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ORIGINAL CONTRIBUTION

FTO rs9939609 A allele influences anthropometric outcome in response to dietary intervention, but not in response to physical exercise program

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Abstract

Purpose The fat mass and obesity-associated (*FTO*) gene is involved in energy homeostasis. The A allele of the rs9939609 (SNP; T>A) is associated with obesity and higher food intake, while its effect in energy expenditure remains unclear. The aim of this study is to examine whether *FTO* rs9939609 is associated with the anthropometric outcomes of a physical exercise program and a dietary intervention.

Methods We studied two independent samples. The first was composed by children and adolescents in which overweight and obese individuals were submitted to a physical exercise program ($n=136$) and normal weight participants served as a control group ($n=172$). The second sample was composed by obese women submitted to a hypocaloric dietary intervention ($n=126$).

Results Physical exercise and dietary intervention were effective, independently of genotype. We found no association of *FTO* rs9939609 with obesity in children and adolescents ($p=0.67$). The rs9939609 affected the response to dietary intervention in obese women: A allele carriers reduced 2.7 cm less of abdominal circumference (AC) than homozygous TT ($p=0.04$), while no effect was observed in response to physical exercise in overweight and obese children and adolescents.

Conclusions The A allele is associated with a worse outcome in response to the hypocaloric dietary intervention regarding abdominal circumference reduction; the same allele did not show interaction with any anthropometric outcomes in response to the exercise program applied.

Keywords *FTO* · rs9939609 SNP · Obesity · Dietary intervention · Physical exercise

Introduction

Common obesity has a complex etiology that results from interactions of endogenous (genetic) and exogenous (lifestyle) factors [1]. Although the role of healthy feeding and lifestyle in the prevention and treatment of common obesity is well established, the impact of genetic factors in this context remains poorly understood. In this sense, many researchers have been trying to identify genetic variants that contribute to phenotypes associated with obesity [2–4]. It is also relevant to analyze the effect of genetic variants in specific contexts to identify the interaction factors (genotype environment) and the direction of these interactions, which may contribute to the predisposition and response to obesity treatments [5, 6].

Gabrielle Araujo do Nascimento and Mayza Dalcin Teixeira contributed equally to this article.

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The fat mass and obesity-associated (*FTO*) gene seems to be an excellent candidate gene, since it has been related to weight gain [2]. *FTO* gene product is a 2-oxoglutarate-dependent nucleic acid demethylase [7] with high affinity for single-strand DNA/RNA [7, 8]. *FTO* is expressed in the whole body, especially in the hypothalamus, which is involved in regulation of energy balance [2, 9]. According to Stratigopoulos et al. [10], fasted mice had a reduced *FTO* expression in hypothalamus compared to fed mice. This result suggests that the variation in FTO levels in hypothalamus can be a signal to promote feeding [9]. *FTO* rs9939609 single-nucleotide polymorphism (SNP) (T>A) is located in the first intron of the gene, and the risk allele (A allele) is associated with a higher body mass index (BMI) and increased food intake [2, 11, 12].

Thus, with the objective of adding efforts in the elucidation of the genotype x environment interactions that interfere in therapeutic approaches to obesity, this study tested whether the *FTO* rs9939609 SNP is associated with anthropometric outcomes in response to two interventions: physical exercise in overweight and obese children and adolescents and hypocaloric dietary intervention in obese women.

Methods

Study design

This study presents the analysis of interaction of the same anthropometric and genetic variables in two independent sample groups, which were structured and submitted to interventions at different times. The experimental design in each sample group was longitudinal.

In total, 434 individuals were analyzed, 308 of which constituted one sample (children and adolescents), and 126 constituted another independent sample (obese women). Both samples were composed of individuals from Curitiba and neighboring cities (Paraná state, Southern Brazil), with predominantly Euro-Brazilian ancestry.

The studies were approved by the ethics committee of the Federal University of Paraná (UFPR) (approval number 765.184/2003-11) and Pontifical Catholic University of Parana's Institutional Ethics Board (IEB approval number: 0005306/11). Informed Consent was obtained from every participant.

Sample groups and interventions

Children and adolescents group—physical exercise program

This group was composed of 308 children and adolescents of both sexes (204 boys and 104 girls), of which 172 had normal weight and 136 were overweight or obese (31 overweight and 105 obese; according to parameters defined by WHO). The mean overall age was 13.55 with standard deviation of 2 years old (aged 8–17 years).

Participants were recruited in public schools at Paraná state, Southern Brazil. The inclusion criteria were the following: medical liberation for practicing physical exercise and do not use drugs that could interfere on weight control and/or lipid levels. Those who were in agreement with the established criteria were invited to participate in this research, and those who accepted, with the legal responsible consent, had the free and informed consent term signed by them. For each participant, blood samples were collected, height and weight measured, BMI was calculated and then centered and scaled to create a *Z*-score (BMI-Z), waist circumference (WC) and abdominal circumference (AC) were measured.

The 136 overweight or obese children and adolescents were subjected to physical exercises composed of four different types of training. The 172 children and adolescents with normal weight were included in some analyzes as a reference group.

The physical exercises were conducted by physical education professionals, and applied three times a week during 12 weeks on students in their home schools.

Four kinds of physical exercise were conducted: land-based aerobic exercise, high-intensity interval training (HIIT), combined training and water walking. Since no significant impact of the different trainings in the analyzed variables was found, the physical exercise groups were analyzed together. Details of the four types of training applied are shown in the supplemental material.

After the conclusion of the exercise program, the anthropometric data were collected again. It was not possible to obtain AC and WC data from all individuals who completed the program ($n = 136$), therefore, the analyzes of these variables count with a smaller number of individuals ($n = 94$ for AC and $n = 58$ for WC).

Obese women—dietetic intervention

This group was initially constituted by 199 obese women (BMI ≥ 30, according to parameters defined by WHO). At the end of the study, 126 women completed the

hypocaloric dietary intervention. Only this group was statistically analyzed.

Women were invited to participate in this study by local radio and television. The inclusion criteria for the women in this group were the following: age ≥ 20 years, body mass index ≥ 30 kg/m^2, pre-menopause, not pregnant, and not breastfeeding. Women in drug treatment for weight control, with hypothyroidism, type I diabetes, kidney disease, hypertension or who have undergone stomach reduction surgery were excluded from the study.

Those who were in agreement with the established criteria were invited to participate in this research, and those who accepted signed the free and informed consent term.

The nutritional intervention design and application was conducted by a multidisciplinary team of professionals and postgraduates of the Nutrition Department of the Pontifical Catholic University of Paraná. Psychologists, nutritionists, nurses and geneticists collected preliminary information from women who fit in the study. The blood samples were collected and BMI, AC and WC were measured. A questionnaire containing eating habits was also applied to provide the basis for a personalized diet.

The dietetic intervention had two following components: (1) group nutritional intervention with two sessions. The first one occurred during the third week of the intervention and consisted in readings about choosing healthy foods and the second was a workshop about food labels offered during the fifth week, and (2) an individual dietetic intervention with three sessions. The nutritional intervention lasted 7 weeks.

The individual dietetic intervention was defined by a nutritionist based on food habits obtained by a 24-h dietary recall. The daily energy expenditure (total energy expenditure) was calculated for each participant and a deficit of 600 kcal/per day was applied to these daily needs, consisting in a hypocaloric diet. Considering all the participants, the diets ranged from 1000 to 2200 kcal/per day [13].

General diet models contemplated the national recommendations for healthy feeding and were designed aiming maximum standardization in calories, macronutrients, calcium and iron quantities. The individual diets consisted in these general models and considered the individual needs and the deficit of 600 kcal/day. Each diet included four meals per day (breakfast, lunch, afternoon snack and dinner). Distributed in these four meals, every individual diet included three portions of fruits, three portions of vegetables, at least a portion of meat, one portion of leguminous and three portion of dairy products. Other simple foods were included: bread, rice, beans, coffee, soy oil, margarine and oats. Individual diets included a dinner rich in salad/vegetables, moderate in protein (chicken, meat or cheese) and poor in carbohydrates (rice or bread) and included two general options for dinner:(1) salad/vegetables, bread and cheese, or (2) salad/vegetables, rice, beans and chicken (or meat).

Individual diets fitted the percentage intervals of energy consumption from fats between 20 and 35%, carbohydrates from 45 to 65% and proteins from 10 to 35%.

The individual dietetic intervention sessions occurred in the second, fourth and sixth weeks and in each session the foods of the diet were changed to avoid food monotony [13]. After 7 weeks of intervention, the anthropometric data were collected again. It was not possible to obtain AC and WC data from all individuals who completed the program ($n = 126$), hence the analyzes of these variables count with a smaller number of individuals ($n = 125$ for AC and $n = 124$ for WC).

The experimental procedure applied in all the sample groups is demonstrated in Fig. 1.

Anthropometric variables

The anthropometric variables were collected according to the Anthropometric Indicators Measurement Guide [14], with the individuals wearing light clothes and without shoes.

Three measurements were obtained and the median between them was considered. The children and adolescents were considered overweight when their BMI *Z*-score was between + 1 and + 2, and obese when their BMI *Z*-score was higher than + 3. Women were classified as obese when BMI ≥ 30 [15].

DNA extraction and genotyping

The DNA was extracted from peripheral blood according to the salting-out technique Lahiri and Numberger [16], and then diluted to 20 ng/µl. The *FTO* rs9939609 SNP was genotyped with a TaqMan SNP genotyping assay (Applied Biosystems). The reactions were performed according to the following conditions: 60 °C for 30 s, 95 °C for 10 min, 50 cycles of 95 °C for 15 s and 60 °C for 1 min, and 60 °C for 30 s. Three previously sequenced control samples, representative of each of the possible genotypes, were included in each reaction.

Statistical analysis

Genotype and allele frequencies were obtained by direct counting and, regarding children and adolescents, compared between the group of overweight/obese and normal weight by Chi-square test. The Hardy–Weinberg equilibrium was verified, also using the Chi-square test.

The continuous variables were tested for normality using the Kolmogorov–Smirnov test with Lilliefors correction. The initial and final mean of the variables (before and after the interventions) were compared by paired parametric

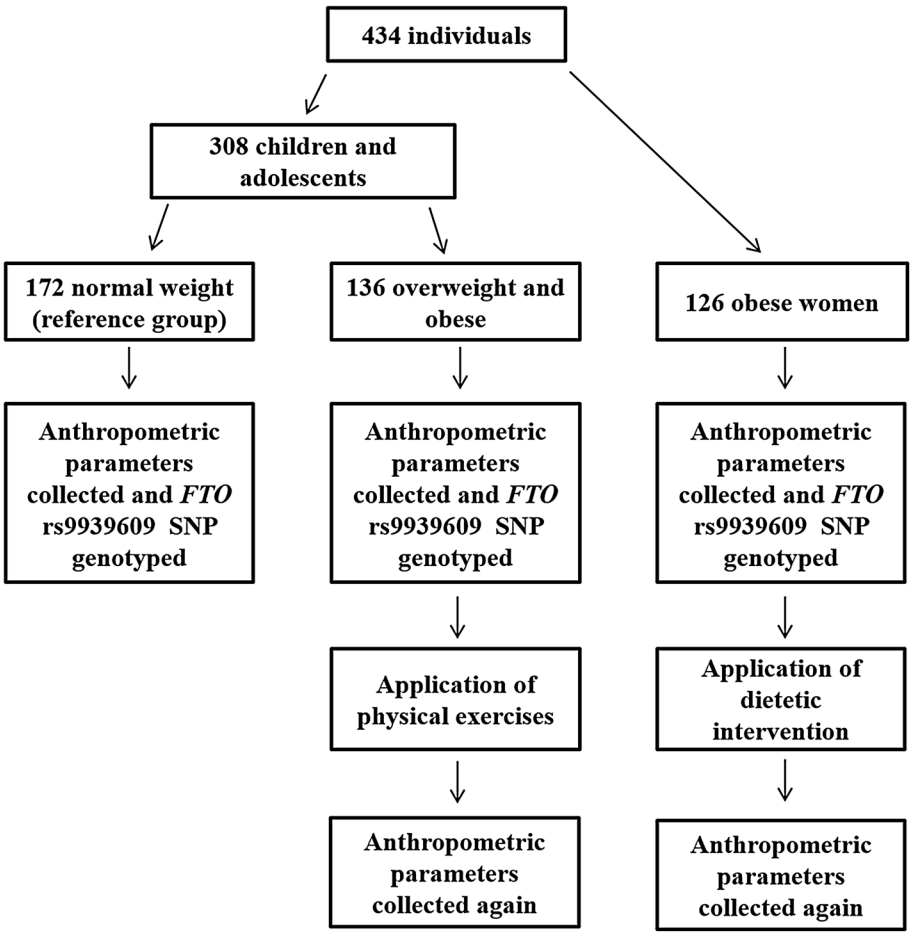

Fig. 1 Study design

or nonparametric tests (*t* test paired or Wilcoxon test, respectively).

The recessive, dominant and co-dominant models of allelic interaction were tested. The dominant model fitted our results, and henceforth adopted for analyzes that involved the sample stratification by rs9939609 SNP genotypes. Independent comparison tests of mean were used to evaluate the mean differences (initial − final) in the anthropometric parameters between genotypes (parametric—*t* test or nonparametric—Mann–Whitney). Multiple regression analyzes were also applied. Due to the adopted statistics design and considering the investigation of only one SNP and its risk allele expected effects, no correction was adopted for multiplicity. Statistical significance adopted for the tests was 0.05 (5%).

Results

Physical exercise and dietary intervention promoted changes in anthropometric variables of overweight/obese children and adolescents and obese women, respectively (Tables 1, 2).

Physical exercise contributed to reduction of 0.23 kg/m^2 in BMI *Z*-score ($p = 10^{-4}$) in overweight/obese children and adolescents (Table 1). The means of the variables analyzed in the normal weight group served as reference to check whether variables that initially were different between overweight/obese and normal weight groups had become similar due to the physical exercise program. Despite the positive changes in the anthropometric outcomes promoted by the physical exercise program, all anthropometric measures that were initially different between these groups remained higher in overweight/obese (Table 1).

Similar to the exercise effect, the diet was also effective: reduction of 0.9 kg/m^2 in BMI ($p = 10^{-4}$), 7.04 cm in AC ($p = 10^{-4}$) and 3.28 cm in WC ($p = 10^{-4}$) was found in obese women (Table 2).

The allele and genotype frequencies of rs9939609 SNP in children and adolescents (overweight/obese and normal weight groups) and in obese women are shown in Table 3. The rs9939609 SNP genotype distributions are in Hardy–Weinberg equilibrium in all sample groups ($p > 0.05$).

The risk allele (A allele), frequently associated with obesity, was found at similar frequency among overweight/

Table 1 Comparisons of initial and final means of anthropometric variables (before and after physical exercise) in overweight and obese children and adolescents, and their comparisons with means of anthropometric variables of normal weight children and adolescents

Children and adolescents								
Variables	Overweight and obese				Normal weight			
	n	Initial mean ± SD	Mean after 12 weeks ± SD	*p*	*n*	Mean ± SD	p^a	p^b
BMI *Z*-score (kg/m^2)	136	2.88 ± 1.09	2.80 ± 1.08	0.0008*	172	−0.21 ± 0.83	10^{-4}*	10^{-4}*
AC (cm)	83	96.84 ± 12.19	96.05 ± 12.62	0.29	129	67.63 ± 6.35	10^{-4}*	10^{-4}*
WC(cm)	55	93.31 ± 10.99	92.84 ± 11.38	0.22	58	67.30 ± 5.74	10^{-4}*	10^{-4}*

BMI body mass index, *AC* abdominal circumference, *WC* waist circumference, *SD* standard deviation, *p* comparison between the initial and after 12 weeks means of physical exercise in overweight and obese children and adolescents, p^a comparison between the initial mean in the overweight and obese individuals and the mean in normal weight individuals, p^b comparison between the mean after 12 weeks in the overweight and obese individuals and the mean in the normal weight individuals

*$p < 0.05$

Table 2 Comparison of initial and final means of anthropometric variables (before and after dietetic intervention) in obese women

Obese women				
Variables	*n*	Initial mean ± SD	Mean after 7 weeks ± SD	*p*
BMI (kg/m^2)	126	35.11 ± 5.15	34.19 ± 5.09	10^{-4}*
AC (cm)	125	109.44 ± 11.56	101.88 ± 10.49	10^{-4}*
WC(cm)	124	95.91 ± 9.77	92.08 ± 10.93	10^{-4}*

BMI body mass index, *AC* abdominal circumference, *WC* waist circumference, *SD* standard deviation, *p* comparison between the initial and after 7 weeks means of nutritional intervention in obese woman

*$p < 0.05$

Table 3 Genotype and allele frequencies of *FTO* rs9939609 SNP in overweight and obese children and adolescents, in normal weight children and adolescents, and in obese women

Genotype	*n*	%	Allele	% ± SE
Children and adolescents—overweight and obese				
TT	53	38.97	T	62.13 ± 0.01
AT	63	46.32		
AA	20	14.71	A	37.87 ± 0.01
Total	136	100		
Children and adolescents—normal weight				
TT	65	37.79	T	63.95 ± 0.01
AT	90	52.33		
AA	17	9.88	A	36.05 ± 0.01
Total	172	100		
Obese women				
TT	35	27.78	T	50.4 ± 0.01
AT	55	43.65		
AA	36	28.57	A	49.6 ± 0.01
Total	126	100		

SE standard error

obese group, compared to children and adolescents with normal weight ($p = 0.67$). To check if there was rs9939609 A allele influence on BMI *Z*-score, multiple regression analysis was performed (corrected for age and sex) considering both normal weight and overweight/obese groups, and no genotype effect on BMI *Z*-score was observed ($p = 0.30$) (Supplementary Table 1).

The rs9939609 A allele effect on anthropometric variables was found only in interaction with dietary intervention. No rs9939609 A allele influence was observed in response to exercise in obese/overweight children and adolescents (Fig. 2a). While obese women A allele carriers reduced on average 2.7 cm less of AC than homozygous TT ($p = 0.04$) (Fig. 2b) in response to diet.

In transversal analyzes (at baseline and at the final moment), in both sample groups, no rs9939609 A allele effect was found (Supplementary Table 2).

Multiple regression analyzes were applied in models in which the anthropometric outcomes were evaluated as a function of possible independent variables in both sample groups. These analyzes confirmed the interaction between rs9939609 SNP and dietary intervention on AC change in obese women ($p = 0.047$) in an A allele-dominant model (Table 4). The AC change was also dependent on the BMI variation ($p = 0.001$), which was expected considering the correlation between these variables. We found no relation between rs9939609 SNP and WC variation ($p = 0.16$). The change in this variable was only dependent on the BMI change ($p = 0.003$) in obese women.

The lack of rs9939609 SNP effect on physical exercise anthropometric outcomes in children and adolescents was also confirmed in obese/overweight children and adolescents, in whom the AC variation was dependent only on the BMI variation ($p = 0.02$) and age ($p = 0.006$) (Table 4).

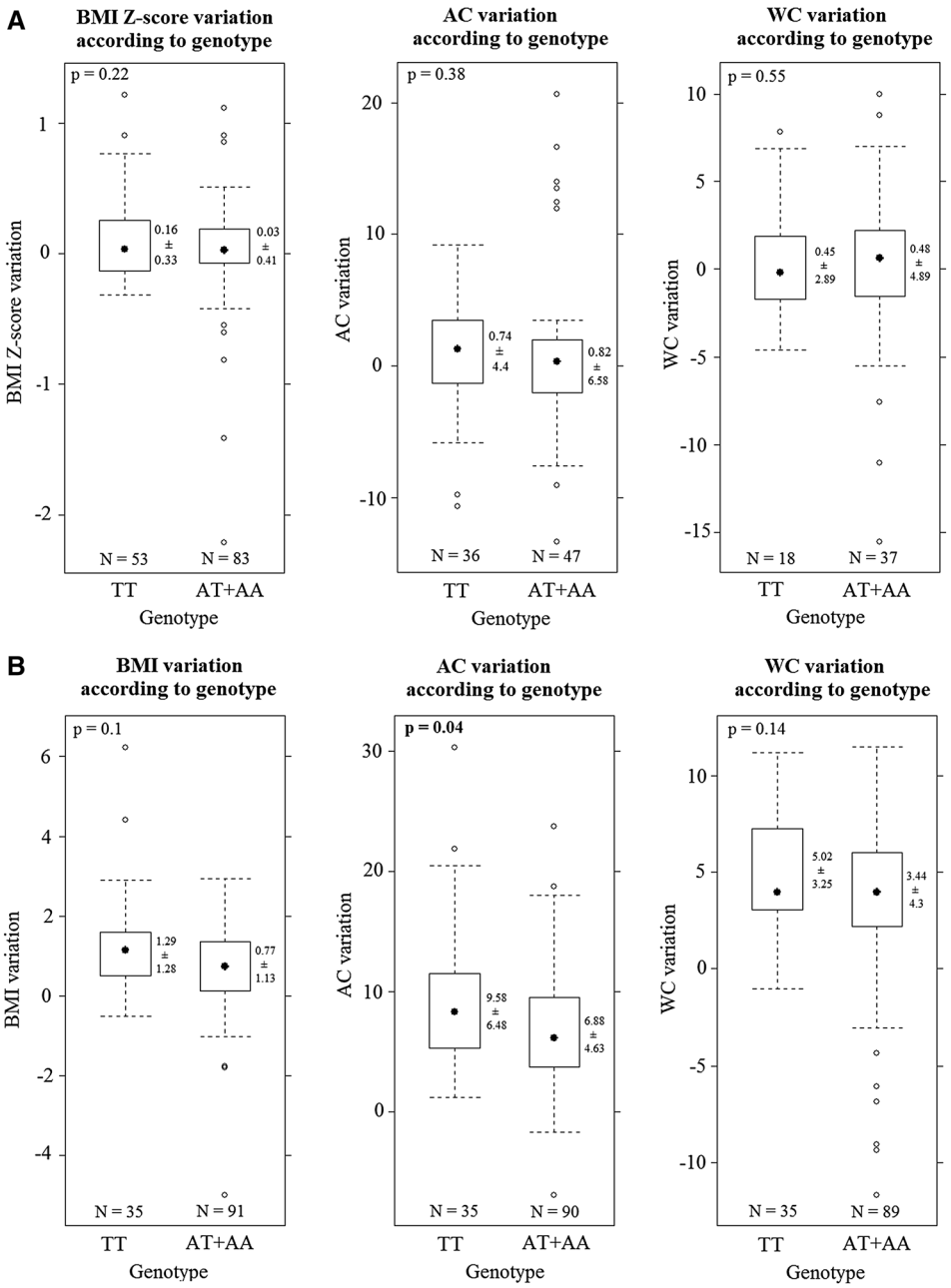

Fig. 2 Comparisons of mean variation (±SD) of anthropometric variables between carriers and non-carriers of rs9939609 A allele. **a** Overweight and obese children and adolescents subjected to physical exercises, mean variation in body mass index (BMI) *Z*-score, abdominal circumference (AC) and waist circumference (WC) according to genotype. **b** Obese woman subjected to dietary intervention, mean variation in BMI, AC and WC according to genotype

Discussion

It is known that environmental factors such as diet and physical exercise play an important role in obesity prevention and are widely used as treatment. Considering that genetic variants may lead to individual variation on diet and physical exercise outcomes, more individualized approaches could be more efficient.

In the present study we evaluated, in two independent samples, the possible interaction between *FTO* rs9939609 SNP and a dietary intervention and a physical exercise program anthropometric outcomes.

In our study, although both interventions were effective on reducing anthropometric measurements, obese women carriers of the A allele appeared to benefit less from the applied diet compared to non-carrier obese women; while the same allele did not influence anthropometric outcomes in children and adolescents submitted to physical exercise. This finding suggests that the A allele, besides contributing negatively to the baseline anthropometric and metabolic profile [17–19], may also influence the results of obesity therapeutic approaches.

Abdominal circumference of obese women A allele carriers decreased 2.7 cm less when compared to non-carriers

Table 4 Models of multiple regression analysis in overweight and obese children and adolescents and in obese women

Dependent variable	Independent variables considered	$\beta \pm$ SD	p
Overweight and obese children and adolescents			
BMI *Z*-score variation	Genotype	−0.17 ± 0.09	0.05
	Age	0.10 ± 0.09	0.27
	Sex	−0.004 ± 0.09	0.97
	Type of training	0.03 ± 0.09	0.72
AC variation	Genotype	0.005 ± 0.10	0.96
	BMI *Z*-score variation	0.25 ± 0.11	0.02*
	Age	0.30 ± 0.11	0.006*
	Sex	0.11 ± 0.10	0.31
	Type of training	−0.04 ± 0.10	0.69
WC variation	Genotype	0.01 ± 0.15	0.94
	BMI *Z*-score variation	0.20 ± 0.15	0.18
	Age	0.28 ± 0.21	0.18
	Sex	0.05 ± 0.15	0.73
	Type of training	0.32 ± 0.21	0.12
Obese women			
AC variation	Genotype	2.03 ± 1.02	0.047*
	BMI	1.27 ± 0.38	0.001*
WC variation	Genotype	0.12 ± 0.09	0.16
	BMI	0.26 ± 0.09	0.003*

BMI body mass index, *AC* abdominal circumference, *WC* waist circumference; β regression coefficient, *SD* standard deviation, *Genotypes* AT + AA and TT (dominant model)

*$p < 0.05$

submitted to the same calorie restriction orientation. This finding is interesting, since the *FTO* genotype did not influence the BMI reduction in response to diet, but specifically modified the fat central deposit in response to it. The harmful effects of increased central fat for whole metabolic health are well known. It has unique characteristics of development and function that differentiate it from the adipose tissue distributed in the rest of the body [20], and its accumulation is positively correlated with susceptibility to various metabolic complications [21–23]. In this context, the A allele effect may be of particular importance for women, since postmenopausal women show an increase in central fat deposit, compared to premenopausal women, consistent with estrogen-protective effect decline [24, 25], which may be aggravated by the presence of the rs9939609 risk allele.

Other polymorphism in *FTO* gene were related to body fat distribution. Haupt et al. [26] found that A allele carriers of rs8050136 *FTO* polymorphism have higher subcutaneous and visceral fat amount, and this association are influenced by gender. Both SNPs show strong linkage disequilibrium ($D¢ = 0.9998$) [27], thus, it is not possible to exclude that this association is due to rs9939609.

The meta-analysis performed by Xiang et al. [28] presents a contrasting effect compared to our results: A allele carriers presented greater weight loss compared to TT genotype carriers in response to diet/lifestyle interventions, but measures of abdominal circumference were not considered. The studies contemplated in this meta-analysis have samples from several regions, and mostly consisted of diet/lifestyle-combined interventions in men and women, which prevents a direct comparison with our results. The observed effects were more persistent in the mixed sample (men and women combined) than in the stratified sample (only women), although the authors did not present the results of this last analysis. In this regard, it is possible that factors inherent to the sample influence the interaction between *FTO* rs9939609 SNP and interventions, mainly the sex of the individuals, since the strong influence of the sex hormones in fat central deposit, is known [29].

Although the way *FTO* rs9939609 influencing specific fat distribution is unclear, some possibilities can be discussed. Several studies demonstrate the association of the *FTO* rs9939609 SNP with obesity and metabolic disorder traits [30–32]. Because of its intronic location, its functional role is not fully understood, but studies suggest that the risk allele is functional, and leads to increased *FTO* expression [33]. Berulava and Horsthemke [33] found higher levels of primary *FTO* transcript from the risk allele, compared to levels obtained from the non-risk allele in blood cells and skin fibroblasts. The association between the A allele and increased *FTO* expression is consistent with the observed in *FTO* knockout mice, which

presented less weight and less fat mass compared to wild-type [34].

It is not well established how *FTO* overexpression affects the demethylase function of the encoded protein, and consequently, its physiological contribution to adiposity and associated metabolic disorders. However, Merkestein et al [35]. demonstrated that mice that overexpressed *FTO* exhibited altered expression of many genes previously associated with obesity. Among these genes, the adiponectin, leptin and adrenergic receptor beta 3 and beta 2 (*ADRB3* and *ADRB2*, respectively), related to food intake control, inflammatory profile and energy expenditure, suggesting that the physiological effect of *FTO* overexpression may involve all these pathways.

In addition to the fact that *FTO* mRNA is found at high levels in the hypothalamus, a region responsible for energy balance regulation [36], studies have associated the presence of the A allele with increased food and fat intake [11, 12, 37].

Considering that *FTO* overexpression in mice was related to changes in expression of genes related to anabolic pathways [35], it is possible that A allele carriers obese women had a differentiated modulation of the energetic pathways mobilized by diet, resulting in greater resistance to fat loss in the central area of the body. Among the possible FTO-modulated genes, the adrenergic receptors may be the most likely involved with the energy balance of fat deposits, since they play central role in lipolysis activation [38]. In this way, *ADRB2* gene presented downregulation in response to *FTO* overexpression in mice muscle [35], which may lead to decreased lipolysis, since knockout in mice beta adrenergic receptors (*ADRB1, ADRB2* and *ADRB3*) showed inability to lose weight in response to a ketogenic diet [39]. However, *FTO* product influence other genes related to metabolism, and further studies are needed to clear the possible interaction between *FTO* and *ADRB2*, and their effects on lipolysis.

On the other hand, it is not possible to rule out the possibility that, in our study, the obese women carriers of the A allele may have ingested a greater amount and more energetic foods, compared to A allele non-carriers, even with the same caloric restriction orientation, which reflected in lower abdominal circumference losses. To elucidate this issue, more studies involving dietary intervention are needed, as well as functional studies considering the energy pathways preferentially activated in function of *FTO* overexpression.

Despite the lack of interaction between A allele and the metabolic changes stimulated by physical exercise in our study, it could be involved in energy expenditure during physical exercise due to its participation in the energy homeostasis regulation via hypothalamus. According to Merkestein et al., [35] this regulation may involve the exacerbated activation of anabolic pathways in white adipose tissue and skeletal muscles due to the *FTO* overexpression, which may contribute negatively to the response to physical exercise, since this route could be preferentially used in detriment of the catabolic pathway.

However, a pathway that clearly explains the effect of *FTO* gene variants on energy expenditure stimulated by physical exercise is unknown, which explains in part the controversial results of studies evaluating this relationship [40].

Our results agree with other studies that found no association of rs9939609 A allele with energy expenditure [11, 12, 41]. However, these comparisons should be interpreted with caution, considering that such studies had different methodologies, some measuring basal energy expenditure, using calorimetric approaches [41], others assessed the physical activity level by questionnaires that allowed to classify the individuals of the sample in physically active or inactive [42]. Our study is one of the few that evaluates the interaction of the rs9939609 SNP with the practice of controlled physical exercise in terms of anthropometric outcomes in obese and overweight children and adolescents.

Other factors also contribute to the lack of consensus in the studies that evaluate the physical activity and rs9939609 SNP interaction, such as the ethnicity, gender and age of participants. Kilpeläinen et al. [43], in a meta-analysis, found that physical activity attenuates the odds ratio for obesity in 27% in adults with the A allele, but in children and adolescents this interaction was not observed.

Despite promising results, our work has some restrictions. The largest of these refers to the sample size, which generally affects the identification of minor effects. This restriction also influenced the analyzes performed in the obese children and adolescents group, which could not be stratified according to sex neither to specific age groups, which could be important for the identification of sex and age-dependent *FTO* interactions.

Knowing the magnitude of contributing factors for obesity and associated co morbidities is extremely important, given the particularities of treatment and prevention that may arise from this knowledge. In this regard, we found that the obese women A allele carriers, who composed our sample, were less benefited by the applied dietary intervention, compared to non-carriers, being this difference represented by the smaller decrease in abdominal circumference, a characteristic that is of great importance in terms of metabolic health.

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Author contributions GAN, MDT: conception, data analysis, manuscript writing. NL: data collection, review of manuscript. RLRS: review of manuscript. LFS, GEM, LRS, JP, WAL, MFAL, ACKT: data collection. LFA: conception, data collection, data analysis, review

of manuscript. LVT: conception, data collection, data analysis, review of manuscript, contribution to discussion.

Compliance with ethical standards

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Conflict of interest The authors have no conflicts of interest to declare.

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