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Prevalence of metabolically healthy obese phenotype and associated factors in South American overweight adolescents: A cross-sectional study

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ABSTRACT

Objective: The aim of this study was to verify the prevalence of metabolically healthy obese (MHO) phenotype and associated factors in South American adolescents who are overweight.
Methods: A cross-sectional study was carried out with 340 overweight adolescent boys and girls between 10 and 18 y of age. The participants were classified as MHO according to two definitions: absence of any metabolic syndrome component and absence of insulin resistance (IR). The MHO phenotype–associated factors analyzed were age, sex, nutritional status, waist circumference (WC), body composition, metabolic profile, and cardiorespiratory fitness. Multivariable logistic regression was used to determine predictors of MHO using odds ratios with 95% confidence intervals.
Results: The prevalence of MHO in South American overweight adolescents was 49.4% and 55.9% according to MS and IR criteria, respectively. Sex and WC were predictors of the MHO phenotype, considering MS classification criterion. For the IR criterion, age, WC, and triacylglycerol levels were independent predictors of MHO in adolescents. Cardiorespiratory fitness did not predict MHO phenotype in any of the criteria used.
Conclusions: The prevalence of MHO in South American overweight adolescents was high and varied according to the definition used. Age, sex, WC, and triacylglycerolslevel were independent predictors of the MHO phenotype in this population.

Introduction

The prevalence of obesity has reached epidemic proportions in adults and among children and adolescents [1]. Over the past 3 decades, the overweight frequency in adolescents increased from 5% to 17.6%, representing an increase of >150% [2]. Childhood obesity has been considered a pivotal risk factor for diseases such as hypertension, dyslipidemia, and type 2 diabetes, and is a strong predictor of adulthood obesity [3].

Conflictingly, scientific evidence has shown the existence of a group of obese individuals with a much lower likelihood of developing such conditions, referred to as metabolically healthy obese (MHO) [4–6]. MHO individuals have shown less health-related general risks than their metabolically unhealthy obese (MUO) counterparts [7,8].

Although the MHO phenotype presents a more favorable condition than MUO, longitudinal studies have confirmed that, compared with metabolically healthy normal-weight individuals, MHO individuals are still at increased risk for type 2I diabetes and cardiovascular diseases (CVDs) [9]. Moreover, studies have indicated that the MHO phenotype is not a permanent state and many of these individuals will transit to an MUO profile, increasing the risk for developing metabolic-related major diseases [10,11].

No standard definition criterion exists to classify MHO, whose prevalence varies from 6% to 75%, depending on the criterion used [12]. In a recent meta-analysis, Lin et al. [13] reported a 35% prevalence of MHO in obese adults. Prevalence varies significantly among regions, with the highest observed in Africa and South America [13].

Pimentel et al. [14] conducted a cross-sectional study with 258 Brazilian obese adults and reported a prevalence of MHO ranging from 70.9% to 72.1%, depending on the applied criterion. The distinct patterns of fat distribution by ethnicity may influence these differences

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[13]. Notwithstanding, studies developed in South America are still scarce, and appropriate ones are needed to better elucidate this issue.

To our knowledge, no study has investigated the prevalence of the MHO phenotype in South American adolescents. Most were performed in the European [15–23], North American [24–28], and Asian [29–31] populations and found a wide variation in prevalence and criterion for the definition of MHO phenotype in this specific age group.

Considering the lack of data regarding the prevalence of MHO in youth and especially the absence of data from South America adolescents, the aim of this study was to verify the prevalence and associated risk factors of MHO phenotype in South American overweight adolescents.

Materials and methods

Study design

This cross-sectional study was conducted under the framework of the NUTRI-BRACOL study, whose aim was to verify the effectiveness of risk behavior–changing programs focusing on nutrition and physical activity in the countries of Brazil and Colombia.

Participants

The sample was composed of 340 overweight adolescent boys and girls between 10 and 18 y of age. They were recruited through television, radio, and social media announcements in addition to meetings in schools near the university between 2009 and 2016.

The inclusion criteria considered to select the participants were as follows:

- Between10 and 18 y of age
- Diagnosed as overweight according to cutoff points proposed by Cole and Lobstein [32]
- Agreement provided by the individual and his or her legal guardian to fully participate in the assessments; signed informed consent form
- No genetic or endocrine diseases present
- Does not consume alcoholic beverages, glucocorticoids, psychotropic drugs, or anything that may influence the appetite regulation
- Does not use diuretics.

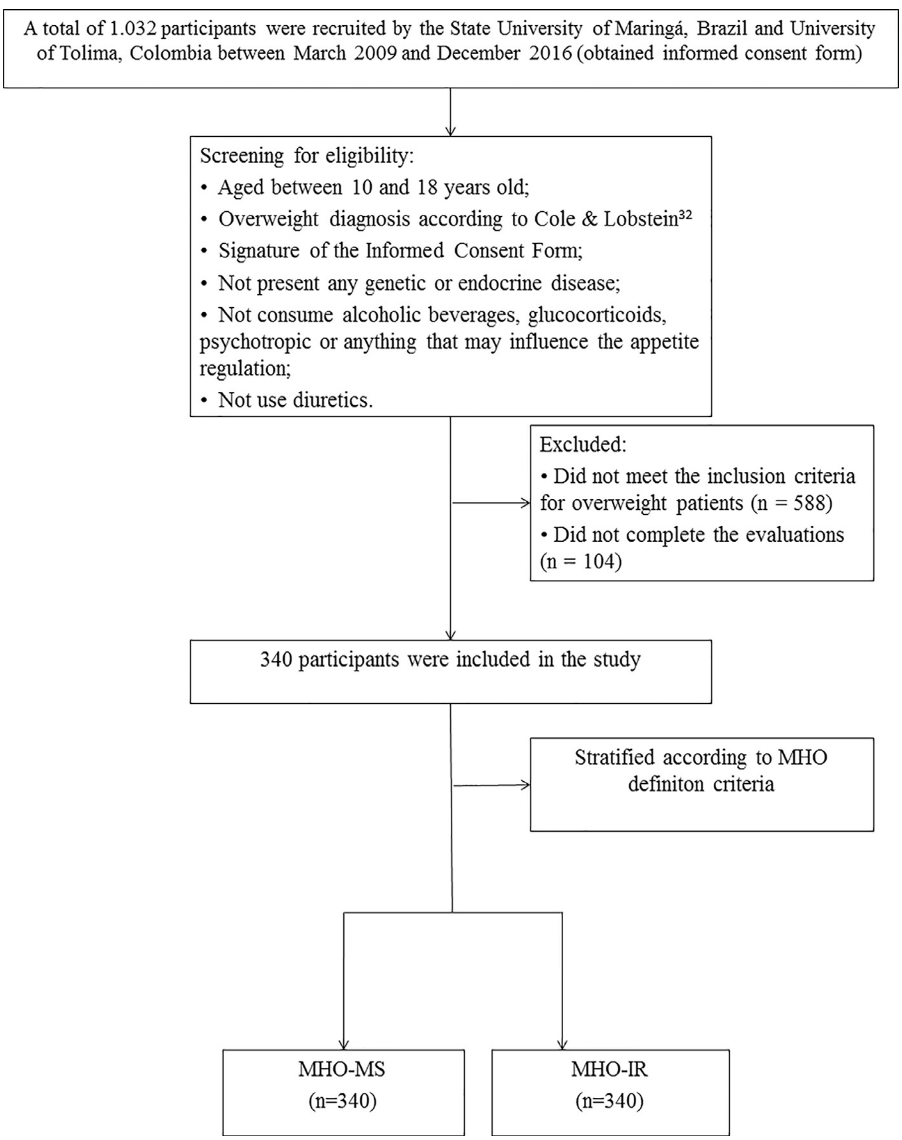

Fig. 1. Flowchart of sample recruitment and inclusion procedures. IR, insulin resistance; MetS, metabolic syndrome; MHO, metabolically healthy obese.

Individuals who did not fulfill the assessment protocols were excluded from the analysis. Recruitment and inclusion procedures are described in Figure 1.

Anthropometric, body composition, and hemodynamic analysis

To assess body mass (BM) and fat mass percentage (FM%), an 8-point tactile electrode multifrequency bioelectrical impedance (Octapolar, InBody 520 model, Korea) was used. Individuals were strongly urged to follow the instructions proposed by Heyward [33]. FM% was classified using specific cutoff points for age and sex proposed by FitnessGram [34]. Stature was measured using a 2.20 m wall-mounted stadiometer (Sanny, Sao Paulo, Brazil). The procedures recommended by Lohman et al. [35] were strictly followed. Body mass index (BMI) was obtained using the equation weight (kg)/ height $(m)^2$ and classified based on the cutoff points proposed by Cole and Lobstein [32]. Waist circumference (WC) was measured using an elastic metric tape (Sanny) at the midpoint between last rib and iliac crest [35]. The percentile 75th of specific age and sex cutoff points were used to classify WC [36]. Blood pressure was measured using an automated sphygmomanometer (Microlife, Rio de Janeiro, Brazil) after a 10-min rest period [37].

Biochemical analysis

Blood samples were collected in the morning (e.g., after 10-h fasting), in vacuum blood collection tubes with gel and centrifuged for 11 min at 3600g/min, to obtain the serum. Serum concentration of fasting plasma glucose (FPG) was determined by the hexokinase method, and total cholesterol (TC) by the enzymatic method. High-density lipoprotein cholesterol (HDL-C) was measured directly in serum, and triacylglycerols (TGs) by the Trinder reaction method. Insulin resistance (IR) was assessed by the homeostasis model assessment insulin resistance (HOMA-IR) [38].

Cardiorespiratory fitness assessment

The multistage 20-m shuttle run test [39] was used to assess cardiorespiratory fitness (CRF). The test started at a fixed velocity of 8.5 km/h and had progressive increments of 0.5 km/h at every stage (i.e., each minute) until the individuals reached volitional exhaustion. Maximal oxygen consumption (VO_2 max) was indirectly estimated using the last attained stage of each individual [39].

Classification of metabolic state

Two main criteria were used to classify the MHO phenotype. The first was based on the traditional metabolic syndrome (MetS) components, in which MHO-classified individuals did not present altered FPG (<5.6 mmol/l), TG (<1.7 mmol/l), systolic blood pressure (SBP; <130 mm Hg), diastolic blood pressure (DBP; <85 mm Hg) or HDL-C (≥1.03 mmol/L and ≥1.29 mmol/L for women ≥16 y), in accordance with the International Diabetes Federation cutoff points [40]. The second criterion considered IR, assessed by HOMA-IR, to classify the MHO phenotype (≤3.16) [41].

Statistical analysis

Data normality was tested by the Kolmogorov–Smirnov test. Descriptive statistic (i.e., median and interquartile range) was used to characterize the sample. Mann–Whitney U test and χ^2 test were performed to compare MHO and MUO groups regarding age, sex, BM, anthropometry, nutritional status, WC, FM%, and metabolic profile. Logistic regression analysis was performed to examine the associations between each variable and MHO phenotype. Subsequently, multivariate testing was performed by entering all of the associated factors of MHO into the final logistic regression model. The significance level adopted was $P \leq 0.05$. The analyses were carried out with the statistical software program SPSS version 20 (IBM, Armonk, NY, USA).

Ethics and trial registration

All study procedures strictly followed the requirements demanded on the Resolution 466/2012 of the Brazilian National Health Council. The research protocol was previously approved by the university ethics committee and registered in the Brazilian Register of Clinical Trials.

Results

Table 1 presents the characteristics of participants by MHO and MUO phenotypes according to two MHO definition criteria (i.e., MetS and IR). The prevalence of MHO individuals ranged from 49.4% to 55.9%, according to MetS and IR definition criteria, respectively. Females presented more prevalence of MHO than in males, in both criteria.

Considering MetS and IR criteria together, MHO individuals differ from MUO group on the following variables: age, stature, BM, BMI, WC, FPG, TG, SBP, DBP, and HOMA-IR. In addition, differences in stature and HDL-C between MHO and MUO phenotypes also were found when considering only the MetS criteria, and for FM% and VO_2 max when considering the IR criterion. Hence, MHO individuals presented a better metabolic profile than MUO individuals in both metabolic health definition criteria.

The predictors of the MHO phenotype after adjustment for age and sex are shown in Table 2. Using MS definition criterion, nutritional status (severe obese: odds ratio [OR], 0.40; 95% confidence interval [CI], 0.22–0.72; $P = 0.002$), WC (OR, 0.37; 95% CI, 0.22–0.62; $P < 0.001$), body fat (OR, 0.48; 95% CI, 0.27–0.87, $P = 0.015$), IR (OR, 0.51; 95% CI, 0.32–0.81; $P = 0.004$), and CRF (OR, 4.66; 95% CI, 1.40–15.51; $P = 0.012$) were significant predictors of

Table 1
Anthropometric, clinical, and biochemical characteristics according to MHO and MUO phenotypes considering both MetS and IR definition criteria*

	MetS (n = 340)			IR (n = 340)		
Variables	MHO (n = 168)	MUO (n = 172)	*P*-value	MHO (n = 190)	MUO (n = 150)	*P*- value
Sex, n (%)			<0.001			0.040
Male	32.8 (39)	67.2 (80)		48.3 (57)	51.7 (61)	
Female	58.4 (129)	41.6 (92)		59.9 (133)	40.1 (89)	
Age (y)	16 (2)	16 (1)	0.013	16 (2)	15 (3)	<0.001
Body mass (kg)	79.9 (20)	90.7 (31.6)	<0.001	80.1(23.5)	88.6 (25.2)	<0.001
Stature (m)	1.65 (0.12)	1.68 (0.15)	0.012	1.64 (0.12)	1.67 (0.15)	0.208
BMI (kg/m^2)	29.4 (5.3)	32.3 (7.8)	<0.001	29.4 (6.2)	32.3 (6.8)	<0.001
WC (cm)	87.5 (11.6)	93 (16.9)	<0.001	87 (12.6)	93.5 (14.5)	<0.001
FM %	41.7 (10.5)	43.5 (9.5)	0.082	41.7 (9.5)	43.8 (9.9)	0.007
FPG (mmol/L)	85 (12)	88 (11)	0.006	83. (12)	89 (9.2)	<0.001
HDL-C (mmol/L)	49 (9.9)	38.8 (10.5)	<0.001	44.7 (12.4)	43.1 (14)	0.093
TG (mmol/L)	79 (43)	95 (61.2)	<0.001	76.5 (40)	102 (51.2)	<0.001
SBP (mm Hg)	114.5 (12)	125.5 (18)	<0.001	118 (15)	122 (17.2)	0.020
DBP (mm Hg)	70.5 (9)	76 (13)	<0.001	71.5 (11.2)	74 (110)	0.012
VO_2 max (mL•kg•min^{-1})	29.8 (5.4)	29.3 (6.1)	0.267	30.1 (4.6)	28.5 (7.8)	0.001
HOMA-IR	2.5 (1.8)	3.4 (3.1)	<0.001	1.8 (1.2)	4.5 (2)	<0.001

BMI, body mass index; DBP, diastolic blood pressure; FM%, % of fat mass; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; IR, insulin resistance; MHO, metabolically healthy obese; MetS, metabolic syndrome; MUO, metabolically healthy obese; SBP, systolic blood pressure; TG, triacylglycerol; VO_2 max, maximal oxygen consumption; WC, waist circumference.
*Data are expressed in median (interquartile range).

Table 2
Association between nutritional status, waist circumference, body fat, cardiorespiratory fitness, and the presence of MHO by two different criteria*

	MetS			IR		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Nutritional status						
Overweight	1	–	–	1	–	–
Obese	0.76	0.44–1.32	0.329	0.41	0.23–0.73	0.002
Severe obese	0.40	0.22–0.72	0.002	0.27	0.15–0.51	<0.001
WC						
Normal	1	–	–	1	–	–
High	0.37	0.22–0.62	<0.001	0.35	0.21–0.58	<0.001
Body fat						
Normal	1	–	–	1	–	–
High	0.48	0.27–0.87	0.015	0.55	0.30–1.01	0.055
SBP						
Normal	–	–	–	1		
High	–	–	–	0.60	0.34–1.08	0.087
DBP						
Normal	–	–	–	1		
High	–	–	–	0.99	0.50–1.97	0.974
FPG						
Normal	–	–	–	1		
High	–	–	–	0.14	0.03–0.68	0.015
TG						
Normal	–	–	–	1		
High	–	–	–	0.26	0.13–0.55	<0.001
HDL-C						
Normal	–	–	–	1		
High	–	–	–	1.10	0.70–1.72	0.686
IR						
<3.16	1	–	–	–	–	–
≥3.16	0.51	0.32–0.81	0.004	–	–	–
CRF						
Normal	1	–	–	1	–	–
High	4.66	1.40–15.51	0.012	3.06	0.93–10.11	0.067

CRF, cardiorespiratory fitness; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; MetS, metabolic syndrome; MHO, metabolically healthy obese; SBP, systolic blood pressure; TG, triacylglycerol; WC, waist circumference.
*Adjusted for both age and sex.

MHO. For IR definition, nutritional status (obese: OR, 0.41; 95% CI, 0.23–0.73; $P = 0.002$, severe obese: OR, 0.27; 95% CI, 0.15–0.51; $P < 0.001$), WC (OR, 0.35; 95% CI, 0.21–0.58; $P < 0.001$), FPG (OR, 0.14; 95% CI, 0.03–0.68; $P = 0.015$), and TG (OR, 0.26; 95% CI, 0.13–0.55; $P < 0.001$) were predictors of MHO.

As a final step, the strongest variables (e.g., age, sex, WC, IR, and CRF for MetS, as well as SBP, HDL-C, and TG for IR) of the logistic regression models were introduced in the final models. Only sex and WC remained significant independent predictors of MHO by the MetS definition criterion. Significant independent predictors of MHO for the IR definition criterion were age, WC, and TG (Table 3).

Discussion

To our knowledge, this is the first study to characterize the prevalence and predictors of the MHO phenotype in South American adolescents who are overweight. The prevalence of the MHO phenotype varied from 49.4% to 55.9%, according to MetS and IR criteria, respectively. Age, sex, WC, and TGs were independent predictors of MHO in South American adolescents who are overweight.

Although several studies have shown the prevalence of MHO in adults [12,13] and young people, most of them involved European [15–23], North American [24–28], and Asian [29–31] populations. The present findings showed a higher prevalence of MHO than those found in European (35.4%), North American (37.6%), and Asian (35.4%) adolescent-based studies that used the same criteria for MHO phenotype [22,28,31]. In a recent meta-analysis, Lin et al. [13] reported an overall MHO prevalence of 35% in studies with obese individuals. However, there was a great variation according to the regions. The highest prevalence was observed in Brazil [14], and Africa [42]. The researchers attributed it to the distinct patterns of fat distribution by ethnicity. Obese individuals in these regions might have less visceral adipose tissue and less ectopic fat deposition than in other ethnicities [14,42].

Similar to previous studies in adults [43] and adolescents [27,29], we confirmed that WC was significantly associated with the MHO phenotype, supporting the hypothesis that visceral fat accumulation is a strong predictor of adverse health in the obese population [6,7]. Although obese individuals have high rates of total body fat, WC has been shown to be a better predictor of the MHO phenotype [43]. In fact, we found that high values of WC reduced the odds of being MHO at 50% to 60%. These findings corroborate with those found by Li et al. [29] in a sample of obese Chinese children and adolescents. However, there is no evidence that South American children and adolescents have lower WC than any other population worldwide and that this could be associated with a higher prevalence of MHO.

The TG level was shown to be a strong independent predictor of MHO phenotype in South American adolescents who are overweight when the IR criterion was used. Hypertriacylglycerolmia is a frequently found condition in patients with MetS and type 2 diabetes and has been considered an independent risk factor for CVDs [44]. In addition, TGs and HDL-C were considered independent predictors for MHO in a non-obese population that were followed for 7.8 y [45]. In agreement with these findings, we verified that individuals with high TG values presented 72% fewer odds of being MHO.

Table 3
Results of binary logistic regression model on the likelihood of MHO phenotypes outcome including clinical and laboratory variables

	OR	95% CI	P-*value*
Model 1: MetS definition			
Age, y	1.01	0.88–1.17	0.855
Sex			
Male	1	–	–
Female	2.23	1.33–3.74	0.002
WC			
Normal	1	–	–
High	0.47	0.27–0.80	0.006
IR			
<3.16	1	–	–
≥3.16	0.64	0.39–1.03	0.066
CRF			
Normal	1	–	–
High	3.09	0.90–10.5	0.072
Model 2: IR definition			
Age, y	1.23	1.06–1.42	0.006
Sex			
Male	1	–	–
Female	1.00	0.58–1.73	0.99
WC			
Normal	1	–	–
High	0.38	0.22–0.66	0.001
SBP			
Normal	1	–	–
High	0.80	0.43–1.50	0.486
HDL-C			
Normal	1	–	–
High	0.78	0.48–1.26	0.315
TG			
Normal	1	–	–
High	0.28	0.13–0.60	0.001
CRF			
Normal	1	–	–
High	1.84	0.53–6.34	0.332

CRF, cardiorespiratory fitness; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; MetS, metabolic syndrome; MHO, metabolically healthy obese; SBP, systolic blood pressure; TG, triacylglycerol; WC, waist circumference.

Age and sex also were predictors of MHO, according to IR and MetS criteria, respectively. Although some studies have shown a higher prevalence of the MHO phenotype in adolescents than in adults [15,25] or the elderly [25], the difference of MHO prevalence between children and adolescents is poorly understood [19,20], mainly during adolescence (i.e., pubertal versus postpubertal) [17]. During puberty, children develop a transient state of IR that starts with puberty, peaks at Tanner stage 3, and returns to prepubertal levels by the end of puberty [46]. This could be understood as a metabolic risk at this stage, considering it is a transient state of metabolic alteration during puberty. In the present sample, which was composed mainly of pubertal and postpubertal adolescents, the older adolescents had 1.2 times more chance of being MHO than their younger counterparts, considering the IR criterion. Although some studies have found higher odds of MHO in prepubertal and pubertal [17,19] populations, it appears that the presence of MHO during puberty does not predict the presence of MHO in later stages of adolescence [17]. However, this issue still needs to be elucidated with prospective studies that follow individuals throughout the adolescence phase. The female sex was an independent predictor of MHO only for the MetS criterion. Female adolescents in the present study presented 2.3 times more likely to be MHO than their male counterparts. These findings corroborated with previous studies with adults [6,7] and adolescents [19]. Girls usually have more body fat than boys and the distribution of body fat is markedly different between them. Girls have lower fat levels in the visceral deposits and higher in the subcutaneous compared with boys. It seems to confer a lower level of systemic inflammation and metabolic risk [47].

Lifestyle behavior, such as physical activity and healthy dietary habits, have been suggested as an important predictor of the MHO phenotype [7]. However, the relationship between physical activity levels and the presence of the MHO phenotype is controversial in the literature. Prince et al. [26] found that greater time in moderate to vigorous physical activities was a significant predictor of MHO. On the other hand, Heinzle et al. [27], in a representative sample of North American children and adolescents, did not find an association between any physical activity domain and the MHO phenotype. These discrepancies might be explained by the use of questionnaires to estimate levels of physical activity [43]. In the present study, we estimated CRF, which is considered a direct physiologic measure of physical activity level and appears to be strongly associated with metabolic risk factors in adolescents [26,48]. Although CRF has been shown to be a strong predictor of the MHO phenotype in the unadjusted analysis, when the model was adjusted for other predictor variables, this prediction disappears. These findings are in line with those found by Sénéchal et al. [24], in which there was no association between high levels of CRF and the presence of the MHO phenotype in adolescents. The association between elevated levels of physical activity or CRF and the presence of MHO are more evident in the adult population owing the notable decline in physical activity levels compared with young people [49]. Other lifestyle predictors might be more related to this phenotype in obese youth.

The present study had several limitations that should be mentioned. First, because of the lack of consensus on the definition of the MHO phenotype, our results are difficult to compare with others. Notwithstanding, we used the two most common criteria to define MHO in the pediatric population. Second, we did not collect a lot of data regarding pubertal development, lifestyle, psychological, and socioeconomic factors that could be included in the predicted model. Third, by the nature of the study (e.g., cross-sectional design), it was not possible to establish a cause-and -effect relationship.

Despite these limitations, however, the strength of the present study was that it was the first to present the prevalence of MHO in overweight adolescents from countries representing South America, and also some predictors of MHO phenotype in this population. Considering the lack of studies with South American samples and the presence of important ethnic differences in the prevalence of these phenotypes in the obese population, the present study brings important contributions to this theme.

Conclusion

The present study demonstrated that 49.4% to 55.9% of South American adolescents who are overweight are metabolically healthy, according to MetS and IR criteria, respectively. The independent predictors of MHO phenotype in this population were age, sex, WC, and TG levels, depending on the criterion used. WC was the only predictor that appeared in both criteria, demonstrating that visceral fat is pivotal on the relationship between obesity and metabolic dysregulation in adolescents. Future longitudinal studies are needed to confirm these predictors throughout childhood and adulthood.

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