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Interaction effects of *FTO* rs9939609 polymorphism and lifestyle factors on obesity indices in early adolescence

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ABSTRACT

Background: The rs9939609 SNP in fat mass and obesity-associated (*FTO*) gene influence obesity, whose effects might be mediated by lifestyle factors. However, evidence was lacked in early adolescents. This study aimed to investigate the interactions effects of *FTO* rs9939609 and lifestyle factors on obesity indices in early adolescence.
Methods: The study included 1149 children aged 10–12 years. Their body mass index (BMI) and body fat percentage (BF%) were measured, and lifestyle factors were surveyed through questionnaires. The rs9939609 SNP in the *FTO* gene was genotyped.
Results: Significant associations were found between *FTO* rs9939609 and obesity indices after adjusting for confounding factors. An interaction effect between rs9939609 and soft drinks was observed with $p = 0.019$ for BMI after adjustment for confounding factors. The children carrying risk allele A had a significantly higher mean BMI (mean=19.67kg/m^2) than those carrying only the wild allele T (mean = 17.987 kg/m^2) when they reported a higher intake of soft drinks (≥3 times/week), but the association was not observed among children with a lower intake of soft drinks. No significant interactions were established between appetite, weekday TV viewing, sleep, exclusive breast feeding in the first four months and *FTO* rs9939609 on BMI or BF%. Bioinformatics revealed that rs9939609 and its linkage disequilibrium (LD) SNPs are potentially implicated in the regulation of gene expression in blood, pancreatic and brain tissue cells.
Conclusion: FTO rs9939609 had an obvious and independent effect on obesity-related indices in early adolescents. Soft drinks may exert a modifying effect on the relationship between *FTO* rs9939609 and BMI.

Introduction

The rs9939609 single nucleotide polymorphism (SNP), which was located within the first intron of fat mass and obesity associated gene (*FTO*), has been most extensively studied and confirmed to have a strong association with obesity in adults, as well as in children and adolescents [1–4]. It is well established that individual susceptibility to obesity is determined by the interplay between genetic component and environmental factors [5]. A growing number of studies have recently shown that the influence of the *FTO* gene on obesity may be modified by lifestyle factors such as diet and physical activity [6–9]. However, the most of relevant studies were conducted in adults, while evidence was lacked in early adolescents even though adolescence is a dynamic period for the development of obesity [10]. The few studies that investigated the potential inter-

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actions in adolescents have generated conflicting results, especially when comparing studies across different cultures or ethnicities [6,11–13]. A recent meta-analysis including 16,097 children and adolescents revealed that an interaction between *FTO* rs9939609 and dietary protein intake on body mass index (BMI) was found only in whites but not in African Americans or Asians [11].

However, the rapid socioeconomic progress, urbanization, globalization, and the changes in governmental policies have led to the emerging and increasing adoption of western dietary patterns by Chinese children [14–17]. Moreover, adolescence involves noticeable changes in a more sedentary activity as well as reduced sleep since youth may increasingly develop autonomy and independence [18,19]. Evidence exists that Chinese adolescents have a shorter sleep duration than their Western counterparts [19]. Therefore, it is pertinent to explore the gene-environment interactions in early adolescents in China.

Our previous study showed that *FTO* rs9939609 and lifestyle factors such as weekday TV viewing, appetite, sleep, exclusive breast feeding in the first four months were associated with obesity indices in early adolescence [20,21]. However, the modification effects of lifestyle factors in the association between *FTO* and obesity were not considered. The present investigation aimed to explore whether gene-environment interactions exist between *FTO* rs9939609 and lifestyle-related risk factors that influence obesity indices.

Methods

Subjects

The study was conducted from November to December 2009 in Shanghai, China [20,21]. Of the children selected from 10 primary schools by stratified cluster random sampling method, 1243 returned the complete questionnaires, 1649 took part in anthropometric assessments, and 1669 had blood samples, leaving 1149 for statistical analysis. The study was approved by the Ethics Committee of Shanghai Children's Medical Center, and written informed consent was obtained from the parents or guardians.

Measures

Questionnaire

Parents filled out our Shanghai Children's Medical Center socio-demographic questionnaire. The following variables were included: age, gender, birth weight, method of birth delivery (vaginal/cesarean delivery), exclusive breast feeding in the first four months (yes/no), weekday TV viewing (<1/1–2/>2 h per day), parental education level (junior high school and below/middle high school/university and above), parental BMI and described in our previous study [21].

Parents were asked to report their child's evening bedtime and wake-up time for weekdays and weekends in the past month. The calculated sleep duration was described in our precious study and classified into three groups: <9 h, 9–10 h, ≥10 h [21].

Dietary information was obtained via self-report which included appetite (more than peers/the same as peers/less than peers) and consumption of various foods. The following information defines the food categories in the dietary survey: fast foods were defined as McDonald's or KFC or other fast foods (i.e.,0 time/month; ≤3 times/month; >3 times/month); soft drinks were defined as carbonated drinks, other noncarbonated sugar-sweetened drinks (water-based beverages that contain sugar), and sport drinks (i.e., <1 times/week; 1–2times/week; ≥3 times/week); and snacks were classified as sweet (candy, candy bars, chocolate, cake, biscuits) and savory (fries, chips and nuts) food (i.e., <1 times/day; 1times/day; ≥2 times /day).

Anthropometric measurements

Weight, height, triceps and subscapular skinfold thicknesses as well as BMI, body fat percentage (BF%) were assessed. The details can be seen in the publications of our previous study [20,21]. Pubertal status was determined based on visual inspection of physical maturity by our experienced pediatric endocrinologist.

Specimen collection and DNA extraction

Approximately 0.2 mL of blood was collected from each subject. DNA extraction and SNP genotyping were performed as described in our precious study [20].

Statistical analysis

Statistical descriptions were made by calculating mean and standard deviation for continuous variables and percentages for categorical variables. Multiple linear regression analysis was applied to evaluate the association of *FTO* rs9930609 with obesity indices under adjustment for covariates. Main effects and interaction terms were included to test gene-environment interactions influencing obesity indices using generalized linear regression models. Quanto software (http://hydra.usc.edu/gxe/) was applied to perform the power calculation for the interaction test [22]. We applied an explorative statistical significance level of $\alpha = 0.05$. Statistical analyses were conducted using SPSS statistical software (version 21.0, SPSS Inc., Chicago).

Bioinformatics analysis

The potential genetic mechanism of rs9939609 effect was explored by bioinformatics analysis of ENCODE reference data. The upstream and downstream 2 mb of rs9939609 were retrieved from the release version 3 of 1000 Genomes Project and the Asian population was extracted to test linkage disequilibrium (LD) by the PLINK software [23,24]. The LD SNPs of rs9939609 are identified as those with squared correlation coefficient (r2)>0.80. The ENCODE uniform peaks of genome-wide sequenced data were analyzed to identify regulatory DNA elements that involve rs9939609 and its LD SNPs for blood, adiposity, pancreas, brain and embryonic stem cells [25].

Results

The final sample included 586 boys (51.0%) and 563 girls (49.0%) with a mean age of 10.82 ± 0.38 years. Minor allele frequencies for rs9939609 (Allele A) were 0.12 in this study and it was within the Hardy–Weinberg equilibrium ($p > 0.05$).

We found that *FTO* rs9939609 was still associated with BMI ($\beta = 0.059$, $p = 0.019$) and BF% ($\beta = 0.078$, $p = 0.004$) after adjusting for gender, age, birth weight, method of birth delivery, weekday TV viewing, appetite, sleep, tanner stage, parental BMI and education level (Supplemental Table 1). The interaction effects of *FTO* rs9939609 and lifestyle factors for obesity indices are presented in Table 1. No significant interactions were found between appetite, weekday TV viewing, sleep, exclusive breast feeding in the first 4 months, and *FTO* rs9939609 on BMI or BF%. After stratification by gender, the results remained insignificant.

We further analyzed the effects of the interaction of fast food, soft drinks, and snack consumption with *FTO* rs9939609. No strong evidence was established for the influence of interactions between *FTO* rs9939609 and fast food and snack consumption on BMI and BF%. Significant interaction between soft drink and *FTO* rs9939609 was observed for children's BMI (F statistic = 4.64, *p*-interaction: soft drink**FTO* rs9939609 = 0.010), presented in Table 1

Table 1
Interactions between *FTO* rs9939609 and lifestyle factors on obesity indices.

		BMI (kg/m^2) *FTO* rs9939609			BF (%) *FTO* rs9939609		
	N (%)	TT (889)	AT/AA (260)	P-interaction	TT (889)	AT/AA (260)	P-interaction
Exclusive breast feeding in the first 4 months				0.28			0.28
Yes	718 (62.5)	18.02 ± 3.07	18.84 ± 3.20		18.81 ± 5.29	20.49 ± 5.79	
No	431 (37.5)	18.44 ± 3.34	18.77 ± 3.29		19.59 ± 5.60	20.41 ± 5.43	
Weekday TV viewing				0.59			0.88
<1 h/day	825 (71.8)	18.02 ± 3.04	18.53 ± 3.11		18.97 ± 5.33	20.26 ± 5.55	
1–2 h/day	278 (23.8)	18.54 ± 3.47	19.55 ± 3.59		19.30 ± 5.68	21.00 ± 5.93	
>2 h/day	51 (4.4)	18.61 ± 3.60	19.69 ± 2.55		19.99 ± 5.40	20.88 ± 5.99	
Appetite				0.47			0.44
More than peers	263 (22.9)	20.47 ± 3.52	20.84 ± 3.40		21.85 ± 6.38	22.52 ± 5.92	
Equal to peers	635 (55.3)	17.91 ± 2.80	18.37 ± 2.91		18.75 ± 5.15	19.96 ± 5.56	
Less than peers	251 (21.8)	16.53 ± 2.27	17.59 ± 2.85		17.21 ± 3.72	19.34 ± 4.94	
Sleep				0.67			0.97
<9 h	201 (17.5)	18.79 ± 3.34	19.79 ± 3.63		20.14 ± 6.01	21.66 ± 6.76	
9–10 h	746 (64.9)	18.12 ± 3.21	18.74 ± 3.15		19.00 ± 5.36	20.34 ± 5.46	
≥10 h	202 (17.6)	17.77 ± 2.82	18.07 ± 2.95		18.42 ± 4.89	19.64 ± 5.01	
Fast food				0.47			0.82
0	395 (34.4)	18.52 ± 3.25	18.96 ± 3.42		19.53 ± 5.54	20.63 ± 6.16	
≤3/month	593 (51.6)	18.04 ± 3.16	18.59 ± 3.15		18.98 ± 5.38	20.34 ± 5.42	
>3 times/month	161 (14)	17.88 ± 3.02	19.17 ± 3.00		18.51 ± 5.23	20.37 ± 4.97	
Soft drink				0.010			*0.077*
<1 time/week	435 (37.9)	18.37 ± 3.36	18.66 ± 3.10		19.28 ± 5.69	20.05 ± 5.59	
1–2 times/week	412 (35.9)	18.11 ± 3.22	18.18 ± 3.00		19.07 ± 5.35	19.91 ± 5.27	
≥3 times/week	302 (26.3)	17.98 ± 2.98	19.67 ± 3.49		18.86 ± 5.12	21.59 ± 6.00	
Snack				0.71			0.99
<1 times/day	414 (36)	18.36 ± 3.16	19.05 ± 3.00		19.19 ± 5.31	20.59 ± 5.45	
1 time/day	363 (31.6)	18.22 ± 3.04	18.60 ± 3.26		19.27 ± 5.43	20.53 ± 5.93	
≥2 times/day	372 (32.4)	17.92 ± 3.32	18.77 ± 3.49		18.82 ± 5.53	20.23 ± 5.62	

BMI: body mass index; BF%: body fat percentage.

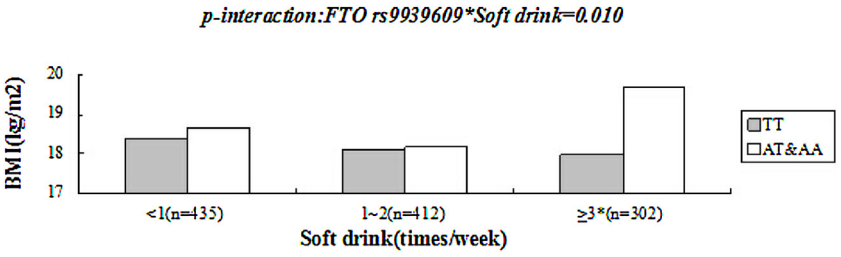

Fig. 1. Interaction between FTO and soft drink on BMI (*: P < 8.05).

and Fig. 1. Children carrying risk allele A (rs9939609 genotypes: AT&AA) have a significantly higher mean BMI (mean = 19.67 kg/m^2) than children carrying only wild allele T (mean = 17.98 kg/m^2) with $p < 0.001$, for children who reported a higher intake of soft drink (≥3 times/week). The association was not observed among children with a lower intake of soft drinks. The interaction between *FTO* rs9939609 and intake of soft drinks on BMI remains significant after adjusting for gender, age, birth weight, method of birth delivery, weekday TV viewing, appetite, sleep, tanner stage, parental BMI and education level, *FTO* rs9939609 and soft drink (*F* statistic = 4.00, *p*-interaction: soft drink***FTO* rs9939609 = 0.019). Stratified by gender, the interaction effects of *FTO* rs9939609 and soft drink on BMI was more significant in girls (*F* statistic = 4.96, *p*-interaction: soft drink***FTO* rs9939609 = 0.007) than in boys (*F* statistic = 2.70, *p*-interaction: soft drink***FTO* rs9939609 = 0.068). However, the interaction between them was not observed for *BF%* (*F* statistic = 1.78, *p*-interaction: soft drink***FTO* rs9939609 = 0.17) when adjusted for confounding factor or stratified by gender. Besides, we found our study had 80% power to detect rs9939609-environment interaction effects with 0.68% and 1.0% heritability for *alpha* = 0.05 and 0.01 respectively.

SNP rs9939609 is situated within the intron of *FTO* gene, and a total number of 66 LD SNPs was observed with the largest distance of 19,573 bp upstream and 24,642bp downstream (Supplementary Table 2). The sequenced peak data of ENCODE was identified for blood, pancreas, brain and embryonic stem cells except the missing adipose cells, representing regulatory DNA elements of transcription factor binding sites (TFBS) based on the SPP (TFBS_SPP) and PeakSeq peak calling (TFBS_SEQ), open chromatin elements based on DNase-seq and FAIRE methods, and histone modifications (Table 2). The covering regulatory elements included BATF binding sites and histone modification of H3k4me1 in the blood cells of GM12878, p300 binding sites in the brain tissue cells of SK-N-SH_RA, histone modification of H3K27ac and H3k4me1 in the brain tissue cells of NH-A, and open chromatin region for different pancreas and brain tissue cells (Table 2).

Discussion

In this study, we found that *FTO* rs9939609 exerted an obvious and independent effect on obesity-related indices in Chinese early adolescents, and only soft drink modified the association between the *FTO* rs9939609 and BMI among several lifestyle factors in early

Table 2
DNA regulatory elements for rs9939609 and the LD SNPs.

Cell*	Tissue	TFBS SEQ	TFBS SPP	DNASE	FAIRE	Histone
GM12878	Blood	BATF	BATF	–	–	H3k4me1
H1-hESC	Embryonic stem cell	–	–	–	–	–
PANC-1	Pancreas	–	–	–		
8988T	Pancreas			+		
HPDE6-E6E7	Pancreas			+		
PanIsletD	Pancreas			–		
PanIslets	Pancreas			+	+	
NH-A	Brain	–	–	+		H3K27ac, H3k4me1
Medullo	Brain			–	–	
PFSK-1	Brain	–	–			
SK-N-SH_RA	Brain	p300	–	–		–
U87	Brain	–	–			
Gliobla	Brain	–	–	–	+	
SH-SY5Y	Brain	–	–			
HBMEC	Brain	–	–	+		–
BE2_C	Brain			–		
HA-h	Brain			+		
SK-N-MC	Brain			–		

Cell*: http://genome.ucsc.edu/ENCODE/cellTypes.html.
"+": the cell DNA regulatory elements cover rs9939609 and/or its LD SNPs; "–": the cell DNA regulatory elements do not cover rs9939609 and/or its LD SNPs; Blank: the cell does not have sequence data of the DNA regulatory elements.

adolescence. Bioinformatics study results revealed rs9939609 and its linkage disequilibrium (LD) SNPs ($r^2 > 0.8$) are potentially implicated in the regulation of gene expression in blood, pancreatic and brain tissue cells.

FTO rs9939609 has been found to contribute to the risk of obesity, and, more specifically, several adult studies established environmental factors interacted with *FTO*, which modify obesity risk [6–10]. Nevertheless, exceedingly insufficient research has been conducted in children especially early adolescents. GWAS with a large sample size (>90,000 subjects) has shown that *FTO* rs9939609 explained 0.34% of the BMI variance [26]. The present study has a smaller sample size of 1149 children and the lower frequency of rs9939609 *A*-risk allele (12%), which may lead to lower power for examining effects of rs9939609, compared with GWAS design in the African American (*A*-risk allele:43.4%) and European populations (*A*-risk allele :43.5%) [26]. Our data showed that the percentage of explained variance in BMI was still similar to GWAS study (0.35% vs. 0.34%) after adjusted for confounding factors (Supplemental Table 1). For Children's BF%, the percentage of explained variance was 0.61% (Supplemental Table 1). These findings suggest that *FTO* rs9939609 may have a more obvious and independent effect on obesity-related indices in Chinese early adolescence.

Our findings further suggested that soft drinks may modify the genetic effect of *FTO* on the obesity-related risk in children, even given that the examined soft drinks was not associated with obesity indices in our sample. To our knowledge, this is the first study linking sugar-sweeten soft drink consumption with the *FTO* rs9939609 polymorphism on obesity risk in early adolescents. Our results are consistent with one obtained in an adult study, which showed the high intake of artificially sweetened beverages was associated with a higher BMI in men with the *FTO* risk-allele but not in men with no *FTO* risk-allele [27]. Previous reports exist that a higher intake of total fat and saturated fatty acids promoted the association between the *FTO* rs9939609 and BMI [28,29]. Given the high amount of sugar (9–24 teaspoons) added in soft drinks [30], it reveals our knowledge that not only fat, carbohydrate, and protein and fiber content but also sugar can modulate the association between *FTO* rs9939609 and BMI. Besides, a stronger interaction effect of *FTO* rs9939609 and soft drink on BMI was found in girls. It may be due to the effect of *FTO* on obesity is also more obvious in girls, who had higher intake of soft drink in our sample [20]. The present findings have public health implications; they show that decreasing the intake of soft drinks has the potential to counteract the effects of a putatively deleterious genotype on obesity.

Among the lifestyles that may modulate the association of the *FTO* SNP with BMI, physical activity has been the most commonly studied. Extensive evidence is available on the effects of low physical activity on obesity and the association of physical activity with the effects of *FTO* risk alleles [6,7]. However, a meta-analysis of 19,268 children did not found an effect interaction between physical activity and *FTO* on obesity [6]. In our study, we used weekday TV as sedentary activity to investigate the interaction effect, and found no significant interaction between weekday TV and *FTO* rs9939609. The missing detection of interaction may not sufficiently explain modification effects of physical activity on *FTO* rs9939609 because weekday TV alone cannot stand for the whole activity level of children. A study conducted in Northern Spain showed that shorter sleep duration was related to BMI in homozygous children of non-risk TT genotype, but not in those carrying the risk allele A for the *FTO* rs9939609 SNP, where frequency of allele A is 41.4% [31]. However, our results indicated that *FTO* rs9939609 and sleep duration independently influence obesity measures and the interaction effect was not present, which might be due to the lower frequency of rs9939609 A-risk allele in our study.

The few studies investigated on the interaction effect of breastfeeding indicated breastfeeding could attenuate the increase in BMI among carriers of the risk allele of *FTO* rs9939609 in children [32,33]. Those findings indicated early interventions that targeted a longer duration of breastfeeding might prevent the risk of overweight/obesity later in life, particularly in children with high genetic predisposition. However, the findings were not replicated in our study. The identification of interactions between genetic variants and lifestyle is challenging as it requires much larger sample sizes than those needed for the detection of the main effects of genes or environment [34]. Further studies with larger samples are needed to accurately determine the interaction effects.

SNP rs9939609 resides in the intron of *FTO* gene, and its genetic mechanism underlying the test effects remains unclear. Our analysis of ENCODE data showed that rs9939609 may exert effects by modifying the transcription factors of *BATF* and *p300*, histone modifications of *H3k4me1* and *H3K27ac*, and open chromatin elements in blood, pancreas, and brain tissue cells. The *BATF* is the transcription factor for the differentiation of IL17-producing T helper cells which involve in coordination of the inflammatory responses [35], and the inflammation is considered as a key mechanism underlying obesity [36]. The *p300* is a transcriptional coactivator, participating in the activities of hundreds of different transcription factors [37]. *H3k4me1* and *H3K27ac* are both known as the enhancers [38].

More specifically, for astrocyte (NH-A), rs9939609 and its LD SNPs are covered by multiple regulatory elements of *H3k4me1*, *H3K27ac* and open chromatin (Supplementary Table 2). These findings contribute to the improved explanation of the effect of rs9939609 and its interaction with soft drink, which will provide initiative for further investigation of the underlying genetic mechanism for obesity development.

The difficulty of measuring lifestyle exposures accurately added difficulties to the interaction analysis. We only used category questions to collect the dietary pattern and sedentary activity (weekday TV) information in our study, which reduced statistical power and led to non-significant results. Further investigations using data of high quality are needed to investigate effects of *FTO* rs9939609 and lifestyle factors on obesity measures. Besides, we did not perform the further exploration concerning the correlation between gene expression and genotype and lifestyle since we did not have expression data. Thus, future studies are required to explore that correlation.

In conclusion, *FTO* rs9939609 had an obvious and independent effect on obesity-related indices in early adolescence. Significant interactions between soft drinks and *FTO* variants on obesity indicated that personalized therapies for subjects with genetic predisposition to obesity might be an effective measure.

Ethical statement

We declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki, and that all procedures were carried out with the adequate understanding and written consent of the subjects.

We also certify that formal approval to conduct the experiments described has been obtained from the human subjects review board of their institution and could be provided upon request.

Conflict of interest

None declared.

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