, setting a threshold for BMI, and staying relatively stable across adulthood [35]. The Baltimore Longitudinal Study of Aging observed a dose-dependent relationship between *FTO rs1421085* and body mass index during ageing, where BMI was highest in CC homozygotes and lowest in TT homozygotes [36]. Interestingly, the trajectories of BMI over time significantly differed between *FTO rs1421085 genotype* ($\chi 2 = 13.7$, df = 4,P= 0.008) [36]. Several GWAS have observed an association between *FTO* intronic variants and BMI variation in children [10,37,38] and adults [9,11], but the onset of the effect is still unknown. Barton et al. (2016) demonstrated that higher placental FTO expression was associated with faster fetal growth between 11 and 34 weeks gestation where *FTO rs9939609* AA homozygous fetuses had faster biparietal diameter and head circumference velocities, but not abdominal circumference growth velocity [39]. However no significant association between *FTO* SNPs and birth weight has been noted [40,41].

FTO is expressed in various tissues throughout the body [6,7,42,43] whereas its levels are particularly high in the hypothalamus [42,43]. Therefore, several studies have assessed the association between *FTO* intronic variants and dietary intake. In mice, FTO overexpression has been associated with obesity and increased in food intake [44]. *FTO* rs1421085 risk allele has also been associated with greater perceived hunger scores ($p = 0.007$) [18]. Harbron et al. (2014) showed that *FTO* rs17817449 GG homozygote individuals had higher intake of high-fat foods (1.74, SE 0.87, $p = 0.049$) and refined starches (0.67, SE 0.30, $p = 0.029$), but no significant association was found with consumption of energy dense drinks or snacks [18]. We observed that female *FTO rs1421085* CC homozygotes had a greater decrease in the rate of change in daily energy intake (kcal) and lipid intake (g/kg) per year from age 15 to 25 years, compared to TT homozygotes. We also found a lower protein (g/kg) and lipid (g/kg) intake and a lower lipid intake (E%), in male heterozygotes, compared to TT homozygotes. Similar results were observed by Livingston et al. (2015) in a systematic review and a meta-analysis, which demonstrated that *FTO* risk allele carriers had significantly lower energy intake ($p = 0.028$) and total fat ($p = 0.004$), carbohydrate ($p = 0.005$) and protein ($p = 0.001$) intake, when adjusted for body weight [20].

Although intronic variants in the *FTO* gene have not been associated with physical activity [45,46], the effect of *FTO* risk allele on obesity has shown to be decreased by physical activity [46,47]. Kilpeläinen et al. (2011) conducted a random effects meta-analysis of cross-sectional data of 218 166 adults and 19 268 children to assess if physical activity affects the effect of *FTO* on obesity. The *FTO rs9939609* SNP or a proxy with linkage disequilibrium $r^2 > 0.8$ in each study was used. They found that physical activity reduces the effect of *FTO* on BMI (p for interaction = 0.005), waist circumference (p for interaction = 0.002) and body fat percentage (p for interaction = 0.02) in adults [46]. In our study, we demonstrated that in

female subjects, physical activity scores were significantly greater in CC homozygotes compared to TT homozygotes in every fixed timepoint, but no statistically significant associations were identified in CRF between *FTO rs1421085* genotype.

The observed reduction in daily energy intake and significantly greater standardized physical activity score among female CC homozygotes from age 15 to 25 years led us to hypothesize that the lack of association in female subjects between *FTO rs1421085* genotype and measures of obesity might be due to lifestyle. Thus, models for measures of obesity and abdominal obesity were adjusted for daily energy intake and standardized physical activity score. Nevertheless, in females, differences in measure of obesity between *FTO* genotype were not observed in the adjusted models. Finally models with sex × *FTO* and sex × time interactions were fitted, which revealed sex and *FTO rs1421085* genotype interactions. Interestingly, we observed an interaction between *FTO rs1421085* genotype and standardized socioeconomic status (SES) score in female subjects, where increasing SES status score led to an increase in measurements of obesity in TT homozygotes, but to a decrease in CC homozygotes. An interaction between *FTO rs9939609* and SES was previously demonstrated by Foraita et al. (2015) in children, where TT homozygotes where more protected by a favourable socioeconomic environment [22]. The mechanism behind such interactions is not clear and should be explored if further studies confirmed the significance of either type of FTO genotype and SES interactions as reported previously [22] and herewith.

Abundant research has been conducted to assess the obesity increasing effect of *FTO* variants through nutrition and physical activity; however, no consistent relationship between *FTO rs1421085* and candidate mechanisms such as eating behaviour traits [16] and altered resting energy expenditure [48] has been found. Research by Claussnitzer et al.

(2015) instead demonstrated that the obesity increasing effect of *FTO rs1421085* SNP T to C causes a disruption in the ARID5B-mediated repression of *IRX3* and *IRX5* expression in preadipocytes which leads to excessive accumulation of triglycerides, increased adipocyte size, reduced mitochondrial oxidative capacity and reduced white adipocyte browning, resulting in reduced mitochondrial thermogenesis [21]. However, the authors did not assess whether carriers of the *FTO rs1421085* C-allele have lower energy expenditure.

The ECPBHS is a longitudinal birth cohort study with population representative sample and comprehensive data, but it has some limitations. The sample of ECPBHS consists of individuals of only European descent and therefore we cannot be sure if the associations are similar in other ethnicities. Additionally, the effect of *FTO rs1421085* genotype on markers of obesity and abdominal obesity in males could already be observed at age 9, the earliest age of observation, and thus we are unable to describe the age when the differences emerge.

Our findings confirm that the effect of *FTO rs1421085* genotype on markers of obesity is already manifested in childhood in males. In females, on abdominal obesity, from adolescence, remaining rather stable from adolescence to young adulthood with no genotype × time interaction. A sex × *FTO rs1421085* and sex × time interaction was also observed. Moreover, in female subjects SES × *FTO rs1421085* interaction was detected. Our findings indicate that the effect of *FTO* rs1421085 risk allele on obesity is not mediated by daily energy intake, macronutrient intake or physical activity, but can differ in age groups and sex and be modified by SES. When analyzing biological mechanisms behind *FTO* obesity increasing effect, further research should consider the potential effect modifying impact of sex, age and socioeconomic environment.

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COMPETING INTERESTS

The authors declare no competing financial interests.

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Table 1. Anthropometric measurements, dietary intake, cardiorespiratory fitness, physical activity score and socioeconomic status score (mean and SD) at age 15 years, 18 years and 25 years of the ECPBHS sample by *FTO rs1421085* genotype and age (n).

	15 years old			18 years old			25 years old		
	TT	**TC**	**CC**	**TT**	**TC**	**CC**	**TT**	**TC**	**CC**
Age (years)	15.2 ± 0.7 (335)	15.2 ± 0.7 (519)	15.2 ± 0.7 (220)	17.8 ± 0.7 (273)	17.9 ± 0.8 (455)	17.9 ± 0.9 (184)	24.7 ± 0.6 (282)	24.8 ± 0.6 (448)	24.8 ± 0.8 (194)
Height (cm)	169.5 ± 8.2 (335)	169.3 ± 8.3 (519)	169.5 ± 7.5 (220)	1737.7 ± 9.3 (268)	173.1 ± 9.0 (444)	173.0 ± 8.5 (177)	174.4 ± 9.4 (282)	173.9 ± 9.2 (447)	174.0 ± 8.7 (194)
Weight (kg)	58.5 ± 9.7 (335)	59.1 ± 10.2 (519)	59.6 ± 11.7 (220)	66.1 ± 11.5 (268)	66.4 ± 12.2 (444)	67.8 ± 13.8 (177)	71.7 ± 15.2 (282)	72.5 ± 15.6 (447)	74.1 ± 17.3 (194)
BMI (kg/m²)	20.3 ± 2.6 (335)	20.6 ± 2.8 (519)	20.7 ± 3.5 (220)	21.8 ± 2.8 (268)	22.1 ± 3.3 (444)	22.6 ± 4.0 (177)	23.4 ± 3.8 (282)	23.8 ± 4.1 (447)	24.4 ± 5.0 (194)
Waist (cm)	68.3 ± 5.8 (335)	68.8 ± 6.4 (519)	69.1 ± 7.5 (220)	73.2 ± 7.4 (268)	73.6 ± 8.5 (444)	74.0 ± 9.6 (177)	78.8 ± 11.0 (282)	79.7 ± 11.5 (447)	80.6 ± 12.2 (194)
Hip (cm)	90.1 ± 6.4 (333)	90.9 ± 6.6 (519)	90.8 ± 7.5 (220)	94.0 ± 6.7 (268)	94.6 ± 6.8 (444)	95.1 ± 8.3 (177)	98.8 ± 8.1 (282)	99.3 ± 8.7 (447)	100.0 ± 9.5 (194)
WHR (units)	0.76 ± 0.05 (333)	0.76 ± 0.05 (519)	0.76 ± 0.05 (220)	0.78 ± 0.06 (268)	0.78 ± 0.06 (444)	0.78 ± 0.06 (177)	0.80 ± 0.07 (282)	0.80 ± 0.07 (447)	0.80 ± 0.07 (194)
WHtR (units)	0.40 ± 0.03 (335)	0.41 ± 0.03 (519)	0.41 ± 0.04 (220)	0.42 ± 0.04 (268)	0.43 ± 0.04 (444)	0.43 ± 0.05 (177)	0.45 ± 0.06 (282)	0.46 ± 0.06 (447)	0.46 ± 0.06 (194)
Sum of 5 skinfolds (mm)	52.3 ± 24.1 (335)	55.5 ± 25.9 (519)	55.4 ± 28.3 (220)	65.6 ± 31.9 (268)	69.5 ± 33.5 (444)	73.5 ± 36.3 (175)	74.2 ± 35.8 (282)	76.6 ± 36.5 (446)	79.4 ± 40.0 (193)
Daily energy intake (kcal)	2236.0 ± 915.1 (331)	2196.5 ± 863.4 (518)	2249.0 ± 1017.4 (220)	2206.0 ± 905.7 (268)	2156.2 ± 906.0 (435)	2216.6 ± 814.3 (176)	2044.0 ± 786.6 (276)	1976.5 ± 696.8 (442)	1960.5 ± 688.9 (195)
Protein (g/kg)	1.2 ± 0.6 (331)	1.2 ± 0.5 (518)	1.2 ± 0.5 (220)	1.1 ± 0.5 (267)	1.1 ± 0.5 (435)	1.1 ± 0.4 (175)	1.1 ± 0.5 (273)	1.1 ± 0.4 (436)	1.1 ± 0.4 (192)
Lipids (g/kg)	1.5 ± 0.8 (331)	1.5 ± 0.7 (518)	1.5 ± 0.9 (220)	1.4 ± 0.6 (267)	1.3 ± 0.6 (435)	1.4 ± 0.6 (175)	1.2 ± 0.5 (273)	1.1 ± 0.5 (436)	1.1 ± 0.4 (192)
Carbohydrates (g/kg)	4.9 ± 2.2 (331)	4.8 ± 2.2 (518)	4.8 ± 2.1 (220)	4.0 ± 1.7 (267)	4.0 ± 1.7 (435)	3.9 ± 1.5 (175)	3.4 ± 1.4 (273)	3.2 ± 1.2 (436)	3.2 ± 1.2 (192)
Protein E%	12.9 ± 3.2 (331)	13.1 ± 3.1 (518)	13.1 ± 3.2 (220)	13.7 ± 3.1 (268)	13.7 ± 3.0 (435)	13.8 ± 2.8 (176)	15.9 ± 4.0 (276)	16.1 ± 4.0 (442)	16.3 ± 4.1 (195)
Lipids E%	35.2 ± 8.4 (331)	35.0 ± 8.0 (518)	35.3 ± 8.0 (220)	36.6 ± 7.6 (268)	35.5 ± 7.9 (435)	37.0 ± 7.0 (176)	35.9 ± 6.9 (276)	35.7 ± 6.2 (442)	35.4 ± 5.4 (195)
Carbohydrates E%	51.9 ± 9.4 (331)	51.9 ± 8.8 (518)	51.6 ± 8.9 (220)	48.8 ± 8.4 (268)	49.4 ± 8.9 (435)	48.5 ± 7.6 (176)	46.0 ± 8.6 (276)	46.1 ± 7.9 (442)	46.2 ± 8.0 (195)
MPO/kg	2.9 ± 0.8 (335)	2.9 ± 0.7 (514)	2.9 ± 0.7 (220)	2.5 ± 0.7 (254)	2.5 ± 0.7 (408)	2.4 ± 0.7 (167)	2.7 ± 0.7 (269)	2.7 ± 0.7 (424)	2.6 ± 0.8 (190)
Activity score	2.6 ± 1.1 (323)	2.7 ± 1.0 (498)	2.7 ± 1.1 (211)	1.2 ± 0.8 (246)	1.2 ± 0.8 (409)	1.2 ± 0.8 (159)	4.5 ± 3.1 (290)	4.4 ± 3.1 (460)	5.0 ± 3.2 (194)
Standardized activity score	–0.07 ± 1.00 (323)	0.02 ± 1.00 (498)	0.06 ± 1.03 (211)	–0.01 ± 1.00 (246)	–0.01 ± 1.0 (409)	0.03 ± 1.05 (159)	–0.02 ± 1.0 (290)	–0.03 ± 1.00 (460)	0.15 ± 1.02 (194)
SES score	14.7 ± 3.3 (242)	14.7 ± 3.4 (411)	14.6 ± 3.4 (165)	15.2 ± 4.0 (237)	15.6 ± 3.8 (396)	15.6 ± 3.7 (153)	14.1 ± 2.6 (285)	14.2 ± 2.5 (460)	14.6 ± 2.6 (187)
sSES score	–0.0001 ± 1.0 (242)	0.01 ± 1.0 (411)	–0.02 ± 1.0 (165)	–0.6 ± 1.0 (237)	0.03 ± 1.0 (396)	0.03 ± 1.0 (153)	–0.06 ± 1.0 (285)	–0.02 ± 1.0 (460)	0.14 ± 1.0 (187)

WHR – waist to hip ratio; WHtR – waist to height ratio; MPO – maximum power output; SES – socioeconomic status; sSES – standardized socioeconomic status

Table 2. Estimated main effects (mean and 95% CI) in male and female subjects of the ECPBHS sample in anthropometric measurements from 15 to 25 years of age between *FTO rs1421085* genotype according to the linear mixed effects regression model.

	MALE[3]			FEMALE[3]			MALE[3]			FEMALE[3]		
	Coeff.[1]	95% CI	p value	Coeff.[1]	95% CI	p value	Adjusted Coeff.[2]	95% CI	p value	Adjusted Coeff.[2]	95% CI	p value
Body weight (kg)												
TC genotype	2.199	0.160; 4.238	**0.035**	0.039	–1.699; 1.777	0.965	1.721	–0.459; 3.901	0.122	–0.309	–2.200; 1.582	0.749
CC genotype	2.137	–0.413; 4.687	0.100	1.623	–0.524; 3.771	0.139	1.687	–1.042; 4.415	0.226	1.560	–0.781; 3.901	0.191
CT genotype × sSES score							0.573	–0.844; 1.990	0.428	0.064	–1.006; 1.135	0.906
CC genotype × sSES score							–0.266	–2.093; 1.561	0.775	–1.400	–2.753; –0.046	**0.043**
BMI (kg/m^2)												
TC genotype	0.740	0.200; 1.280	**0.007**	0.083	–0.467; 0.633	0.767	0.619	0.040; 1.197	**0.036**	–0.011	–0.618; 0.596	0.973
CC genotype	0.836	0.160; 1.512	**0.015**	0.449	–0.231; 1.129	0.196	0.671	–0.053; 1.396	0.069	0.434	–0.318; 1.186	0.258
CT genotype × sSES score							0.054	–0.314; 0.422	0.773	–0.078	–0.436; 0.280	0.670
CC genotype × sSES score							–0.121	–0.593; 0.352	0.616	–0.392	–0.843; 0.060	0.089
Sum of 5 skinfolds (mm)												
TC genotype	8.046	3.957; 12.135	**< 0.001**	0.126	–4.461; 4.713	0.957	7.233	2.743; 11.722	**0.002**	–1.051	–6.037; 3.934	0.679
CC genotype	6.837	1.717; 11.956	**0.009**	2.965	–2.699; 8.630	0.305	5.911	0.284; 11.538	**0.039**	2.471	–3.705; 8.647	0.433
CT genotype × sSES score							1.031	–2.534; 4.596	0.571	–1.452	–5.050; 2.146	0.429
CC genotype × sSES score							1.304	–3.271; 5.879	0.576	–5.284	–9.776; –0.792	**0.021**
BF (%)												
TC genotype	1.682	0.751; 2.613	**< 0.001**	–0.004	–0.790; 0.782	0.992	1.492	0.472; 2.512	**0.004**	–0.241	–1.096; 0.613	0.580
CC genotype	1.590	0.426; 2.755	**0.007**	0.272	–0.699; 1.243	0.583	1.484	0.207; 2.761	**0.023**	0.098	–0.961; 1.157	0.857
CT genotype × sSES score							0.192	–0.604; 0.988	0.636	–0.179	–0.795; 0.437	0.568
CC genotype × sSES score							0.054	–0.963; 1.071	0.918	–0.712	–1.479; 0.055	0.069
WC (cm)												
TC genotype	0.986	–0.189; 2.161	0.100	0.482	–0.689; 1.653	0.420	0.782	–0.502; 2.066	0.232	0.298	–1.008; 1.605	0.654
CC genotype	1.173	–0.297; 2.642	0.118	1.157	–0.289; 2.603	0.117	0.715	–0.893; 2.323	0.383	1.248	–0.372; 2.868	0.131
CT genotype × sSES score							0.228	–0.720; 1.175	0.638	–0.223	–1.106; 0.661	0.621
CC genotype × sSES score							0.298	–0.915; 1.510	0.630	–1.473	–2.577; –0.370	**0.009**
HC (cm)												
TC genotype	1.860	0.649; 3.071	**0.003**	0.074	–1.108; 1.256	0.902	1.482	0.207; 2.756	**0.023**	0.052	–1.237; 1.341	0.937
CC genotype	1.524	0.009; 3.039	**0.049**	0.362	–1.098; 1.821	0.627	1.270	–0.326; 2.866	0.119	0.388	–1.206; 1.982	0.633
CT genotype × sSES score							0.329	–0.578; 1.236	0.477	0.153	–0.698; 1.004	0.724
CC genotype × sSES score							–0.207	–1.368; 0.953	0.726	–1.073	–2.138; –0.007	**0.048**
WHR (units)												
TC genotype	–0.0060	–0.0123; 0.0002	0.056	0.0046	–0.0021; 0.0113	0.181	–0.0051	–0.0118; 0.0016	0.133	0.0034	–0.0038; 0.0107	0.350
CC genotype	–0.0013	–0.0091; 0.0065	0.751	0.0088	0.0005; 0.0171	**0.037**	–0.0049	–0.0133; 0.0035	0.255	0.0095	0.0005; 0.0184	0.038
CT genotype × sSES score							0.0025	–0.0032; 0.0082	0.394	–0.0046	–0.0102; 0.0010	0.110
CC genotype × sSES score							0.0050	–0.0022; 0.0123	0.173	–0.0069	–0.0138; 0.0001	0.052

WHtR (units)												
TC genotype	0.0057	–0.0008; 0.0123	0.084	0.0032	–0.0036; 0.0100	0.360	0.0049	–0.0021; 0.0119	0.173	0.0026	–0.0051; 0.0103	0.515
CC genotype	0.0081	–0.0001; 0.0162	0.052	0.0056	–0.0029; 0.0140	0.196	0.0047	–0.0041; 0.0136	0.294	0.0061	–0.0034; 0.0157	0.210
CT genotype × sSES score							0.0001	–0.0050; 0.0052	0.967	–0.0021	–0.0073; 0.0030	0.419
CC genotype × sSES score							0.0014	–0.0051; 0.0079	0.677	–0.0072	–0.0137; –0.0008	**0.028**

[1]Coefficient (Coeff.) can be interpreted as the mean difference in anthropometrical measurements between *FTO rs1421085* TC and TT genotype or between CC and TT genotype at each timepoint

[2]Coefficient (Coeff.) can be interpreted as the mean difference, adjusted to daily energy intake, standardized physical activity score and *FTO* × sSES interaction, in anthropometrical measurements between *FTO rs1421085* TC and TT genotype or between CC and TT genotype at each timepoint

[3]Average sample size by sex and *FTO rs1421085* genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC= 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

Table 3. The rate of change per standardized socioeconomic status (sSES) score unit in anthropometric measurements (mean and 95% CI) in the female subjects of the ECPBHS sample according to the linear mixed effects regression model with *FTO rs1421085* genotype × sSES interaction.

	TT genotype	**TC genotype**	**CC genotype**
Body weight (kg)	0.176 (–0.646; 0.998)*	0.240 (–0.445; 0.925)	–1.224 (–2.299; –0.149)*
BMI (kg/m^2)	0.052 (–0.223; 0.328)#	–0.025 (–0.255; 0.204)	–0.339 (–0.697; 0.018)#
Sum of 5 skinfolds (mm)	2.510 (–0.270; 5.290)*	1.058 (–1.227; 3.344)	–2.774 (–6.303; 0.754)*
BF (%)	0.429 (–0.047; 0.905)#	0.250 (–0.141; 0.641)	–0.283 (–0.884; 0.318)#
WC (cm)	0.505 (–0.177; 1.187)*	0.282 (–0.280; 0.844)	–0.968 (–1.836; –0.101)*
HC (cm)	0.266 (–0.392; 0.923)*	0.419 (–0.122; 0.959)	–0.807 (–1.645; 0.031)*
WHR (units)	0.0018 (–0.0026; 0.0061)#	–0.0028 (–0.0063; 0.0008)	–0.0051 (–0.0105; 0.0003)#
WHtR (units)	0.0028 (–0.0012; 0.0067)*	0.0006 (–0.0027; 0.0039)	–0.0045 (–0.0095; 0.0006)*

* $p < 0.05$ significant difference in the rate of change between *FTO rs1421085* genotype TT and CC

$0.05 \leq p < 0.10$ trend in the rate of change between *FTO rs1421085* genotype TT and CC

Table 4. Estimated main effects (mean and 95% CI) in male subjects and estimated main and interaction effects (mean and 95% CI) in female subjects of the ECPBHS sample in daily energy intake (kcal), nutrient intake (g/kg) and nutrient intake as a percentage from daily energy intake (E%) from 15 to 25 years of age between *FTO rs1421085* genotype according to the linear mixed effects regression model.

	MALE[3]			FEMALE[3]		
	Coefficient[1]	**95% CI**	**p value**	**Coefficient**[2]	**95% CI**	**p value**
Energy intake (kcal)						
TC genotype	–103.172	–231.644; 25.301	0.115	234.711	–74.469; 543.892	0.137
CC genotype	–43.858	–203.413; 115.697	0.590	402.881	23.857; 781.904	**0.037**
TC genotype × time				–12.441	–28.445; 3.563	0.128
CC genotype × time				–20.426	–39.967; –0.885	**0.040**
Protein (g/kg)						
TC genotype	–0.089	–0.166; –0.013	**0.022**	0.194	–0.019; 0.407	0.075
CC genotype	–0.081	–0.176; 0.015	0.097	0.164	–0.098; 0.425	0.221
TC genotype × time				–0.010	–0.020; 0.001	0.063
CC genotype × time				–0.008	–0.020; 0.005	0.219
Lipids (g/kg)						
TC genotype	–0.137	–0.224; –0.051	**0.002**	0.136	–0.156; 0.427	0.361
CC genotype	–0.055	–0.163; 0.052	0.313	0.367	0.010; 0.724	**0.044**
TC genotype × time				–0.007	–0.022; 0.008	0.338
CC genotype × time				–0.020	–0.038; –0.001	**0.035**
Carbohydrates (g/kg)						
TC genotype	–0.214	–0.475; 0.047	0.108	0.576	-–0.213; 1.364	0.153
CC genotype	–0.219	–0.544; 0.106	0.187	0.798	–0.171; 1.767	0.106
TC genotype × time				–0.030	–0.067; 0.006	0.102
CC genotype × time				–0.044	–0.089; 0.001	0.053
Protein E%						
TC genotype	–0.152	–0.616; 0.311	0.520	0.568	–1.196; 2.333	0.528
CC genotype	–0.286	–0.863; 0.291	0.332	–0.793	–2.954; 1.367	0.472
TC genotype × time				–0.015	–0.109; 0.078	0.746
CC genotype × time				0.076	–0.038; 0.190	0.189
Lipids E%						
TC genotype	–1.018	–1.990; –0.046	**0.040**	–0.178	–4.137; 3.782	0.930
CC genotype	–0.102	–1.309; 1.105	0.869	3.044	–1.815; 7.904	0.219
TC genotype × time				0.008	–0.189; 0.204	0.939
CC genotype × time				–0.154	–0.394; 0.087	0.210
Carbohydrates E%						
TC genotype	0.839	–0.342; 2.020	0.164	–0.079	–4.460; 4.302	0.972
CC genotype	0.424	–1.043; 1.892	0.571	–1.506	–6.877; 3.865	0.583
TC genotype × time				–0.014	–0.239; 0.212	0.906
CC genotype × time				0.043	–0.233; 0.318	0.762

[1]Coefficient can be interpreted as the mean difference in daily energy intake (kcal), nutrient intake (g/kg) and nutrient intake as a percentage from daily energy intake (E%) between *FTO rs1421085* TC and TT genotype or between CC and TT genotype at each timepoint.

[2]Difference in the rate of change in daily energy intake (kcal), nutrient intake (g/kg) and nutrient intake as a percentage from daily energy intake (E%) between *FTO rs1421085* TC and TT genotype or between CC and TT genotype can be calculated as the sum of main effect coefficient and time × interaction coefficient at given timepoint.

[3] Average sample size by sex and *FTO rs1421085* genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC= 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

Table 5. The rate of change per year in daily energy intake (kcal), nutrient intake (g/kg) and nutrient intake as a percentage from daily energy intake (E%) (mean and 95% CI) in the female subjects of the ECPBHS sample according to the linear mixed effects regression model with *FTO rs1421085* genotype × time interaction.

	TT genotype	TC genotype	CC genotype
Energy intake (kcal/kg)	–11.362 (–23.903; 1.179)*	–23.803 (–33.746; –13.861)	–31.788 (–46.774; –16.802)*
Protein (g/kg)	0.004 (–0.004; 0.012)#	–0.006 (–0.012; 0.001)#	–0.004 (–0.013; 0.006)
Lipids (g/kg)	–0.017 (–0.029; –0.005)*	–0.024 (–0.034; –0.015)	–0.037 (–0.051; –0.022)*
Carbohydrates (g/kg)	–0.089 (–0.118; 0.061)	–0.120 (–0.142; –0.097)#	–0.133 (–0.168; –0.099)#
Protein E%	0.274 (0.201; 347)	0.259 (0.201; 0.316)	0.350 (0.263; 0.437)
Lipids E%	0.088 (–0.066; 0.243)	0.096 (–0.026; 0.218)	–0.065 (–0.250; 0.119)
Carbohydrates E%	–0.048 (–0.657; –0.304)	–0.494 (–0.634; –0.354)	–0.438 (–0.649; –0.226)

* $p < 0.05$ significant difference in the rate of change between *FTO rs1421085* genotype TT and CC

$0.05 \leq p < 0.10$ trend in the rate of change between *FTO rs1421085* genotype TT and TC or TT and CC

Table 6. Estimated main effects (mean and 95% CI) of the ECPBHS sample in maximum power output per kilogram body mass (MPO per kg) and standardized physical activity score from 15 to 25 years of age between *FTO rs1421085* genotype according to the non-linear mixed effects regression model.

	MALE[2]			FEMALE[2]		
	Coefficient[1]	95% CI	p value	Coefficient[1]	95% CI	p value
MPO per kg						
TC genotype	–0.095	–0.201; 0.011	0.080	0.058	–0.010; 0.126	0.092
CC genotype	–0.088	-0.220; 0.044	0.192	–0.001	–0.085; 0.082	0.975
Standardized physical activity score						
TC genotype	–0.040	–0.178; 0.097	0.563	0.103	–0.025; 0.232	0.116
CC genotype	0.099	–0.072; 0.270	0.255	0.162	0.003; 0.321	**0.046**

[1]Coefficient can be interpreted as the mean difference in MPO per kilogram body mass and standardized physical activity score between *FTO rs1421085* TC and TT genotype or between CC and TT genotype at every fixed timepoint.

[2] Average sample size by sex and *FTO rs1421085* genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC= 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

Table 7. Estimated main effects (mean and 95% CI) in male and female subjects of the ECPBHS sample in standardized socioeconomic status (SES) score from 15 to 25 years of age between *FTO rs1421085* genotype according to the linear mixed effects regression model.

	MALE[2]			FEMALE[2]		
	Coefficient[1]	95% CI	p value	Coefficient[1]	95% CI	p value
Standardized SES score						
TC genotype	0.198	0.038; 0.358	**0.015**	–0.032	–0.196	0.132
CC genotype	0.240	0.038; 0.441	**0.020**	0.075	–0.127	0.277

[1]Coefficient (Coeff.) can be interpreted as the mean difference in standardized socioeconomic status score between *FTO rs1421085* TC and TT genotype or between CC and TT genotype at each timepoint.

[2] Average sample size by sex and *FTO rs1421085* genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC= 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

FIGURE LEGENDS

Figure 1. Association between *FTO rs1421085* genotype and body mass index (BMI), daily energy intake (kcal/day), standardized physical activity (sPA) score and standardized socioeconomic status (sSES) score from 15 to 25 years of age in male (graph A) and female (graph B) subjects.

Colors need not be used for any figures in print.