



ORIGINAL ARTICLE

Association between overweight and obesity in schoolchildren with rs9939609 polymorphism (FTO) and family history for obesity<sup>☆,☆☆</sup>



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Abstract

**Objective:** To determine the association between overweight/obesity in schoolchildren with FTO rs9939609 polymorphism (fatmass and obesity associated) and family history of obesity.

**Methods:** Cross-sectional study comprising a sample of 406 children aged 7–17 years in a city in southern Brazil. Overweight/obesity in schoolchildren was assessed by body mass index (BMI), and family history of obesity was self-reported by parents. Polymorphism genotyping was performed by real time PCR (polymerase chain reaction). The association between the nutritional status of schoolchildren with the presence of family obesity, stratified by polymorphism genotypes (AA [at-risk for obesity], AT, and TT), was assessed by prevalence ratio values (PR) through Poisson regression.

**Results:** Among schoolchildren with the AA genotype, 57.4% had overweight/obesity; the percentage was lower for the AT and TT genotypes (33.1% and 28.9%, respectively). Overweight/obesity in schoolchildren was associated with a family history of obesity, especially among children with the AA genotype. The prevalence was higher among those with an obese mother (PR: 1.28;  $p < 0.001$ ), obese maternal or paternal grandmother (PR: 1.22;  $p = 0.047$ ), and obese paternal grandfather (PR: 1.32;  $p < 0.001$ ).

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**PALAVRAS-CHAVE**

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**Conclusions:** There is an association between the AA genotype of rs9939609 polymorphism and BMI among schoolchildren. The association between overweight/obesity in schoolchildren with a family history of obesity was found mainly among students with the AA genotype.

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### Associação entre sobrepeso e obesidade em escolares com o polimorfismo rs9939609 (FTO) e histórico familiar de obesidade

#### Resumo

**Objetivo:** Verificar se existe relação entre o sobrepeso/obesidade de escolares com o polimorfismo rs9939609, do gene FTO (*fatmass and obesity associated*) e com o histórico familiar de obesidade.

**Métodos:** Estudo transversal composto por uma amostra de 406 escolares, de sete a 17 anos, de um município do sul do Brasil. O sobrepeso/obesidade dos escolares foi avaliado por meio do índice de massa corporal (IMC) e o histórico familiar de obesidade por questões autorreferidas pelos pais. A genotipagem do polimorfismo foi feita por PCR (*polymerase chain reaction*) em tempo real. A associação entre o estado nutricional dos escolares com a presença de obesidade familiar, estratificada pelos genótipos do polimorfismo (AA – risco para obesidade, AT e TT), foi avaliada pelos valores de razão de prevalência (RP), por meio da regressão de Poisson.

**Resultados:** Entre os escolares com o genótipo AA, 57,4% apresentaram sobrepeso/obesidade; para os genótipos TT e AT, o percentual é inferior (33,1% e 28,9%, respectivamente). O sobrepeso/obesidade do escolar associou-se com o histórico familiar de obesidade, principalmente entre os escolares portadores do genótipo AA, foi superior entre os que apresentam mãe obesa (RP: 1,28;  $p < 0,001$ ), avó materna e paterna obesas (RP: 1,22;  $p = 0,047$ ) e avô paterno obeso (RP: 1,32;  $p < 0,001$ ).

**Conclusões:** Há relação entre o genótipo AA, do polimorfismo rs9939609, com o IMC dos escolares avaliados. A relação entre sobrepeso/obesidade do escolar com o histórico familiar de obesidade foi encontrada, principalmente, entre os escolares com o genótipo AA.

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## Introduction

Obesity is a multifactorial condition, determined by environmental and genetic factors, and is a facilitator of several other diseases.<sup>1,2</sup> Associated with cardiovascular diseases and metabolic disorders, conditions previously observed mostly in adults, childhood obesity has currently become a major public health issue.<sup>3</sup> Some fat mass and obesity-associated (FTO) polymorphisms have been associated with fat mass and obesity, especially the rs9939609 polymorphism, with increased risk for obesity in carriers of allele A.<sup>1</sup> Each copy of allele A with the rs9939609 polymorphism is associated with an increase of 0.4 kg/m<sup>2</sup> in BMI and higher chance (1.31-fold increase) of developing obesity.<sup>4</sup> Berentzen et al.<sup>5</sup> and Cecil et al.<sup>3</sup> found an association between a higher percentage of fat and the presence of AA genotype in Danish adults and Scottish children, respectively. Berentzen et al.<sup>5</sup> observed that individuals from Denmark homozygous for allele A are more likely to experience an increase of 10 kg of fat mass (1.3-fold higher chance) when compared to carriers of the TT genotype.

The FTO gene is expressed in the arcuate nucleus of the hypothalamus, a relevant region for appetite behavior, having an effect on homeostasis. Although the FTO gene functions and pathways are unknown, analysis of its structure has shown it is involved in post-translational

modification, repair of deoxyribonucleic acid (DNA, which protects the genome from damage that leads to mutations), and fatty acid metabolism.<sup>2,6</sup> The FTO was identified for the first time as a susceptible gene to obesity in two genome studies.<sup>7</sup> Since then, studies have focused on the association of the FTO gene with excessive fat accumulation and its interaction with behavioral factors.<sup>2</sup>

Conversely, it is known that obesity is a multifactorial condition with a strong lifestyle influence and that physical activity acts as a protective factor, regardless of rs9939609 polymorphism genotype.<sup>2</sup> In addition to physical activity, inadequate eating habits are associated with the development of obesity, and parents' behavior has great influence on the consumption of high-calorie foods. Therefore, parents are role models for their children's behavior, influencing their food preferences since early childhood.<sup>8</sup>

Thus, this study aimed to verify whether there is an association between overweight/obesity of children with rs9939609 polymorphism of the FTO gene and their family history of obesity.

## Methods

This cross-sectional study included 406 children and adolescents (203 males), aged 7–17, from six schools in the city

of Santa Cruz do Sul, state of Rio Grande do Sul, Brazil. At the start of the study, a minimum of 392 students was estimated for an error of 5% and considering a prevalence of overweight and obesity of 30%<sup>9</sup> for the sample to be representative of the municipality.<sup>10</sup> The students whose free and informed consent form was signed by parents or guardians were included in the study. Initially, the sample had 420 students; however, 14 parents/guardians did not complete the questionnaire on family history of obesity and were excluded.

The study was previously submitted to the Ethics Committee on Human Research of Universidade de Santa Cruz do Sul (UNISC), and was approved under protocol No.2525/10. All parents or guardians of the schoolchildren signed the consent form authorizing participation in the study. The form provided information on the purpose of the study and its procedures, as well as possible discomforts and benefits of the study.

Anthropometric assessment of the schoolchildren comprised the body mass index (BMI), calculated using the weight and height values, which were measured through a scale and stadiometer (Welmy, Santa West Barbara, SP, Brazil), by a Physical Education teacher experienced in this type of assessment, performed with the schoolchildren wearing light clothing and barefoot. At the beginning of each evaluation day, the scale was calibrated. Subsequently, the formula:  $BMI = \text{weight}/\text{height}^2$  was applied.

BMI was classified according to the percentile curves of the World Health Organization,<sup>11</sup> according to gender and age, considering overweight/obesity as  $\geq 85$ th percentile. Family history of obesity was assessed through self-reported questions by the parents. The questionnaire contained a box for parents to indicate with an "X" the presence of obesity in the following family members: father, mother, siblings, paternal grandfather, paternal grandmother, maternal grandfather, and maternal grandmother. Obesity in siblings was not included in the models, as it was not associated with child obesity and adolescents. Obesity for each family member was classified as "present" when the box had the "X" mark, or "absent," without this mark.

The choice of the rs9939609 polymorphism (T>A) of the FTO gene was made through allele frequency search for the Caucasian population, as the study population is of German descent.<sup>12</sup> The study was carried out using the HapMap data (International HapMap Project). Of the total number of schoolchildren, 74.9% were Caucasians. This fact, self-reported by the students, was used to adjust the analyses involving the rs9939609 polymorphism.

Blood collection was carried out at the Laboratory of Exercise Biochemistry of Universidade de Santa Cruz do Sul, following the biosafety standards. DNA was extracted from whole blood in vials containing EDTA, using commercial kits from Qiagen (QIAamp DNA Blood Mini Kit; Qiagen<sup>TM</sup>, Germany). Subsequently, the DNA was quantified in Qubit<sup>®</sup> 2.0 Fluorometer (Invitrogen, CA, USA) and diluted to the necessary concentration. The real-time polymerase chain reaction (PCR) technique was used for the rs9939609 polymorphism genotyping using 96-well plates. The reactions were performed in duplicate using a 10  $\mu$ L sample containing 10 ng of genomic DNA. TaqMan probes were used, labeled with the VIC/FAM fluorophores (Applied Biosystems, CA, USA) in StepOnePlus equipment (Applied Biosystems, CA, USA).

Data were entered and analyzed using SPSS (IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. NY, USA), using descriptive statistics (frequency and percentage). The association between the genotypes of the rs9939609 polymorphism with BMI of schoolchildren and family history of obesity was tested using the chi-squared test; differences were considered significant when  $p < 0.05$ . Poisson regression was used to test the association between the student's BMI (dependent variable considering underweight/normal weight *versus* overweight/obesity) with a family history of obesity, stratified by the three genotypes of the rs9939609 polymorphism (TT, AT, and AA). The analysis was adjusted for the student's ethnicity. The Hardy-Weinberg equilibrium was tested using the GraphPadPrism<sup>®</sup> 5.0 software (GraphPad Software, CA, USA), considering  $p > 0.05$  when comparing the expected values with the observed values.

## Results

Table 1 shows the sample characteristics, which are similar regarding gender and school network. The percentage of students with overweight/obesity was 34.5%. The distribution of genotypes (AA, AT, and TT) and allele frequency (A allele and T allele) of the rs9939609 polymorphism of the FTO gene indicates that the data was in Hardy-Weinberg

**Table 1** Sample characterization. Santa Cruz do Sul, RS, Brazil, 2012.

	n (%)
<i>Gender</i>	
Male	203 (50.0)
Female	203 (50.0)
<i>Ethnicity</i>	
Caucasian	304 (74.9)
Black	36 (8.9)
Mixed-race	65 (16.0)
Asian	1 (0.2)
<i>BMI</i>	
Underweight/normal weight	266 (65.5)
Overweight/obesity	140 (34.5)
<i>Public school network</i>	
Municipal	202 (49.8)
State	204 (50.2)
Age <sup>a</sup>	10.9 (2.5)
<i>FTO (rs9939609)<sup>b</sup></i>	
AA (at-risk genotype for obesity)	54 (13.3)
AT	180 (44.3)
TT	172 (42.4)
A Allele	288 (35.5)
T Allele	524 (64.5)

BMI, body mass index; FTO, fat mass and obesity-associated gene.

<sup>a</sup> Expressed as mean (standard deviation).

<sup>b</sup> Significance level, according to the chi-squared test for evaluation of Hardy-Weinberg equilibrium ( $p = 0.955$ ) when comparing the expected values (51 – AA; 186 – AT; and 169 – TT) and observed values (54 – AA; 180 – AT; and 172 – TT).

**Table 2** Association between the genotypes of rs9939609 polymorphism, student's BMI, and family history of obesity.

	Student's BMI classification		<i>p</i>
	Underweight/normal weight	Overweight/obesity	
	<i>n</i> (%)	<i>n</i> (%)	
<i>rs9939609</i> polymorphism ( <i>FTO</i> )			
AA genotype <sup>a</sup> ( <i>n</i> = 54)	23 (42.6)	31 (57.4)	0.001
AT genotype ( <i>n</i> = 180)	128 (71.1)	52 (28.9)	
TT genotype ( <i>n</i> = 172)	115 (66.9)	57 (33.1)	
<i>Father</i>			
Yes ( <i>n</i> = 16)	5 (31.3)	11 (68.8)	0.003
No ( <i>n</i> = 390)	261 (66.9)	129 (33.1)	
<i>Mother</i>			
Yes ( <i>n</i> = 31)	18 (58.1)	13 (41.9)	0.364
No ( <i>n</i> = 375)	248 (66.1)	127 (33.9)	
<i>Maternal grandmother</i>			
Yes ( <i>n</i> = 28)	13 (46.4)	125 (33.1)	0.028
No ( <i>n</i> = 378)	253 (66.9)	15 (53.6)	
<i>Maternal grandfather</i>			
Yes ( <i>n</i> = 13)	6 (46.2)	7 (53.8)	0.135
No ( <i>n</i> = 393)	260 (66.2)	133 (33.8)	
<i>Paternal grandmother</i>			
Yes ( <i>n</i> = 22)	13 (59.1)	9 (40.9)	0.514
No ( <i>n</i> = 384)	253 (65.9)	131 (34.1)	
<i>Paternal grandfather</i>			
Yes ( <i>n</i> = 10)	4 (40.0)	6 (60.0)	0.086
No ( <i>n</i> = 396)	262 (66.2)	134 (33.8)	

BMI, body mass index.

<sup>a</sup> At-risk genotype for obesity.

equilibrium, i.e., the observed values were similar to the expected ( $p = 0.955$ ).

Table 2 shows a significant association between the student's BMI with the at-risk genotype for obesity (AA) of the rs9939609 polymorphism. Thus, the schoolchildren with the AA genotype have a higher percentage of overweight/obesity (57.4%) when compared to the children with the AT (28.9%) and TT (33.1%) genotypes. Moreover, the presence of obesity in the father and the maternal grandmother were associated with the student's overweight/obesity ( $p = 0.003$  and  $p = 0.028$ , respectively).

In a regression model, the association between the schoolchildren's BMI with a family history of obesity was identified mainly in students with the at-risk genotype for obesity (AA) for the rs9939609 polymorphism (*FTO*). Thus, the prevalence of obesity in the students is higher among those with an obese mother (PR: 1.28;  $p < 0.001$ ), obese maternal and paternal grandmother (PR: 1.22;  $p = 0.047$ ), and obese paternal grandfather (PR: 1.32,  $p < 0.001$ ). Among the students with the TT and AT genotypes, an association was found between schoolchildren's overweight/obesity and an obese father and obese maternal grandfather (Table 3).

## Discussion

This study showed a significant association between the genotypes of the rs9939609 polymorphism and BMI;

the percentage of overweight and obesity in the at-risk genotype for this condition was higher (57.4%) when compared with the TT (33.1%) and AT (28.9%) genotype. Similar results were found in the study by Cecil et al.,<sup>3</sup> with 97 prepubertal students from Scotland aged 4–10 years, which found that the A allele was associated with BMI ( $p = 0.003$ ) and increased fat mass ( $p = 0.01$ ).

The study by Wardle et al.,<sup>13</sup> with 131 children aged between 4 and 5 years, with overweight/obesity, observed the at-risk genotype for obesity (AA) in 18% of their sample, although no association was found with BMI, and those with the highest percentage of fat were the AA genotype carriers. Liu et al.<sup>14</sup> observed an association of BMI with rs9939609 polymorphism (*FTO*), both among young Europeans and among young African Americans. In a study with 289 subjects aged 6–19 years, individuals with at least one A allele had significantly higher BMI and fat mass.<sup>15</sup> Furthermore, in Chinese children and adolescents, an increased risk for obesity was found in subjects with AA or AT genotypes, when compared with subjects with the TT genotype.<sup>16</sup> In another study, carried out in 3503 children and adolescents from Beijing, China, an association was found between the rs9939609 polymorphism and obesity, in which each A allele was associated with an increase of 0.79 in BMI.<sup>17</sup>

Another study carried out in Chinese children and adolescents aged 6–18 years, aiming to evaluate the association of rs9939609 *FTO* with BMI and the risk of obesity, as well as

**Table 3** Association between the student's BMI and family history of obesity, according to the genotypes of rs9939609 polymorphism.

Family history of obesity	Student's BMI	
	PR (95% CI)	<i>p</i>
<i>TT genotype</i>		
Father	1.27 (1.00–1.61)	0.047
Mother	1.05 (0.86–1.28)	0.623
Maternal grandmother	1.03 (0.83–1.28)	0.771
Maternal grandfather	1.38 (1.12–1.69)	0.002
Paternal grandmother	0.89 (0.72–1.09)	0.254
Paternal grandfather	1.05 (0.76–1.44)	0.770
<i>AT genotype</i>		
Father	1.32 (1.04–1.66)	0.021
Mother	0.90 (0.74–1.09)	0.285
Maternal grandmother	1.21 (1.00–1.47)	0.054
Maternal grandfather	0.78 (0.73–0.82)	<0.001
Paternal grandmother	1.10 (0.80–1.53)	0.553
Paternal grandfather	1.17 (0.74–1.87)	0.505
<i>AA genotype<sup>a</sup></i>		
Father	1.15 (0.88–1.49)	0.305
Mother	1.28 (1.14–1.43)	<0.001
Maternal grandmother	1.22 (1.01–1.48)	0.043
Maternal grandfather	1.04 (0.78–1.39)	0.789
Paternal grandmother	1.22 (1.01–1.48)	0.043
Paternal grandfather	1.32 (1.20–1.46)	<0.001

BMI, body mass index; Poisson regression considering two variables (underweight/normal weight *versus* overweight/obesity), adjusted for ethnicity; family history of obesity: the absence of this condition was considered as reference; PR, prevalence ratio; 95% CI, 95% confidence interval.

<sup>a</sup> At-risk genotype for obesity.

to determine the age at which this association is evident, observed that this association did not appear until the children reached 12–14 years. After this age, the association increased in the female gender between 15 and 18 years, but not in the male gender. In a subgroup that was followed-up, the association of rs9939609 with BMI and obesity were observed only six years later, and in the female gender,<sup>18</sup> in agreement with the study of Henriksson et al.,<sup>19</sup> in which there was no rs9939609 association with fat mass in the first twelve weeks of life.

In the study by Silva et al.,<sup>20</sup> carried out with 348 Brazilian children who were evaluated at ages 1, 4, and 8 years, no differences were observed at age 1 year between the mean BMI and genotypes. A significant association was observed between AA genotype and higher mean BMI at 4 years, and at the age of 8 years, individuals with the AA genotype had higher mean BMI and sum of skinfold thickness.

In populations of the oceanic islands (Polynesia, Malaysia, and Micronesia), no association was found between the AA, TT, and AT alleles with BMI, and 73% of the subjects were obese.<sup>21</sup> Similarly, in a study with students from Queretaro (Mexico), no association was observed between the alleles and overweight or metabolic risk indicators.<sup>22</sup>

The study by Lopez-Bernejó et al.<sup>23</sup> found no significant difference in body fat at birth in babies with the A allele.

After 13 days, it was observed that babies homozygous for the A allele had higher fat mass. In the study by Solak et al.,<sup>24</sup> there was no significant association between the rs9939609 genotype of the FTO gene and anthropometric indicators (BMI, WHR, and body composition). In the study by Souza et al.,<sup>25</sup> with Brazilian children and adolescents, no significant association was found between the FTO gene and anthropometric and metabolic parameters, a result that can be attributed to the miscegenation of the Brazilian population and ethnic heterogeneity.

Currently, it is not entirely known how the A allele of the rs9939609 polymorphism influences the accumulation of body fat. It is suggested that, because of its role in the hypothalamus through direct connection to appetite control and fat accumulation, there is a stimulation in this region, resulting in fat use limitation and sparing.<sup>2</sup>

In a study of 289 young individuals aged 6–19 years, it was observed that subjects with one or two A alleles (AT or AA) had more frequent loss of control eating and preference for foods with higher fat content.<sup>15</sup> Similarly, Wardle et al.<sup>13</sup> observed that children with the TT genotype ate less than children with the AA genotype. A study of Chinese children and adolescents showed that while subjects with the TT genotype had a preference for a plant-based diet, those with the AA genotype had a preference for a meat-based diet.<sup>16</sup>

Wahlén et al.<sup>26</sup> suggested an association between the rs9939609 polymorphism and the cellular metabolism of fats, in which carriers of the AT allele had higher glycerol release from adipocytes and a greater concentration of glycerol in plasma than subjects with the AA allele, indicating that carriers of the AT allele have a higher degradation of lipids.

In the present study, it was observed that the association between the students' BMI and family history of obesity was found mainly among children and adolescents with the at-risk genotype for obesity (AA) of the rs9939609 polymorphism. Factors associated with overweight/obesity were: an obese mother (PR: 1.28; *p* < 0.001), obese maternal and paternal grandmother (PR: 1.22; *p* = 0.047) and obese paternal grandfather (PR: 1.32; *p* < 0.001). Lee et al.<sup>27</sup> indicate that genetic predisposition plays an important role in the family descent, with the risk of obesity in a person who has an obese first-degree relative varying from 1.5 to 5, when compared to an individual who has only first-degree relatives with normal weight. Conversely, Mustelin et al.<sup>28</sup> point out that exposure to different environments, for instance, a high level of physical activity, can modify the inheritable levels of obesity. In their study, exposure to physical activity significantly modified BMI. In schoolchildren from Santa Cruz do Sul, RS, Brazil, the rs9939609 polymorphism was associated with overweight and obesity, also showing an association with cardiorespiratory fitness levels.<sup>29</sup>

This is a relevant study, as few studies with children and adolescents that analyzed the rs9939609 polymorphism in the FTO gene were carried out in Brazil. Additionally, it featured a relevant sample, with data on family history of obesity. However, the study has limitations, such as the fact that data on family history of obesity was self-reported by the parents. Moreover, socioeconomic and environmental factors were not included in the regression model; it is known that environmental factors influence the increase in

childhood obesity trends, as they influence eating behaviors and practice of physical activity.<sup>30</sup> These variables can influence the association between the polymorphism and the clinical phenotype of obesity, considering this is a multifactorial condition.

The authors conclude that there is a significant association between the risk genotype for obesity (AA) of the rs9939609 (FTO) polymorphism with the student's BMI. Moreover, the association between overweight/obesity of students with a family history of obesity was identified mainly in students with the AA genotype.

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## Conflicts of interest

The authors declare no conflicts of interest.

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