Pediatric RESEARCH

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POPULATION STUDY ARTICLE

Uric acid reference values: report on 1750 healthy Brazilian children and adolescents

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BACKGROUND: Our purpose was to determine reference values and determinants of serum uric acid (SUA) in children and adolescents.

METHODS: A fasting blood sample was collected from 1750 schoolchildren and adolescents (6–17 years). Puberty was defined according to the Tanner scale. Bodyweight, muscle mass, and body fat percentage were determined by bioimpedance. Data are given as cut-offs and mean ± standard deviation.

RESULTS: SUA level was higher in children that had already entered puberty (4.2 ± 1.1 mg/dL) than among prepubescent (3.6 ± 0.8 mg/dL; $p < 0.01$). Considering the 90 percentile (p90) as the upper reference value, the following values are proposed for boys and girls, respectively: <10 years or prepubescent: ≤4.5 mg/dL and ≤4.8 mg/dL; from 10 to 13 years: ≤5.7 mg/dL and ≤5.2 mg/dL; from 14 to 17 years: ≤6.4 mg/dL and ≤5.3 mg/dL. Muscle mass explained part of the variability in SUA after pubescence, acting as an independent variable for higher levels of SUA.

CONCLUSIONS: The sex, age, and phase of puberty influence SUA reference levels, and part of this influence could be explained by the higher muscle mass, mainly after the adolescence onset.

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IMPACT:

- The key message of this study is that high levels of uric acid in the blood are associated with metabolic syndrome and cardiovascular risk factors. These diseases should be prevented since the infancy
- However, it is necessary to establish reference values of uric acid (SUA) for children and adolescents.
- The Brazilian population is highly admixed and these values were not determined so far.
- We studied a robust sample of Brazilian schoolchildren and adolescents (6–17 years) and defined the 90th percentile of uric acid as the upper limit of normality for sex, age, and pubertal stage.
- These values can be used as a reference for other populations with similar characteristics.

INTRODUCTION

Increased levels of uric acid in the blood are often associated with cardiovascular risk factors in adults. While serum uric acid levels for adults have been well determined in the literature, values characterizing increases in serum uric acid (SUA) levels in children are still under discussion because such values can change according to sex, age, and pubertal development. Therefore, it is necessary to describe the determinants of SUA levels in this population, as well as to establish reference values for the different stages of this phase of the life cycle. However, the definition of reference values for SUA is not a simple task since the concentration of this substance in the blood depends on a complex interaction of dietary factors, muscle mass, and renal excretory capacity, and in children and adolescents, these parameters depend on sex, age, and pubertal phase.[1–3]

The prevalence of hyperuricemia has increased over the last decades, and it varies according to sex, age, and ancestry; the prevalence tends to be higher among males and non-white individuals.[4,5] Age seems to be a variable that shows a strong positive correlation with SUA levels. Previous studies have shown increases in uric acid levels over the years, with important differences evident in the average SUA levels between children and adolescents.[6,7]

A review of hyperuricemia in children has shown that different reference values are currently used to determine this condition; these values range from 4.9 mg/dL as the lowest cut-off point to 8.0 mg/dL as the highest one. There is not a well-established pattern among studies.[8] Isolated high SUA levels in children who have no presence of gout or nephrolithiasis might not be properly taken into account by pediatricians. However, studies such as the present one conducted by our group could emphasize the importance of pediatricians to examine a high SUA concentration as a marker of an increased risk for the development of cardiovascular diseases, such as hypertension and atherosclerosis in adulthood.

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From this standpoint, it seems important to determine the distribution of uric acid in healthy children, in our case in Brazilian children, evaluating the limits to be established based on the rationale of good medical judgment, clinical relevance, and statistical findings. Therefore, the aim of the present study was to determine the distribution of SUA in a sample of Brazilian children and adolescents.

METHODS

A cross-sectional study was conducted in a sample of children and adolescents (6–17 years) recruited in a social project (*Estação Conhecimento*, Serra/Espírito Santo-ES, Brazil), a project resulting from a partnership between the public sector and VALE mining company. Other subjects in the same age group were recruited from public schools in Vitória/ES, a municipality in the neighborhood of Serra. At the beginning of recruitment, ~2000 children and adolescents attended the social project in Serra, which provide free academic support and the opportunity to practice sports and participate in artistic activities. From 2014 to 2017, 1800 children and adolescents attended the Cardiovascular Investigation Clinic located at the Federal University of Espírito Santo for clinical and laboratory exams. Fifty children who met at least one of the following criteria were excluded from the analysis: the presence of comorbidities; the use of drugs that could influence the results, such as oral antidiabetics, insulin, statins, and corticosteroids; and/or missing data. Thus, a total of 1750 children and adolescents were ultimately included in this analysis (1442 from *Estação Conhecimento* and 308 from the public schools of Vitória). All the participants from *Estação Conhecimento* regularly attended public schools in the Serra municipality. All the data were collected in a single visit by trained investigators who were previously certified by a senior investigator. The exams were carried out the morning after an overnight fast.

The study was conducted according to the tenets of the Declaration of Helsinki, and the project was approved by the institutional Ethics Committee (registration number: 725.488). Written informed consent was obtained from parents or legal guardians, and assent terms were also obtained from adolescents.

Anthropometric measurements

Bodyweight was measured to the nearest 50 g and was measured using a previously calibrated electronic scale with participants barefoot and wearing only underclothes. Height was obtained to the nearest 0.1 cm with a wall-mounted scale. Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the top of the iliac crest and classified as normal or increased.[9] The waist-to-height ratio (WHtR) was calculated as the ratio between the waist circumference and height. Body composition, including determined muscle mass and body fat percentage (BFP), was obtained by tetrapolar bioimpedance (InBody 230, Biospace, Seoul, South Korea). For the classification of BFP, the parameters adopted by Freedman et al.[10] were used to determine normal body fat or high body fat (i.e., when BFP was higher than 26–42%, according to sex and age group).

The Tanner Scale was adopted to define the phases of sexual development according to secondary sex characteristics, with stage 1 being prepubertal, stages 2–4 being pubertal and stage 5 being postpubertal.[11,12] In addition, the participants were also divided into age groups that roughly corresponded to the prepubescent (6–9 years old), pubescent (10–13 years old), and adolescent (14–17 years old) phases.

Race/color was determined according to the Instituto Brasileiro de Geografia e Estatística (IBGE) standard,[13] and individuals were classified as either "white", "black", "indigenous" or "brown" ("*Pardo*"). "*Pardo*" individuals are generally defined as those with an admixed ancestry, which refers to a variable degree of European, African, and Native American ancestry.

Blood pressure was measured three times on the left arm after the participant rested for 5 min in a seated position with the arm at the level of the heart using an automated and validated digital oscillometric sphygmomanometer (Omron 705CP, Japan). The readings were taken with a 1-min interval between measurements, and the mean value of the two last readings was defined as the clinical blood pressure. In case of a variation of more than 5 mmHg between measures 2 and 3, a fourth measurement was performed, and the two measures with a difference closer to 5 mmHg were averaged.[14]

Biochemical measurements

Venous blood samples were collected under fasting conditions from the forearm using standard techniques. Samples were sent to a central laboratory (Laboratório Tommasi, Vitoria, Brazil) for determination of serum levels of total cholesterol (Chol), high-density lipoprotein cholesterol (HDLc), triglycerides (TG), glucose, creatinine, insulin, and uric acid. For those with TG levels <400 mg/dL, the low-density lipoprotein cholesterol (LDLc) level was calculated using Friedewald's formula.[15] Serum insulin levels were measured using an electrochemiluminescence immunoassay, and all assessments were performed with commercially available kits. Insulin resistance (IR) was estimated using the HOMA-IR index:[2] [fasting insulin (U/mL) × fasting glucose (mmol/L)/22.5].[16]

Statistical analysis

Continuous variables are shown as the mean ± standard deviation. Means were compared using Student's *t*-test for independent samples. Categorical variables are expressed as the numbers of individuals (*n*), percentages (%), and 95% confidence intervals (95% CIs). Pearson correlation was performed to estimate the relation between uric acid and body composition (body fat percentage and muscle mass). Multiple linear regression was performed to estimate the contribution of each variable to the total uric acid variability. Data were analyzed using SPSS 20.0 software (IBM, Chicago, IL), and statistical significance was set at $p < 0.05$.

RESULTS

Of the 1750 participants included in the present analyses, 1188 were children (6–12 years old—68%), 562 adolescents (13–17 years old—32%); 993 were boys and 757 girls (Fig. 1). Both

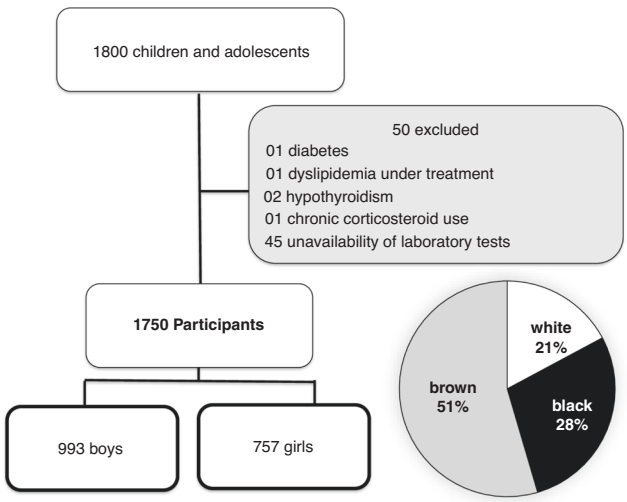

Fig. 1 Enrollment diagram of study participants. Of the 1800 children and adolescents included, 50 were excluded due to one or more exclusion criteria, given the final sample of 1,750 participants.

boys and girls showed similar characteristics with regard to age (mean = 11 years old), skin color (21.1% white, 27.6% black and 51.3% brown), and pubertal stage (24.8% prepubertal, 66.0% pubertal, and 9.2% postpubertal) (Table 1).

The distribution of SUA among boys and girls is shown in Fig. 2. The SUA concentration ranged from 0.6 and 8.4 mg/dL, and the mean was 4.0 ± 1.1 mg/dL, with higher SUA levels among boys. Examining only the adolescents (13–17 years old), the mean was 4.6 ± 1.1 mg/dL.

In Fig. 3, we observe differences in SUA levels between boys and girls at each pubertal stage. In the prepubertal stage, the values of SUA are similar in boys and girls. However, in the puberty and postpubertal stages, SUA levels are higher in boys than in girls. These findings were observed when the whole sample was considered and also when analyzing boys and girls separately, with higher values among boys. It was also observed that the age groups—6–9 years old, 10–13 years old, and 14–17 years old—showed values of uric acid that were similar to those found in the groups classified based on pubertal stage, with values that increased over the years and that were higher among boys, the difference being noticeable from 14 years old.

Table 1. General characteristics of the sample.

	Total ($n = 1750$)	Boys ($n = 993$)	Girls ($n = 757$)	p-value
Age (years)	11.1 (2.6)	11.1 (2.5)	11.2 (2.6)	0.496
Race/skin color				
White	356 (21.1)	198 (20.6)	158 (21.6)	0.592
Black	467 (27.6)	273 (28.4)	194 (26.6)	0.382
Brown	868 (51.3)	490 (51.0)	378 (51.8)	0.724
Pubertal staging				
Prepubertal	422 (24.8)	243 (25.2)	179 (24.3)	0.643
Pubertal	1123 (66.0)	630 (65.4)	493 (66.8)	0.551
Postpubertal	156 (9.2)	90 (9.3)	66 (8.9)	0.775

Continuous values are expressed as mean ± standard deviation and were analyzed using the Student's *t*-test. Proportions are expressed in *n* (%) and were analyzed using the chi-square test.

Therefore, clustering by age group was performed to identify the 90th percentile for each age group, according to sex, aiming to determine the superior limits. Considering the 90th percentile (p90) as the upper reference value, the following values are proposed for boys and girls, respectively: <10 years or prepubescent: ≤4.5 mg/dL and ≤4.8 mg/dL; from 10 to 13 years: ≤5.7 mg/dL and ≤5.2 mg/dL; from 14 to 17 years: ≤6.4 mg/dL and ≤5.3 mg/dL.

Considering the p90 for sex and age group, 11.4% of the entire sample was considered to have high SUA. When performing the analysis using the cut-off point of 5.5 mg/dL (reference value used in other studies), the prevalence of high SUA was 10.3% in the general sample and 21.5% among adolescents. The prevalence rates using different cut-off points and according to age groups are shown in Table 2. Using a cut-off point of 5.5 mg/dL, compared to the 90th percentile, the prevalence was very underestimated among children aged 6–9 years (prepubertal stage), and the prevalence was very low when the reference values for adults were used.

The mean age for the onset of puberty (Tanner stage 2) was 11.8 ± 2.2 years (11.9 ± 2.1 years for boys and 11.7 ± 2.2 for girls). SUA level was higher among individuals who had already entered puberty (4.2 ± 1.1 mg/dL) than among prepubescent (3.6 ± 0.8 mg/dL; $p < 0.01$). Regarding SUA distribution, the results indicated no differences in the average SUA level ($p = 0.946$) or in the frequency of high SUA ($p = 0.863$) between white and non-white individuals.

The relationship between corporal composition variables and SUA levels is shown in Fig. 4. Muscle mass is significantly correlated with SUA and is higher in boys ($r = 0.64$; $p < 0.01$) than in girls ($r = 0.39$; $p < 0.01$). Body fat percentage shows only a significant correlation with girls ($r = 0.20$; $p < 0.01$).

To determine which anthropometric and biochemical markers presented stronger interactions with SUA ($r > 0.20$), Pearson's correlation was used. SUA shower strong correlation to age, abdominal circumference, muscle mass, systolic blood pressure, creatinine, insulin, and HOMA-IR index. A stepwise multiple linear regression analysis was then performed for these variables. In boys, the model that better explained SUA variability within the sample

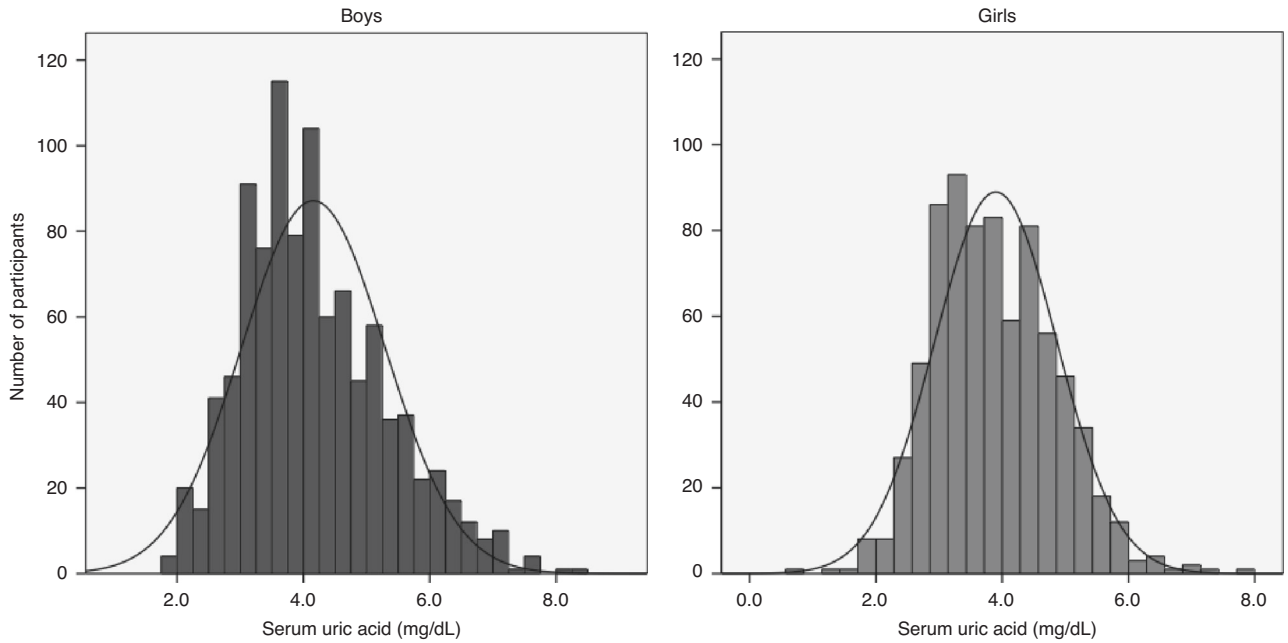

Fig. 2 Histograms of serum uric acid distribution in boys and girls. Observe that girls follow a normal distribution. In boys, however, there is shift to right of the distribution.

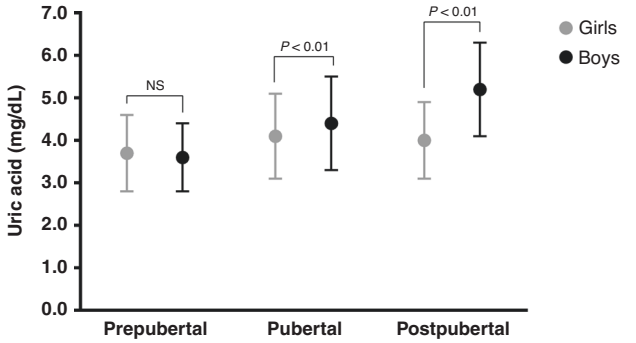

Fig. 3 Uric acid levels by sex, according to pubertal status. Data are the means and standard deviations. Observe that in the pubertal stage there is no difference between boys and girls. This difference become significant when pubertal or postpubertal boys and girls were compared. NS non significant.

Table 2. Prevalence of high serum uric acid (SUA) levels for boys and girls, according to age group and different cut-off values.

Age groups	Prevalence of high SUA > 90th percentile[a]	Prevalence of high SUA > 5.5 mg/dL	Prevalence of high SUA adult cut-off[b]
Boys			
6–9 years	13.1%	1.7%	0.3%
10–13 years	10.7%	12.5%	0.6%
14–17 years	12.5%	34.5%	3.0%
Girls			
6–9 years	10.9%	2.9%	0.8%
10–13 years	10.6%	6.4%	1.9%
14–17 years	11.9%	8.2%	1.9%

[a]90th percentile cut-off points: for boys, 4.5 mg/dL for 6–9 years, 5.7 mg/dL for 10–3 years, and 6.4 for 14–17 years; for girls, 4.8 mg/dL for 6–9 years, 5.2 mg/dL for 10–13 years, and 5.3 for 14–17 years.
[b]Reference value for adults: >7.2 mg/dL for men and >6.0 mg/dL for woman.

included muscle mass, waist circumference, and creatinine; these factors explained ~43% of SUA variability ($R^2 = 0.428$; $p < 0.001$), resulting in a linear equation in which uric acid mg/dL = 0.70 + 0.052 × muscle mass (kg) + 0.034 × waist circumference + 0.58 × creatinine (mg/dL). In girls, the only continuous variable that remained in that model was muscle mass; this variable explained 22.4% of SUA variability within the sample ($R^2 = 0.224$; $p < 0.001$).

DISCUSSION

To our knowledge, this is the first robust study of SUA distribution in a healthy Brazilian population including individuals in a wide age range (6–17 years old). A previous Brazilian study described the prevalence of high SUA levels and their association with cardiovascular risk factors in 129 children from the State of Paraíba, but the participants were all obese children and patients attended in the obesity center for children.[17] Another Brazilian study involved 350 children aged 8–9 years.[18]

The Brazilian study that examined only obese children and adolescents[17] used 5.5 mg/dL as the cut-off value and identified the prevalence of high SUA as 12.4%, which is a value higher than the percentage found in the present study (10.3%); this outcome suggests the influence of obesity on SUA levels.

Using the reference value of 5.5 mg/dL, the prevalence of hyperuricemia among the adolescents who participated in the present study was 21.5%, which is a value lower than that reported for North American adolescents in the NHANES study (30.2%).[19] It is interesting to note that among these North American adolescents, the SUA distribution showed a plateau that was more elevated than that found among the adolescents of the present study. In the NHANES study, the SUA concentration ranged from 1.9 to 12.1 mg/dL, with a mean of 5.1 mg/dL, while in the present study, the SUA concentration ranged from 1.5 to 8.4 mg/dL, with a mean of 4.6 mg/dL.

The KNHANES study, examining Korean children, defined hyperuricemia as SUA level >6.6 mg/dL for individuals 10–11 years old (both sexes) and >7.7 mg/dL and >5.7 mg/dL for males and females, respectively, within the age group of 12–18 years old.[20] In Japan, using a cut-off point of 7.0 mg/dL, the prevalence of hyperuricemia in participants aged 9–15 years old was found to be 8.8%.[21] Nonetheless, these reference values seem to be high, given that the reference SUA values in adults are 7.2 mg/dL for men and 6.0 mg/dL for women. Above 7.0 mg/dL, there would be a higher risk of uric acid crystallization and tissue deposition, with higher concentrations being associated with diseases traditionally linked to hyperuricemia, such as gout and nephrolithiasis. This solubility point of SUA is also used in studies to define the cut-off point for normality in adults. Thus, our reference values established from p90 for sex and age groups seem to be more suitable for the screening of children and adolescents with high SUA levels, who could prospectively develop cardiovascular risk factors that are associated with this prognostic biomarker.[22,23]

From our results, it is clear that one of the mechanisms involved in the increase in SUA throughout the life cycle is pubertal stage/sexual and hormonal maturation. However, our findings also demonstrate that the age groups of 6–9 years old, 10–13 years old, and 14–17 years old are almost similar to the classification based on the pubertal stage. Notably, age is a variable that is easier to use in the clinical setting than that of sexual maturation.

Laboratory assessments using reference values determined according to the pubertal stage are unusual, because this would, among other reasons, hinder the identification and understanding of the results by lay parents. In this context, there was an attempt to identify the superior limits (based on p90) for the age groups to determine reference values for each of these groups.

In individuals under 10 years old, the SUA values are similar in boys and girls and a unique reference value around 4.7 mg/dL is suggested by our data. Then, the values increase and beginning at 14 years old, there is a substantial elevation in males. Such low values among younger children were also observed in previous studies by Clifford et al.[6] and Kubota et al.,[8] in which it was demonstrated that SUA increases over the years and that differences between the sexes emerge beginning at 12 years old.

With regard to the differences between sexes, a plausible explanation may be linked to a genetic predisposition to higher renal urate reabsorption. A Japanese study showed that the renal uric acid receptor ABCG2 has differences in its expression among different ethnicities.[24] The increased renal expression of ABCG2 in males compared to females may partially account for the higher SUA levels observed in this sex.[25] Nonetheless, a mutation in the ABCG2 gene in females is associated with hormonal modifications.[26]

From this standpoint, the odds of detecting hyperuricemia would also be, in part, associated with a nonmodifiable factor, i.e., genetic inheritance. There are genetic polymorphisms that influence the expression of urate receptors, and previous studies have shown that gene–environment interactions might exist.[27]

Despite previous studies indicating a higher prevalence of hyperuricemia in African Americans[4] and Africans[5] than in white individuals, a Brazilian study did not show a relation between ethnicity and the prevalence of hyperuricemia in white and non-white adults, which could be explained by the high level of racial miscegenation among the Brazilian population.[28] Consistently, the present study also did not show such a difference, a result likely

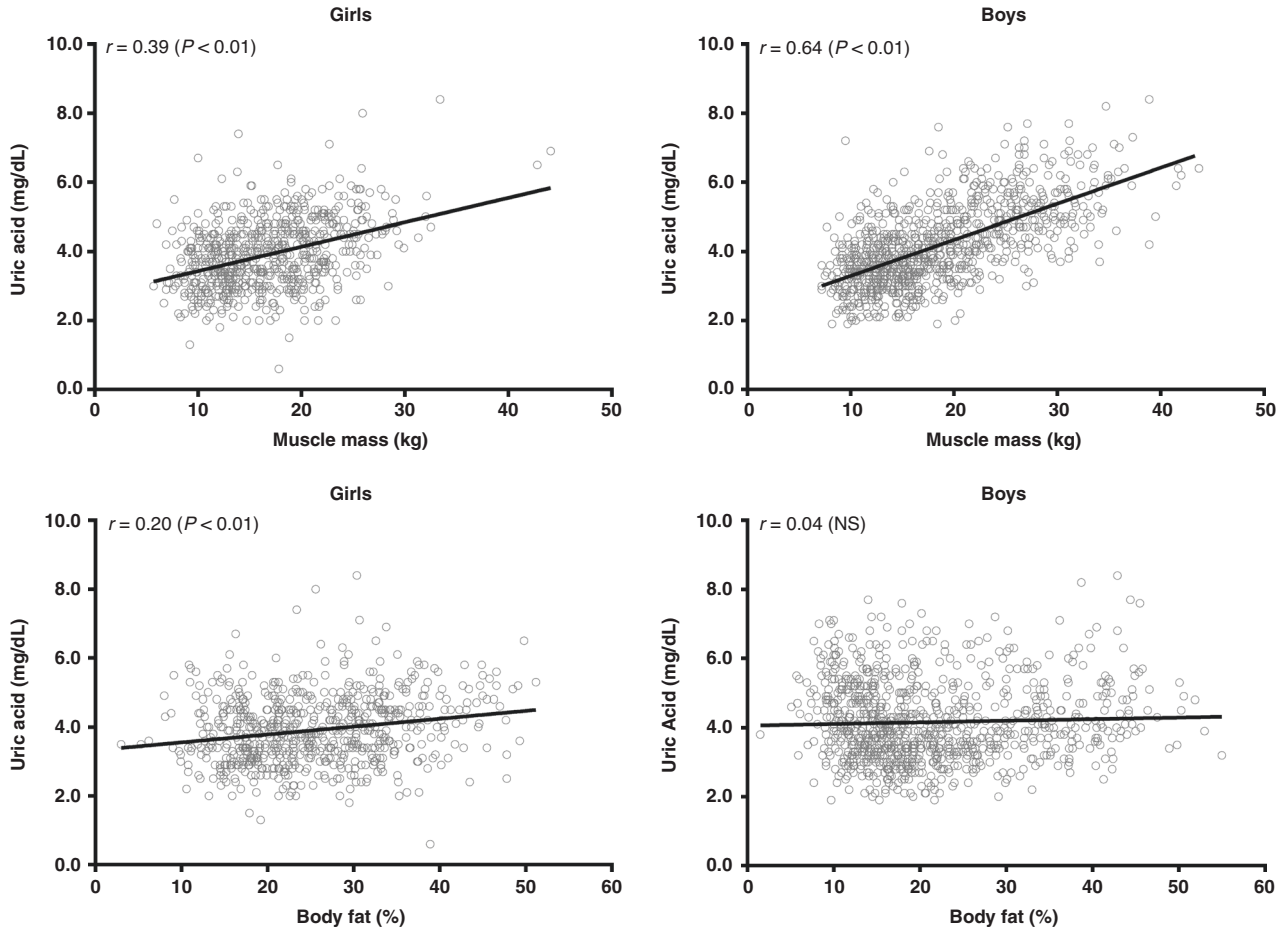

Fig. 4 Relationship between serum uric acid and body composition components (e.g., muscle mass and body fat percentage) in girls and boys. Regression line were calculated by the least square method. r = Pearson correlation coefficient. Observe the different contribution of fat mass in boys and girls. NS non significant.

associated with a high percentage (51%) of brown subjects included in our study.

Our findings suggest that a mediator of the effect of age on SUA could be muscle mass, represented mostly by the volume of muscular mass. The fast increase of muscle mass that accompanies the onset of adolescence in boys corroborates this interpretation of the present data. This finding is even more reasonable when it is considered that the stage of puberty influences body composition. Morphological modifications include changes in muscle mass, body fat distribution, and growth velocity.[29] SUA was higher in girls with high BFP. A study performed using part of our sample identified BFP as a good indicator of weight status.[30] Furthermore previous study of our group showed BMI has a direct correlation with BFP, girls were found to be more frequently overweight/obese.[31]

An advantage of our study in relation to previous studies is the large number and the large age range of participants. All the participants were regularly attending public schools within the two municipalities. Those individuals who presented with health conditions and/or the use of medications that could potential interfere with the results were removed. Therefore, we can consider the sample as composed of an apparently healthy group that is adequate for generating reference values for the general population. Suitable reference values for SUA were determined for each age group and sex, therefore avoiding underestimating increases in SUA levels that would already be considerably high for a certain age. Performing the analysis by age group allowed for an easier assessment by the healthcare professional who addressed these patient profiles.

Limitations

The data were collected from a convenient and nonrandom sample of students attending public schools in two municipalities. Therefore, the sample is not representative of the whole Brazilian population. Thus, such data should be used cautiously in regard to other populations.

CONCLUSION

The degree of puberty, age, and sex influence the distribution of SUA, and the average SUA level was higher among individuals who had already entered puberty. Muscle mass explained part of the variability in SUA, showing itself to be an independent predictor of higher levels of SUA.

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AUTHOR CONTRIBUTIONS

S.R.A.M.-M.: Drafting the article, data analysis, and interpretation. Approval of the final version of the manuscript. D.Z.: Data acquisition and article revision. P.R.O.: Data acquisition and article revision. R.O.A.: Concepcion and design of the project, data analysis, and article revision. J.P.B.: Data analysis and article revision. J.G.M.:

Conception and design of the project, data analysis, and final approval of the manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Statement regarding patient consent: The project was approved by the Ethics Committee of Universidade Federal do Espírito Santo (registration number: 725.488). Written informed consent was obtained from parents or legal guardians, and assent terms were obtained from adolescents. The procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

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