European Journal of Clinical Nutrition (2017), 1–6

www.nature.com/ejcn

ORIGINAL ARTICLE

C-reactive protein in Brazilian adolescents: distribution and association with metabolic syndrome in ERICA survey

DT Giannini[1], MCC Kuschnir[2], CL de Oliveira[3], KV Bloch[4], BD Schaan[5], FV Cureau[6], KMB de Carvalho[7], GM Dias[8] and M Szklo[9]

BACKGROUND/OBJECTIVES: C-reactive protein (CRP) is a marker of inflammation that has been shown to be predictive of cardiovascular diseases in adults. To evaluate the distribution of CRP as well as its association with metabolic syndrome and its components.

SUBJECTS/METHODS: This is a cross-sectional study on adolescents aged 12–17, participants in the Study of Cardiovascular Risk in Adolescents (ERICA). Anthropometric, biochemical and blood pressure data were collected from 6316 adolescents, selected from a random sample of students in the cities of Brasilia, Fortaleza, João Pessoa, Manaus, Porto Alegre and Rio de Janeiro. Metabolic syndrome was defined by the criteria proposed by International Diabetes Federation for adolescent. Poisson regression model with robust variance, taking into consideration the study's complex sampling design, was used to determine multivariate-adjusted prevalence rate ratios expressing the relationship of metabolic syndrome with CRP.

RESULTS: In adolescents with metabolic syndrome, CRP concentrations were five times higher (1.01 mg/l; interquartile range (IQR): 0.54–3.47) compared with those without metabolic syndrome (0.19 mg/l; IQR: 0.10–0.78). In multivariate Poisson regression analysis adjusted by sex, age and skin color, the prevalence of elevated CRP (>3.0 mg/l) was almost three times higher in adolescents with metabolic syndrome than in those without this condition (prevalence ratio (PR): 2.9; 95%CI: 2.0–4.3; $P<0.001$). Of the metabolic syndrome components, elevated waist circumference, low high-density lipoprotein-cholesterol and high triglycerides were significantly related to CRP in a graded (dose–response) manner.

CONCLUSIONS: The association of CRP with metabolic syndrome and its components suggests that inflammation may be useful in assessing cardiovascular risk in adolescents.

European Journal of Clinical Nutrition advance online publication, 24 May 2017; doi:10.1038/ejcn.2017.74

INTRODUCTION

Cardiovascular disease and type 2 diabetes,[1] are responsible for high mortality rates in the world.[2] C-reactive protein (CRP) is a marker of inflammation related to obesity and other cardiovascular risks in adults.[3] Although the data are scarce, the associations between CRP concentrations and cardiovascular disease (CVD) risk have been reported in children and adolescents.[1]

Metabolic syndrome (MS) is associated with subclinical inflammation,[4] and is an independent predictor of cardiovascular risk and type 2 diabetes in adults[5] and in children and adolescents.[6]

In contrast with adults, associations in youth are less likely to be confounded by chronic conditions. Therefore, studies on pediatric populations may contribute to the understanding of the relationship between obesity, inflammation, insulin resistance and metabolic syndrome. In addition, CRP may be a useful marker in when screening of children and adolescents for risk of developing CVDs and diabetes in adult life.[7]

Previous studies have assessed the prevalence of MS in Brazilian adolescents.[8,9] However, few studies[10] have investigated the association between components of MS and inflammatory markers in a representative sample. The aim of this study was to evaluate the distribution of CRP as well as its association with MS and its components in this population.

METHODS

This study is part of the Study of Cardiovascular Risk in Adolescents (ERICA, *Estudo de Risco Cardiovascular em Adolescentes*), which is a national, cross-sectional, school-based study, aimed to estimate the prevalence of MS and other cardiovascular risk factors in adolescents aged between 12 and 17 years.

Sampling weight was calculated by the products of the inverse of the probabilities of inclusion in each selection stage, and calibrated by age and sex, considering the estimated number of adolescents enrolled in schools located in the geographic strata included in the study. Sample size calculation was based on an expected prevalence of MS of 4%,[11] a maximum estimation error of 0.9%, a confidence level of 95%, and a design effect of 2.97. The sampling process has been fully described previously.[12]

The sample was divided into 32 strata, comprised of 27 capitals of Brazilian States and five cities with more than 100 000 inhabitants from each of the five geographic regions of the country. Stratification was done according to three categories: schools, year/shift classes combinations and

[1]Universidade do Estado do Rio de Janeiro, Hospital Universitário Pedro Ernesto, Divisão de Nutrição, Rio de Janeiro, Brazil; [2]Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas, Programa de Pós-Graduação em Ciências Médicas, Rio de Janeiro, Brazil; [3]Universidade do Estado do Rio de Janeiro, Instituto de Nutrição, Rio de Janeiro, Brazil; [4]Universidade Federal do Rio de Janeiro, Instituto de Estudos em Saúde Coletiva, Rio de Janeiro, Brazil; [5]Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [6]Postgraduate Program in Endocrinology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [7]Universidade de Brasília, Faculdade de Ciências da Saúde, Programa de Pós Graduação em Nutrição Humana, Brasília-DF, Brazil; [8]Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil and [9]The Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD, USA. Correspondence: Dr DT Giannini, Universidade do Estado do Rio de Janeiro, Hospital Universitário Pedro Ernesto, Av 28 de setembro, Universidade do Estado do Rio de Janeiro, 77 – Vila Isabel, Rio de Janeiro 20551-030, Brazil.
E-mail: denisegiannini@uol.com.br
Received 17 September 2016; revised 7 February 2017; accepted 14 April 2017

classrooms. Thus, the sample was representative at national, regional levels and also at the State capitals.

In this study, sample consists of 15 154 adolescents aged 12 through 17 years that attended morning classes in schools in six capitals: Brasilia, Fortaleza, João Pessoa, Manaus, Porto Alegre and Rio de Janeiro. These schools are located in all five Brazilian regions (two of them to the northeast), therefore, is a representative sample of these capitals. Excluded were adolescents who were pregnant, those who reported use of corticoids, anti-inflammatories, and antibiotics, and those with CRP levels $\geqslant 10$ mg/l (in order to remove the influence of acute inflammatory processes).[13]

Information about sex, age, type of school (public or private), sexual maturation, skin color, smoking and physical activity were obtained from a self-administered questionnaire using a personal digital assistant for entering the data.

Sexual maturation was determined using pictures depicting Tanner's sexual maturation stages.[14] The participants were classified into pre-pubertal stage (Tanner 1), pubertal (Tanner 2–4) and post-pubertal stage (Tanner 5).

Skin color was self-reported as white, brown, black, yellow and native, according to the Brazilian Institute of Geography and Statistics classification.[15] Adolescents who reported smoking on one or more days in the past 30 days were considered smokers, by following the Centers for Disease Control and Prevention[16] and the Brazilian National Cancer Institute's recommendations.[17]

Physical activity level was assessed by the Self-Administered Physical Activity Checklist, validated by Farias Júnior *et al*.[18] for the Brazilian population. The level was determined by the sum of the product of the time spent in each physical activity and the respective frequency. Adolescents who spent less than 300 min per week in moderate to vigorous physical activity were considered inactive.[19]

Measures of weight, height and waist circumference were performed by trained investigators, according to standardized procedures.[11] Body weight was measured using an electronic scale (Líder, Araçatuba, São Paulo, Brazil, Model P200M), with 300 kg and 50 g readability. Height was measured to the nearest 0.1 cm, in duplicate, using a portable stadiometer (Alturexata, Belo Horizonte, Minas Gerais, Brazil), and calculated as the mean of these two measures (a maximum variation of 0.5 cm between the two readings was considered acceptable). Waist circumference was measured to the nearest 0.1 cm using an inelastic measuring tape (Sanny, São Bernardo do Campo, São Paulo, Brazil), with the participant standing with arms along the body, feet slightly apart and abdomen relaxed. A horizontal measure was taken at the midway between the lowest rib and the upper border of iliac crest.

Weight status was based on the body mass index (BMI = weight (kg)/(height $(m)^2$) curves proposed by Onis *et al*.[20] Adolescents with a *Z*-score < -2 were classified as 'underweight', those with a *Z*-score $\geqslant -2$ and $< +1$ were classified as 'normal weight', a *Z*-score $\geqslant +1$ and $< +2$ as 'overweight', and those with a *Z*-score $\geqslant +2$ were classified as 'obese'.

Blood pressure was measured according to The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children

Table 1. Demographic, behavioral characteristics and weight status data of adolescents from six capitals included in the ERICA CRP study

Variables	*Brasília*	*Fortaleza*	*João Pessoa*	*Manaus*	*Porto Alegre*	*Rio de Janeiro*	*Total*
	% (95%CI)	*% (95%CI)*	*% (95%CI)*	*% (95%CI)*	*% (95%CI)*	*% (95%CI)*	*% (95%CI)*
Sex							
Male	49.6	49.2	50.4	49.8	50.3	49.8	49.9
Female	50.4	50.8	49.6	50.2	49.7	50.2	50.1
Age, years							
12–14	47.6	50.3	47.5	55.4	50.3	52.7	51.2
15–17	52.4	49.7	52.5	44.6	49.7	47.3	48.8
Type of school							
Public	54.0 (37.0–70.0)	55.1 (33.1–75.3)	81.7 (61.9–92.5)	88.0 (70.8–95.7)	75.8 (53.3–89.6)	70.2 (50.6–84.4)	67.9 (58.7–75.9)
Private	46.0 (30.0–63.0)	44.9 (24.7–66.9)	18.3 (7.5–38.1)	12.0 (4.3–29.2)	24.2 (10.4–46.7)	29.8 (15–6–49.4)	32.1 (24.0–41.3)
Pubertal stage							
1	0.4 (0,1–0.8)	0.3 (0–0.9)	0.3 (0–0.9)	0.9 (0.4–1.9)	0 (0–0.6)	0.2 (0–0.6)	0.3 (0.2–0.5)
2–3–4	56.3 (52.5–60.0)	65.4 (61.1–69.5)	61.7 (57.0–66.1)	72.4 (69.4–75.2)	58.6 (54.1–62.9)	60.9 (57.2–64.5)	62.0 (60.1–63.8)
5	43.3 (39.6–47.1)	34.3 (30.2–38.6)	38.0 (33.4–42.9)	26.7 (23.8–29.8)	41.3 (37–45.7)	38.9 (35.2–42.6)	37.7 (35.9–39.6)
Skin color							
White	37.8 (32.3–43.6)	31.0 (26.2–36.2)	33.0 (28.9–37.4)	21.7 (19.0–24.5)	67,1 (56.1–76.5)	38.6 (33.0–44.6)	37.6 (34.8–40.5)
Black	6.0 (4.3–8.2)	4.2 (3.6–5.8)	8.2 (5.5–12.3)	4.2 (3.2–5.6)	13.3 (8.3–20.6)	11.3 (8.1–15.5)	8.4 (6.9–10.1)
Brown	53.4 (48.3–58.4)	61.5 (56.7–66.1)	54.2 (49.7–58.6)	70.2 (67.0–73.1)	18.1 (12.9–24.7)	47.9 (43.9–51.9)	51.3 (49.2–53.4)
Yellow	2.6 (1.7–3.9)	3.0 (2.0–4.4)	3.4 (1.9–5.8)	2.5 (1.8–3.5)	1.1 (0.2–5.8)	1.8 (1.1–2.9)	2.2 (1.8–2.8)
Native	0.2 (0–0.8)	0.3 (0.1–1.0)	1.2 (0.6–2.8)	1.4 (0.8–2.4)	0.4 (0–2.5)	0.3 (0.1–0.7	0.5 (0.3–0.7)
Smoking							
Smokers	2.9 (2.0–4.1)	1.2 (0.6–2.3)	1.1 (0.4–3.2)	1.2 (0.7–2.0)	1.4 (0.8–2.3)	0.9 (0.5–1.7)	1.4 (1.1–1.8)
Non-smokers	97.1 (95.9–98.0)	98.8 (97.7–99.4)	98.9 (96.8–99.6)	98.8 (98.0–99.3)	98.6 (97.7–99.2)	99.1 (98.3–99.5)	98.6 (98.2–98.9)
Physical activity							
Active	56.8 (52.9–60.6)	53.8 (49.8–57.8)	50.7 (45.8–55.5)	55.7 (52.3–58.5)	48.0 (43.7–52.4)	50.4 (45.8–55.1)	52.6 (50.4–54.7)
Inactive	43.2 (39.4–47.1)	46.2 (42.2–50.2)	49.3 (44.5–54.1)	44.3 (41.5–47.2)	52.0 (47.6–56.3)	49.6 (44.9–54.2)	47.4 (45.3–49.6)
Weight status							
Underweight	2.5 (1.7–3.7)	2.4 (1.4–3.8)	4.2 (2.7–6.3)	2.1 (1.4–3.2)	0.7 (0.4–1.6)	2.2 (1.2–4.0)	2.2 (1.7–2.9)
Normal weight	74.1 (70.8–77.0)	67,2 (6.4–7.1)	70.1 (64.8–74.9)	75.3 (71.7–78.6)	66.1 (60.1–70.8)	67.1 (63.1–70.9)	69.4 (67.5–71.3)
Overweight	14.8 (12.4–17.6)	20.3 (18.0–22.8)	19.0 (15.1–25.0)	14.5 (11.7–17.8)	23.7 (19.6–28.2)	19.3 (15.6–23.7)	18.5 (16.7–20.4)
Obesity	8.6 (6.6–11.1)	10.1 (7.6–13.3)	6.7 (4.9–9.2)	8.1 (6.7–9.6)	9.5 (6.6–14.5)	11.4 (8.0–15.5)	9.9 (8.3–11.7)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ERICA, Estudo de Risco Cardiovascular em Adolescentes (Study of Cardiovascular Risk in Adolescents). χ^2-test.

and Adolescents,[21] using the Omron 705 IT oscillometric device, validated for adolescents.[22] The measurements were taken in triplicate at 3-min intervals, and the mean of the two last readings was used in the analysis.

Blood samples were analyzed at the reference laboratory, and quality control was based on the criteria from the Clinical Pathology Society.[11] Fasting plasma glucose levels were measured by the hexokinase method using a Siemens ADVIA 2400. Total cholesterol, high-density lipoprotein-cholesterol (HDL-c) and triglycerides levels were measured by enzymatic colorimetric test (Roche, Indianapolis, IN, USA; Modular analyzer). MS was defined according to the International Diabetes Federation criteria adapted by Zimmet *et al*.[23] MS components included central adiposity (<16 years: $\geqslant$90th waist cincunference percentile; $\geqslant 16$ years—male: $\geqslant 90$ cm and female: $\geqslant 80$ cm;) plus at least two of the following criteria: (1) triglycerides $\geqslant 150$ mg/dl; (2) HDL-c: <16 years: <40 mg/dl, $\geqslant 16$ years—male: <40 mg/dl and female: <50 mg/dl) systolic blood pressure $\geqslant 130$ mm Hg or diastolic blood pressure $\geqslant 85$ mm Hg; and 3) glucose $\geqslant 100$ mg/dl or previously diagnosed type 2 diabetes.

Given the lack of cutoff values of high CRP levels for adolescents, we adopted >3 mg/l proposed by the Food and Drug Administration.[24]

The CRP measurements performed in the two laboratories used the same techniques (immunoturbidimetry—Kit Bio Systems) and equipment brand and model (Siemens, Munich, Germany, Advia 2400 chemistry analyzer). The analysis of CRP was performed by the reference laboratory for the capitals with immediately collected blood, Fortaleza, João Pessoa and Manaus; for Brasília, Rio de Janeiro and Porto Alegre, the analysis was performed in the other laboratory using frozen serum least 80 °C. The correlation observed between laboratories was 0.94 (Bland-Altman test) and when categorized, 3 mg/l κ was 0.86.

Statistical analyses took into account the complex sampling that consider all sources of variability of the ERICA sample.[12] Normally distributed variables were expressed as means and 95% confidence intervals (95% CI), those with non-normal distribution as median and interquartile range (p25-p75), and categorical variables as proportions and 95%CI. The χ^2-test was used to compare categorical variables, and the Wilcoxon–Mann–Whitney and Kruskal–Wallis tests were used for comparisons between continuous variables.

We examined the independent contribution of the MS and its five components to CRP using Poisson regression model with robust variance to estimate the prevalence ratios. The following potentially confounding variables were entered in the model: sex, age, sexual maturation stage, skin color, physical activity and smoking, and kept when $P \leqslant 0.20$ (a higher *P*-value was used to minimize the beta error).

The analyses were performed using the Stata software package (College Station, TX, USA), version 14, and a significance level of 5% was adopted in all analyses.

Ethical issues

The ERICA study was approved by the Research Ethics Committee of the Institute of Studies on Public Health, Federal University of Rio de Janeiro (no. 45/2008) and by the Ethics Committee of each participating institution. Adolescents who agreed to participate in the study were included after obtaining informed consent from their parents/guardians.

RESULTS

In total eligible students in the morning classes of the capitals Brasilia, Fortaleza, João Pessoa, Manaus, Porto Alegre and Rio de Janeiro, around 55.2%, 46.7%, 57.6%, 47.1%, 48.9% and 44.1%, respectively, had data collected of questionnaire, anthropometric, blood pressure and blood sample. Of these, 824 adolescents who did not have CRP measured and 1088 with CRP $\geqslant 10$ mg/l and/or who reported use of anti-inflammatory, antibiotic or corticoid were excluded. Thus, data from 6316 adolescents were included in the analyses; 1,034 from Brasilia, 893 from Fortaleza, 813 from João Pessoa, 1296 from Manaus, 790 from Porto Alegre and 1490 from Rio de Janeiro.

Demographic, behavioral and weight status data, adjusted for the sample design and stratified by city, are presented in Table 1.

The mean BMI in the total sample was 21.4 kg/m^2 (95%CI: 21.3–21.6) and waist circumference was 72.2 cm (95%CI: 71.7–72.6). Mean levels of the metabolic parameters were as follows: glucose 86.8 mg/dl (95%CI: 86.3–87.2), HDL-c 47.4 mg/dl (95%CI: 46.9–47.9) and triglycerides 77.6 mg/dl (95%CI: 76.1–79.1). Mean systolic and diastolic blood pressures were 110.4 mm Hg (95%CI: 109.8-110.9) and 65.7 mm Hg (95%CI: 65.3–66.1), respectively.

Median CRP concentrations were similar in females and males, and were higher in the older than in the younger age group. White adolescents showed the highest concentrations of CRP, from the 50th through the 90th percentiles. Higher CRP levels were found in adolescents with excessive weight than in those with normal weight ($P < 0.001$).

Thirty-three percent (95%CI: 31.0–34.6%) of participants had CRP concentration below the detection limit (0.10 mg/l) and 9.6%

Table 2. Percentiles of CRP concentration (mg/l) of adolescents, from six capitals included in the ERICA

	Percentiles			
	25	50	75	90
All	0.10	0.20	0.81	2.81
Capitals				
Brasília	0.10	0.14	0.64	2.38
Fortaleza	0.10	0.10	0.80	2.90
João Pessoa	0.10	0.20	0.80	3.20
Manaus	0.10	0.10	0.70	2.90
Porto Alegre	0.10	0.32	0.94	3.11
Rio de Janeiro	0.10	0.21	0.87	2.82
Sex				
Female	0.10	0.20	0.87	2.80
Male	0.10	0.18	0.74	2.83
Age, years				
12–14	0.10	0.10	0.65	2.30
15–17	0.10	0.25	1.00	3.20
Skin color				
White	0.10	0.23	0.91	3.00
Black	0.10	0.10	0.80	2.14
Brown	0.10	0.18	0.72	2.90
Yellow	0.10	0.10	0.76	1.99
Native	0.10	0.25	0.70	1.74
Weight status				
Underweight	0.10	0.10	0.22	0.86
Normal weight	0.10	0.10	0.50	1.81
Overweight	0.10	0.41	1.50	3.29
Obesity	0.40	1.25	3.10	5.97

Abbreviations: CRP, C-reactive protein; ERICA, Estudo de Risco Cardiovascular em Adolescentes (Study of Cardiovascular Risk in Adolescents).

Table 3. C-reactive protein (median level and CI) by components of metabolic syndrome

Metabolic syndrome Components[a]	*Median (95%CI)—mg/l*		
	Present	*Absent*	P-*value*
High waist circumference	1.00 (0.80–1.40)	0.13 (0.12–0.16)	<0.001
Hyperglycemia	0.47 (0.21–0.90)	0.19 (0.15–0.20)	0.005
Low HDL-cholesterol	0.30 (0.26–0.40)	0.14 (0.12–0.18)	<0.001
High triglycerides	0.40 (0.28–0.66)	0.19 (0.15–0.20)	<0.001
High blood pressure	0.42 (0.29–0;68)	0.18 (0.14–0.20)	<0.001

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein. [a]According to the International Diabetes Federation (2007).

(95%CI: 8.7–10.6) had CRP >3.0 mg/l, with the highest proportion seen in Porto Alegre (11.1%; 95%CI: 8.7–14.0), followed by João Pessoa (10.6%; 95%CI: 8.7–13.0), Rio de Janeiro (9,7%; 95%CI: 8.0–11.8), Manaus (9.5%; 95%CI: 7.8–11.6), Fortaleza (9.3%; 95%CI: 8.0–10.8) and Brasília (8.2%; 95%CI: 6.7–10.1) ($P=0.472$). CRP percentiles of the reference population are presented in Table 2.

MS prevalence rates were 2.1% (95%CI: 1.7–2.5): 3.0% (95%CI: 1.8–5.0) in João Pessoa, 2.6% (95%CI: 1.7–3.8) in Fortaleza, 2.2% (95%CI: 1.5–3.2) in Manaus, 2.2% (95%CI: 1.3–3.7) in Porto Alegre, 1.9% (95%CI: 1.3–2.7) in Rio de Janeiro and 1.7% (95%CI: 1.1–2.6) in Brasilia, with no statistically significant differences between the cities ($P=0.515$).

Among the components of the MS, the most prevalent was low HDL-c, observed in 31.3% (95%CI: 29.5–33.1) of the adolescents, followed by increased waist circumference (11.7%; 95%CI: 10.4–13.1), elevated blood pressure (7.6%; 95%CI: 6.7–8.6), hyperglycemia (4.4%; 95%CI: 3.6–5.4) and high triglycerides (4.6%; 95%CI: 3.9–5.5). For each of these cardiovascular risk factors the association with higher median CRP levels was consistent with expectation: high levels of BP, triglycerides and glucose, and low levels of HDL-C (Table 3).

Median CRP levels were five times higher in adolescents with than in those without MS (Figure 1a), and the prevalence of adolescents with CRP >3 mg/l according to the presence or absence of MS was 31.0% (95%CI: 22.1–41.6) and 9.2% (95%CI: 8.3–10.2) ($P<0.001$), respectively. CRP levels were progressively higher in adolescents with higher number of MS components (Figure 1b).

The associations between CRP and MS with selected variables are presented in Table 4.

Statistically significant age-, sex- and skin color-adjusted associations of CRP with MS, and three of its components—high waist circumference, low HDL and high triglycerides—we observed (Table 5).

However, after adjustment by BMI, the association between CRP with MS (PR: 1.1; 95%CI: 0.7–1.5; $P=0.78$) was eliminated and only the association of elevated CRP and low HDL-c (PR: 1.4; 95%CI: 1.1–1.7; $P=0.002$) remained statistically significant.

Table 4. Association of CRP and metabolic syndrome with selected variables

Variable	*PR (95%CI)*	P-*value*
Sex		
Female	1	
Male	1.12 (0.9–1.3)	0.20
Age, years		
12–14	1	
15–17	1.3 (1.0–1.6)	0.03
Pubertal stage		
1	1	
2–3–4	2.2 (0.4–11.6)	0.35
5	2.3 (0.4–12.3)	0.32
Skin color		
White	1	
Black	0.6 (0.4–1.0)	0.05
Brown	0.9 (0.7–1.1)	0.37
Yellow	0.7 (0.3–1.4)	0.27
Native	0.3 (0.1–1.5)	0.15
Physical activity		
Active	1	
Inactive	1.1 (0.9–1.4)	0.41
Smoking		
Non-smokers	1	
Smokers	1.0 (0.5–2,0)	0.90
Weight status		
Normal weight	1	
Underweight	0.9 (0.3–2.7)	0.93
Overweight	2.1 (1.7–2.6)	<0.001
Obesity	4.3 (3.2–5.7)	<0.001

Abbreviations: CI, confidence interval; CRP, C-reactive protein; PR, prevalence ratio.

DISCUSSION

In our study of random samples of adolescents living in six Brazilian cities, a significant association between MS and CRP was observed after adjustment for age, sex and skin color. This finding suggests the possibility of using CRP as a marker of MS in adolescents. The association of MS with PCR was also found in the study by DeBoer *et al*. of a representative sample of American adolescents.[25]

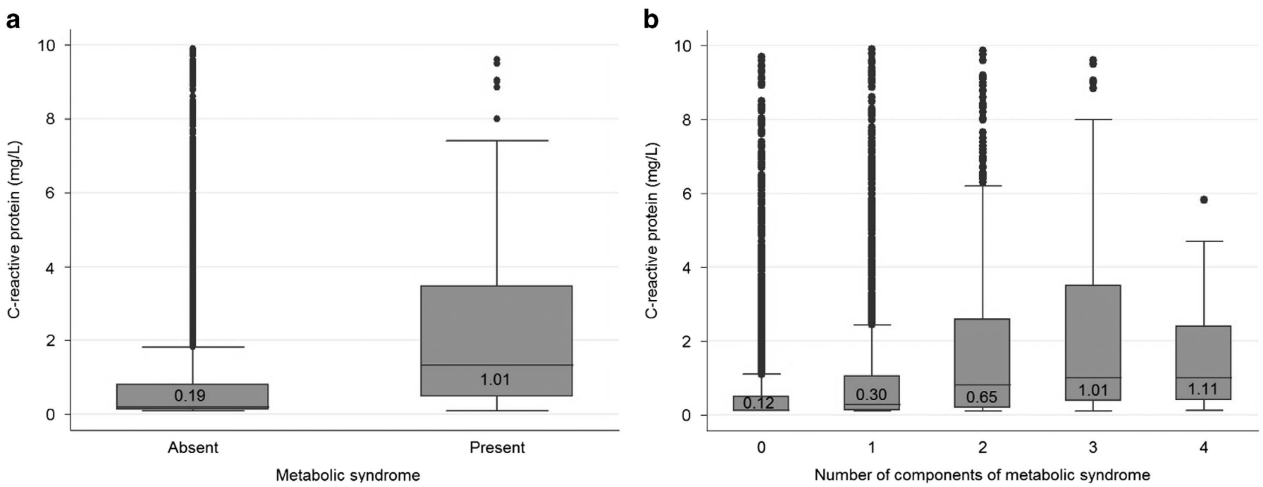

Figure 1. Median CRP concentration according to the presence of metabolic syndrome (**a**) and according to the number of components of metabolic syndrome (**b**). The boxplot shows minimum and maximum values and 25th, 50th (median) and 75th percentile of CRP concentration.

Table 5. Association of elevated levels of CRP (>3 mg/l) with metabolic syndrome and its components

Variable	*PR (95%CI)*	P-*value*	[a]*Adjusted PR (95%CI)*	P-*value*
Metabolic syndrome	3.1 (2.1–4.5)	< 0.001	2.9 (2.0–4.3)	< 0.001
Components				
High waist circumference	3.1 (2.5–3.9)	< 0.001	3.2 (2.6–4.0)	< 0.001
Low HDL-cholesterol	1.7 (1.4–2.1)	< 0.001	1.7 (1.4–2.0)	< 0.001
High triglycerides	2.0 (1.5–2.7)	< 0.001	1.9 (1.5–2.7)	< 0.001
High blood pressure	1.1 (0.8–1.6)	0.535	1.0 (0.7–1.4)	0.895
Hyperglycemia	1.2 (0.7–2.2)	0.450	1.3 (0.7–2.3)	0.355

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HDL, high-density protein; PR, prevalence rate ratio. [a]Adjusted for age (12–14; 15–17), sex and skin color (white, black, brown, yellow and native).

Although CRP concentrations were lower in our adolescent population than typical values in adults, 9.6% of adolescents had CRP concentration >3.0 mg/l, the proposed threshold to define high levels of CRP in adults.[24] As in adults,[26] the distribution of CRP concentrations in adolescents in our study was positively skewed. Also in agreement with some previous reports,[26,27] CRP concentration varied by age and skin color, but not by sex.

Median concentrations of CRP were higher among adolescents living in Porto Alegre than in the other cities included in our study. Evidence suggests[28] that higher prevalence of obesity in Porto Alegre,[29] may be responsible for much of this difference in concentration of CRP among capitals.

In this study, serum level CRP was significantly elevated in adolescents with excessive weight, and Roh et al.[30] confirmed that obese adolescents had similar levels of inflammatory markers as those found in obese adults. In Brazil, a study conducted with adolescents in the city of São Paulo also showed CRP levels to be higher in those with excess weight.[31]

These results indicate that, although there is no established cutoff points of CRP levels for adolescents, obesity-related subclinical inflammation is observed in this population.[31]These findings are biologically plausible, since the adipose tissue releases pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-6, which can stimulate hepatic production of CRP.[32] Thus, the close relationship between obesity and CRP, as shown in our and previous studies,[33,34] is as expected. This pro-inflammatory and prothrombotic state in obesity is associated with the exacerbation of the atherosclerotic process, and the risk of development of MS and CVDs.

In the present study, CRP levels were five times higher in adolescents with MS than in those that did not meet the criteria for MS. which is corroborated for others researchs[25,26,35,36] as Visser et al's study,[37] that compared, normal weight subjects, overweight children and adolescents had higher CRP levels and a seven times higher risk of developing MS as adults. In addition, and as expected we have observed that the higher the number of components of MS, the higher the CRP levels in the study group, a finding that has been previously reported.[38]

In our study, after adjustment for age, sex and skin color, there were significant associations of CRP with MS and three of its five components (high waist circumference, low HDL and high triglyceride levels, suggesting that CRP levels in adolescents may be an important cardiometabolic predictor of CVD later in life, as proposed by Soriano-Guillén *et al*.[36] Wu *et al*.'s study,[39] 1438 children and adolescents in Taiwan, found positive correlations of CRP with BMI, triglycerides, insulinemia and HOMA-IR, and negative correlations with HDL-c. Similar findings have been found in the study by Cardoso-Saldanã *et al*.[35] of 325 adolescents aged between 12 and 16 years and in the study by Lambert *et al*.[27]

In the present study, statistically significant associations between components of MS and CRP disappeared after adjustment by BMI, with the exception of HDL-c. Our findings were compatible with previously published articles, as Brasil *et al*.,[40] that reported the relationship with TG and CRP lost its significance upon adjustment for BMI. Oliveira *et al*.[41] observed a significant association ($P < 0.001$) between CRP with insulin resistance, metabolic syndrome, waist circumference, BMI, hypertension, TG and HDL-C. However, after adjustment for BMI, associations became nonsignificant.

In the cross-sectional study by Yoshida *et al*.[42] involving 568 children, those with higher CRP levels had a worse lipid profile. However, after adjusting for BMI, only HDL-c had a significant correlation with CRP levels in both sexes. The association between CRP and HDL-c could be mediated by different cytokines of adipose origin that in some genetically predisposed individuals are elevated in individuals with higher adiposity. However, prospective studies are needed to confirm this relationship.

Among adults and adolescents, components of the MS and the MS itself are associated with measures of inflammation. Low-grade inflammation may be the mechanism explaining the increased risk of CVDs in individuals with MS.[43] However, our findings that obesity is associated with a mild chronic inflammatory response suggests that it important in the development of cardiometabolic alterations.

Our study had some limitations. First, its cross-sectional nature does not allow us to establish temporal relationships. The other limitation of cross-sectional studies, survival bias, is unlikely in our study, given the young age of our study sample. Another potential limitation is the absence of a well-established cutoff point to define high values for CRP in adolescents. However, in view of the concordance between our findings and findings of may other studies, the cutoff point of 3.0 mg/dl seems to be reasonable to establish associations. Although the laboratory that measured CRP concentration in Porto Alegre, Rio de Janeiro and Brasília were different from that of the other cities, quality control measures were equivalent in both laboratories and sensitivity analysis based on excluding the laboratory of Porto Alegre Clinical Hospital did not materially change our results. Our study also had important strengths, including standardization of procedures and geographic representativeness.

CONCLUSION

In a representative sample of adolescents from six Brazilian capitals, a high 9.6% of participants had elevated CRP concentrations based on a threshold of 3.0 mg/l (which defines the adult high-risk category.) We observed strong age- sex- and skin color-adjusted associations of elevated CRP with MS and three of its components: elevated waist circumference, low HDL-c and high triglycerides. Accordingly, in adolescents with MS, median CRP levels were higher than in those without MS, and the higher the number of MS components, the higher the CRP levels. Elevated CRP may be a useful tool for the early detection of adolescents at higher risk of developing CVD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The study ERICA was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos/FINEP and Conselho Nacional de Pesquisa/CNPq) (grants FINEP: 01090421, CNPq: 565037/2010-2, 405009/2012-7 and 457050/2013-6).

REFERENCES

1 Wang G, Christoffel KK, Brickman WJ, Hong X, Arguelles L, Zhang S *et al.* C-reactive protein in adolescent twins: patterns and relationship to adiposity. *J Clin Endocrinol Metab* 2011; **96**: 3226–3233.
2 Chu NF, Rimm EB, Wang DJ, Liou HS, Shieh SM. Clustering of cardiovascular disease risk factors among obese schoolchildren: the Taipei Children Heart Study. *Am J Clin Nutr* 1998; **67**: 1141–1146.
3 Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347**: 1557–1565.
4 Ferranti S, Mozaffarian D. The perfect storm: obesity, adipocyte dysfunction, and metabolic consequences. *Clin Chem* 2008; **54**: 945–955.
5 Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM *et al.* Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 2005; **112**: 666–673.
6 Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr* 2008; **152**: 201–206.
7 Guran O, Akalin F, Ayabakan C, Dereli FY, Haklar G. High-sensitivity C-reactive protein in children at risk for coronary artery disease. *Acta Paediatr* 2007; **96**: 1214–1219.
8 Giannini DT, Kushnir MCC, Szklo M. Metabolic syndrome in overweight and obese adolescents: a comparison of two different diagnostic criteria. *Ann Nutr Metab* 2014; **64**: 71–79.
9 Kuschnir MC, Bloch KV, Szklo M, Klein CH, Burafaldi LA, Abeu GA *et al.* ERICA: prevalence of metabolic syndrome in Brazilian adolescents. *Rev Saude Publica* 2016; **50**: 11s.
10 Lourenco BH, Cardoso MA. ACTION Study Team.Cardoso,C-reactive protein concentration predicts change in body mass index during childhood. *PLoS One* 2014; **9**: e90357.
11 Bloch KV, Szklo M, Kuschnir MC, Abreu GA, Barufaldi LA, Klein CH *et al.* The Study of Cardiovascular Risk in Adolescents--ERICA: rationale, design and sample characteristics of a national survey examining cardiovascular risk factor profile in Brazilian adolescents. *BMC Public Health* 2015; **15**: 94.
12 Vasconcellos MTL, Silva PLN, Szklo M, Kuschnir MCC, Klein CH, Abreu GA *et al.* Sampling design for the Study of Cardiovascular Risks in Adolescents (ERICA). *Cad Saude Publica* 2015; **31**: 921–930.
13 DeBoer MD. Obesity, systemic inflammation, and increased risk for cardiovascular disease and diabetes among adolescents: a need for screening tools to target interventions. *Nutrition* 2013; **29**: 379–386.
14 Tanner JM. *Growth at Adolescence.* 2nd ed. Blackwell Scientific Publications: Oxford, 1962.
15 Instituto Brasileiro de Geografia e Estatística (IBGE). *Um Estado das Categorias de Classificação de Cor ou Raça*. IBGE: Rio de Janeiro, 2008.
16 Department of Health and Human Services USA. Preventing tobacco use among young people. *A report of the Surgeon General: US Department of Health and Human Services*. Atlanta, Georgia, 1994.
17 Global Youth Tobacco Survey Collaborating Group. Differences in worldwide tobacco use by gender: findings from the Global Youth Tobacco Survey. *J Sch Health* 2003; **73**: 207–215.
18 Farias Júnior JC, Lopes AS, Mota J, Santos MP, Ribeiro JC, Hallal PC. Validade e reprodutibilidade de um questionário para medida de atividade física em adolescentes: uma adaptação do Self-Administered Physical Activity Checklist. *Rev Bras Epidemiol* 2012; **15**: 198–210.
19 Biddle S, Cavill N, Sallis JF. *Young and Active? Young People and Health-enhancing Physical Activity: Evidence and Implications*. Health Education Authority: London, 1998, pp 17–48.
20 Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007; **85**: 660–667.
21 National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; **114**: 555–576.
22 Stergiou GS, Yiannes NG, Rarra VC. Validation of the Omron 705 IT oscillometric device for home blood pressure measurement in children and adolescents: the Arsakion School Study. *Blood Press Monit* 2006; **11**: 229–234.
23 Zimmet P, Alberti KGM, Kaufman F, Tajima N, Silink M, Arslanian S *et al.* The metabolic syndrome in children and adolescents–an IDF consensus report. *Pediatr Diabetes* 2007; **8**: 299–306.
24 U.S. Food And Drug Administration (FDA). *Guidance for Industry - Review Criteria for Assessment of C Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays*. FDA: Silver Spring, MD, 2005.
25 DeBoer MD, Gurka MJ, Sumner AE. Diagnosis of the metabolic syndrome is associated with disproportionately high levels of high-sensitivity C-reactive protein in non–Hispanic Black adolescents an analysis of NHANES 1999–2008. *Diabetes Care* 2011; **34**: 734–740.
26 Ford ES, Giles WH, Myers GL, Rifai N, Ridker PM, Mannino DM. C-reactive protein concentration distribution among US children and young adults: findings from the National Health and Nutrition Examination Survey, 1999–2000. *Clin Chem* 2003; **49**: 1353–1357.
27 Lambert M, Delvin EE, Paradis G, O'Loughlin J, Hanley JA, Levy E. C-reactive protein and features of the metabolic syndrome in a population-based sample of children and adolescents. *Clin Chem* 2004; **50**: 1762–1768.
28 Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005; **28**: 2745–2749.
29 Bloch KV, Klein CH, Szklo M, Kuschnir MCC, Abreu GA, Barufaldi LA *et al.* ERICA: prevalências de hipertensão arterial e obesidade em adolescentes Brasileiros. *Rev Saude Publica* 2016; **50**(Suppl 1): 9s.
30 Roh EJ, Lim JW, Ko KO, Cheon EJ. A useful predictor of early atherosclerosis in obese children: serum high-sensitivity C-reactive protein. *J Korean Med Sci* 2007; **22**: 192–197.
31 Silva IT, Sanches LB, Mello AP, Damasceno NR. Impact of C-reactive protein on cardiovascular risk in adolescents. *Arq Bras Cardiol* 2010; **94**: 585–591.
32 Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem* 2008; **54**: 24–38.
33 Cushman M, McClure LA, Howard VJ, Jenny NS, Lakoski SG, Howard G. Implications of increased C-reactive protein for cardiovascular risk stratification in black and white men and women in the US. *Clin Chem* 2009; **55**: 1627–1636.
34 Blaha MJ, Rivera JJ, Budoff MJ, Blankstein R, Agatston A, O'Leary DH *et al.* Association between obesity, high-sensitivity C-reactive protein $\geqslant$2mg/l, and subclinical atherosclerosis: implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2011; **31**: 1430–1438.
35 Cardoso-Saldaña G, Juárez-Rojas J, Zamora-González J, Raygoza-Pérez M, Martinez-Alvarado R, Posadas-Sánchez R *et al.* C-reactive protein levels and their relationship with metabolic syndrome and insulin resistance in Mexican adolescents. *J Pediatr Endocrinol Metab* 2007; **20**: 797–806.
36 Soriano-Guillén L, Hernández-García B, Pita J, Domínguez-Garrido N, Del Río-Camacho G, Rovira A. High-sensitivity C-reactive protein is a good marker of cardiovascular risk in obese children and adolescents. *Eur J Endocrinol* 2008; **159**: R1–R4.
37 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low-grade systemic inflammation in overweight children. *Pediatrics* 2001; **107**: E13.
38 Barja S, Acevedo M, Arnaiz P, Berríos X, Bambs C, Guzmán B *et al.* Marcadores de aterosclerosis temprana y síndrome metabólico en niños. *Rev Med Chil* 2009; **137**: 522–530.
39 Wu DM, Chu NF, Shen M-H, Wang SC. Obesity, plasma high sensitivity c-reactive protein levels and insulin resistance status among school children in Taiwan. *Clin Biochem* 2006; **39**: 810–815.
40 Brasil AR, Norton RC, Rossetti MB, Leão E, Mendes RP. Proteína C reativa como indicador de inflamação de baixa intensidade em crianças e adolescentes com e sem obesidade. *J Pediatr (Rio J)* 2007; **83**: 477–480.
41 Oliveira AC, Oliveira AM, Adan LF, Oliveira NF, Silva AM, Ladeia AM. Retraction: update to 'C-reactive protein and metabolic syndrome in youth: a strong relationship?'. *Obesity (Silver Spring)* 2009; **17**: 1113.
42 Yoshida T, Kaneshi T, Shimabukuro T, Sunagawa M, Ohta T. Serum C-reactive protein and its relation to cardiovascular risk factors and adipocytokines in Japanese children. *J Clin Endocrinol Metab* 2006; **91**: 2133–2137.
43 El-shorbagy HH, Ghoname IA. High-sensitivity C-reactive protein as a marker of cardiovascular risk in obese children and adolescent. *Health* 2010; **2**: 1078–1084.