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DOI
10.1038/ijo.2014.156

Published in
International Journal of Obesity

Document version
Accepted manuscript

Online publication date
19 August 2014

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Citation
Foraita R, Günther F, Gwozdz W, Reisch LA, Russo P, Lauria F, et al. Does the *FTO* gene interact with the socioeconomic status on the obesity development among young European children? Results from the IDEFICS study. Int J Obes. 2015;39(1):1-6.

19-June-14

Does the *FTO* gene interact with the socio-economic status on the obesity development among young European children? Results from the IDEFICS study.

Running title: *FTO*×socio-economic status interaction on obesity

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Abstract

Background: Various twin studies revealed that the influence of genetic factors on psychological diseases or behaviour is more expressed in socio-economically advantaged environments. Other studies predominantly show an inverse association between socio-economic status (SES) and childhood obesity in western developed countries. The aim of this study is to investigate whether the fat mass and obesity associated (*FTO*) gene interacts with the socio-economic status on childhood obesity in a subsample (N=4 406) of the IDEFICS (Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS) cohort.

Methods: A structural equation model (SEM) is applied with the latent constructs obesity, dietary habits, physical activity and fitness habits, and parental SES to estimate the main effects of the latter three variables and a *FTO* polymorphism on childhood obesity. Further, a multiple group SEM is used to explore whether an interaction effect exists between the single nucleotide polymorphism rs9939609 within the *FTO* gene and SES.

Results: Significant main effects are shown for physical activity and fitness (standardised $\hat{\beta}^S$=-0.113), SES ($\hat{\beta}^S$=-0.057) and the *FTO* homozygous AA risk genotype ($\hat{\beta}^S$=0.177). The explained variance of obesity is about 9%. According to the multiple group approach of SEM, we see an interaction between SES and *FTO* with respect to their effect on childhood obesity ($\Delta\chi^2$=7.3, df=2, p=0.03).

Conclusion: Children carrying the protective *FTO* genotype TT seem to be more protected by a favourable social environment regarding the development of obesity than children carrying the AT or AA genotype.

Keywords

3-6 Keywords: Childhood obesity, education, gene-environment interaction, income, multiple group comparison, occupation

Introduction

Childhood obesity is a complex disorder where lifestyle factors, socio-economic status (SES), and genetic factors play an important – and interconnected – role. The steep increase of the obesity epidemic in the past two decades might be largely caused by changes in the living environment that promotes both: excessive food intake and sedentary lifestyles.[1] Such changes may have an impact on the effect of the genetic predisposition of an individual since genetic factors within a given environment do not only influence an individual's body weight and body composition, but also the susceptibility to unhealthy behaviours. The investigation of interactions between genes and social environment may hence help to find answers to public health questions as whether individuals with a specific genetic makeup are more susceptible to a particular social environment and hence more influenceable by a prevention strategy or therapeutic interventions.

Some authors have reported a more pronounced influence of genetic factors on psychological characteristics or behaviour in socio-economically privileged rather than in a socio-economically disadvantaged environment.[2,3] Disadvantaged social groups may be more exposed to social and economic risk factors which might mask the genetic influence on certain phenotypes. Especially with respect to obesity, for instance, Pigeyre et al.[4] revealed an interaction between a neuromedin B polymorphism and maternal education.

For sure, modelling obesity and its determinants is a highly complex task. There are many potentially influential determinants that have been reported to have an impact on obesity[5]; and many of them are interconnected. Moreover, not all of these determinants can be

88 measured directly and are therefore considered as latent constructs. For instance, SES can only
89 be assessed by measuring different facets such as income, occupation, and education. While
90 obesity is commonly assessed by the body mass index (BMI [kg/m^2]), other anthropometric
91 measurements such as waist circumference, waist-to-height ratio, or skinfold thickness are
92 used in addition to assess obesity, in particular in children. In view of the assumed high
93 correlations between these measurements, we propose here treating also obesity as latent
94 construct.

95 In general, regression methods fail to capture the influence of a network of latent constructs
96 on the development of obesity. Thus, we would like to exploit a statistical model that can
97 mirror highly complex association structures and is able to model latent constructs. Here, the
98 method of choice is a structural equation model (SEM) that combines a network of latent
99 constructs with the measurements of their observed indicators. In addition, SEM allows for
100 modelling the correlations between the determinants. The model is then assessed by a
101 comparison of the observed variance-covariance structure with the one implied by the
102 network structure.

103 The aim of the present study is to examine whether the single nucleotide polymorphism (SNP)
104 rs9939609 in the fat mass and obesity-associated gene (*FTO*) interacts with the parental SES on
105 obesity in children aged 2-9 years. For this purpose, we apply a multiple group approach
106 (MGA) of SEM. This exploratory approach consists of multiple comparisons between several
107 distinctive groups. In our case, we consider three groups based on the three genotypes in our
108 database.

109 The paper is organised as follows: In the following section, we present the European study
110 IDEFICS on childhood obesity on which our analysis is based. We then describe how the SEM is
111 designed and introduce the multiple group approach. Next, we present the results of our

112 analysis in detail and critically discuss these results. The paper concludes with a summary of
113 the main results and a brief sketch of implications for research and policy.

114

115 Subjects and Methods

116 IDEFICS (Identification and prevention of Dietary- and lifestyle-induced health EFfects In
117 Children and infantS) is a multi-centre population-based longitudinal study that explores
118 health effects with focus on childhood overweight/obesity.[6] A cohort of 16 228 children aged
119 2-9 years was enrolled in eight European countries (Belgium, Cyprus, Estonia, Germany,
120 Hungary, Italy, Spain, Sweden) according to a standardised protocol to collect data on
121 anthropometric and demographic characteristics, physical activity and fitness (PAF), and
122 dietary habits (DIET) amongst others. PAF was measured by accelerometry, self-administered
123 questionnaires, and a shuttle-run test. DIET was, amongst others, assessed using a 24-h dietary
124 recall of one day. Genotyping of rs9939609 within the *FTO* gene (A<T, minor allele
125 frequency=40.4%) was done in a subsample of 4 500 children (for detailed information about
126 genotyping see[7]). The analysis sample was further reduced to 4 406 children by exclusion of
127 unsuccessfully genotyped participants.

128 Means (±standard deviation (SD)) or proportions are calculated for baseline characteristics of
129 the study population. An SEM[8] is applied to investigate whether the rs9939609 SNP interacts
130 with SES on childhood obesity. SES, DIET, PAF, and obesity are modelled as latent constructs
131 with multiple causal indicators: For SES we consider the measured indicators “household
132 income level”, “maximum parental level of education”, and “maximum parental level of
133 occupational position” where all country-specific answer categories of these indicators were
134 recoded to international standardised classification systems to make them comparable across
135 countries.[9] The latent construct DIET is captured by the indicators “usual energy intake per day

136 in kcal", "usual intake per day of protein in gram", "usual intake per day of fat in gram", and
137 "usual intake per day of water in gram", which are corrected for within-person variability. The
138 latent construct PAF is reflected by "percentage of time spent in moderate-to-vigorous
139 activity" (MVPA, cut-points according to[10]), "average activity counts per minute" (both
140 measured by accelerometers), "self-reported hours per week the child was physically active"
141 and "maximum oxygen uptake VO_{2max}" (estimated from a shuttle-run test). Obesity is modelled
142 as latent construct involving "age- and sex-standardised BMI z-scores"[10,11], "waist-to-height
143 (WH) ratio", "percentage of body fat" (calculated from a bioelectrical impedance analysis
144 according to Tyrrell et al.[12]), and "subcutaneous skinfold thickness" (sum of subscapular and
145 triceps) as indicators. PAF, DIET, SES, and *FTO* are modelled as determinants of obesity. Using
146 linear regressions, the indicators of DIET and PAF are adjusted for age, sex, and country and
147 the indicators of obesity are adjusted for age and sex. The obtained residuals are then used as
148 observed indicators for all further analyses. In addition, the endogenous latent construct
149 obesity is adjusted for sex, age, and country to allow for estimating the impact of *FTO*, SES, PAF
150 and DIET on obesity.

151 The basic SEM is depicted in Figure 1: ovals reflect latent constructs, boxes reflect observed
152 indicators; error and disturbance terms as well as the reference categories (i.e. *FTO* - TT
153 genotype and Germany) are not represented. Single-headed arrows between latent constructs
154 symbolise postulated pathways and double-headed arrows symbolise covariances between
155 latent constructs. A confirmatory factor analysis (CFA) is employed to examine the reliability
156 and validity of the measurement model. This enables us to investigate whether the four latent
157 constructs are well represented by the indicator variables. The subsequent SEM additionally
158 includes the structural relations between the latent constructs.

159 The basic SEM is fitted to estimate main effects on obesity. To test for an interaction between
160 SES and *FTO,* the multiple group approach (MGA) is exploited. The objective of the MGA is to
161 compare distinct sets of parameters for each genotype, some of them restricted by assuming

that they are equal across genotypes. The MGA follows a step-up approach and compares different nested models. That is, each of these models is estimated under additional constraints (see Table 1) and then compared to the preceding model with respect to its model fit. This procedure continues as long as the models do not significantly differ. In the final step, the only unconstrained parameter reflects the path from SES to obesity. This parameter is then tested to be equal across the three *FTO* genotypes.[13] If the effect of SES on obesity is not equal for all *FTO* genotypes, we conclude that there is an interaction between SES and *FTO*. We use robust weighted least square estimators to fit SEM and $\Delta\chi^2$ difference tests to conduct MGA.

Additional power calculations[14] for this exploratory approach revealed that the sample size of our study is sufficient to detect a significant difference in the model fits for each of the $\Delta\chi^2$ difference tests conducted (see Table 1 for the considered degrees of freedom and Table 2 for the resulting power).

We report the root mean square error of approximation (RMSEA) and the comparative fit index (CFI) as fit indices. RMSEA values <0.05 and CFI values >0.95 indicate good fit.[15] We also report the χ^2 statistic although we do not use it as fit index because of its drawback being sensitive to large sample sizes.[16] Standardised parameter estimates are reported where standardised estimated structural regression parameters indicate changes in units of standard deviations. The residual variances for usual energy intake and for MVPA are fixed to 0.033 and 0.059, respectively, based on the results of two exploratory factor analyses to ensure that all estimated variances are positive.

Results

In the following, we first present basic descriptive results. Then, we give the overall model fits of the measurement model and of the basic SEM before we discuss the estimated basic SEM. Finally, we present the results of the MGA. For this purpose, we describe the results of the first

model of this approach (model MG; see Table 1) which is estimated without any constraints on the model parameters in some more detail before we report the results of the $\Delta\chi^2$ difference test on interaction between *FTO* and SES.

Basic demographic characteristics are shown in Table 3. Mean age (±SD) is 6.0 years (1.8) in boys and 6.1 years (1.8) in girls. The most frequent *FTO* genotype is AT (47.3%), whereas the homozygous AA genotype only occurs in 16.7%. At least one parent has the highest educational level in 40.1% and the highest occupational level in 30.3%; however, the most frequent parental income level belongs to the medium category (28.2%).

The overall model fit of the CFA model is very good (RMSEA=0.036; CFI=0.96) which supports the postulated measurement model before introducing the path structure into the SEM.

Table 1 presents the model fit indices of all SEMs leading to an inconsistent assessment of the model fit (e.g. basic SEM: RMSEA=0.05; CFI=0.79). According to RMSEA the fitted models are acceptable; CFI values indicate, however, poor model fits.

Table 4 shows estimated paths coefficients, covariances and variances for the basic SEM. Standardised main effects are also shown in Figure 1. Non-standardised estimates are interpreted as in ordinary least squares (OLS) regression and are used to compare equal paths between genotypes. Standardised estimates are interpreted in units of standard deviations and should be used to compare different paths within one genotype. The rs9939609 homozygous risk genotype AA is a statistically significant positive predictor for obesity ($\hat{\beta}$=0.154 (p<0.001), standardised $\hat{\beta}^S$=0.177). The standardised coefficient implies that the AA genotype increases obesity by 0.177 SDs compared to the reference TT. PAF ($\hat{\beta}$=-0.101 (p<0.001), $\hat{\beta}^S$=-0.113) and SES ($\hat{\beta}$=-0.079 (p=0.002), $\hat{\beta}^S$=-0.057) have a statistically significant negative main effect on obesity. An increase of the latent construct PAF or SES by 1 SD decreases obesity by 0.113 and 0.057 SDs, respectively. There is no statistically significant main effect for DIET ($\hat{\beta}$=-0.005 (p=0.758), $\hat{\beta}^S$=-0.006). The only statistically significant association

within the endogenous variables is between PAF and DIET (covariance: 0.056 ($p<0.037$)). The basic SEM shows country-specific differences of obesity. The total explained variance of obesity is about 9%.

The multiple group model with complete heterogeneity (model MG) reveals that the path from PAF to obesity is statistically significant in all three genotype groups (TT: $\hat{\beta}$=-0.109 ($p<0.001$), AT: $\hat{\beta}$=-0.103 ($p<0.001$), AA: $\hat{\beta}$=-0.086 ($p=0.050$)). SES is a statistically significant inverse predictor of obesity for the TT genotype (TT: $\hat{\beta}$=-0.170 ($p<0.001$)), but not statistically significant for the other genotypes (AT: $\hat{\beta}$=-0.030 ($p=0.424$), AA: $\hat{\beta}$=-0.051 ($p=0.354$)) (results not shown).

The MGA reveals significant differences between the regression parameters for the latent constructs of the rs9939609 genotype groups (Table 2). In the first three steps, factor loadings, intercepts, thresholds for categorical variables, and path coefficients besides the path between SES and obesity are shown to be equal across all three *FTO* genotypes. In the last step, the $\Delta\chi^2$ difference test yields a statistically significant difference between the model fits of the model with freely estimated regression parameters for SES on obesity (MG 3) in comparison with the model MG 4 where all regression parameters are assumed to be equal across genotypes ($\Delta\chi^2$=7.3, df=2, $p=0.03$).

Discussion

Due to our results, parental SES may interact with the polymorphism rs9939609 (*FTO*) in its influence on childhood obesity. The results of the MGA implied that the advantage of favourable socio-economic conditions in which the child grows up is especially apparent for children carrying the protective *FTO* genotype TT. We found a strong positive association of the AA risk genotype with obesity scaled to units of BMI z-score. The basic SEM showed in addition that an increase of 1 SD of PAF reduces obesity around twice as much as a 1 SD

increase on the parental SES scale. Furthermore, the model suggested that if carriers of the AA genotype increase their PAF by around 1.5 SDs they may compensate for their genetic predisposition which can be seen from the following equation: $\hat{\beta}_{AA}^{S} + 1.5 \cdot \hat{\beta}_{PAF}^{S} = 0.177 - 1.5 \cdot 0.113 \approx 0$. The only statistically significant association within the endogenous variables is between PAF and DIET. We were unable to detect an association between SES and both: DIET or PAF.

There are some other studies that investigated whether socio-economic factors modify the effects of genetic variations on health outcomes[17,18,19,20,21] but only a few examined the *FTO* gene in this context. Our finding is supported by Corella et al.[22] who reported an interaction between education and *FTO* rs9939609 regarding their influence on BMI in adults. However, other investigators[23] could not reveal an interaction between two other *FTO* polymorphisms with education and income on BMI in adults. Besides the interaction which is of interest in here, i.e. between SES and *FTO*, interactions between the environmental variable physical activity and *FTO* SNPs are reported in the literature.[24,25]

FTO has been long considered "a gene of unknown function in an unknown pathway"[26] that has frequently been associated with fat mass and predisposes to childhood and adult obesity.[27,28,29,30] Human *FTO* presents high homology with the murine *Fto*, located on mouse chromosome 8.[31] In recent years, several papers shed light on its physiological role but a complete understanding of the "true cellular function of FTO remains a puzzle", as reviewed by Larder et al..[32] However, it is frequently reported that the FTO protein is expressed in multiple tissues with particularly high expression levels in the brain and the hypothalamus, which is a key location for regulation of energy balance and the regulation of appetite.[26,33,34,35] According to Way and Lieberman[36], especially genes affecting brain function appear to influence adaptive behaviours and the degree to which a person is emotionally responsive under favourable or unfavourable social environments.

In accordance to other studies, the polymorphism rs9939609, SES, and PAF have significant direct effects on obesity with inverse associations of SES and PAF.[7,26,33,37,38,39] However, our results did not show any evidence for an association between DIET and obesity. A possible explanation may be that the diet indicators used for the present analysis only capture one dimension of diet and may miss important information. Moreover, misreporting and measurement errors, that are a special problem when measuring diet in children, may affect or even mask associations between diet and obesity.[39]

We applied structural equation models because they allow to model and test a complex association network incorporating several indicator variables simultaneously. Thus, it is possible to assess significance and importance of relationships in the context of the overall structure, even between predictor variables, which might lead to more valid conclusions than several single regression analyses. However, contradictory overall model fit values indicate a weakness of our results. While RMSEA attests a good fit, CFI values lower 0.95 might indicate that the postulated network does not match the true structure or that the correlations between the selected indicators are too weak. This inconsistent assessment of the model fit may also be due to reverse causation which cannot completely be ruled out because of the cross-sectional study design which does not allow conclusions on causal associations.

Strengths of our study are, amongst others, the heterogeneity of the study sample reflecting various European cultures, the highly standardised examination programme, and the objective assessment of lifestyle factors.

In summary, our study suggested an interaction between the *FTO* polymorphism rs9939609 and socio-economic status on childhood obesity, which reflects the sensitivity of the *FTO* gene to the social environment. More insights into the biology of *FTO* are needed to understand if and how it regulates gene expression under different socio-economic conditions. Despite this limitation, our analysis showed that an individual genetic susceptibility to obesity could be

compensated by adopting and maintaining a lifestyle in families that reduces sedentary behaviour. However, as long as the complex underlying biology of *FTO* is not yet understood, the interpretation of the moderating effect is speculative. Further research in how genes and social environment can moderate each other will be needed to fully understand this complex relationship and to use it as a robust evidence-base for health policy. This holds particularly true against the current intense discussion of how patterns of fat metabolism that are influenced by genetic architecture represent an adaptive response to psychosocial environment.[40]

Acknowledgements

This work was done as part of the IDEFICS Study (www.idefics.eu). We gratefully acknowledge the financial support of the European Community within the Sixth RTD Framework Program Contract No. 016181 (FOOD). We thank the IDEFICS children and their parents for taking the time to participate in this extensive examination programme. We are grateful for the support provided by school boards, headmasters, teachers, school staff, communities, and for the effort of all study nurses and our data managers, especially Claudia Brünings-Kuppe and Birgit Reineke.

Conflict of Interest

The authors declare no conflict of interest.

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Tables

Table 1: Description of models and model fit indices for the basic SEM, the basic multiple group model MG, and multiple group models MG 1 through MG 4 using data from the IDEFICS study (N=4 406)

Table 2: $\Delta\chi^2$ difference tests for nested and constrained models; the power of each test has been calculated based on the degrees of freedom of the respective χ^2 test given in Table 1, assuming α=0.05 and RMSEA values of 0.045 for both models under the alternative hypothesis that both models are not equal (N=4 406)

Table 3: Demographic characteristics of 4 406 children included in the analysis

Table 4: Parameter estimates for the basic SEM using IDEFICS data (N=4 406)

Figures

Figure 1: Structural equation model estimating the main effects of SES, dietary habits (DIET), physical activity and fitness (PAF) habits and the rs9939609 (*FTO*) polymorphism. Standardised parameter estimates are shown; bold lines indicate statistically significant parameter estimates and fixed factor loadings (α=0.05). Ovals reflect latent constructs, boxes reflect observed indicators; error and disturbance terms as well as the reference categories (i.e. *FTO* - TT genotype and Germany) are not represented. Arrows between latent constructs represent postulated pathways.

Table 1

Model	Characteristics and model constraint	Description	χ^2; df	RMSEA; (90%-CI); p-close [a]	CFI
Basic SEM	Main effect model	Information on *FTO* is included as observed variable in the regression on obesity	2886; 240	0.050; (0.048,0.052); 0.486	0.789
MG	All parameters genotype-specific and freely estimated	Complete heterogeneity	3225; 636	0.053; (0.051,0.054); 0.008	0.781
MG 1	MG and homogeneity of factor loadings	Weak factorial measurement invariance	3256; 658	0.052; (0.050,0.054); 0.043	0.780
MG 2	MG 1 and homogeneity of mean levels	Strong measurement invariance	3266; 692	0.050; (0.049,0.052); 0.375	0.782
MG 3	MG 2 and constraints on coefficients (exclusive of SES→obesity)	Homogeneity of remaining coefficients; coefficient of SES across genotypes are freely estimated	2898; 714	0.046; (0.044,0.047); 1.000	0.815
MG 4	MG 3 and homogeneity of all coefficients	Interaction between *FTO* and SES	2882; 716	0.045; (0.044,0.047); 1.000	0.817

Abbreviation: CFI, comparative fit index; MG, multiple group model; RMSEA, root mean square error of approximation; SEM, structural equation model; SES, socioeconomic status. [a]p-close is the probability of RMSEA ≤ 0.05

Table 2

Nested models	Test (for equality of)	$\Delta\chi^2$ difference test	df	p-value	Power
MG 1 versus MG	Factor loadings	26.6	22	0.23	100%
MG 2 versus MG 1	Mean	37.0	34	0.33	100%
MG 3 versus MG 2	Coefficients, without consideration of SES	18.1	22	0.70	100%
MG 4 versus MG 3	Interaction	7.3	2	0.03	83%

Table 3

	Total (N=4 406)	Girls (N=2 114 (48%))	Boys (N=2 292 (52%))
		N (%)	
Country			
Belgium	539 (12.2%)	248 (11.7%)	291 (12.7%)
Cyprus	493 (11.2%)	239 (11.3%)	254 (11.1%)
Estonia	567 (12.9%)	295 (14.0%)	272 (11.9%)
Germany	587 (13.3%)	266 (12.6%)	321 (14.0%)
Hungary	549 (12.5%)	257 (12.2%)	292 (12.7%)
Italy	566 (12.8%)	275 (13.0%)	291 (12.7%)
Spain	558 (12.7%)	264 (12.5%)	294 (12.8%)
Sweden	547 (12.4%)	270 (12.8%)	277 (12.1%)
***FTO* (rs9939609)**			
Genotype TT	1 582 (35.9%)	739 (35.0%)	843 (36.8%)
Genotype AT	2 086 (47.3%)	1 016 (48.1%)	1 070 (46.7%)
Genotype AA	738 (16.7%)	359 (17.0%)	379 (16.5%)
Parents' income level (7)			
Low	643 (14.6%)	319 (15.1%)	324 (14.1%)
Medium low	681 (15.5%)	334 (15.8%)	347 (15.1%)
Medium	1244 (28.2%)	571 (27.0%)	673 (29.4%)
Medium high	723 (16.4%)	356 (16.8%)	367 (16.0%)
High	798 (18.1%)	387 (18.3%)	411 (17.9%)
Missing	317 (7.2%)	147 (7.0%)	170 (7.4%)
Maximum parents' educational level (7)			
Low	82 (1.9%)	40 (1.9%)	42 (1.8%)
Medium low	334 (7.6%)	151 (7.1%)	183 (8.0%)
Medium	1 415 (32.1%)	693 (32.8)	722 (31.5%)
Medium high	797 (18.1%)	369 (17.5%)	428 (18.7%)
High	1 769 (40.1%)	858 (40.6%)	911 (39.7%)
Missing	9 (0.2%)	3 (0.1%)	6 (0.3%)
Maximum parents' occupational level (7)			
Low	730 (16.6%)	361 (17.1%)	369 (16.1%)
Medium low	603 (13.7%)	255 (12.1%)	348 (15.2%)
Medium	569 (12.9%)	289 (13.7%)	280 (12.2%)
Medium high	1 043 (23.7%)	490 (23.2%)	553 (24.1%)
High	1 333 (30.3%)	660 (31.2%)	673 (29.4%)
Missing	128 (2.9%)	59 (2.8%)	69 (3.0%)
		Mean (SD)	
Age	6.1 (1.8)	6.1 (1.8)	6.0 (1.8)
BMI z-score	0.3 (1.1)	0.3 (1.1)	0.2 (1.1)
Waist-to-height ratio	0.46 (0.04)	0.46 (0.04)	0.46 (0.04)
Subcutaneous skinfold thickness (in mm)	16.8 (4.4)	17.8 (4.4)	15.9 (4.3)
Percentage of body fat (%)	31.4 (7.7)	34.6 (7.2)	28.4 (7.0)
Usual energy intake (in kcal) per day	1534.9 (173.3)	1514.6 (168.2)	1554.1 (175.9)

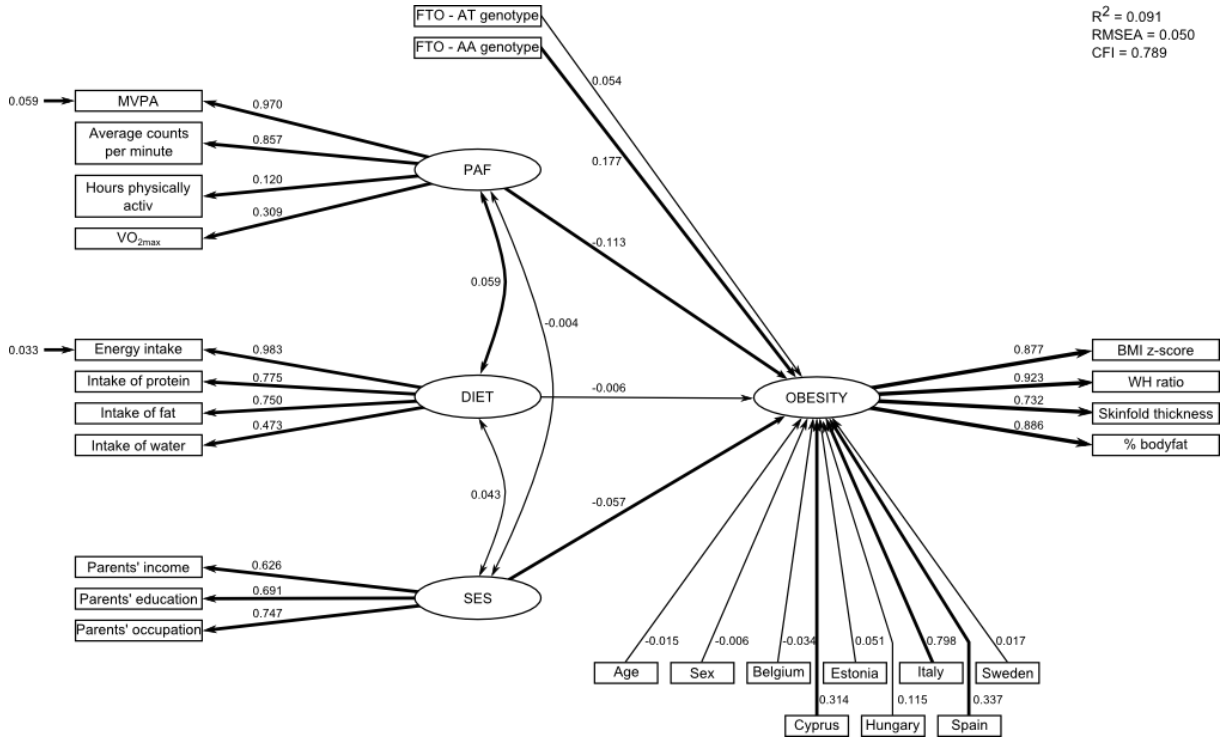
	Total (N=4 406)	Girls (N=2 114 (48%))	Boys (N=2 292 (52%))
Usual intake of protein (in g) per day	58.7 (8.7)	58.1 (8.6)	59.4 (8.7)
Usual intake of fat (in g) per day	55.3 (5.5)	54.9 (5.4)	55.7 (5.6)
Usual intake of water (in g) per day	1208.8 (225.5)	1191.9 (223.7)	1224.9 (226.1)
Percentage of time spent in MVPA	5.4 (2.6)	4.9 (2.4)	5.9 (2.8)
Average activity counts per minute	585.3 (151.7)	559.4 (145.6)	609.1 (153.3)
Hours per week the child was physically active	16.7 (8.3)	16.5 (8.3)	16.9 (8.3)
Predicted VO_{2max} (in ml·min^{-1})	47.5 (2.6)	47.2 (2.4)	47.9 (2.8)

Abbreviation: MVPA, moderate-to-vigorous activity.

Table 4

		Estimate	SE[a]	p-value[b]	Standardised estimate
Paths					
	PAF → Obesity	-0.101	0.019	0.000	-0.113
	DIET → Obesity	-0.005	0.017	0.758	-0.006
	SES → Obesity	-0.079	0.026	0.002	-0.057
	FTO (AT) → Obesity	0.047	0.029	0.104	0.054
	FTO (AA) → Obesity	0.154	0.039	0.000	0.177
	Age	-0.013	0.013	0.310	-0.015
	Sex (female)	-0.005	0.026	0.845	-0.006
	Sex (male, ref.)	1			
	Country (Italy)	0.696	0.050	0.000	0.798
	Country (Estonia)	0.045	0.053	0.399	0.051
	Country (Cypress)	0.274	0.052	0.000	0.314
	Country (Belgium)	-0.030	0.056	0.599	-0.034
	Country (Sweden)	0.015	0.055	0.783	0.017
	Country (Hungary)	0.100	0.051	0.050	0.115
	Country (Spain)	0.294	0.053	0.000	0.337
	Country (Germany, ref.)	1			
Covariances					
	PAF <-> DIET	0.056	0.027	0.037	0.059
	SES <-> PAF	-0.003	0.016	0.871	-0.004
	SES <-> DIET	0.026	0.016	0.090	0.043
Variances					
	PAF	0.946	0.033	0.000	1
	DIET	0.960	0.029	0.000	1
	SES	0.391	0.019	0.000	1

Abbreviations: DIET, dietary intakes; PAF, physical activity and fitness; SES, socioeconomic status. [a] Standard error. [b] All p-values are two-sided


R^2 = 0.091
RMSEA = 0.050
CFI = 0.789
FTO - AT genotype
FTO - AA genotype
0.054
0.177
0.059
MVPA
0.970
Average counts per minute
0.857
Hours physically activ
0.120
VO_{2max}
0.309
PAF
-0.113
0.059
-0.004
0.033
Energy intake
0.983
Intake of protein
0.775
Intake of fat
0.750
Intake of water
0.473
DIET
-0.006
OBESITY
0.877
BMI z-score
0.923
WH ratio
0.732
Skinfold thickness
0.886
% bodyfat
0.043
-0.057
Parents' income
0.626
Parents' education
0.691
Parents' occupation
0.747
SES
-0.015
Age
-0.006
Sex
-0.034
Belgium
0.051
Estonia
0.798
Italy
0.017
Sweden
0.314
Cyprus
0.115
Hungary
0.337
Spain