

ORIGINAL INVESTIGATION

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Effects of *FTO* RS9939906 and *MC4R* RS17782313 on obesity, type 2 diabetes mellitus and blood pressure in patients with hypertension

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Abstract

Background: Genetic variants of the *FTO* gene rs9939609 A/T and the *MC4R* gene rs17782313 C/T have been associated with obesity. Individuals with mutations in *MC4R* gene have lower blood pressure (BP), independently of obesity. This study aimed to investigate the association of *FTO* rs9939609 and *MC4R* rs17782313 with anthropometric indexes, BP, and type 2 diabetes mellitus among hypertensive patients.

Methods: We genotyped 217 individuals (86 men and 131 women) with hypertension (systolic or diastolic BP \geq 140/90 mmHg or using antihypertensive drugs). Diabetes mellitus was diagnosed according to the American Diabetes Association criteria. Waist and neck circumferences (cm), Body Adiposity Index (BAI,%), Lipid Accumulation Product Index (LAP, cm.mmol.l) and body mass index (BMI, kg/m²) were analyzed using analysis of covariance or modified Poisson's regression.

Results: Rare allele frequencies were 0.40 for A for *FTO* rs9939609 and 0.18 for C for *MC4R* rs17782313. A positive association of *FTO* rs9939609 and *MC4R* rs17782313 with BMI was observed in the overall sample. Among men and women, neck circumference was associated with the *FTO* genotype and, for women, *MC4R* genotype. In contrast, in men we found a negative association of *MC4R* rs17782313 with diastolic BP (TT 90.1 \pm 12.2, TC/CC 83.2 \pm 12.1; P = 0.03) and borderline association for systolic BP after controlling for age and BMI.

Conclusions: Common genetic variants of *FTO* rs9939609 have positive associations with BMI and neck circumference and *MC4R* rs17782313 in women, but a negative association with diastolic and mean blood pressure in men with hypertension.

Keywords: Diabetes mellitus, Hypertension, *FTO* rs9939609, *MC4R* rs17782313, Waist circumference, Neck circumference, Lipid Accumulation Product index, Body mass index

Introduction

Obesity is a well-known risk factor for hypertension and type-2 diabetes mellitus [1]. Genetic factors play an important role in the development of obesity [2], but the underlying genetic pathways are poorly understood.

FTO (*fat mass and obesity-associated*) gene was first identified in mouse [3] and it has been associated with energy balance [4,5]. *MC4R* (*melanocortin 4 receptor*) gene was the first loci in which mutations were associated with morbid obesity in human beings [6,7]. The most common genetic variant of the *FTO* gene (rs9939609 A/T) [8] and a variant near the *MC4R* gene (rs17782313 C/T) [9] were detected recently and both single nucleotide polymorphisms (*SNPs*) have been associated mainly with overall [8,9] and, in some cases, abdominal obesity [10-12]. Cardiovascular risk factors as type-2 diabetes mellitus [13,14], insulin resistance [15], and hypertension [16] were associated with the risk

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allele A for *FTO* rs9939609 and the risk allele C for *MC4R* rs17782313, regardless body mass index [13,14].

FTO gene is strongly expressed in hypothalamus [17,18], a brain structure involved in the control of energy homeostasis [5] and regulation of blood pressure [19]. The association between the risk allele A for *FTO* rs9939609 polymorphism and elevated blood pressure was demonstrated in Caucasian populations [16]. *MC4R* gene is also expressed in the hypothalamus [18,20], but when inactivated is associated with lower blood pressure, independently of obesity [21]. However, this association has been shown only in individuals with mutations [21]. In the overall population, individuals carrying the risk allele C for near *MC4R* rs17782313 did not have different blood pressure levels comparing to non-carriers [22]. For type-2 diabetes mellitus risk, studies that evaluated both polymorphisms in the overall population are inconclusive [8,23,24].

Among individuals with hypertension, who are often obese and have type-2 diabetes [25], the contribution of both polymorphisms on obesity, blood pressure control and type-2 diabetes mellitus had not been investigated. The aim of this study was to investigate the association between *FTO* rs9939609, *MC4R* rs17782313 with anthropometric indicators, blood pressure, and type-2 diabetes in patients with hypertension.

Methods

This is a cross-sectional study, which enrolled men and women, aged 18 to 80 years, who had been diagnosed with hypertension, living in the urban area of Porto Alegre, southern Brazil. In total, a sub-sample of 217 patients was genotyped (38.8%) and examined in an outpatient clinic of a reference hospital. The study was approved by the Ethical Committee of our institution, and all patients accepted to participate and signed a consent form.

Genotyping

DNA was extracted from peripheral blood using NucleoSpin® Blood (Macherey-Nagel GmbH & Co. KG, Germany). StepOne™ Real-Time PCR Systems (Applied Biosystems Inc., Foster City, CA) was used to genotype the *FTO* locus rs9939609 and the *MC4R* locus rs17782313 using TaqMan-based assays (Applied Biosystems Inc., Foster City, CA).

Outcome variables

Trained research assistants carried out six standardized blood pressure measurements [26], obtained in three visits, using an aneroid sphygmomanometer with an adequate sized cuff to the arm circumference and the average was used to calculate mean blood pressure [(Systolic BP + 2*Diastolic BP)/3]. Hypertension was diagnosed by

systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive lowering agents [27]. Type-2 diabetes mellitus was diagnosed by fasting blood glucose ≥ 126 mg/dl, glycated hemoglobin $\geq 6.5\%$, or use of anti-diabetic agents [28].

Other covariates

Demographic data and information regarding education (years at school), smoking (ex-smoker or current smoker), abusive alcohol consumption (≥ 30 g ethanol/day in men and ≥ 15 g/day in women), and physical activity (short version of the *International Physical Activity Questionnaire*, IPAQ [29], categorized as low/moderate or high intensity) were collected using standardized questionnaires by trained interviewers.

Weight (kg) was measured with patients in light clothes, barefoot, in a 100 g scale (Filizola®, model 31, IN Filizola – SA, Sao Paulo, Brazil) and height was obtained with patient in Frankfurt plane, using a Tonelli® stadiometer with 0.1 cm scale, model E120 A (IN Tonelli – SA, Santa Catarina, Brazil). Body mass index (BMI) was calculated by the weight (kg)/height (m)².

Waist circumference was obtained with a plastic, flexible, inelastic measuring tape positioned in the middle point, between the last costal rib and the iliac crest, in a perpendicular plane, with patient standing in both feet, approximately 20 cm apart, and with both arms hanging freely at the side, with palms facing thighs. Neck circumference was measured with the head straight and eyes staring forward, horizontally, one inch below the laryngeal prominence, and hip circumference at the level of the higher diameter over the buttocks. The anthropometry was carried out in duplicate, with a one week break, by interviewers trained independently and periodically reassessed. Body Adiposity Index (BAI) was calculated using the formula: hip (cm)/[height (m)^{1.5}]-18 [30].

Serum triglycerides were measured by calorimetric enzymatic method using standardized techniques. Lipid Accumulation Product Index (LAP) was calculated from waist circumference, in centimeters, plus serum triglycerides, in mmol, for men [(WC-65)*TG] and women [(WC-58)*TG] [31].

Analyses

Statistical analyses were performed using SPSS (*Statistical Package for the Social Science*, SPSS®, version 17.0, IL, USA). Means \pm SD and percentages were compared using analysis of variance or Pearson's chi-square test. We tested the potential relationship of genotype and blood pressure, using analysis of covariance models, with the adjustment for age and BMI. Modified Poisson's regression (expressed as risk ratio and 95% CI) was used to analyze the association between genotype and type-2 diabetes, after adjustment for age and BMI. A P value

between 0.05 and 0.1 was considered as a trend toward association and less than 0.05 as statistically significant.

Results

Characteristics of individuals included in the study for each polymorphism are shown in Table 1. Rare allele frequencies were 0.40 for A for *FTO* rs9939609 and 0.18 for C for *MC4R* rs17782313. Genotype frequencies did not differ from those predicted by the Hardy-Weinberg equilibrium ($P = 0.8$ for *FTO* and $P = 0.8$ for *MC4R*).

In total, 86 men and 131 women were assessed, aged 59.8 ± 11.2 years, systolic blood pressure of 152.1 ± 20.6 mmHg, and diastolic blood pressure of 87.7 ± 13.0 mmHg. The prevalence of type-2 diabetes mellitus was 44.7%; 4.2% of the sample reported abusive alcohol consumption and 43.8% were current or ex smokers.

Obesity

FTO rs9939609 individuals with AT and AA genotypes had higher BMI than those with TT, as well as those who had *MC4R* rs17782313 with CT and CC genotypes. In addition, neck circumference was higher among AT/AA carriers than TT carriers according to *FTO* risk allele. For other anthropometric indices, the *P* values remained as a trend toward association, as seen for waist circumference (*FTO* and *MC4R*) and Body Adiposity Index (BAI).

Analyses conducted according to gender (Table 2) showed that men and women who were carriers of AT/AA genotype had higher neck circumference than those homozygotes TT for *FTO* rs9939609, while a trend toward association was verified for body mass index. Women carrying risk alleles AA/AT also had higher Body Adiposity Index versus TT for *FTO* genotype.

According to *MC4R* rs17782313 genotype, there were no significant differences among anthropometric indexes for men with CT/CC genotype, in comparison to homozygotes TT (Table 3). Waist circumference and Lipid Accumulation Product Index had a trend to be higher in women with CT and CC genotypes and neck circumference was significantly higher among women carrying risk allele C.

Type-2 diabetes mellitus

There was no difference in prevalence of type-2 diabetes according to *FTO* rs9939609 genotype. The trend toward association detected for *MC4R* rs17782313 (Table 1), further analyzed by gender showed that women who had *MC4R* rs17782313 CT/CC genotype had higher prevalence of diabetes than those with TT allele (Table 3). The multivariate analysis taking into account age and BMI showed that the allele C for *MC4R* was associated with higher risk of type 2 diabetes mellitus in women (RR = 1.5 95%CI: 1.1 – 2.2, $P = 0.03$),

Table 1 Characteristic of participants according to polymorphism [mean \pm SD, n (%)]

	rs9939609			rs17782313		
	TT (n = 75)	TA/AA (n = 142)	P value	TT (n = 146)	TC/CC (n = 71)	P value
Age (years)	59.6 \pm 11.4	60.2 \pm 11.1	0.7	60.3 \pm 11.3	59.2 \pm 10.8	0.5
Sex			0.9			0.02
Men	30 (34.9)	56 (65.1)		66 (76.7)	20 (23.3)	
Women	45 (34.4)	86 (65.4)		80 (61.1)	51 (38.9)	
Vigorous physical activity			0.7			0.2
Yes	11 (31.4)	24 (68.6)		27 (77.1)	8 (22.9)	
No	64 (35.4)	117 (64.6)		118 (65.2)	63 (34.8)	
Body mass index (kg/m ²)	28.9 \pm 4.6	30.7 \pm 5.2	0.02	29.6 \pm 4.8	31.1 \pm 5.4	0.04
Waist circumference (cm)	99.5 \pm 11.5	102.1 \pm 11.6	0.1	100.3 \pm 11.2	103.1 \pm 12.1	0.1
Neck circumference (cm)	37.7 \pm 3.4	38.9 \pm 3.8	0.03	38.5 \pm 3.8	38.5 \pm 3.3	0.9
Body Adiposity Index (%)	33.6 \pm 5.8	34.9 \pm 6.9	0.2	33.9 \pm 6.5	35.7 \pm 6.6	0.07
LAP* (cm.mmol/l)	4.1 \pm 0.8	4.2 \pm 0.6	0.4	4.1 \pm 0.6	4.2 \pm 0.7	0.2
Type-2 Diabetes			0.7			0.07
Yes	32 (33.0)	65 (67.0)		59 (60.8)	38 (39.2)	
No	43 (35.8)	77 (64.2)		87 (72.5)	33 (27.5)	
SBP [§] (mmHg)	155.2 \pm 22.7	150.8 \pm 19.7	0.1	154.3 \pm 21.8	147.9 \pm 18.1	0.04
DBP [¶] (mmHg)	88.9 \pm 13.2	87.1 \pm 13.1	0.3	88.5 \pm 13.4	86.1 \pm 12.4	0.2
Mean blood pressure (mmHg)	111.0 \pm 14.1	108.3 \pm 13.1	0.2	110.5 \pm 13.9	106.7 \pm 12.3	0.06

*LAP Lipid Accumulation Product, log-transformed; § systolic blood pressure; ¶ diastolic blood pressure.

Table 2 Characteristic of men and women according to polymorphism risk allele A for *FTO* rs9939609 [mean ± SD, n (%)]

	Men			Women		
	TT (n = 30)	TA/AA (n = 56)	P value	TT (n = 45)	TA/AA (n = 86)	P value
Age (years)	63.9 ±8.8	58.9 ±11.1	0.03	56.7 ±12.2	60.9 ±11.1	0.04
Body mass index (kg/m ²)	28.3 ±4.4	29.7 ±4.1	0.1	29.5 ±4.7	31.3 ±5.8	0.07
Waist circumference (cm)	101.3 ±12.4	104.1 ±10.7	0.3	98.2 ±10.8	100.9 ±11.9	0.2
Neck circumference (cm)	40.5 ±3.0	41.7 ±2.6	0.04	35.9 ±2.8	36.9 ±3.1	0.04
Body Adiposity Index (%)	29.4 ±3.2	29.4 ±3.5	0.9	36.4 ±5.3	38.6 ±6.1	0.04
LAP* (cm.mmol.l)	4.1 ±0.8	4.3 ±0.6	0.2	4.1 ±0.7	4.1 ±0.6	0.9
SBP [§] (mmHg)	155.2 ±22.5	150.1 ±19.9	0.3	155.1 ±23.1	151.2 ±19.6	0.3
DBP [¶] (mmHg)	88.5 ±14.7	88.5 ±11.6	0.9	89.4 ±12.2	86.3 ±13.9	0.2
Type-2 Diabetes			0.9			0.5
Yes	14 (35.9)	25 (64.1)		18 (31.0)	40 (69.0)	
No	16 (34.0)	31 (66.0)		27 (37.0)	46 (63.0)	

*LAP Lipid Accumulation Product, log-transformed; § systolic blood pressure; ¶ diastolic blood pressure.

but not among men (RR = 0.9 95%CI: 0.6 – 1.7, P = 0.9). *FTO* was not associated to diabetes among men (RR = 1.1 95%CI: 0.7 – 1.7, P = 0.9) and women (RR = 1.0 95%CI: 0.7 – 1.6, P = 0.9).

Blood Pressure

Carriers of risk alleles (A for *FTO* rs9939609 and C for *MC4R* rs17782313) had average diastolic blood pressure similar to non-carriers, but systolic blood pressure was significantly lower among *MC4R* rs17782313 individuals with CT/CC genotype and for *FTO* variant there was a trend toward association.

Table 4 shows systolic, diastolic, and mean blood pressure adjusted for age and BMI, among men and women

according to the genotype. *FTO* was not associated with blood pressure for both genders, but among men with risk allele C for *MC4R* rs17782313, diastolic blood pressure was significantly lower (P = 0.03), and there was a trend for systolic blood pressure (P = 0.05). Therefore, mean blood pressure was markedly lower among those with allele C for *MC4R*, independently of age and BMI.

Discussion

As far as we know, this is the first study showing the association of a common genetic variant near *MC4R* gene with blood pressure in patients with hypertension. The negative association of *MC4R* common variant with blood pressure in men is a novelty, as it had been

Table 3 Characteristic of men and women according to polymorphism risk allele C for *MC4R* rs17782313 [mean ± SD, n (%)]

	Men			Women		
	TT (n = 66)	TC/CC (n = 20)	P value	TT (n = 80)	TC/CC (n = 51)	P value
Age (years)	61.1 ±10.3	59.2 ±11.3	0.5	59.7 ±12.1	59.2 ±10.8	0.8
Body mass index (kg/m ²)	28.9 ±4.4	30.1 ±4.1	0.3	30.1 ±5.4	31.5 ±5.7	0.2
Waist circumference (cm)	102.5 ±11.1	105.1 ±11.9	0.4	98.5 ±11.1	102.3 ±12.2	0.07
Neck circumference (cm)	41.3 ±2.9	41.2 ±2.7	0.9	36.1 ±2.8	37.4 ±2.9	0.01
Body Adiposity Index (%)	29.4 ±3.4	29.4 ±3.5	0.9	37.6 ±6.0	38.1 ±5.9	0.7
LAP* (cm.mmol.l)	4.2 ±0.7	4.3 ±0.8	0.9	4.0 ±0.6	4.2 ±0.7	0.07
SBP [§] (mmHg)	154.3 ±21.2	143.8 ±18.1	0.04	154.3 ±22.4	149.7 ±17.9	0.2
DBP [¶] (mmHg)	89.8 ±12.8	84.1 ±11.7	0.08	87.5 ±13.9	86.9 ±12.8	0.8
Type-2 Diabetes			0.9			0.02
Yes	30 (76.9)	9 (23.1)		29 (50.0)	29 (50.0)	
No	36 (76.6)	11 (23.4)		51 (69.9)	22 (30.1)	

*LAP Lipid Accumulation Product, log-transformed; § systolic blood pressure; ¶ diastolic blood pressure.

Table 4 Systolic and diastolic blood pressure adjusted-means* among men and women according to genotype [mean ± SD, (95% CI)]

		Men			Women		
	Genotype	n	Mean ± SD (95% CI)	P value	Genotype	n	Mean ± SD (95% CI)
rs9939609	TT				TT		
		(n = 30)				(n = 45)	
						(n = 86)	
Systolic BP (mmHg)	153.7 ± 20.7 (146.1 – 161.3)	150.8 ± 20.9 (145.3 – 156.4)	0.6	155.9 ± 21.5 (149.6 – 162.2)	150.8 ± 20.4 (146.4 – 155.3)	0.2	
Diastolic BP (mmHg)	89.9 ± 12.5 (85.4 – 94.4)	87.7 ± 12.7 (84.5 – 91.0)	0.5	87.5 ± 12.7 (83.7 – 91.2)	87.2 ± 12.1 (84.6 – 89.9)	0.9	
Mean BP (mmHg)	111.1 ± 13.7 (106.2-116.0)	108.8 ± 13.5 (105.2-112.3)	0.5	110.6 ± 13.7 (106.5-114.7)	108.2 ± 13.7 (105.3-111.2)	0.5	
rs17782313	TT				TT		
		(n = 66)				(n = 80)	
						(n = 51)	
Systolic BP (mmHg)	154.2 ± 20.3 (149.2 – 159.1)	144.2 ± 20.1 (135.3 – 153.2)	0.05	154.1 ± 20.6 (149.5 – 158.6)	150.2 ± 20.7 (144.3 – 155.9)	0.3	
Diastolic BP (mm Hg)	90.1 ± 12.2 (87.2 – 92.9)	83.2 ± 12.1 (77.9 – 88.5)	0.03	87.5 ± 12.5 (84.8 – 90.2)	86.9 ± 12.9 (83.5 – 90.5)	0.8	
Mean BP (mmHg)	111.3 ± 13.5 (108.1-114.6)	103.9 ± 13.4 (98.0-109.8)	0.02	109.8 ± 13.4 (106.8-112.7)	107.9 ± 13.5 (104.1-111.7)	0.5	

* Means adjusted for age and BMI.

described only in morbidly obese individuals with rare mutations in the *MC4R* gene and in animal models. The association was further evaluated in analyses by gender, showing that men carrying the C allele for *MC4R* had lower diastolic and mean blood pressure compared with TT homozygotes.

Genome-wide association studies have been identified a number of genetic variants associated with obesity and their role in obesity-related vascular diseases [32]. Frayling et al. [8] showed for the first time the contribution of the SNP rs9939609 in *FTO* on excess of weight, and this result has been replicated in several populations [4,5,10,11]. As expected, common variant of *FTO* was associated with BMI in our overall population, but the analysis by gender confirmed only a trend toward association. Body Adiposity Index, a simple index which detects the percentage of total fat was significantly higher among women carrying *FTO* risk allele, and the effect of the gene on women body weight could be essentially over body fat. Among men, the association between *FTO* and BMI has not been confirmed [33] or it was weakened [34]. Another simple measure correlated with total and abdominal obesity is neck circumference [35], which was higher in men and women with risk allele A. This association has also been confirmed in European adolescents [36].

For the overall population, common variant near *MC4R* rs17782313 was associated with BMI and there was a trend to have subjects with higher BAI among CT/CC carriers. Analyses conducted by gender showed that in addition to the association of neck circumference

with *MC4R* genotype, the trend toward higher waist circumference and Lipid Accumulation Product suggest an effect of the risk allele C on visceral obesity in women with hypertension. Mutation carriers on *MC4R* had increased lean mass [7] and the variant near *MC4R* could reflect this effect among in men, who had proportionally more free-fat mass comparing to women. Furthermore, men and women had differences regarding metabolism of free fatty acids, which increased accumulation on visceral adipose tissue in women when compared with men [37]. Among Chinese, no association was found between *MC4R* rs17782313 and abdominal obesity detected by waist circumference [38] and, in a European cohort, *MC4R* rs17782313 plus *FTO* rs1421085 were associated with abdominal obesity and metabolic syndrome. However, when analyzed separated, neither *MC4R* nor *FTO* were associated with any individual metabolic syndrome feature, including waist circumference [39].

In this study, type-2 diabetes mellitus was associated with women carriers of risk allele C for *MC4R* rs17782313, which remained significant after control for age and BMI. Studies that assessed the contribution of polymorphisms in *FTO* and *MC4R* genes on type-2 diabetes mellitus are controversial, probably due to ethnic differences regarding body composition and lifestyle among populations (significant differences about the frequencies of several common obesity susceptibility variants in or near *FTO* and *MC4R* were found in class III obese Hispanic patients, i.e.) [40]. Among hypertensive women, the effect of risk allele C for *MC4R* rs17782313 on type-2 diabetes mellitus could be mediated by

increased visceral adipose tissue. *MC4R* showed higher expression in mesenteric fat among obese and diabetic rats when compared with lean rats [18]. Besides, studies support that the association of *FTO* rs9939609 and the *MC4R* rs17782313 polymorphisms with type-2 diabetes and obesity could be modulated and depended on diet [23]. It is also suggested that both type-2 diabetes and obesity had a common genetic etiology from the same 16.3 encoding region where *FTO* is located, and probably this is not the only susceptibility gene on this region which share the risk for both obesity and type-2 diabetes [41]. Genetic predisposition to obesity and *FTO* common variants contributed to increased insulin resistance among Europeans, but weakly increased type-2 diabetes risk, which is mediated by BMI itself [42].

As seen in morbid obese - with no hypertension and with rare mutations in *MC4R* gene, this sample of hypertensive individuals carrier of risk allele C for common variant near *MC4R* had lower levels of blood pressure in comparison to homozygote non-carriers. After adjustment for age and BMI, the association remained significant in men. It has been widely demonstrated in animal models the contribution of melanocortin system on cardiovascular function [43], and, in human beings, it has been shown how centrally expressed melanocortin 4 receptor (*MC4R*) not only conveys hypothalamic signals suppressing food intake, but it is also involved in blood pressure control [21]. Common variants near *MC4R* could reflect the same effect, but is unknown if anti-hypertensive drugs or changes in lifestyle could modify the expression of these genes or the effects of both polymorphisms on blood pressure, as it has been shown [44]. Among different model species, it has been demonstrated signaling cascades and transcription factors for several obesity genes that could be useful for development of new drugs and for translational research [45].

This study has some limitations and strengths that should be taken into account when interpreting the results. The analysis of genotype by gender is exploratory and it is underpowered to detect small differences. Therefore, some associations that achieved statistical significance in the overall analysis remained only as a trend toward association (BMI and *FTO* genotype, for instance). In the other side, some associations remained significant, as neck circumference and *FTO* genotype, while others came up only for women (*FTO* and BAI). The associations of gene variants with anthropometric indexes should be confirmed in further studies, with statistical power to carry out analysis by gender.

In conclusion, this study shows a negative effect of *MC4R* rs17782313 on mean arterial pressure and diastolic blood pressure among men. Associations of some anthropometric indexes with polymorphisms are exploratory for both, men and women. The pathways for

these associations are not completely understood, but genetic variants near the *MC4R* gene may reflect the complexity of such mechanisms.

Abbreviations

BAI: Body Adiposity Index; BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; DNA: Deoxyribonucleic acid; *FTO*: Fat mass and obesity-associated; IPAQ: International Physical Activity Questionnaire; LAP: Lipid Accumulation Product Index; *MC4R*: Melanocortin 4 receptor; RR: Risk ratio; SNP: Single nucleotide polymorphism; TG: Triglycerides; WC: Waist circumference.

Competing interest

No potential competing interest relevant to this article were reported.

Authors' contributions

AM, LBM, FDF, SCF have made substantial contributions to conception and design; AM, USM, FS, SCF analyzed and interpreted the data; AM, LBM, FS have been involved in drafting the manuscript, and USM, FDF, SCF in the reviewing it critically for important intellectual content. The authors had full access to all of the data in the study and AM and SCF take responsibility for the contents of the article. All authors have given final approval of the version to be published.

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