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Severe asthma is associated with metabolic syndrome in Brazilian adolescents



To the Editor:

Asthma is a serious health problem in developing countries, with increasing prevalence over the last decades, especially among children and adolescents.¹ In Brazil, according to the International Study of Asthma and Allergies in Childhood, the prevalence of active asthma in children aged 6 to 7 years and adolescents aged 13 to 14 years was, respectively, 24.3% and 19%, one of the highest among Latin American countries.²

Metabolic syndrome (MS) is an important health issue associated with increased cardiovascular risk. The Study of Cardiovascular Risk in Adolescents (Portuguese acronym "ERICA") involving Brazilian students showed a 2.6% prevalence of MS.³

The association between asthma and MS components such as insulin resistance and high blood pressure (BP) has been observed regardless of body mass index (BMI).^{4,5} More recently, a study with adolescents found association between insulin resistance and MS, with worsened lung function in overweight/obese individuals.⁶ Thus, hyperinsulinemia and dyslipidemia, which are silent precursors of diabetes and cardiovascular disease, could be associated with development of asthma.⁴

Considering that asthma and MS are both inflammatory conditions, our hypothesis was that MS and its components could be more prevalent among patients with asthma. To investigate this association, we performed a cross-sectional study using data from ERICA, a multicenter, school-based country-wide study in a complex sample of adolescents aged 12 to 17 years. The study stratified the sample by region and grouped according to schools and classes, with representativeness to the set of cities with more than 100,000 inhabitants of the country.⁷ Detailed descriptions of subject recruitment and data collection have been reported previously.⁷ Data were collected by a self-administered questionnaire using a personal digital assistant, including questions about sociodemographic characteristics, lifestyle, and asthma. A total of 72,508 students from public and private schools were assessed and submitted to anthropometric, weight, height, waist circumference (WC), and BP measurements. Fasting blood samples were collected from a subsample of 40,732 participants for measurements of glucose, insulin, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides (TGs). The homeostasis model assessment-estimated insulin resistance

(HOMA-IR) was also estimated. Participants fasting for less than 12 hours, refusing phlebotomy, pregnant, or disabled were excluded.⁷ Current asthma (CA) was defined by the presence of at least 1 attack in response to the question "In the last 12 months, how many attacks of wheezing you had?" and severe asthma (SA) defined by 4 or more asthma attacks according to previously established criteria.⁸ Metabolic abnormalities were defined according to International Diabetes Federation Consensus 2005.⁹ All procedures for anthropometric measurements, BP evaluation, and biochemical determinations are described in the article's [Methods](#) section in the Online Repository at www.jacionline.org. All analyzes were performed using SURVEY procedure in STATA 14.0 software (StataCorp, College Station, Tex). Detailed description of statistical analysis is in this article's [Methods](#) section. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Federal University of Rio de Janeiro (no. 45/2008).⁷

Between 2013 and 2014, 37,410 adolescents were evaluated (see [Fig E1](#) in this article's Online Repository at www.jacionline.org). Mean age was 14.6 ± 1.6 years; 50.1% were females. Regarding skin color/ethnicity, 58.1% were black/brown and about 40% white. The prevalence of CA and SA was 13.8% (95% CI, 12.4-15.2) and 2.09% (95% CI, 1.95-2.24), respectively. MS was present in 2.3% of the populations sampled (95% CI, 2.14-2.45).

Main sociodemographic and metabolic characteristics of participants according to presence or absence of asthma are summarized in [Table I](#). Adolescents with nonsevere asthma were more likely to be female, white skin color, current smoker, and student from a private school than those without disease. Except for the latter, there were no significant differences in relation to these variables between those without asthma and those with SA. In this group of adolescents, the means of BMI, WC, and TGs differed significantly from those without the disease.

[Table II](#) presents the relationship between the prevalence of components of MS and CA/SA. Only increased prevalence of altered WC was significantly associated with CA (prevalence ratio [PR], 1.19; 95% CI, 1.00-1.43). However, significant associations between SA and obesity (PR, 1.28; 95% CI, 1.02-1.62), increased WC (PR, 1.74; 95% CI, 1.16-2.61), hyperglycemia (PR, 1.78; 95% CI, 1.05-2.98), hyperinsulinemia (PR, 1.55; 95% CI, 1.03-2.33), and HOMA-IR (PR, 1.02; 95% CI, 1.01-1.04) were observed. SA was also significantly associated with MS (PR, 2.43; 95% CI, 1.39-4.27), and this association remained after adjustment for age, sex, current smoking, and BMI by Poisson regression (PR, 1.71; 95% CI, 1.03-2.82) (see [Table E1](#) in this article's Online Repository at www.jacionline.org).

To our knowledge, this is the first study of asthma and MS and its components in a representative sample of Brazilian adolescents. CA was associated with increased WC but not with MS. However, SA was significantly associated with MS, and this association remained after adjustment for age, sex, current smoking, and BMI. In addition, significant associations were observed between SA and obesity, increased WC, hyperglycemia, and hyperinsulinemia. Elevated WC seems to be an important factor linking MS to asthma in our sample. Besides that, insulin resistance, another known component of MS, was associated with SA, which may represent a subgroup of patients with SA with metabolic abnormalities without alteration of BMI. Surprisingly,

TABLE I. General characteristics of study participants according to presence of asthma

Characteristic	CA (n = 4,705)							
	No asthma (n = 32,705)		Nonsevere asthma (n = 3,913)			SA (n = 792)		
	Mean or %	95% CI	Mean or %	95% CI	P value	Mean or %	95% CI	P value
Age (y)	14.6	14.5-14.6	14.6	14.5-14.8	.63	14.7	14.3-15.2	.552
Female	49.0	48.5-49.4	58.3	54.7-61.8	.000*	51.5	42.2-60.7	.781
White	38.6	36.7-40.6	45.9	41.1-50.8	.002*	44.8	34.7-55.4	.33
Private school	21.2	17.1-26.1	27.5	19.4-37.3	.035*	31.7	21.8-43.7	.029*
Current smoker	1.69	1.43-2.0	3.6	2.4-5.5	.012*	4.2	2.4-7.4	.065
Sedentary lifestyle	48.0	47.0-49.0	43.9	38.3-49.8	.174	45.4	35.7-55.5	.695
BMI (kg/m ²)	21.3	21.2-21.4	21.7	21.3-21.9	.07	22.2	21.3-23.1	.048†
WC (cm)	72.0	71.7-72.4	72.5	71.5-73.5	.416	74.6	72.1-77.1	.036†
HDL (mg/dL)	47.2	46.6-47.9	47.8	46.9-48.6	.208	46.3	44.9-47.6	.145
TG (mg/dL)	77.4	76.2-78.7	79.2	76.4-81.9	.283	84.8	78.8-90.8	.021†
Glucose (mg/dL)	86.4	85.9-86.8	86.1	85.1-87.1	.587	86.2	84.8-87.6	.843
Insulin (mU/L)	9.4	9.1-9.7	9.7	9.1-10.3	.283	10.3	9.0-11.5	.163

Results are shown as means for continuous variables and percentages (%) for categorical variables.

HDL, High-density lipoprotein.

*Chi-square test.

†t test with survey data (reference: no asthma).

TABLE II. Prevalence of adiposity measures, metabolic abnormalities, and MS according to asthma status

Characteristic	CA			SA		
	PR	95% CI	P value	PR	95% CI	P value
Obesity	1.08	0.99-1.18	.087	1.28	1.02-1.62	.034*
Increased WC	1.19	1.00-1.43	.047*	1.74	1.16-2.61	.007*
Hyperglycemia	1.18	0.79-1.77	.417	1.78	1.05-2.98	.029*
Low HDL	1.02	0.90-1.16	.714	1.35	0.94-1.92	.102
Hypertriglyceridemia	0.95	0.73-1.24	.716	1.72	0.91-3.26	.095
High BP	0.68	0.51-0.89	.007*	1.16	0.68-1.99	.585
Hyperinsulinemia	1.12	0.91-1.37	.293	1.55	1.03-2.33	.034*
HOMA-IR	1.01	0.99-1.03	.108	1.02	1.01-1.04	.002*
MS	0.94	0.67-1.31	.719	2.43	1.39-4.27	.002*

HDL, High-density lipoprotein; HDL-C, high-density lipoprotein-cholesterol.

Obesity: Z score > 2; increased WC: >P90; hyperglycemia: serum glucose ≥100 mg/dL; low HDL: <40 mg/dL or <50 mg/dL for 16-17-year-old females; hypertriglyceridemia: TG ≥ 150 mg/dL; high BP: ≥130/85 mm Hg; hyperinsulinemia: insulin ≥ 15 mU/L.

HOMA-IR value was calculated as follows:

Fasting insulin (mU/L) × (fasting glucose (mg/dL) × 0.0555)/22.5.

MS was considered when abdominal obesity (WC > P90) was present and at least 2 of the following criteria: (1) high BP, (2) hypertriglyceridemia, (3) low HDL-C, and (4) hyperglycemia.

*Poisson regression.

a protective association between elevated BP and CA, not observed in adolescents with SA, was found. This finding may reflect only a statistical effect but deserves further analysis.

Our study has some limitations. Cross-sectional design does not allow establishing the temporality of relationships to infer causality between MS and its components and SA. In addition, known correlated factors of asthma were not included, for example, family and personal history of atopy and medication use for asthma control. Unfortunately, we could not perform objective measures of pulmonary function because of sample size and logistic issues, and this may have led to a misdiagnosis of asthma, especially among obese individuals. However, a large and representative sample and utilization of standardized procedures by uniformly trained personnel represent considerable strengths of our findings.

In conclusion, MS, some of its components, and insulin resistance were significantly associated with SA in Brazilian adolescents, independent of BMI. Thus, further research is needed

to establish causality and possible common pathophysiological mechanisms, as well as the consequent clinical and therapeutic implications, between these 2 conditions.

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Farm dust reduces viral load in human bronchial epithelial cells by increasing barrier function and antiviral responses



To the Editor:

Early-life respiratory infections caused by rhinoviruses (RVs) and/or respiratory syncytial virus can lead to recurrent wheezing and constitute one of the most dominant risk factors for the development of asthma.¹ Multiple studies show that growing up on farms is associated with protection against allergies, rhinitis, and asthma.² Similarly, farm children also suffer less from virus-induced wheezing in the first years of life.² An increased susceptibility to RVs and respiratory syncytial virus could be related to a weakened epithelial barrier function facilitating viral penetration and/or reduced antiviral responses, such as, a lower IFN production.^{1,3} Interestingly, polymorphisms were identified in genes involved in regulation of the epithelial (barrier) function and linked to a higher susceptibility to develop allergies and asthma.⁴ Furthermore, epithelial cells isolated from patients with asthma demonstrate a defective barrier function,

characterized by a lower transepithelial electrical resistance, higher permeability, and reduced expression of adhesion molecules,⁵ suggesting that a reduced epithelial barrier function may also contribute to the pathophysiology of asthma.^{3,5} In the gut, epithelial recognition of commensal microbes by Toll-like receptors (TLRs) is crucial in maintaining intestinal homeostasis and integrity.⁶ We hypothesized that microbe-rich farm dust decreases susceptibility to RV infection in human airway epithelium by increasing barrier function, and maintaining mucosal tolerance.

All experimental procedures were performed as described in this article's Online Repository at www.jacionline.org. Farm dust extract pre-exposure (18 hours) of undifferentiated primary bronchial epithelial cells (PBECs) followed by RV1b infection caused a significant reduction in viral load at 48 hours postinfection compared with medium, as shown by viral RNA and titer (Fig 1, A). Despite lower viral load, farm dust exposure significantly increased expression of the antiviral IFN-stimulated gene viperin, whereas the expression of other IFN-stimulated genes was not significantly different (Fig 1, B; see Fig E1, A, in this article's Online Repository at www.jacionline.org). This effect could not be attributed to a significant enhancement of production of IFN- α , IFN- β , and IFN- λ by farm dust in RV-infected cells (Fig E1, B), nor to increased responsiveness of farm dust-treated cells to IFN as shown by the inability of farm dust to modulate IFN- β -induced expression of viperin mRNA (Fig E1, C). Interestingly, induction of transcriptional activator IFN regulatory factor (IRF)-1, which regulates viperin expression via IFN-independent pathways,⁷ was increased by farm dust exposure (Fig 1, B). These findings suggest that enhanced viperin expression during treatment of infected cells with farm dust is independent of IFN pathways and mediated by IRF-1 (Fig 1, B).⁷ In addition to enhanced antiviral defenses, the reduction in viral load upon farm dust treatment may also be explained by the reduced binding and subsequent receptor-mediated endocytosis of RV1b. This is supported by our finding of decreased cell-associated RV1b RNA directly after viral exposure in farm dust-treated cells (Fig 1, C), which may have resulted from an increased barrier resistance. Indeed, after 2 hours of farm dust exposure, we observed a dose- and time-dependent increase in resistance (see Fig E2, A, in this article's Online Repository at www.jacionline.org), reaching a maximal 1.7-fold increase compared with medium. In intestinal epithelium, TLR2 was identified to modulate the formation of intercellular junctions.⁶ Similarly, we observed that TLR2-ligand Pam3CSK4 also increased resistance in PBECs to a similar extent as farm dust (Fig E2, A). These observations were supplemented by a reduced transport of macromolecules (fluorescein isothiocyanate-dextran) across the epithelial layer (Fig 1, D, and Fig E2, B), indicating that farm dust exposure affects both ionic and macromolecular permeability. Interestingly, while Pam3CSK4 strongly increased barrier resistance, the TLR4-ligand LPS did not affect permeability (Fig E2, C). This inability may result from the absence of MD-2 in human airway epithelial cells and the lack of TLR4-mediated signaling. We next studied farm dust in the context of recovery from epithelial injury by exposing fully differentiated air-liquid interface (ALI) PBEC cultures to cigarette smoke followed by farm dust. The initial decrease in barrier activity observed at 1 hour after cigarette smoke exposure could not be prevented by farm dust, but recovery was enhanced as shown by an increased transepithelial electrical resistance at 4 hours (Fig E2, D). Thus, farm dust not only improves airway epithelial barrier

METHODS

Adiposity measures

Anthropometric measurements were performed with the student wearing light clothes and bare feet. Height was measured to the nearest 1 mm using a calibrated stadiometer (portable stadiometer Altuxata, Minas Gerais, Brazil) with millimeter resolution and height up to 213 cm. Weight was measured to the nearest 50 g using a digital scale (model P150m, 200 kg of capacity and 50 g of precision, Líder, São Paulo, Brazil).^{E1}

BMI was calculated using the following formula: $\text{BMI (kg/m}^2\text{)} = \text{weight in kilograms divided by the height in meters squared}$. To determine weight categories of adolescents, World Health Organization reference curves, with the index BMI/age, according to sex, was used. The cutoff points were as follows: very low weight, Z score less than -3 ; low weight, Z score -3 or more and less than -1 ; normal weight, Z score -1 or more and 1 or less; overweight, Z score more than 1 and 2 or less; obesity, Z score more than 2.^{E2}

WC was measured to the nearest 1 mm using a fiberglass anthropometric tape, with millimeter resolution and length of 1.5 m (Sanny, São Paulo, Brazil). Measurement was done horizontally, at half the distance between iliac crest and lower costal margin.^{E3}

BP evaluation

BP measurements were based on the 4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, published in 2004.^{E4} Systolic and diastolic BP and pulse were measured using the automatic oscillometric device Omron 705-IT (Omron Healthcare, Bannockburn, Ill). Three BP measurements were taken, with the mean of the final 2 being used in the hypertension classification. Systemic BP was considered high if the systolic BP was greater than or equal to 130 mm Hg, and the diastolic BP was greater than or equal to 85 mm Hg.^{E5}

Metabolic abnormalities

The blood samples were processed and plasma and serum separated within 2 hours after collection and kept between 4°C and 10°C, and then sent to the study's central reference laboratory for analysis. Biochemical determinations were performed using serum samples obtained under fasting conditions. The Friedewald equation was used to calculate low-density lipoprotein-cholesterol. HOMA-IR value was used as a measure of insulin resistance and was calculated as follows: $\text{fasting insulin (mU/L)} \times (\text{fasting glucose (mg/dL)} \times 0.0555)/22.5$. All measurements were performed in automatic analyzers at reference laboratory following uniform standard procedures and quality controls, as detailed elsewhere.^{E6}

In this study, metabolic abnormalities were defined according to International Diabetes Federation Consensus 2005.^{E7} MS was considered when abdominal obesity ($\text{WC} > \text{P90}$) was present and at least 2 of the following criteria were met: (1) high BP ($\geq 130/85$ mm Hg); (2) hypertriglyceridemia ($\text{TGs} \geq 150$ mg/dL); (3) low high-density lipoprotein-cholesterol (<40 mg/dL or <50 mg/dL for 16-17-year-old females); (4) hyperglycemia (serum glucose ≥ 100 mg/dL). The cutoff points that were used for these tests are presented in Table 1.

Lifestyle

This variable was defined by the time in minutes of weekly physical activity, being classified, respectively, as sedentary (<300 min/wk) and active (≥ 300 min/wk).^{E8}

Current smoking

Current smokers were defined as those who smoked cigarettes at least 1 day in the last 30 days.^{E9}

Statistical analysis

Primary sampling units and strata for the complex design of ERICA were taken into account for data analysis. Sampling weights, stratification, and clusters provided in ERICA data set were incorporated into the analysis to obtain proper estimates and SE. Descriptive statistics were reported by frequency, means, and SD. Bivariate analysis between asthma and components of MS was performed using chi-square test, PR, and its respective 95% 95% CIs. Then, those significant associations ($P < .20$) were included in multivariate models adjusted by potential confounders or interaction factors, such as age, sex, race, physical activity, smoking, and school type (private or public) by Poisson regression. For analysis of final models, P value of less than .05 was considered to be statistical significant. All analyzes were performed using SURVEY procedure in STATA 14.0 software (StataCorp, College Station, Tex).

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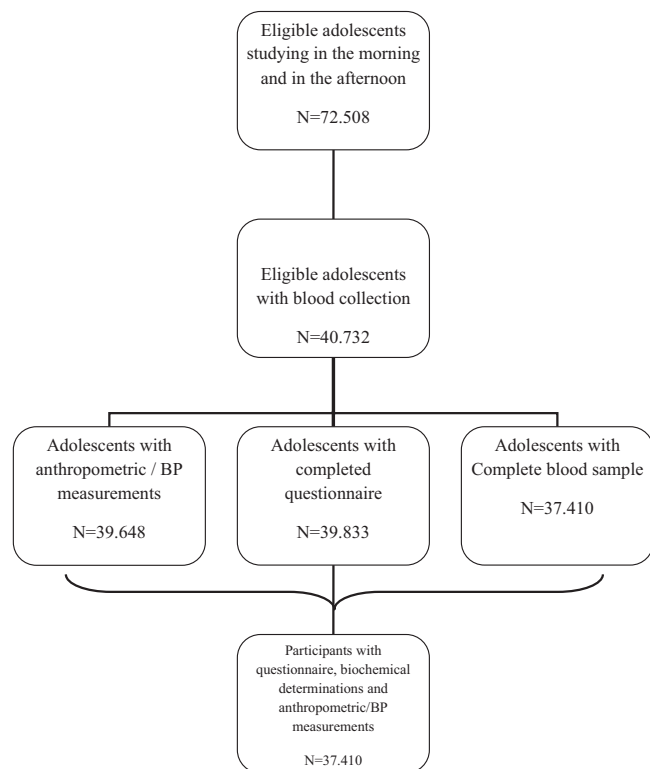


FIG E1. Flowchart of participants with completed data on questionnaire, anthropometric measurements, and biochemical determinations used to define MS.

TABLE E1. Parameters of multivariate analysis* for the association of SA with MS and with its components

Characteristic	SA	
	PR	95% CI
Increased WC	1.46	0.85-2.51
Hyperglycemia	1.77	1.08-2.91
Hyperinsulinemia	1.29	1.01-1.64
MS	1.71	1.03-2.82

*Poisson regression, adjusted for age, sex, current smoking, and BMI.

TABLE E2. Classification criteria: Cutoff points used for blood testing results^{E6}

Examination	Method*	Cutoff points		
		Desirable	Borderline	High
Cholesterol (mg/dL)	Enzymatic kinetics	<150	150-169	≥170
LDL-C (mg/dL)	Enzymatic colorimetric assay	<100	100-129	≥130
HDL-C (mg/dL)	Enzymatic colorimetric assay	≥45	—	—
TGs (mg/dL)	Enzymatic kinetics	<100	100-129	≥130
Glucose (mg/dL)	Hexokinase method	70-99	100-125.9	≥126
Insulin (mU/L)	Chemiluminescence	<15	15-20	≥20

LDL-C, Low-density cholesterol; *HDL-C*, high-density cholesterol.

*Brazilian Society of Pathology.