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ORIGINAL ARTICLE

Nutritional status, adiposity and asthma severity and control in children

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Aim: To investigate association between nutritional status, adiposity and asthma severity and control in children.

Methods: We conducted a case control study at two teaching hospitals in Brazil. Cases were children (3–12 years) with persistent asthma and age-matched controls were those with intermittent asthma. Nutritional status was assessed by body mass index (BMI). Adiposity was assessed by sum of skinfolds and waist circumference (WC). Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using conditional logistic regression or multinomial logistic regression as appropriate.

Results: Two hundred sixty-eight cases and 126 controls were included. Obesity (>2 BMI *z*-score for age) was significantly associated with persistent asthma (adjusted OR 2.62; 95% CI 1.39–4.95). There was a significant linear relationship between BMI *z*-scores (≤1, >1 to ≤2, >2) and risk of having persistent asthma ($P = 0.003$ for linear trend). Children with WC >90th percentile had a higher risk of persistent asthma when compared with those with WC ≤90th percentile (adjusted OR 3.38; 95% CI 1.26–9.06). No significant difference was found in terms of nutritional status and adiposity between children whose asthma was controlled by inhaled corticosteroids and those requiring inhaled corticosteroids plus other medications for asthma control.

Conclusions: Obesity measured by BMI and increased abdominal adiposity are significantly associated with risk of persistent asthma but not type of controller medications.

Key words: adiposity; asthma; body mass index; case control study; child; obesity.

What is already known on this topic

1 Prevalence of both asthma and obesity has increased in the last decades.
2 Obesity is a risk factor for childhood asthma.

What this paper adds

1 Obesity measured by body mass index (BMI) and increased abdominal adiposity is associated with more severe asthma (i.e. persistent asthma).
2 There is a linear relationship between nutritional status assessed by BMI (from normal, overweight to obesity) and risk of having persistent asthma.
3 Neither nutritional status nor adiposity is associated with type of controller medications.

Asthma and obesity are considered as global public health problems. The prevalence of both asthma and obesity has increased in the last decades that may indicate a potential link between two conditions. Several epidemiological studies have shown an association between overweight/obesity and risk of childhood asthma.[1–4] A possible association between overweight/obesity and asthma severity and control in children has also been studied; however, the number of such studies is still limited. Some studies showed that obesity was associated with increased asthma severity and worse disease control,[5–7] but other studies did not confirm these findings[8,9] or showed such association only in a subgroup of patients (females).[10] Moreover, most of the previous studies used only body mass index (BMI) as an indicator of nutritional status, but the distribution of body fat may vary significantly, even within the same BMI range.[11]

This study aimed to investigate association between nutritional status, adiposity and asthma severity and control in children.

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Conflict of interest: None.

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Methods

Study design

We conducted a case control study at the paediatric pulmonary outpatient clinics of two university teaching hospitals in southern Brazil between April 2012 and May 2013. These clinics are the two only public specialised services for asthmatic children covering a region with around 500 000 inhabitants. Most of children with asthma attending these public clinics were from low- and middle-income families and referred by general paediatricians. After initial assessment and investigation, patients were regularly followed up at the clinics. The research project was approved by the Research Ethics Committee of the two universities, and informed consent was obtained from all parents or guardians.

Participants

Children aged 3–12 years with diagnosis of asthma were eligible for the study. Asthma was diagnosed if a child met all of the following criteria:[12,13] (i) recurrent episodes (≥3 episodes) of one or more of the following symptoms – wheeze, cough, breathing difficulties and chest tightness, particularly at night or in the early hours of the morning; (ii) respiratory symptoms improve spontaneously or after treatment (bronchodilators associated or not with corticosteroids); (iii) presence of triggers or aggravating factors such as exposure to allergens or irritants, physical exercise, weather changes or emotional stress; (iv) personal history of atopy (allergic rhinitis or eczema) and/or family history of atopy (asthma, allergic rhinitis or eczema) in first-degree relatives.

Asthma severity was classified as intermittent or persistent (mild, moderate or severe), based on the criteria of the National Heart Lung and Blood Institute (NHLBI).[14] If children were under use of controller medications at study entry, their medical records before the start of treatment were reviewed for confirmation of asthma severity. Asthma controller medications were checked and adjusted if needed at regular follow-up visits based on patient's response.

Children with persistent asthma were considered as the cases, whereas those with intermittent asthma were considered as the controls. Due to limited number of children with intermittent asthma attending the clinics, we recruited one control for two cases matched by age groups: 36–72 months and 73–144 months.

We excluded from the study children with bronchopulmonary dysplasia, cystic fibrosis, congenital cardiopulmonary diseases, immunodeficiency and chronic encephalopathy.

Study variables and data collection

Asthma severity and control were considered as dependent variables (outcomes). Given that asthma was controlled or partly controlled in all participants during study period according to the Global Initiative for Asthma (GINA) criteria,[13] we classified asthma control in three categories based on the need and type of controller medications: (i) asthma controlled with inhaled corticosteroids (ICSs) alone; (ii) asthma controlled with ICS plus other medications such as long-term beta 2-agonists or leukotriene receptor antagonists; (iii) and asthma controlled without use of maintenance medications. The clinical data for diagnosis and classification of asthma were obtained by physicians at regular visits through interviews with parents or caretakers using a standardised data form. The frequency of respiratory symptoms, use of bronchodilators and limitation to physical activities in the last 30 days and the frequency of acute exacerbations, use of systemic corticosteroids, emergency room visits and hospitalisation in the last 12 months were asked. In children over 6 years of age, lung function was assessed using peak expiratory flow meter and/or spirometry. The diagnosis and classification of asthma were performed by three senior pulmonologists who provided specialised cares for asthmatic children at two study settings.

Independent variables included nutritional status, demographic and socio-economic data (gender, age and skin colour, family income and educational level of parents), smoking during pregnancy, presence of any sources of allergens in the home (curtains, carpets, fluffy toys or pets), gestational age (preterm: <37 weeks), birthweight (low birthweight: <2.500 g), family history of asthma (first-degree relatives) and personal history of allergic rhinitis. These data were collected by five well-trained investigators through interview with patient's parents or caretakers using a standardised pre-coded questionnaire. All investigators were blinded to the classification of asthma severity and control.

Nutritional status assessed by BMI (body weight in kg/height in m^2) was classified in three categories according to the WHO Growth Curves: (i) normal: BMI z-score for age ≤1; (ii) overweight: BMI z-score for age >1 and ≤2; (iii) obese: BMI z-score for age >2.[15] The weight (kg) was measured by a mechanical platform scale with capacity up to 150 kg (Filizola, Brás, São Paulo, Brazil), and height (m) was measured by a stadiometer (Altura Exata, Santa Efigênia, Belo Horizonte, Brazil) using standardised methodology.[16] Adiposity was assessed using sum of skinfolds (SSFs) and waist circumference (WC). The SSF was obtained from the sum of triceps and subscapular skinfolds based on methodology proposed by Jelliffe.[17] For the purposes of analysis, the SSF was categorised in tertiles. The WC was measured at the midpoint between the last rib and iliac crest using an inextensible measuring tape with a 0.1 cm precision, according to standardised methodology.[16] The WC was classified in two categories using the distribution of our study sample: >90th percentile and ≤90th percentile.

Statistical analysis

Double data entry was performed using the software EPI-data 3.2 (EpiData Association, Odense, Denmark). Analyses were carried out using Stata 11 (Stata Corp. College Station, TX, USA). A descriptive analysis was conducted for each group with calculation of absolute and relative frequencies for independent variables. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to estimate the degree of association between independent variables and outcomes. For the outcome 'asthma severity', we used conditional logistic regression due to matching of cases and controls by age groups. For the outcome 'asthma control', we used multinomial logistic regression given that this outcome had three categories. This method allows to estimate OR for each independent variable simultaneously without multiple tests. The multivariable

analysis was used for the control of potential confounding factors, being included in the final model only those with *P* value ≤ 0.21 in the bivariate analysis. The *P*-value < 0.05 in two-tailed tests was defined as statistically significant.

Results

A total of 404 patients were screened for eligibility, of which 10 were excluded due to diagnosis of bronchopulmonary dysplasia ($n = 3$), chronic neurological disease ($n = 2$), pulmonary tuberculosis ($n = 1$), congenital heart diseases ($n = 3$) and not having a diagnosis of asthma ($n = 1$). Thus, 394 patients were included in the study, of whom 268 were classified as the cases and 126 as the controls. Table 1 shows the characteristics of 394 patients. Only male gender and maternal smoking during pregnancy were significantly associated with persistent asthma, with OR (95% CI) of 1.58 (1.03–2.42) and 1.90 (1.07–3.37), respectively.

Table 2 shows association between nutritional status, adiposity and asthma severity. Three patients with BMI *z*-score for age <2 (two from persistent asthma group and one from intermittent asthma group) were excluded from the analysis. Obesity (BMI *z*-score for age >2) was significantly associated with persistent asthma (adjusted OR 2.62; 95% CI 1.39–4.95). There was a significant linear relationship between nutritional status

Table 1 Characteristics of study participants ($n = 394$)

Variables	Persistent asthma ($n = 268$)		Intermittent asthma ($n = 126$)		OR (95% CI)	*P* value*
	n	%	*n*	%		
Gender						0.03
Female	109	40.7	65	51.6	1.00	
Male	159	59.3	61	48.4	1.58 (1.03–2.42)	
Race						0.85
White	187	70.0	87	69.1	1.00	
Non-white	80	30.0	39	30.9	0.96 (0.60–1.52)	
Family income						0.86**
1st tercile	94	37.3	41	33.9	1.00	
2nd tercile	76	30.2	38	31.4	0.89 (0.52–1.52)	
3rd tercile	82	32.5	42	34.7	0.88 (0.52–1.48)	
Maternal smoking during pregnancy						0.02
No	200	75.2	107	85.6	1.00	
Yes	66	24.8	18	14.4	1.90 (1.07–3.37)	
Any sources of indoor allergens						0.68
No	13	4.9	5	4.0	1.00	
Yes	254	95.1	121	96.0	0.81 (0.28–2.31)	
Gestational age						0.21
≥37 weeks	207	81.5	98	86.7	1.00	
<37 weeks	47	18.5	15	13.3	1.49 (0.79–2.79)	
Birthweight						0.83
≥2.500 g	218	85.5	99	84.6	1.00	
<2.500 g	37	14.5	18	15.4	0.93 (0.51–1.72)	
Maternal educational level						0.21
≥9 years	139	52.3	56	44.8	1.00	
<9 years	127	47.7	69	55.2	0.76 (0.49–1.17)	
Paternal educational level						0.41
≥9 years	88	35.1	35	31.0	1.00	
<9 years	163	64.9	78	69.0	0.82 (0.51–1.32)	
Family history of asthma						0.55
No	108	40.5	55	44.0	1.00	
Yes	159	59.5	70	56.0	1.13 (0.74–1.75)	
Personal history of allergic rhinitis						0.19
No	72	27.2	41	32.8	1.00	
Yes	193	72.8	84	67.2	1.37 (0.86–2.18)	
Passive smoking						0.08
No	144	53.9	80	63.5	1.00	
Yes	123	46.1	46	36.5	1.47 (0.95–2.27)	

**P* value estimated by Wald test for heterogeneity **Wald test for linear trend.

Table 2 Crude and adjusted association between nutritional status, adiposity and asthma severity

Variables	Persistent asthma *n* (%)	Intermittent asthma *n* (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)*	*P* value
Nutritional status				0.003**		0.003**
Normal	109 (43.3)	60 (57.0)	1.00		1.00	
Overweight	60 (23.8)	30 (24.8)	1.27 (0.75–2.17)		1.34 (0.76–2.37)	
Obesity	83 (32.9)	22 (18.2)	2.39 (1.37–4.16)		2.62 (1.39–4.95)	
Waist circumference				0.005		0.016
≤90th percentile	215 (85.0)	116 (95.1)	1.00		1.00	
>90th percentile	38 (15.0)	8 (4.9)	3.67 (1.49–9.08)		3.38 (1.26–9.06)	
Sum of skinfolds				0.364**		0.751**
1st tercile	76 (32.2)	42 (36.5)	1.00		1.00	
2nd tercile	81 (34.3)	37 (32.2)	1.25 (0.72–2.14)		1.13 (0.62–2.06)	
3rd tercile	79 (33.5)	36 (31.3)	1.29 (0.74–2.28)		1.10 (0.59–2.07)	

*Adjusted for: sex, maternal educational level, smoking during pregnancy, gestational age, allergic rhinitis personal history, exposition to passive smoking.
***P* value for linear trend.

assessed by BMI (from normal, overweight to obesity) and risk of having more severe asthma (persistent asthma) ($P = 0.003$ for linear trend). Children with WC above 90th percentile also had a higher risk of having persistent asthma when compared with those with WC equal or below 90th percentile (adjusted OR 3.38; 95% CI 1.26–9.06). There was no significant association between SSF and asthma severity.

Adjusted association between nutritional status, adiposity and asthma control is shown in Table 3. Obesity assessed by BMI and by WC percentile was significantly associated with use of controller medications, either ICS alone or ICS plus other medications. However, no significant difference was found in terms of nutritional status and adiposity between children whose asthma was controlled by ICS alone and those requiring ICS plus other medications for asthma control. The prevalence of obesity (BMI *z*-score for age >2) and WC > 90th percentile were 31.4% and 13.7% among patients using ICS as maintenance therapy, and 37.5% and 19.0% among those requiring ICS plus other medications for asthma control.

Table 3 Adjusted association between nutritional status, adiposity and asthma control§

Variables	Controlled by ICS†	Controlled by ICS plus other medications†	*P* value‡
Nutritional status			0.68
Normal	1.00	1.00	
Overweight	1.37 (0.75–2.50)	1.24 (0.55–2.83)	
Obese	2.54 (1.31–4.92)	2.93 (1.30–6.60)	
Waist circumference			0.40
≤90th percentile	1.00	1.00	
>90th percentile	2.95 (1.08–8.09)	4.10 (1.32–12.76)	
Sum of skinfolds			0.26
1st tercile	1.00	1.00	
2nd tercile	1.12 (0.60–2.08)	1.09 (0.46–2.62)	
3rd tercile	0.95 (0.50–1.82)	1.48 (0.64–3.35)	

†Reference category: controlled without use of maintenance medications (intermittent asthma). ‡Heterogeneity between categories: 'controlled by ICS' and 'controlled by ICS plus other medications'. §Adjusted for sex, maternal educational level, smoking during pregnancy, gestational age, allergic rhinitis personal history, exposition to passive smoking.

Discussion

This study showed that obesity assessed by BMI and increased abdominal adiposity measured by WC were significantly associated with risk of having more severe asthma, that is, persistent asthma classified by the NHLBI criteria, in children aged 3–12 years old. To the best of our knowledge, this is the first study showing a significant dose–response relationship between the increase in BMI *z*-scores (from normal, overweight to obesity) and risk of having persistent childhood asthma, that is, asthma is severe enough to require regular use of controller medications. No significant difference was found in nutritional status and adiposity between children with asthma controlled by ICS and those requiring ICS plus other medications for asthma control.

Two large population-based studies have investigated association between BMI *z*-scores and asthma severity in children and adolescents. In one study,[4] asthma severity was categorised as mild, controlled, under-treated and severe, based on number of short-acting β-agonists canisters dispensed and need for controller medications. In another study,[5] asthma severity was classified as mild, moderate or severe according to reported symptom burden. Both studies showed significant association between obesity measured by BMI and asthma severity. In contrast, two other studies did not find such association. One study involving children with physician-diagnosed mild to moderate asthma did not show significant association between BMI and asthma severity assessed by reported symptom burden.[8] Another

hospital-based study showed that the prevalence of obesity (BMI ≥85th percentile) was similar between children with mild asthma (30/156, 19.2%) and moderate/severe asthma (35/208, 16.8%).[9] Variation in study design and criteria used for diagnosis and classification of asthma may contribute to inconsistent results across studies.

Given the limitation of BMI in assessing body fat distribution, other adiposity indicators have been used by studies assessing association between obesity and asthma severity/control in children. The percentage of body fat (PBF) measured by dual-energy X-ray absorptiometry was shown to be a more sensitive adiposity indicator associated with asthma morbidity outcomes in female patients compared with BMI.[10] It was also reported that PBF estimated from skinfolds and WC provided additional data than BMI alone in assessing association between adiposity and asthma severity.[7] In this study, we used WC and sum of skinfolds as additional adiposity indicators. We found that WC rather than sum of skinfolds was significantly associated with asthma severity. However, WC identified less cases of obesity in our study sample compared with BMI.

Few studies have investigated association between obesity and asthma control in children. A prospective 1-year study involving adolescents with moderate-to-severe asthma found that PBF measured by DEXA rather than BMI was significantly associated with poorer asthma control assessed by asthma control test in female but not in male subjects.[10] In contrast, analysis of the data from two multicentre case control studies showed that worse asthma control was uniformly associated with obesity measured by BMI in boys.[18] For girls, this association depended on race and ethnicity. In a *post hoc* analysis of the data from the Childhood Asthma Management Program trial,[19] it was found that patients with overweight/obese measured by BMI had a decreased response to budesonide on measures of lung function and emergency department visits/hospitalisations for asthma. In our study, no significant difference was found in nutritional status and adiposity between patients whose asthma was controlled by ICS alone and those requiring ICS associated with other medications for asthma control.

The mechanisms underlying the association between obesity and asthma remain not well understood but may include genetic predisposition, mechanical effects of excessive weight on the lungs and adipose tissue-derived proinflammatory cytokines.[20]

This study has two main strengths. Firstly, the diagnosis of asthma and classification of asthma severity and control were done by pulmonologists based on widely used asthma guidelines. Secondly, anthropometric measures were prospectively obtained by trained investigators who were blind to group status. However, some methodological aspects should be taken into account when interpreting the results. Classifications of asthma severity and control are challenging and controversial.[21,22] Asthma severity generally describes the intrinsic intensity of the disease process, whereas asthma control refers to the extent to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are reduced or removed by treatment.[14] It is generally believed that asthma severity and asthma control are two different concepts and should not be replaced each other.[14,21] In this study, we classified asthma severity as intermittent or persistent (mild, moderate and severe), based on NHLBI criteria. Such classification continues to be recommended by current asthma guidelines[23,24] and widely used by recent studies of asthma.[25–28] In the Australian Asthma Guideline,[29] classification of asthma into intermittent and persistent refers to pattern of asthma rather than severity of disease. However, we believe that the pattern of a newly diagnosed asthma classified as intermittent and persistent mainly reflects the underlying severity of the disease. We combined mild, moderate and severe persistent asthma into a single 'persistent asthma' category given that such combination can improve interobserver agreement on classification.[30] Moreover, asthma severity classified into two categories has practical implication because only children with persistent asthma need long-term use of controller medications, and ICSs are the first-line treatment for the majority of these patients. Children with persistent asthma, especially those with worse asthma control, are more likely to have reduced activity that may contribute to obesity. We did not collect information regarding children's activity level, and this potential confounding factor was not controlled in this study. The case control design of this study does not permit to establish a causal relationship between obesity and asthma severity and control.

In conclusion, this hospital-based case control shows that obesity measured by BMI and increased abdominal adiposity are significantly associated with risk of having persistent childhood asthma but not type of controller medications.

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