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ORIGINAL ARTICLE

Body mass index, adipokines and insulin resistance in asthmatic children and adolescents

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Abstract

Objective: This study aimed to describe the body mass index, insulin resistance, levels of adipokines and inflammatory markers in Brazilian asthmatic children and adolescents and to investigate their possible association with the severity and control of asthma. **Methods:** Cross-sectional study ($n = 92$; age: 3–18 years). Assessed data: Body weight and height, used to calculate the body mass index (BMI) and height-for-age (HAZ). Laboratory measurements: Lipid profile; glycemia and insulin for homeostasis model assessment (HOMA); adipokines; tumor necrosis factor alpha (TNF- α), C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1); total immunoglobulin E (IgE) and specific IgE against aeroallergens. **Results:** The median age was 9.6 years (3.0–16.6); most participants were male ($n = 52$, 56.5%), pre-pubertal ($n = 54$, 58.6%) and had atopic asthma ($n = 85$, 92.4%). Overweight/obesity (38%) showed an inverse correlation with age (adjusted odds ratio [OR] = 0.781; 95% confidence interval [CI] 0.66–0.92) and a direct correlation with the leptin concentration (adjusted OR = 1.13; 95% CI 1.04–1.22). Insulin concentration was independently associated with moderated persistent asthma (adjusted OR = 1.31; 95% CI 1.09–1.52). HOMA showed a direct correlation with the leptin ($\beta = 0.475$; 95% CI 0.117–0.268) and total IgE ($\beta = 0.197$; 95% CI 0.002–0.096) levels and an inverse correlation with the TNF- α levels ($\beta = -0.255$; 95% CI: -0.366–0.055). **Conclusions:** Asthma was associated with insulin resistance and a systemic inflammatory response possibly mediated by adipokines, with leptin levels standing out among the participants with excess weight.

Keywords

Adipokines, adolescent, asthma, child, insulin resistance, obesity

History

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Introduction

Asthma is a chronic inflammatory disease with a multifactorial etiology and a high prevalence among children. The multicentre study ISAAC (International Study of Asthma and Allergies in Childhood) phase 3 found that among Brazilian schoolchildren, the prevalence of active asthma (wheezing in the past 12 months) was 24.3%, 6.1% had severe asthma and 10.3% had a medical diagnosis of asthma. Among adolescents, the prevalence of active asthma was 19%; the prevalence rate of severe asthma was 4.7%, and the prevalence of medically diagnosed asthma was 13.6% [1].

Obesity is also a chronic disease; it is characterized by the accumulation of fatty tissue resulting from a positive energy balance and is influenced by genetic and environmental factors [2]. As is the case in many other countries [3], the prevalence of obesity has increased significantly in Brazil.

One in three children (5–9 years old) is overweight. In adolescents (10–19 years), obesity has increased in both males (from 3.7% in 1975 to 21.7% in 2009) and females (from 7.6% in 1975 to 19.4% in 2009) [4].

Observational studies have shown an increased risk of asthma among obese children and adolescents and a direct relationship between asthma severity and a higher body mass index (BMI) [5]. Several mechanisms might account for this association, including the exacerbation of the systemic inflammatory response that occurs when adipose tissue increases and is infiltrated by macrophages. Under such conditions, the production of proinflammatory mediators such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) increases, as does the secretion of adipokines (leptin and resistin), which are also associated with bronchial hyper-responsiveness and insulin resistance (IR) [6].

Adipokines are proteins secreted by adipocytes that play complex and contradictory roles within the systemic inflammatory response. Adipokines such as leptin, chemerin and resistin usually exhibit proinflammatory actions and are considered to be markers of IR, whereas adiponectin has essentially anti-inflammatory properties [7]. Indeed, it

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perhaps unsurprising therefore to find that, chronic low-grade inflammation is a common feature of obesity and virtually all other non-communicable diseases [8].

This study aimed to describe the body mass index, the degree of IR (using homeostasis model assessment index, HOMA), and concentrations of adipokines and other inflammatory markers in asthmatic children and adolescents and to investigate the possible association between the above features/measures with the severity and control of asthma.

Methods

This study is a cross-sectional study with 92 asthmatic children and adolescents aged 3–18 years who received regular care from the *Children with Asthma Management Program* at basic health units in Embu das Artes City (São Paulo metropolitan area, Brazil) [9].

Patients were excluded if, at the time of the study, they were younger than 3 years old; had genetic syndromes, congenital heart defects, immunodeficiency, cystic fibrosis or endocrinopathy (hypothyroidism, type 1 or 2 diabetes); and/or used medication for dyslipidemia (statins, fibrates), hypoglycemic drugs (metformin) or oral corticosteroids.

A total of 219 children and adolescents were enrolled in the Program from 2007 to 2012, 102 (46.5%) remained under regular care, met the inclusion and exclusion criteria at the time of data collection and were invited to participate. Ten individuals did not complete all of the required clinical and laboratory assessments and were excluded from the final case series.

This study was approved by the ethics committee of the Municipal Health Secretary of Embu das Artes City and the Research Ethics Committee of the Federal University of São Paulo. The children's parents signed the informed consent form, and participants above 10 years of age signed the assent form.

A clinical diagnosis of asthma and a determination of its severity and control were performed according to the 2012 Global Initiative for Asthma (GINA) recommendations [10]. The participants were evaluated to determine their sensitivity to aeroallergens (*Dermatophagoides pteronyssinus*; *Blatella germanica*; *Periplaneta americana*) via the measurement of the serum concentration of specific immunoglobulin E (IgE) (ImmunoCAP System). Sensitization was considered present when at least one measurement was over 0.35 kU/l.

Data on the participant's family history, birth weight, gestational age, total breastfeeding duration, personal history of diseases, medication used in the past year for asthma control (duration and dose), number of asthma attacks and number of visits to the emergency services were collected from the clinical records. The inhaled corticosteroid beclomethasone dipropionate (chlorofluorocarbon propellant) was used by patients because it was offered free of charge by the Municipal Health System.

The participants underwent an objective assessment of puberty stage (M1/P1 or G1/P1: pre-puberty) [11], and systemic arterial pressure was measured using the auscultatory method. Pressure values (systolic and/or diastolic) over the 95th percentile for gender, age and height were considered high [12].

To collect anthropometric data, body weight and height were measured to calculate the anthropometric indicators height-for-age (HAZ) and body mass index (BMIZ) as *z* scores using WHO Anthro Plus® (WHO, 2006/2007) [13,14].

After 12-h fasting, peripheral blood was collected to measure:

- Total cholesterol, high density lipoprotein (HDL-c), low density lipoprotein (LDL-c) and triglycerides (colorimetric method). The cut-off points used were those suggested by the American Academy of Pediatrics [15].
- Glycemia (colorimetric method) and insulin (chemiluminescence), used in the homeostasis model assessment [$\text{HOMA} = \text{glycemia (mmol/l)} \times \text{insulin } (\mu\text{U/ml}) / 22.5$]; IR was defined as present when $\text{HOMA} > 3.16$ [16].
- Adipokines (adiponectin, resistin, leptin, adipon, lipocalin and chemerin) and inflammatory markers (TNF- α , CRP and monocyte chemoattractant protein-1 (MCP-1)); immunoassay Luminex™ xMAP Technology, Millipore, Billerica, MA.
- Total IgE and specific IgE (*D. pteronyssinus*; *B. germanica*; *P. Americana*) (ImmunoCAP System, Thermo Scientific®, Waltham, MA).

Statistical analyses were performed using the SPSS 20.0 software package (IBM®, Armonk, NY). The distributional normality of the continuous variables was investigated using the Shapiro–Wilk test. Non-normal variables are presented as the median (minimum–maximum) and were compared using the Mann–Whitney test. Qualitative variables are presented as absolute numbers and percentages and were compared using the Chi-square test. The Spearman correlation test was used to analyze possible associations between the continuous variables. Forward multivariate stepwise linear regression, after logarithmic transformation of non-normal continuous variables, was used for analysis of variables with significant Spearman correlation coefficient ($p < 0.05$). The variables with p values < 0.1 in bivariate analysis were included in the multivariate forward stepwise binary logistic regression (LR). The final significance level was 5%.

Results

Participant characteristics are described in Table 1. The median age was 9.6 years (2.9; 16.6); most of the participants were male ($n = 52$, 56.5%) and in the pre-pubertal stage ($n = 54$, 58.6%). Atopic asthma was found in 85 (92.4%) participants; the median total IgE concentration was 676.0 IU/mL (9.63; 5000). Rhinitis or atopic dermatitis was present in 82 (89.1%) participants. Regarding the severity of disease, intermittent and mild persistent forms of asthma prevailed (82 patients; 89.1%); in most of the participants, the asthma was under control at the time of assessment (76 patients; 82.6%; Table 1).

Regarding nutritional status (body mass index and height for age), 15 (16.3%), 20 (21.7%), 3 (3.2%) and 4 (4.3%) participants exhibited obesity, overweight, underweight and short stature, respectively (Table 1). The systolic and diastolic pressure was increased in 10 (10.9%) and 8 (8.7%) participants, respectively. Dyslipidemia affecting total cholesterol was detected in 12 (13.0%), LDL-c in 13 (14.1%), HDL-c in

Table 1. General characteristics of the 92 children and adolescents included in the study.

Variable		N (%)
Gender	Male	52 (56.5)
Birth weight	<2500 g	3 (3.3)
	2500–4000 g	79 (85.8)
	>4000 g	5 (5.4)
Total breastfeeding duration	≥4 months	65 (70.6)
Pubertal stage	Pre-pubertal	54 (58.6)
	Pubertal	39 (42.4)
Asthma classification	Intermittent	60 (65.2)
	Mild persistent	22 (23.0)
	Moderate persistent	10 (10.8)
Use of nasal corticosteroids	Yes	40 (43.4)
Use of inhaled corticosteroids	Yes	28 (30.4)
Dose of inhaled corticosteroids	Low	15 (16.3)
	Medium	13 (13.1)
Asthma control	Uncontrolled	16 (17.4)
	Controlled	76 (82.6)
Body mass index z score (BMIZ)	Obesity	15 (16.3)
	Overweight	20 (21.7)
	Normal BMI	54 (58.7)
	Underweight	3 (3.2)
Short stature (height for age z score, HAZ)	Yes	4 (4.3)
	No	88 (95.6)
Systolic arterial pressure	Increased	10 (10.9)
Diastolic arterial pressure	Increased	8 (8.7)
Total cholesterol	>200 mg/dL	12 (13.0)
LDL-c	>130 mg/dL	13 (14.1)
HDL-c	<40 mg/dL	15 (16.3)
Triglycerides	>100 mg/dL	23 (25.0)
Glycemia	>100 mg/dL	0 (0.0)
HOMA	>3.16	13 (14.1)

BMI, body mass index; HOMA, homeostatic model assessment; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein.

15 (16.3%), triglycerides in 23 (25%) and HOMA >3.16 was found in 13 (14.1%) participants.

There was no statistically significant association between the patient's BMIZ and severity and control of asthma. The overweight/obese individuals were younger and exhibited higher CRP, TNF- α and leptin levels compared with the participants with normal BMI (Table 2). Multivariate analysis demonstrated that overweight/obesity, in asthmatic children and adolescents, was inversely associated with age (adjusted odds ratio [OR] = 0.78; 95% confidence interval [CI] 0.66–0.92) and directly associated with leptin concentration (adjusted OR = 1.13; 95% CI 1.04–0.22; Table 2).

Patients with moderate persistent asthma exhibited higher insulin concentrations (adjusted OR = 1.31; 95% CI 1.09–1.52; Table 3). Regarding the asthma control, only inhaled corticosteroids were independently associated with uncontrolled asthma (adjusted OR = 5.0; 95% CI 1.6–15.7; Table 4). HOMA was higher among the patients who used inhaled corticosteroids ($n = 28$) than among those who did not [1.9 (0.8–5.3) versus 1.4 (0.2–2.7); $p = 0.009$] (data not shown).

HOMA correlated directly to leptin concentration (Spearman's correlation $r = 0.436$; $p < 0.001$), total IgE ($r = 0.274$; $p = 0.009$) and inversely to TNF- α concentration ($r = -0.258$; $p = 0.014$). Similarly, linear regression showed a direct association between HOMA with leptin concentration ($\beta = 0.475$; 95% CI 0.117–0.268) and total IgE ($\beta = 0.197$;

95% CI 0.002–0.096); and an inverse correlation with TNF- α levels ($\beta = -0.255$; 95% CI –0.366 to 0.055; Table 5).

Discussion

In this study, excess weight (overweight/obesity) was not associated with asthma severity or worse asthma control. Insulin concentration and HOMA were higher among patients with moderate persistent asthma and those who used inhaled corticosteroids. The leptin and total IgE levels were directly correlated with insulin resistance.

Epidemiological findings indicating associations between obesity and asthma have prompted investigation into common mechanisms that may underlie both conditions. Results from research into the possible connection between overweight/obesity and asthma are controversial [17]. An association between the severity of asthma and overweight/obesity was not found in this study. It should be noted that although the frequency of overweight/obesity in the sample was similar to the Brazilian average (38.0%), most of the study participants exhibited mild and controlled asthma. In the literature, an association between these conditions is more prevalent in studies that include participants with more severe asthma and obesity [18].

Leptin levels were higher among overweight/obese patients. The adipokines leptin and adiponectin play a significant role in the pathogenesis of asthma during periods of both stability and exacerbation [7]. Leptin with pro-inflammatory activity stimulates the production of inflammatory cytokines in bronchial and alveolar cells. Adiponectin with predominantly anti-inflammatory action is also expressed in lung cells [7].

In this study, no association was found between CRP levels and the severity or control of asthma. CRP is considered to be an obesity inflammatory marker associated with endothelial dysfunction and atherosclerosis. It is also a predictor of cardiovascular events [19]. In a prospective study, Kattan et al. [20] analyzed respiratory symptoms, nutritional status and inflammatory processes in adolescents with moderate or severe asthma. The results showed increased CRP levels in association with increased BMI and decreased pulmonary function; however, there was no association between CRP and respiratory symptoms or asthma exacerbations. The authors thus concluded that there was no correlation between CRP and asthma severity.

Homeostasis model assessment (HOMA) is a simple and indirect marker of IR that is widely used to assess children and adolescents because it is easy to calculate and exhibits a satisfactory association with the oral glucose tolerance test [16]. Indeed, HOMA is based on fasting blood glucose and insulin samples, seeking to demonstrate the relationship between the insulin production capacity of the pancreas and its ability to maintain adequate blood glucose levels [21]. HOMA was higher among patients with moderate asthma and those who used inhaled corticosteroids.

Inflammation can be more intense in the most severe forms of asthma and among those who use corticosteroids. In the literature, there are few studies evaluating the association between insulin resistance, use of inhaled corticosteroids and asthma. One cohort study conducted in Canada with adults

Table 2. Comparison of the studied variables between asthmatic children and adolescents with overweight/obesity or normal body mass index.

		Overweight/obesity (<i>n</i> = 35)	Normal body mass index (<i>n</i> = 54)	<i>p</i> value
Age	Years	8.2 (2.9;14.7)	9.7 (3.4;16.5)	0.027^a
Gender	Male	19/35 (54.3)	30/54 (55.5)	0.539 ^b
Pubertal stage	Pre-pubertal	13/35 (37.1)	23/54 (42.5)	0.663 ^b
Asthma severity	Moderate	3/35 (8.6)	5/53 (9.4)	0.602 ^b
Asthma control	Uncontrolled	7/35 (20.0)	8/53 (15.1)	0.574 ^b
Inhaled corticosteroids	Yes	10/35 (28.6)	15/53 (28.3)	0.515 ^b
Inhaled corticosteroids	mcg/day	500.0 (250.0;500.0)	500.00 (250.0;1000.0)	0.186 ^a
Systolic blood pressure	mmHg	91.6 (60.0;133.3)	93.3 (70.0;193.3)	0.986 ^a
Diastolic blood pressure	mmHg	60.0 (28.0;90.0)	60.0 (40.0;80.0)	0.856 ^a
Insulin	μU/mL	9.2 (2.4;21.5)	7.4 (1.2;24.5)	0.162 ^a
HOMA		1.75 (0.4;4.4)	1.50 (0.2;5.3)	0.209 ^a
Glycaemia	mg/dL	78.0 (65.0;89.0)	81.0 (60.0;93.0)	0.393 ^a
Triglycerides	mg/dL	81.0 (34.0;167.0)	75.0 (27.0;269.0)	0.725 ^a
Total cholesterol	mg/dL	166.5 (105.0;217.0)	157.0 (73.0;213.0)	0.177 ^a
HDL-c	mg/dL	47.0 (32.0;76.0)	47.0 (13.0;73.0)	0.966 ^a
LDL-c	mg/dL	100.0 (54.0;154.0)	90.5 (26.0;149.0)	0.126 ^a
MCP-1	pg/mL	260.0 (99.3;476.0)	204.0 (43.77;553.0)	0.081 ^a
CRP	mg/dL	3.7 (0.05;16.81)	1.4 (0.11;14.6)	0.013^a
TNF-α	pg/mL	3.9 (1.17;10.17)	3.3 (0.33;10.90)	0.041^a
IL-6	pg/mL	3.9 (0.51;18.28)	3.0 (0.51;25.89)	0.602 ^a
Leptin	pg/mL	7.1 (1.11;29.94)	2.0 (0.21; 44.1)	<0.001^a
Adiponectin	pg/mL	51172 (7762;210090)	61747 (7294;679967)	0.079 ^a
Lipocalin	pg/mL	183.0 (69.3;456.0)	162.0 (61.37;1906.0)	0.326 ^a
Resistin	pg/mL	34.8 (2.61;117.0)	44.2 (4.03;183.0)	0.128 ^a
Adipsin	pg/mL	5587.0 (3865;9311)	5168.0 (3302;11351)	0.105 ^a
Chemerin	pg/mL	47.4 (28.94;100.42)	43.8 (27.90;67.43)	0.077 ^a
Total IgE	IU/mL	641.0 (9.63;5000)	726.0 (18.7;5000)	0.346 ^a

HOMA, homeostatic model assessment; LDL-c, low density lipoprotein; HDL-c, high density lipoprotein; MCP-1, monocyte chemotactic protein 1; CRP, C-reactive protein; IL-6, interleukin 6; IgE, immunoglobulin E; TNF-α, tumor necrosis factor alpha.

^aMedian (minimum;maximum) and *p* value on the Mann–Whitney test.

^b*n*/*N* (percentage) and *p* value on the Chi-square test.

Multivariate analysis: age (adjusted odds ratio [OR] = 0.78; 95% confidence interval [CI] 0.66–0.92) and leptin concentration (adjusted OR = 1.13; 95% CI 1.04–0.22) were associated with overweight/obesity asthma. Bold values *p* < 0.05.

Table 3. Comparison of the studied variables between groups in relation to asthma severity.

		Moderate persistent asthma (<i>n</i> = 10)	Intermittent/mild persistent asthma (<i>n</i> = 82)	<i>p</i>
Age	Years	11.8 (4.9;15.4))	8.9 (3.0;16.5)	0.177 ^a
Gender	Male	8/10 (80.0)	33/82 (40.2)	0.021^b
Pubertal stage	Pre-pubertal	7/10 (70.0)	32/82 (39.0)	0.090 ^b
Inhaled corticosteroids	Yes	10/10 (100.0)	18/79 (22.8)	<0.001^b
Inhaled corticosteroids	mcg/day	750.0 (250.0;1000.0)	425.0 (250.0;500.0)	0.004^a
Systolic blood pressure	mmHg	103.3 (70.0;123.0)	93.3 (60.0;133.0)	0.043 ^a
Diastolic blood pressure	mmHg	60.0 (40.0;80.0)	60.0 (30.0;90.0)	0.680 ^a
Insulin	μU/mL	16.1 (5.0;24.0)	7.6 (1.2;24.5)	0.004^a
HOMA		3.1 (0.8;5.3)	1.6 (0.2;3.7)	0.010^a
Glycemia	mg/dL	79.0 (63.0;89.0)	79.0 (60.0;92.0)	0.388 ^a
Triglycerides	mg/dL	93.0 (60.0;160.0)	76.0 (27.0;269.0)	0.128 ^a
Total cholesterol	mg/dL	151.0 (122.0;184.0)	162.0 (73.0;217.0)	0.221 ^a
HDL-c	mg/dL	44.0 (37.0;56.0)	47.0 (32.0;74.0)	0.399 ^a
LDL-c	mg/dL	79.5 (63.0;116.0)	95.0 (28.0;154.0)	0.871 ^a
MCP-1	pg/mL	205.5 (135.0;455.0)	237.5 (43.8;553.0)	0.726 ^a
PCR	mg/dL	2.2 (0.1;22.8)	1.5 (0.2;10.6)	0.955 ^a
TNF-α	pg/mL	3.4 (1.5;5.1)	3.8 (0.3;10.9)	0.773 ^a
IL-6	pg/mL	4.1 (0.9;16.6)	3.3 (0.5;25.9)	0.547 ^a
Leptin	pg/mL	8.3 (0.4;18.1)	2.9 (0.2;34.5)	0.042^a
Adiponectin	pg/mL	55633 (19540;88679)	55025 (7294;679967)	0.900 ^a
Lipocalin	pg/mL	168.0 (61.4;1906.0)	169.5 (72.3;1244.0)	0.841 ^a
Resistin	pg/mL	34.7 (4.8;66.5)	41.2 (2.6;117.0)	0.196 ^a
Adipsin	pg/mL	5677 (4235;10701)	5415 (3302;11351)	0.643 ^a
Chemerin	pg/mL	50.7 (35.2;100.4)	44.6 (27.9;84.7)	0.185 ^a
Total IgE	IU/mL	1376.0 (338.0;2173.0)	663.0 (9.6;5000.0)	0.281 ^a

HOMA, homeostatic model assessment; LDL-c, low density lipoprotein; HDL-c, high density lipoprotein; MCP-1, monocyte chemotactic protein 1; CRP, C-reactive protein; IL-6, interleukin 6; IgE, immunoglobulin E.

^aMedian (minimum;maximum) and *p* value on the Mann–Whitney test.

^b*n*/*N* (percentage) and *p* value on the chi-square test.

Multivariate analysis: insulin concentration was independently associated with moderated persistent asthma (adjusted OR = 1.31; 95% CI 1.09–1.52). Bold values *p* < 0.05.

Table 4. Comparison of the studied variables in relation to asthma control.

		Uncontrolled asthma* (n = 16)	Controlled asthma (n = 76)	p value ^c
Age	Years	6.9 (2.9;15.4)	9.9 (3.4;16.5)	0.946 ^a
Gender	Male	12/16 (75)	39/76 (51.3)	0.102 ^b
Pubertal stage	Pre-pubertal	6/16 (37.5)	33/76 (43.4)	0.784 ^b
Inhaled corticosteroids	Yes	10/16 (62.5)	18/73 (24.6)	0.006^b
Inhaled corticosteroid dose	mcg/day beclo	500.0 (250.0;1000.0)	250.0 (250.0;500.0)	0.123 ^a
Systolic blood pressure	mmHg	100.0 (60.0;130.0)	93.3 (70.0;133.3)	0.201 ^a
Diastolic blood pressure	mmHg	60.0 (28.0;90.0)	60.0 (40.0;80.0)	0.643 ^a
Insulin	μU/mL	9.85 (3.7;18.1)	7.6 (1.2;24.5)	0.031^a
HOMA		1.95 (0.8;3.6)	1.50 (0.2;5.3)	0.041^a
Glycemia	mg/dL	81.0 (62.0;89.0)	78.0 (60.0;93.0)	0.753 ^a
BMIZ	score z	0.55 (− 2.1;5.6)	0.58 (−3.2;4.3)	0.903 ^a
Triglycerides	mg/dL	84.0 (49.0;170.0)	76.0 (27.0;269.0)	0.489 ^a
Total cholesterol	mg/dL	157.0 (73.0;209.0)	161.0 (89.0;217.0)	0.513 ^a
HDL-c	mg/dL	50.0 (13.0;76.0)	47.0 (32.0;76.0)	0.727 ^a
LDL-c	mg/dL	91.5 (26.0;141.0)	95.0 (28.0;154.0)	0.505 ^a
MCP-1	pg/mL	217.0 (98.3;476.0)	237.5 (43.8;553.0)	0.909 ^a
CRP	pg/mL	1.57 (0.12;104.6)	1.58 (0.5;46.7)	0.899 ^a
TNF-alpha	pg/mL	4.55 (1.06;10.9)	3.64 (0.33;10.1)	0.161 ^a
IL-6	pg/mL	3.4 (0.5;16.5)	3.3 (0.5;25.9)	0.357 ^a
Leptin	pg/mL	3.5 (0.4;15.3)	2.97 (0.21;44.1)	0.219 ^a
Adiponectin	pg/mL	54 643.0 (14 158;179 470)	55 633.5 (7294;679 967)	0.593 ^a
Lipocalin	pg/mL	166.5 (69.2;1906.0)	169.5 (61.4;1244.0)	0.718 ^a
Resistin	pg/mL	32.73 (10.8;117.0)	38.07 (2.6;106.0)	0.270 ^a
Adipsin	pg/mL	5547.0 (3559;10701)	5420.0 (3302;11351)	0.760 ^a
Chemerin	pg/mL	45.8 (35.3;64.6)	44.6 (27.9;100.4)	0.579 ^a
Total IGE	IU	834.5 (135.0;3324.0)	689.0 (9.6;5000.0)	0.121 ^a

*Partially controlled + uncontrolled asthma.
HOMA, homeostatic model assessment; LDL-c, low density lipoprotein; HDL-c, high density lipoprotein; MCP-1, monocyte chemotactic protein 1; CRP, C-reactive protein; IL-6, interleukin 6; IgE, immunoglobulin E.
^aMedian (minimum;maximum) and ^bp value ³on the Mann-Whitney test.
^bn/N (percentage) and significance level on the Chi-square test.
Multivariate analysis: only inhaled corticosteroids was independently associated with uncontrolled asthma (adjusted OR = 5.0; 95% CI 1.6–15.7). Bold values p < 0.05.

Table 5. Regression coefficient corresponding to leptin, TNF-α and total IgE in relation to HOMA in asthmatic children and adolescents.

	β	95% confidence interval	p
Leptin (log)	0.475	0.117; 0.268	<0.001
TNF-α (log)	−0.255	−0.366; −0.055	0.009
Total IgE (log)	0.197	0.002; 0.096	0.041

log, logarithmic transformation; HOMA, homeostatic model assessment; MCP-1, monocyte chemotactic protein 1; CRP, C-reactive protein; IL-6, interleukin 6; IgE, immunoglobulin E; ZBMI, body mass index z-score.
Dependent variable: HOMA (log). Independent variables in the model: IL-6 (log), MCP-1 (log), CRP (log), lipocalin (log), chemerin (log), adipsin (log), resistin (log) and BMIZ (log).

with chronic obstructive pulmonary disease who had used inhaled corticosteroids for many years showed a 34% increase in the incidence of type 2 diabetes mellitus [22]. No study has examined such an association in pediatric patients.

An association between IR and asthma severity has been described in asthmatic and obese children/adolescents. However, few pediatric studies have included patients both with and without excess weight. Al-Shawwa et al. [18] studied adolescents with severe obesity and observed that IR was more common among the asthmatic patients. Jimenez et al. [23] assessed a population of obese youths and found that HOMA was associated with allergic sensitization and a diagnosis of allergic asthma. A Danish population-based study of adults showed that IR was associated with sensitization to aeroallergens and atopic asthma, even after adjustment

for overweight/obesity [24]. However, Ma et al. [25] did not find an association between IR and atopic or non-atopic asthmatic adults.

The response to increased insulin levels varies among different body tissues, and the effect of elevated insulin on lung tissue is not yet fully understood. This interaction is complex and is thought to depend on the developmental stage of the bronchial epithelium and on the length of exposure to high insulin levels [26]. Systemic inflammation (low grade inflammatory process) has been suggested as the primary mechanism connecting IR and asthma [26]. This situation is associated with a reduced tolerance of antigens and increased adipokines that promote bronchial hyper-responsiveness and airway inflammation [27].

The understanding of the action of insulin on lung epithelium will likely increase in the near future as a result of the recent approval of inhaled insulin for the treatment of diabetes mellitus. Preliminary results suggest that inhaled insulin reduces the forced expiratory volume in one second (FEV1). The related mechanisms include exacerbation of the Th2 lymphocyte response, mast cell degranulation and bronchial hyper-responsiveness, which result in bronchoconstriction [27,28].

In this study, HOMA was directly associated with leptin concentration and inversely associated with TNF-α levels. A study conducted in Australia compared children/adolescents with and without allergic asthma and did not find differences in nutritional status between the groups. However, IL-6, IL-4, IL-5, leptin levels and HOMA were higher in the group with

asthma; HOMA exhibited a direct correlation with IL-6 and an inverse correlation with TNF- α [29].

The co-existence of diseases like obesity, asthma and insulin resistance can lead to interactions among different inflammatory, immunologic and metabolic mediators, which can modify the severity and evolution of the clinical conditions and increase the long-term risk of non-communicable diseases, such as cardiovascular illnesses. In a cohort of healthy adults who were followed for 10 years, an association was found between reduced forced vital capacity with type 2 diabetes mellitus and higher risk of cardiovascular death [30]. To date, no studies have assessed the long-term cardiovascular risk of asthmatic children/adolescents.

The limitations of this study derive from a lack of control group (with normal weight and without asthma). It should also be highlighted that the patients did not undergo pulmonary function testing and it was a convenience sample. Finally, as our findings derived from a cross-sectional study, causality cannot be inferred.

To conclude, asthma was associated with insulin resistance and a systemic inflammatory response possibly mediated by adipokines, with leptin levels standing out among the participants with excess weight. This association strengthens the importance of careful asthma control measures in overweight children. It also adds weight to the association between increased insulin concentration and the long-term development of various pathological conditions. New strategies are called for in the care of asthmatic patients, especially in those who are overweight/obese with uncontrolled asthma. Long-term, multidisciplinary follow up is very important for such patients and care should be taken to monitor their nutritional status, asthma control and to reduce morbidities such as obesity to decrease the risk of future damage and morbidity.

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Declaration of interest

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