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Cutoff values for HOMA-IR associated with metabolic syndrome in the Study of Cardiovascular Risk in Adolescents (ERICA Study)

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ABSTRACT

Objective: The aim of this study was to determine the distribution of homeostatic model assessment of insulin resistance (HOMA-IR) values and define its cutoff associated with metabolic syndrome (MetS) in the participants of the Study of Cardiovascular Risk in Adolescents (Estudo de Risco Cardiovascular em Adolescentes).
Methods: MetS was defined according to the International Diabetes Federation criteria. HOMA-IR values were calculated and tabulated by corresponding percentiles for age and sex. Receiver operating characteristic curves were constructed to identify the optimal cutoff values of HOMA-IR associated with MetS in the total population and by sex.
Results: We evaluated 37 815 adolescents ages 12 to 17 y. The highest HOMA-IR medians were found among girls and boys ages 12 and 14 y, respectively. Thereafter, values tended to decrease with age. The optimal cutoff values of the HOMA-IR associated with MetS in the total population, in female adolescents, and in male adolescents were 2.80, 2.32, and 2.87, respectively. Insulin resistance was prevalent in 19.1% (95% confidence interval, 17.7–20.7) of the total population, and the prevalence was higher among girls and overweight Brazilian adolescents.
Conclusions: These findings may serve as new reference points for detecting insulin resistance in Brazilian adolescents.

Introduction

Metabolic syndrome (MetS) is characterized by a group of metabolic dysfunctions that occur simultaneously, leading to an increased risk for cardiovascular diseases (CVDs) and type 2 diabetes mellitus [1,2]. MetS is prevalent in 2.6% (95% confidence interval [CI], 2.3–2.9) of Brazilian adolescents, with the prevalence slightly higher in male adolescents than in female adolescents (2.9%; 95% CI, 2.5–3.4 versus 2.2%; 95% CI, 1.8–2.8) [3].

Although the etiology of MetS remains unclear, there is strong evidence suggesting that insulin resistance (IR) triggers the development of hyperglycemia, hypertension, and dyslipidemia, which are all components of MetS [2,4]. A transient, physiologic IR usually occurs during puberty, and is aggravated by obesity [5–8].

The hyperinsulinemic-euglycemic clamp is the gold standard for assessing IR, but its application in both clinical practice and population studies is limited owing to its high cost and complexity [9,10]. Among the alternative methods, the homeostatic model assessment of insulin resistance (HOMA-IR) [9,10] is a simple mathematical model that provides an indirect measurement of IR, requiring only one fasting glucose and insulin measurement value. The HOMA-IR index represents the relationship between pancreatic insulin secretion and the capacity to maintain adequate glycemic levels [9,10].

The HOMA-IR index has been validated in adolescents via comparisons with the hyperinsulinemic-euglycemic clamp method [11], and cutoff points have been proposed for this age group [12–18]. A study in China with a representative sample of school-aged children (i.e., those ages 6–18 y) has suggested a cutoff point of 2.6 for pubertal adolescents

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[12]. However, to the best of our knowledge, there are no studies on a representative sample of Brazilian adolescents that have suggested HOMA-IR cutoff points for this population. Thus, this study aimed to determine the distribution of the HOMA-IR values and establish the cut-off values associated with MetS among Brazilian adolescents.

Material and methods

Study design and sample

This study is part of the Estudo de Risco Cardiovascular em Adolescentes (ERICA; Study of Cardiovascular Risks in Adolescents), which is a national, cross-sectional, school-based study that enrolled adolescents between 12 and 17 y of age. The ERICA study was conducted between the first semester of 2013 and November 2014 [19]. The selected adolescents attended public and private schools in Brazilian cities with >100 000 inhabitants. Adolescents who were physically disabled or pregnant were excluded.

The sample size calculation and sampling design were fully described by Vasconcellos et al. [20]. Briefly, the researchers studied a complex sample, which was geographically stratified into 32 strata that comprised 27 capitals of Brazilian states and five cities with >100 000 inhabitants from each of the five Brazilian macro-regions. Sample selection was performed in three stages. First, in each stratum, the researchers identified schools that had a probability that was proportional to the number of students enrolled in the last 3 y of elementary school and in the last 3 y of high school, together with an inverse proportion of the distance between the city where the school was located and the capital of the Federated State. Second, in these schools, three combinations of school year and school shift (morning or afternoon) were selected. Finally, in each combination, one class was selected, and all of the students from this class were invited to participate in the study. In all, 1251 schools in 124 cities with >100,000 inhabitants were selected. The results of the ERICA study were nationally representative for the 32 strata and the five macro-regions of Brazil.

The sample weight was calculated using the products of the inverse of the probabilities of inclusion in each stage of the sample selection; these were calibrated by age and sex, considering the estimated number of adolescents enrolled in schools located in the geographic strata. The sample was calculated based on the 4% prevalence of MetS in adolescents, with a maximum estimation error of 0.9%, and a confidence level of 95%. Because sample selection was performed by school, shift and year, and class, a design effect of 2.97 was considered.

Assessments

Each selected school was contacted for the enrollment of the eligible participants and the planning of the data collection. All students (both those attending morning and afternoon shifts) who agreed to participate answered a self-reported questionnaire and were assessed for their anthropometric data and blood pressure measurements. Blood samples were collected after a 12-h overnight fast; as such, only students attending the morning classes were included in the analyses and in the study. The study protocols were described in detail by Bloch et al. [21].

Anthropometric assessment was performed by trained investigators. Body weight was measured to the nearest 50 g, using an electronic scale (Lider Balanças, São Paulo, Brazil). Height was measured in duplicate to the nearest 0.1 cm, using a portable stadiometer (AlturaExata, Belo Horizonte, Brazil), and the mean of the two measurements was used for the analyses. Body weight and height measurements were used to calculate the body mass index (BMI), and the BMI percentile curves by age and by sex, as developed by the World Health Organization, were used to classify the participants' nutritional status [22].

Waist circumference was measured to the nearest 0.1 cm, using a non-elastic tape (Sanny, São Bernardo do Campo, Brazil), at the midpoint between the lowest rib and the iliac crest.

Blood pressure was measured following the recommendations of the Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents [23]. Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured via the oscillometric method using an Omron 705-IT monitor, which has already been validated for adolescents [24]. Blood pressure was measured from the right arm with the participant in a sitting position. Three measurements were obtained within a 3-min interval, after a 5-min rest. The mean of the last two measurements was used for the analyses.

All biochemical tests were performed in a single certified laboratory. Plasma glucose levels were measured by the hexokinase method using an ADVIA 2400 Clinical Chemistry System. Insulin levels were measured via electrochemiluminescence assays using a Modular E170s (Roche, Indianapolis, IN, USA) unit. The serum lipid profile, which included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triacylglycerols (TGs), was analyzed using the enzymatic colorimetric method on a Modular Analyser (Roche, Indianapolis, IN, USA) [25]. HOMA-IR index was calculated using the equation proposed by Matthews et al. [26]:

$$\text{plasma glucose(mmol/L)} \times \text{insulin}(\mu\text{U/L})/22.5.$$

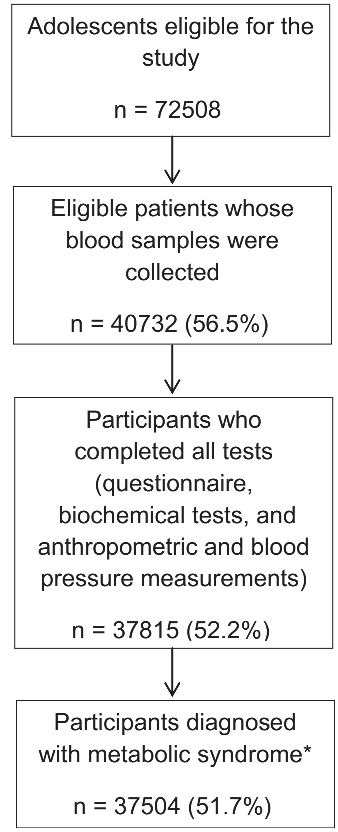

Fig. 1. Participant inclusion flowchart. *Results of all the tests required for metabolic syndrome diagnosis for 311 adolescents were not available.

Table 1
General characteristics of the adolescents by sex (N = 37 815)

Characteristic	Girls (n = 22 682)	Boys (n = 15 133)
	Mean (95% CI)	Mean (95% CI)
SBP (mm Hg)	108.4 (108–108.9)	114.4 (113.8–114.9)
DBP (mm Hg)	66.8 (66.4–67.2)	66 (65.6–66.4)
Fasting glucose (mg/dL)	85.1 (84.6–85.6)	87.6 (87.2–88.1)
Insulin (mg/dL)	10.3 (9.9–10.8)	8.6 (8.3–8.9)
HOMA-IR	2.2 (2.1–2.3)	1.9 (1.8–2)
Triacylglycerols (mg/dL)	79.3 (77.9–80.7)	76.9 (75.1–78.6)
HDL-C (mg/dL)	49.6 (49–50.3)	44.9 (44.3–45.5)
Waist circumference (cm)	71 (70.6–71.5)	73.4 (72.8–73.9)
BMI (kg/m^2)	21.6 (21.4–21.8)	21.2 (21–21.4)

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; SBP, systolic blood pressure

Table 2
Percentile distribution of HOMA-IR index by age and sex (N = 37 815)

	Girls (n = 22 682)					Boys (n = 15 133)				
Age, y	5th	25th	50th	75th	90th	5th	25th	50th	75th	90th
12	0.80	1.46	2.10	2.89	4.29	0.58	1.12	1.48	2.25	3.50
13	0.78	1.35	1.93	2.70	3.86	0.66	1.20	1.67	2.31	3.35
14	0.66	1.31	1.96	2.76	3.64	0.54	1.09	1.68	2.52	3.56
15	0.70	1.31	1.82	2.56	3.52	0.51	1.03	1.48	2.20	3.28
16	0.66	1.22	1.82	2.53	3.48	0.51	0.99	1.49	2.34	3.14
17	0.52	1.08	1.64	2.39	3.19	0.45	0.98	1.33	2.07	3.03

HOMA-IR, homeostatic model assessment of insulin resistance.

Definition of metabolic syndrome

MetS was diagnosed according to the International Diabetes Federation criteria [27] as follows: increased waist circumference (≥90th percentile for those aged <16 y and ≥90 cm for boys and ≥80 cm for girls aged ≥16 y) along with two or more of the following components:

- TG ≥ 150 mg/dL;
- HDL < 40 mg/dL for those aged <16 y and < 40 mg/dL for boys and < 50 mg/dL for girls aged ≥16 y;
- Glucose ≥ 100 mg/dL; and
- SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg.

Statistical analyses

Numerical variables were expressed as means with their 95% CI, whereas categorical variables were expressed as frequencies with their 95% CI. The distribution of the HOMA-IR values was tabulated corresponding to the 5th, 25th, 50th, 75th, and 90th percentiles. The HOMA-IR cutoff points associated with MetS were determined using the receiver operating characteristic (ROC) curves. The Youden index was calculated using the following equation:

$[(\text{sensitivity} + \text{specificity}) - 1]$.

The HOMA-IR values with the highest Youden index were set as the cutoff points.

All statistical analyses were performed using the Survey Module of Stata Software, version 14 (StataCorp, College Station, TX, USA), which corrects for the estimations of a complex sampling design. When the test was not available in the Survey Module, the researchers used weighted estimates that were based on calibrated weights (after the data stratifications).

Ethical considerations

This study was approved by the Research Ethics Committee of the Institute of Studies on Public Health, Federal University of Rio de Janeiro and by the Ethics Committees of each participating institution. Informed consent for participation was obtained from the parents/guardians.

Results

Of the 72 508 eligible students, 40 732 (56.2%) attended the morning shift and had their blood samples collected. Completed data (questionnaire responses, blood pressure measurements, anthropometric data, and biochemical results) were obtained from 37 815 (52.2%) adolescents. The mean age was 14.6 y in both sexes, and 60% of the participants were girls. MetS could be assessed in 37 504 (51.7%) adolescents, as 311 did not have the results of all the tests required for MetS diagnosis (Fig. 1). MetS was prevalent in 2.6% (95% CI, 2.3–2.9), 2.2% (95% CI, 1.8–2.8), and 2.9% (95% CI, 2.5–3.4) of the total population, girls, and boys, respectively.

Of the adolescents, 832 (2.2%; 95% CI, 1.9–2.7) were underweight; 26 849 (71%; 95% CI, 69.4–72.5) were normal weight; 6655 (17.6%, 95% CI, 16.5–18.7) were overweight; and 3479 (9.2%; 95% CI, 8.5–10) were obese. Table 1 shows the general characteristics of the adolescents.

Table 2 shows the percentile distribution of HOMA-IR by age and sex. HOMA-IR values were higher among girls than boys in all

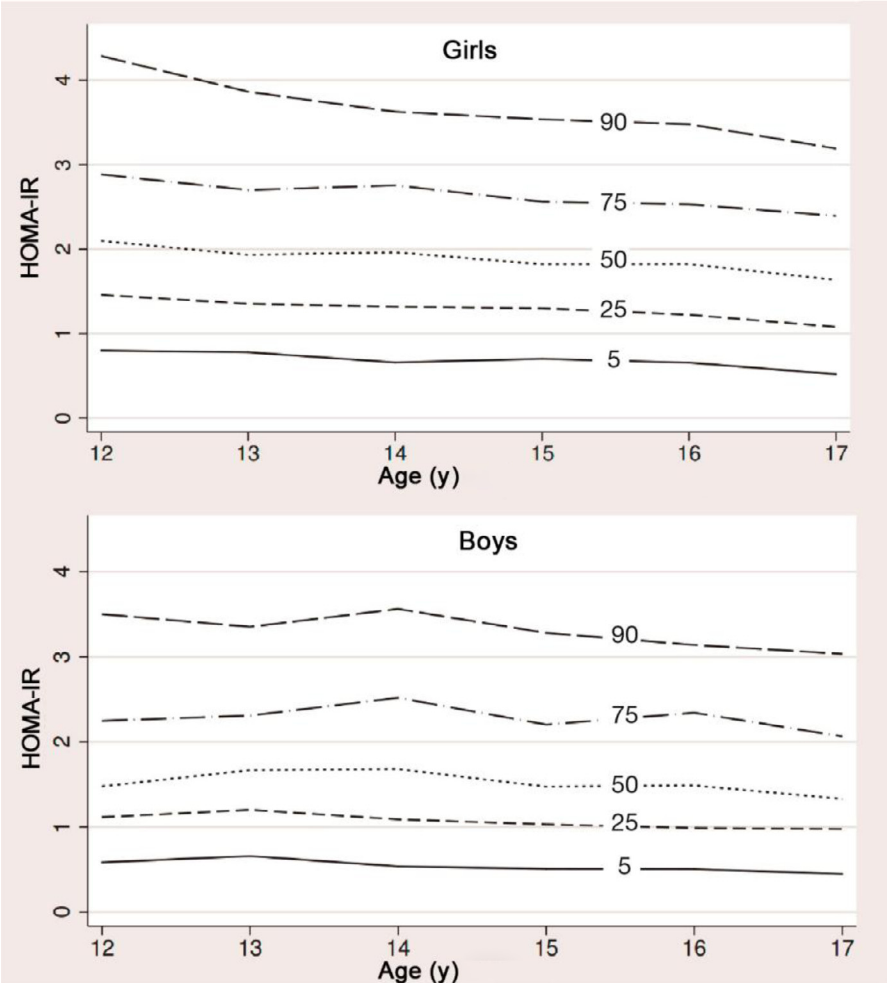

Fig. 2. Percentile distribution of the HOMA-IR index by age for Brazilian adolescent girls (n = 22 682) and boys (n = 15 133). HOMA-IR, homeostatic model assessment of insulin resistance.

age ranges, with median values ranging from 1.64 to 2.10 and 90th percentile values ranging from 3.19 to 4.29 among girls and median values ranging from 1.33 to 1.68 and 90th percentile values varying from 3.03 to 3.56 among boys. The median HOMA-IR was highest in girls ages 12 y of age and boys 14 y of age. Thereafter, values tended to decrease with age (Fig. 2).

The optimal HOMA-IR cutoff value associated with MetS was 2.80 (sensitivity, 73.1%; specificity, 83%; Youden index, 0.561) in the overall population, 2.32 (sensitivity, 86.8%; specificity, 67.4%; Youden index, 0.542) for girls, and 2.87 (sensitivity, 71.3%; specificity, 87.4%; Youden index, 0.588) for boys. The areas under the curves were 0.8417, 0.8333, and 0.8529 in the total sample, the girls, and the boys, respectively (Fig. 3).

According to the established HOMA-IR cutoff for the overall population, IR was prevalent in 19.1% (95% CI, 17.7–20.7) of the participants. Meanwhile, the prevalence rate according to nutritional status was 11.5% (95% CI; 10.4–12.8), 29.4% (95% CI, 26.3–32.7), and 61% (95% CI, 56.4–65.4) for normal weight, overweight, and obese adolescents, respectively. Prevalence by sex was assessed according to the determined cutoffs of 2.32 for girls and 2.87 for boys, and the results showed that IR was prevalent in 15.1% (95% CI, 13.7–16.8) of boys and 34.6% (95% CI, 32.4–36.9) of girls.

Discussion

To our knowledge, this was the first nationwide multicenter study to include a representative sample of Brazilian adolescents and define HOMA-IR cutoff points for this population. The HOMA-IR is a simple, low-cost mathematical equation [9,10] that has been widely used in clinical and epidemiologic studies [12,28–30] for an indirect measurement of IR. However, given that insulin sensitivity may be affected by several factors, such as age, sex, nutritional status, pubertal status, and ethnic differences [5–8,31–33], the accuracy of HOMA-IR in a population depends on age-, sex-, and ethnicity-specific cutoff points.

Among the most widely used statistical methods to determine the HOMA-IR cutoff is the construction of the ROC curves [29,30,34], which yield the best cutoff value of the variable in question based on the sensitivity and the specificity values [35]. The cutoff values obtained in the present study were similar to those reported by Yin et al. (2.6; 78% sensitivity and 67% specificity) [12], Singh et al. (2.5; >70% sensitivity and > 60% specificity) [13], and Burrows et al. (2.6; 59% sensitivity and 87% specificity) [14]. All of these studies considered MetS an undesirable outcome. MetS can begin during adolescence and persist through adult life [36,37]. Therefore, the cutoff point is defined on the basis of the diagnosis of MetS in adolescence, as morbidity and mortality owing to cardiovascular risk factors usually appear at a more advanced age.

Similar to the present study, these studies were cross-sectional investigations that included normal weight and overweight adolescents. They established their HOMA-IR cutoff points by attributing a similar importance to the sensitivity and the specificity values. However, none of these studies proposed cutoff points by sex, and the only study that included a representative population was that involving Chinese adolescents [12].

The prevalence of IR was not markedly different between the present study and the study by Burrows et al. [14], in which 16.3% of Chilean adolescents had IR according to a cutoff point of 2.6 (versus 19.1% prevalence rate in the present study at a cutoff of 2.80).

With respect to the prevalence of IR by nutritional status, the rate was 2.6 and 5.3 times higher among overweight and obese adolescents, respectively, than those with normal weight. These results were expected because being overweight is associated with IR [8].

As previously mentioned, insulin sensitivity is influenced by sex [5,33], and studies have shown that insulin sensitivity is lower in female adolescents than in male adolescents [7,38]. This may be due to differences in the changes in the body composition between boys and girls during adolescence [5,39]. Although boys tend to gain more lean mass, reflecting an increase in their muscle mass and a decrement in their fat percentage, girls gain body fat mass, which is necessary for menarche and the regulation of their menstrual cycle [39]. The results of this study support these reports, as IR was 2.3 times more frequent in female adolescents than in male teenagers. Additionally, the HOMA-IR medians and 90th percentile values were higher in girls than in boys at all ages.

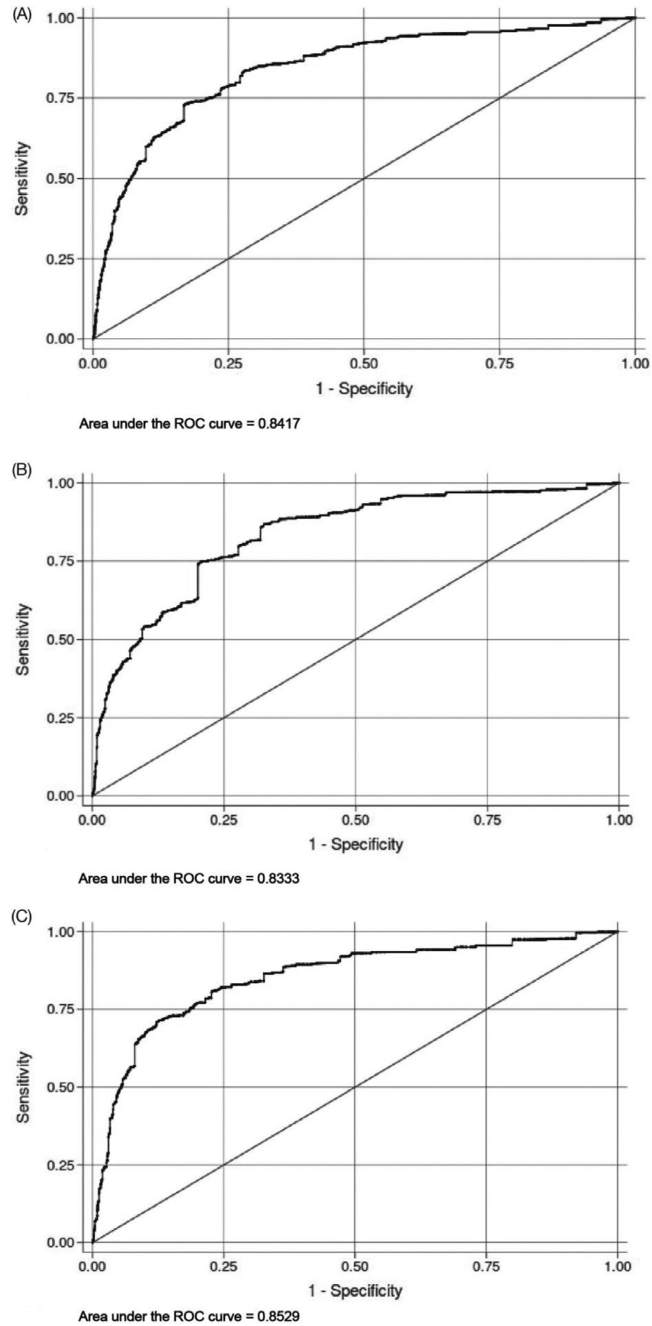

Fig. 3. ROC curve of the HOMA-IR cutoff points associated with metabolic syndrome. ROC curve analyses (**A**) in the overall population, (**B**) in the female adolescents, and (**C**) in the male adolescents. HOMA-IR, homeostatic model assessment of insulin resistance; ROC, receiver operating characteristic.

Furthermore, the median HOMA-IR values in the present study were the highest in girls and boys ages 12 and 14 y, respectively, whereas they were the lowest at the end of puberty (~17 y). This tendency of decreased HOMA-IR values as age increases is attributed to the physiologic decline of insulin sensitivity at the onset of puberty, with a subsequent recovery of normality at the end of this period [6,7].

According to the cutoff points established for each sex, we found that it can be more appropriate to consider 75th percentile for females and 90th percentile for males in the assessment of HOMA-IR values through their distribution in percentiles in the present study.

Several limitations regarding HOMA-IR should be discussed. First, the index is calculated from fasting parameters [26], a condition in which glucose is being taken up primarily by insulin-independent tissues [40]. The second limitation is the proportionality between insulin levels and the degree of IR [40]. Another point is that HOMA-IR assumes that IR is similar in the liver and peripheral tissues [9,40]. Finally, to our knowledge, there is no standardization between the laboratories as to the types of assays used for the determination of plasma insulin. The most appropriate assays are those that are not influenced by proinsulin levels [9]. Despite these issues, HOMA-IR remains a useful tool for population studies because of its convenience and its strong and significant correlation with the hyperinsulinemic-euglycemic clamp method [11,26]. Although the hyperinsulinemic-euglycemic clamp method is considered the gold standard for evaluating IR, it is costly, thus limiting its application in clinical and epidemiological studies. Accordingly, HOMA-IR is more commonly used because of its convenience.

Aside from the issues in HOMA-IR, this study had other limitations. The information about sexual maturation was self-reported; hence, it was susceptible to bias [41]. As such, these data were not included in the analyses. Moreover, the study was cross-sectional in design, and thus cause−effect analysis could not be conducted. However, the present study has strengths such as sample strategy and sample size.

Conclusions

The optimal HOMA-IR cutoff values associated with MetS were 2.80, 2.32, and 2.87 for the overall study sample, female adolescents, and male adolescents, respectively. According to these cutoff points, IR was more prevalent in girls and overweight Brazilian adolescents. These cutoff points may serve as new reference for detecting IR in Brazilian adolescents.

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