Trabajo Original

Obesidad y síndrome metabólico

Waist-to-height ratio cut-off points to predict obesity in adolescents and association with inflammatory markers

Puntos de corte de la relación cintura-altura para predecir la obesidad en adolescentes y asociación con marcadores inflamatorios

Wyllyane Rayana Chaves Carvalho, Ana Karina Teixeira da Cunha França, Alcione Miranda dos Santos, Luana Lopes Padilha, Eduarda Gomes Bogeа


Introduction: obesity increases inflammatory molecules and cardiovascular risk even in young populations. New indicators are being investigated, including the waist-to-height ratio (WHtR) to predict obesity and the relationship with inflammatory markers in childhood and adolescence.

Objective: to identify the cut-off points of the WHtR to determine obesity and its association with inflammatory markers in adolescents in São Luís, state of Maranhão, Brazil.

Methods: this is a cross-sectional study, with 2,209 adolescents aged 18 and 19, belonging to the third phase of the birth cohort entitled “RPS”, carried out in 2016. The total area under the ROC curve (AUC) was identified to assess the predictive capacity of WHtR in relation to body fat percentage (%BF), obtained by air displacement plethysmography (ADP). The association of WHtR with inflammatory markers interleukin-6 (IL-6), tumor necrosis factor (TNF-α) and C-reactive protein (CRP) was evaluated.

Results: prevalence of obesity by the %BF was 10.3 % in males and 40.4 % in females. The cut-off points for the WHtR were 0.50 for females and 0.51 for males, with an AUC of 0.90 (95 % CI: 0.88-0.92) and 0.93 (95 % CI: 0.90-0.97). There was an association of elevated WHtR with higher levels of IL-6 and CRP (p < 0.05).

Conclusion: the predictive capacity of WHtR for obesity was excellent. Elevated values of the WHtR were associated with early inflammatory markers. This study contributed to the identification of cut-off points for simple and low-cost anthropometric indicators.

Keywords: Obesity. Waist-to-height ratio. ROC curve. Inflammation.

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INTRODUCTION

Over the past four decades, obesity in younger individuals has increased worldwide from less than 1% (11 million) in 1975 to near 6% in girls and near 8% in boys (124 million) in 2016. In general, the number of obese aged between five and 19 years has grown more than ten times (1).

In Brazil, the obesity prevalence is even higher in this population, with rate at 8.4% in the age group 12 to 17 years in 2015 (2). The growth of the disease in individuals ages 18 and over is also relevant, increasing by 11.8% in 2006 to 19.8% in 2018 (3). Evidence shows that comorbidities may be associated with obesity even in childhood and adolescence (4), inducing changes in adipose tissue function and increasing the amount of inflammatory mediators such as CRP and pro-inflammatory interleukins (5).

Therefore, measuring obesity in individuals is crucial for early intervention (6). The existing measurement methods have great variability in accuracy, complexity, costs, and availability of each one (7,8). Body mass index (BMI) is the most used in population studies to monitor obesity, although it does not measure adipose tissue (9). To this end, other measures and anthropometric indices have emerged to assess abdominal adiposity, including the waist-to-height ratio (WHtR) (10), which is a good indicator also in adolescents (11). Some researches show that WHtR has a good correlation with visceral fat and cardiovascular diseases (11-15).

National and international studies proposed the cut-off point for WHtR at 0.50 or close to this point, based on BMI and bioimpedance. However, despite its relevance, there is a lack of studies using robust samples and gold standard methods to propose WHtR cut-offs for adolescents (11-16).

Considering the practicality of simple and accurate anthropometric methods and indices to assess obesity in adolescents, the association with cardiovascular diseases, and changes in inflammatory markers, this study aimed to define the cut-off points for WHtR with better level of sensitivity and specificity, using more accurate methods to determine obesity and its association with inflammatory markers in adolescents.

METHODS

STUDY DESIGN

This is a cross-sectional study based on data from the RPS Birth Cohort Consortium (Ribeirão Preto, Pelotas, and São Luís). This work was based on the data of the third phase of the birth cohort from the municipality of São Luís (1997/1998). The detailed methodology of the cohort is described in other publications (17,18).

POPULATION AND SAMPLE IN THE STUDY

The third phase of the cohort was carried out with participants aged 18-19 years to assess nutritional outcomes, chronic diseases, mental health, and human capital, in 2016. In this phase, 2,515 adolescents were evaluated, of which 654 belonged to the birth phase and 1,861 were born in São Luís-MA in 1997, who were selected from the four Military Enlistment office in São Luís island, the 2014 school census, and universities and included to increase the power of the sample and predict future losses. The adolescents included later made all the tests and responded the questionnaires that were carried out with the adolescents in the birth cohort. A questionnaire was also applied to the mothers to collect perinatal data.

This study included individuals from the third-phase cohort of both sexes and those having anthropometric and body composition data. Participants lacking data on the WHtR and body fat percentage (%BF) were not included. After applying the criteria, 2,209 adolescents were eligible to compose the sample of the study. The loss was calculated at 12.1% of the sample due to lack of data.

DATA COLLECTION

This study used data on socioeconomic, demographic, anthropometric body composition, and inflammatory markers of adolescents. They were collected by trained researchers using ques-
tionnaires and measurement instruments. Data were entered in the web-based application Research Electronic Data Capture (Redcap®) (19), which is a secure web application for recording and storing research data.

Socioeconomic and demographic variables assessed: sex (male and female); age 18 years and 19 years (only two individuals were 17 years old, thus they were grouped into the 18 year old category); socioeconomic class according to the Brazilian Economic Classification-CEB (20) (A/B, C, and D/E); currently studying (yes and no); currently working (yes and no); self-declared skin color (black, brown, and white); and schooling (elementary school, high school, high school technical course, vocational technical course, higher education in progress, pre-university course, adult education). Anthropometric indices measured were body weight, height, and waist circumference. Weight (in kg) was measured on a scale attached to the COSMED BOD POD® Gold Standard ADP. Participants were instructed to stand in the center of the scale, barefoot and wearing lycra form-fitting clothing, tops for women and shorts for both sexes. Height (in cm) was measured using an Alturexata® stadiometer, with adolescents standing in the center of the equipment, arms alongside the body, upright position, looking at a point straight ahead, and wearing the same clothing used for measuring. Waist circumference (WC) was measured (in cm) using a 3-dimensional photonic scanner (3DPS) (TC manufacturer). This technology is used for body surface analysis to detect anatomical structure, through photogrammetry.

BMI was used to assess the ratio between weight (kg) and height (m²) and classified according to Z-score adjusted for sex and age. The recommendations by the WHO and used by the Ministry of Health of Brazil (21) were as follows: underweight (< Z-score -2); eutrophy (≥ Z-scores -2 and < Z-scores +1); overweight (≥ score-Z +1 and < Z-score +2); and obesity (≥ score-Z +2). To evaluate abdominal fat, the WHtR was calculated using the Slaghter’s equation (1998) and classified as obese (≥ 25 % for men and ≥ 30 % for women) and non-obese (< 25 % for men and < 30 % for women) (22).

The inflammatory markers interleukin 6 (IL-6), tumor necrosis factor (TNF-ALFA), and C-reactive protein (CRP) were measured in blood samples from a subsample of 533 individuals. Serum was separated and stored in Eppendorf Tubes® at -80 °C until analysis, using sterile and disposable material in compliance with biosafety regulations for biological material. Four (4) blood samples were collected by venipuncture from non-fasting adolescents in relation to the percentage of body fat obtained by ADP. The areas under the ROC curve (AUC) and the confidence intervals were determined and the WHtR values with the best balance between sensitivity and specificity were identified.

The ROC curve is a graphical method for evaluating, organizing and selecting diagnostic and/or prediction systems. AUC describes the probability of correctly identifying individuals who are true-positive and those who are not (23). AUC values close to 1.0 and between 0.90 and 1.0 are considered as highly accurate tests (24) and are statistically significant when the lower limit of the 95 % confidence interval (95 % CI) is greater than 0.50 (25). The Mann-Whitney test was used to compare the inflammatory markers in relation to the cut-offs identified for WHtR. Data were exported from the REDCap system and analyzed using the STATA® statistical program (version 14.0), with significance level of 5 % and CI of 95 % (95 % CI).

**ETHICAL ASPECTS**

The base project for this research, the RPS cohort, was approved by the Research Ethics Committee of the University Hospital - UFMA with Opinion No. 1,302,489.

**RESULTS**

The study included 2,209 adolescents with a prevalence of 18 years old (73.6 %), female (51.6 %), single (96.7 %), self-declared brown (64 %), and economic class A/B (51.6 %). Data indicated that 42.8 % of the adolescents reported having completed high school and 21.3 % had a paid activity (Table I). The prevalence of obesity among adolescents, according to BMI, was 4.1 % in males and 4.7 % in females (p value = 0.104) and, according to %BF, 10.3 % in males and 40.4 % in females (p value < 0.001) (Table II). The median WHtR (interquartile range) was 0.48 (0.45-0.52). In the comparison by gender, males had a lower WHtR median (0.47 vs 0.49; p value < 0.001) (data not inserted into a table).

The area of the ROC curve between WHtR and obesity was 0.93 (95 % CI: 0.90-0.97) for males and 0.90 (95 % CI: 0.88-0.92) for females, showing statistically significant predictive ability to identify obese individuals (lower limit of the 95 % CI [AUC] was > 0.50) (Fig. 1).

Table III describes the sensitivity and specificity values for the WHtR cut-offs.

**STATISTICAL ANALYSIS**

Categorical variables were described using absolute and relative frequencies and quantitative variables using means and standard deviation. Coefficients of asymmetry and kurtosis were calculated, and the Shapiro–Wilkinson Kolmogorov-Smirnov tests were performed to verify the normality of the numerical variables. The receiver operating characteristic (ROC) curve was used to analyze the predictive validity of WHtR in discriminating obese adolescents in relation to the percentage of body fat obtained by ADP. The areas under the ROC curve (AUC) and the confidence intervals were determined and the WHtR values with the best balance between sensitivity and specificity were identified.

The study included 2,209 adolescents with a prevalence of 18 years old (73.6 %), female (51.6 %), single (96.7 %), self-declared brown (64 %), and economic class A/B (51.6 %). Data indicated that 42.8 % of the adolescents reported having completed high school and 21.3 % had a paid activity (Table I). The prevalence of obesity among adolescents, according to BMI, was 4.1 % in males and 4.7 % in females (p value = 0.104) and, according to %BF, 10.3 % in males and 40.4 % in females (p value < 0.001) (Table II). The median WHtR (interquartile range) was 0.48 (0.45-0.52). In the comparison by gender, males had a lower WHtR median (0.47 vs 0.49; p value < 0.001) (data not inserted into a table).

The area of the ROC curve between WHtR and obesity was 0.93 (95 % CI: 0.90-0.97) for males and 0.90 (95 % CI: 0.88-0.92) for females, showing statistically significant predictive ability to identify obese individuals (lower limit of the 95 % CI [AUC] was > 0.50) (Fig. 1).

Table III describes the sensitivity and specificity values for the WHtR cut-offs.
Table I. Socioeconomic and demographic characteristics of adolescents from the RPS birth cohort (third stage), São Luís, Maranhão, Brazil, 2016

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,070</td>
<td>48.4</td>
</tr>
<tr>
<td>Female</td>
<td>1,139</td>
<td>51.6</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 years</td>
<td>1,629</td>
<td>73.7</td>
</tr>
<tr>
<td>19 years</td>
<td>580</td>
<td>26.3</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>2,136</td>
<td>96.7</td>
</tr>
<tr>
<td>Stable union</td>
<td>72</td>
<td>3.2</td>
</tr>
<tr>
<td>Widower</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>421</td>
<td>19.2</td>
</tr>
<tr>
<td>Black</td>
<td>368</td>
<td>16.7</td>
</tr>
<tr>
<td>Brown/mulatto/cabocla/brunette</td>
<td>1,406</td>
<td>64.0</td>
</tr>
<tr>
<td>Yellow/oriental</td>
<td>2</td>
<td>0.1</td>
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</table>

Table I (Cont.). Socioeconomic and demographic characteristics of adolescents from the RPS birth cohort (third stage), São Luís, Maranhão, Brazil, 2016

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's education in years</td>
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<td></td>
</tr>
<tr>
<td>Fundamental</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Complete high school</td>
<td>642</td>
<td>42.8</td>
</tr>
<tr>
<td>High school technical course</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>Technical or vocational course</td>
<td>120</td>
<td>8.0</td>
</tr>
<tr>
<td>Higher education in progressive</td>
<td>559</td>
<td>37.2</td>
</tr>
<tr>
<td>Pre-university course</td>
<td>112</td>
<td>7.5</td>
</tr>
<tr>
<td>Adult education</td>
<td>51</td>
<td>3.4</td>
</tr>
<tr>
<td>Economic classic*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/B</td>
<td>1,138</td>
<td>51.6</td>
</tr>
<tr>
<td>C</td>
<td>832</td>
<td>37.6</td>
</tr>
<tr>
<td>Total</td>
<td>2,209</td>
<td>100</td>
</tr>
</tbody>
</table>

*Brazilian Economic Classification Criteria (CEB).

Table II. Nutritional status of adolescents from the RPS birth cohort (third phase), São Luís, Maranhão, Brazil, 2016

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total n (%)</th>
<th>Men n (%)</th>
<th>Women n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>86 (3.9)</td>
<td>43 (4.0)</td>
<td>43 (3.8)</td>
<td>&lt; 0.104</td>
</tr>
<tr>
<td>Eutrophy</td>
<td>1,699 (77.0)</td>
<td>845 (79.0)</td>
<td>854 (75.1)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>324 (14.7)</td>
<td>138 (13.0)</td>
<td>186 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>98 (4.4)</td>
<td>44 (4.1)</td>
<td>54 (4.7)</td>
<td></td>
</tr>
<tr>
<td>%BF, by ADP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not obese</td>
<td>1,639 (74.2)</td>
<td>960 (89.7)</td>
<td>679 (59.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Obese</td>
<td>570 (25.8)</td>
<td>110 (10.3)</td>
<td>460 (40.4)</td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; %BF: percentage of body fat; ADP: air displacement plethysmography.

Figure 1.
Area under the ROC curve and 95 % CI between WHtR and obesity in adolescents of both sexes from the RPS (third phase) birth cohort, São Luís, Maranhão, Brazil, 2016. A. Male; area under the ROC curve 0.93, and 95 % CI: 0.90-0.97. B. Female; area under the ROC curve 0.90, and 95 % CI: 0.88-0.92.

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For females, WHtR of 0.50 was the cut-off showing the best balance between sensitivity (80.0 %) and specificity (80.1 %) to detect obesity. For males, 0.51 was found the most accurate cut-off (90.9 % sensitivity and 83.8 % specificity), and 0.50 also showed good sensitivity (92.7 %) and specificity (76.4 %). Female adolescents classified as obese (WHtR > 0.50) had significantly higher median values of inflammatory CRP and IL-6 markers (p < 0.001), whereas for males, only CRP showed significance for the cut-offs 0.50 and 0.51 (p < 0.001) (Table IV).

**DISCUSSION**

In this study, the predictive capacity of WHtR in determining obesity in Brazilian adolescents was evaluated in relation to the percentage of body fat assessed by ADP and its association with inflammatory markers. For females, the WHtR cut-off at 0.50 showed the best balance between sensitivity and specificity and was associated with higher levels of CRP and IL-6. For males, the cut-off at 0.51 showed the best balance, but the cut-off at 0.50 was also satisfactory, maintaining good sensitivity and specificity, and both were associated with higher levels of CRP only.

Positive aspects of this study include using ADP, which is considered as a gold standard for detecting obesity, as well as being the first Brazilian study to use ADP to identify the cut-off values for WHtR to predict obesity in adolescents associated with inflammatory markers. In addition, waist circumference for calculating WHtR was obtained from photonic scanner (3DPS) through photogrammetry, where cameras inside the equipment project light onto the individual’s body. From the calculation of the distance between the projected light beams and the extremities of the body, a three-dimensional model of the body surface is calculated.
formed. In studies with large samples, the great advantage of this technique is the average time to obtain the body image, which is much faster than traditional anthropometry. On the other hand, some limitations are the result of the fact that non-randomized sampling and inflammatory markers were carried out in only one subsample, although the sample size is considered to be valid for studies on this theme.

Adolescents classified as obese by BMI were 4.1 % of males and 4.7 % of females, which were lower than values described by the Brazilian literature with prevalence of around 8.4 % in this age group (2). The low prevalence of obesity in adolescents assessed by BMI may be related to the fact that São Luís is one of the state capitals with the lowest overall prevalence of overweight and obesity, according to the Surveillance of Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel), of the Ministry of Health (3).

Despite the low prevalence of obesity identified by BMI in these adolescents, percentage of body fat assessed by ADP showed higher values: 40.4 % of girls and 10.3 % of boys. This finding points to an increase in body fat, especially in females.

These data corroborate recent reports from a study carried out by the Imperial College of London and the World Health Organization (WHO) on the increase in body fat in increasingly younger individuals. In the last four decades, the number of obese children and adolescents between 05 and 19 years of age has increased worldwide, from 11 million in 1975 to 124 million in 2016 (1).

This trend is worrying, since studies show that adolescents with obesity have greater chances of becoming obese adults and body composition in this phase predicts that of adult life. In addition, it is at the stage of transition between adolescence and early adulthood that the disease manifests itself most often (26-28). It is of note the difference in the prevalence of obesity between the methods used in this study, which may be due to the characteristics inherent to each of them. BMI is calculated from simple anthropometric measurements, even though it makes no difference between fat mass and lean mass (29). Body fat percentage was determined by ADP, which is an accurate and reliable method of measuring body fat in adolescents, but it is costly and operationally complex for use in healthcare (12).

It is already clear that, besides the general obesity indicators, the central obesity indicators are important, including WHtR, which is useful for assessing the distribution of body fat and diagnosing high abdominal fat in adolescents (11). Studies have demonstrated that WHtR is a good indicator for children and adolescents’ health in comparison with other anthropometric indicators, as it is based on the assumption that for a given height, there is an acceptable degree of fat stored in the upper portion of the body. Some studies point to this indicator as having a good correlation with visceral fat and cardiovascular diseases (11,15). In this respect, it is pivotal to determine cut-off values for these age groups.

In this study, WHtR showed a high predictive capacity to identify obese adolescents in both genders, since the area under the ROC curve was equal to or greater than 90 % and the lower limit of the 95 % CI was greater than 0.50 (25). In addition, the cut-offs for WHtR at 0.50 for girls and 0.51 for boys were identified as having the best balance between sensitivity and specificity for detecting obesity.

These WHtR agree among the cut-off points found in literature. National and international studies (11,14,30-33) indicate WHtR close to 0.50 as the cut-off point to predict high body fat and risk of developing cardiovascular diseases in individuals of both sexes and populations of different age groups. However, the authors assessed obesity using less accurate anthropometric parameters such as BMI and WC and only Lin et al. (30) and Lins et al. (14) investigated adolescents.

Lin et al. (30) investigated 55,563 adolescents and young adults in Taiwan. The WHtR cut-off points to predict obesity were 0.48 for men and 0.45 for women, with the areas under the ROC curve below 80 %. In Brazil, Lins et al. (14) assessed the relationship of WHtR and metabolic changes in 37,815 adolescents aged 12 to 17 years and found cut-off points of 0.45 for girls and 0.44 for boys and the areas under the ROC curve of 0.74 and 0.70, respectively. It is worth noting that the abovementioned studies did not use more accurate methods to measure fat and showed regular area under the ROC curve (between 0.70 to 0.80). In addition, Lins et al. (14) evaluated adolescents a little younger than those in the present study.

Although in this study the 0.51 cut-off point for males is taken as the best balance between sensitivity and specificity, the 0.50 cut-off was also considered as adequate for detecting obesity and could be an option with still higher sensitivity (92.7 %) and good specificity (76.4 %). It is acknowledged that it would be practical for clinical application to use a single cut-off value for WHtR and 0.50 is already accepted for adults (11).

In addition to determining the cut-off points, the association of WHtR with cardiovascular risk was investigated. In general, research shows that this index is strongly associated with several cardiovascular risk factors and recommends its use in population studies in different age groups (34).

In the present study, high WHtR values were associated with CRP and IL-6 in females and only CRP in males. This finding is important to broaden the discussion about high levels of early inflammatory markers in obese adolescents and clarify this relationship. Notably, Brazilian and international studies that related WHtR to inflammatory markers were not found. CRP acts as a regulator of nitric oxide production in the endothelium and coordinates the production and secretion of various cytokines, increasing the pro-inflammatory activity of different adipokines. Elevated plasma CRP levels are considered as the greatest independent predictors of coronary artery disease (35).

Other studies have also investigated the relationship between inflammatory markers and obesity (36,37). The National Health and Nutrition Examination Survey (NHANES) in the United States evaluated 16,335 children between one and 17 years of age and found an increase in CRP in overweight and obese children and adolescents, by BMI, occurring in early childhood, continuing into adolescence and peaking between the ages 9-14 years (36).

In Brazil, only Bragança et al. (18) reported the association between higher IL-6 and CRP concentrations with obesity clas-
sified by BMI in the same sample of adolescents of the present study. Similarly, Oliveira (37) studied 53 adolescent girls and found association between fat mass and body fat percentage assessed by dual-energy X-ray absorptiometry (DXA) with CRP, but not with IL-6.

Mantovani et al. (38) evaluated inflammatory markers in 104 children and adolescents in Belo Horizonte and observed that plasma levels of tumor necrosis factor type 1 (sTNFR1) were significantly higher in the obese group. And all adipokines differed significantly when lean subjects were compared to overweight and obesity individuals. Jaleel et al. (2013) (39) evaluated 90 individuals (60 control and 30 obese) aged between five and 18 years in Pakistan and found an increase in serum levels of TNF-α, which were significantly higher in obese subjects compared to the control group. A study carried out in three cities in Spain with 446 children and adolescents aged 6-12 years old found that CRP, IL-6, and TNF-α were increased in obese individuals, as well as in those with the highest WHR, where TNF-α was associated with WHR, a sensitive indicator of central obesity (40).

The present study found high prevalence of obesity in adolescents, especially in females, according to the percentage of body fat measured by ADP. It also identified the cut-off points of WHR at 0.50 for girls and 0.51 for boys as having the best balance between sensitivity and specificity to diagnose obesity. However, it also recognizes that the cut-off at 0.50 could be chosen for males, since a single standardized value can be applied for both sexes, which would facilitate its use in healthcare. This cut-off value is also adequate for males as it maintained satisfactory sensitivity and specificity. Finally, from these cut-off points an association was observed between obesity and higher levels of IL-6 and CRP inflammatory markers.

In view of the increase in the prevalence of obesity, especially in young individuals such as adolescents, and the concomitant increase in health complications related to it, this study contributed to the determination of the cut-off value for WHR in adolescents. Given that WHR is a simple, fast and low-cost anthropometric indicator, it will help to improve the diagnosis of obesity in healthcare and, as it is related to changes in inflammatory markers, it will help to prevent early cardiovascular outcomes.

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