



Phenotypes of asthma in low-income children and adolescents: cluster analysis

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ABSTRACT

Objective: Studies characterizing asthma phenotypes have predominantly included adults or have involved children and adolescents in developed countries. Therefore, their applicability in other populations, such as those of developing countries, remains indeterminate. Our objective was to determine how low-income children and adolescents with asthma in Brazil are distributed across a cluster analysis. **Methods:** We included 306 children and adolescents (6-18 years of age) with a clinical diagnosis of asthma and under medical treatment for at least one year of follow-up. At enrollment, all the patients were clinically stable. For the cluster analysis, we selected 20 variables commonly measured in clinical practice and considered important in defining asthma phenotypes. Variables with high multicollinearity were excluded. A cluster analysis was applied using a two-step agglomerative test and log-likelihood distance measure. **Results:** Three clusters were defined for our population. Cluster 1 (n = 94) included subjects with normal pulmonary function, mild eosinophil inflammation, few exacerbations, later age at asthma onset, and mild atopy. Cluster 2 (n = 87) included those with normal pulmonary function, a moderate number of exacerbations, early age at asthma onset, more severe eosinophil inflammation, and moderate atopy. Cluster 3 (n = 108) included those with poor pulmonary function, frequent exacerbations, severe eosinophil inflammation, and severe atopy. **Conclusions:** Asthma was characterized by the presence of atopy, number of exacerbations, and lung function in low-income children and adolescents in Brazil. The many similarities with previous cluster analyses of phenotypes indicate that this approach shows good generalizability.

Keywords: Asthma/classification; Asthma/etiology; Child; Adolescent.

INTRODUCTION

Asthma is a syndrome of recurrent respiratory symptoms triggered by various factors, such as viral respiratory infections, environmental allergens, pollution, and climate changes. It is characterized by chronic airway inflammation and variable expiratory airflow limitation.⁽¹⁾ Asthma is not a single disease; rather, it comprises a syndrome with complex phenotypes. Various previous studies have attempted to subclassify asthma according to the symptoms, airway function, presence of atopy, and type of airway inflammation. Numerous asthma phenotypes have been described by using computational techniques, such as clustering; however, those studies predominately included adults,⁽²⁻⁴⁾ and the results suggested a weak correlation between pathological processes and treatment response.⁽¹⁾

Limited studies have focused on childhood asthma.⁽⁵⁻⁸⁾ Fitzpatrick et al.⁽⁶⁾ described four clusters in a group of 161 children and adolescents who primarily exhibited severe asthma; the obtained clusters were distinct from the clusters identified in adults because they were differentiated by the age at asthma onset, pulmonary

function, presence of atopy, airflow limitation, and comorbidity. Howrylak et al.⁽⁷⁾ described five clusters in a group of 1,041 children with mild-to-moderate asthma, which were differentiated by atopic burden, lung function, and history of exacerbation. Just et al.⁽⁸⁾ only investigated children with allergic asthma and described three clusters according to sensitization and presence of severe exacerbation.

According to the 2014 Global Initiative for Asthma (GINA) strategy report,⁽⁹⁾ the severity of asthma may be classified into five levels, and the key factors to determine asthma severity include symptom magnitude, pulmonary function, and dose of inhaled corticosteroid (ICS) to maintain asthma control. However, this classification does not reflect the heterogeneous characteristics of childhood asthma, which may lead to suboptimal treatments and increased risks of hospitalization, as well as loss of pulmonary function. For example, a great number of children and adolescents with severe asthma have normal lung function during symptom-free days, because FEV₁ does not correlate well with the symptoms; in addition, FEV₁ values lower than 80% are predicted

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to have a low sensitivity to distinguish among the levels of asthma severity in children.⁽¹⁰⁻¹²⁾ Moreover, asthma symptoms vary in frequency and intensity through time and are triggered by various stimuli, such as viral infections and allergens. The reasons why some children exhibit only sporadic symptoms that are improved by short-acting bronchodilators and other children exhibit daily symptoms that require high doses of ICS and ongoing airway inflammation remain poorly understood.

Accurate asthma assessment is essential to avoid impairment and future risks of exacerbations, as well as to guide proper disease management.⁽¹⁾ Moreover, the identification of asthma phenotypes does not provide a better approach to asthma treatment, improve control, avoid adverse effects, or decrease the risk of serious asthma outcomes, such as exacerbations and loss of pulmonary function.⁽¹³⁾ This suggests the importance of additional studies in order to establish the actual clinical utility of phenotype classification. In addition, the previously described asthma phenotypes⁽⁶⁻⁸⁾ have been investigated in developed countries, and their applicability to other populations of children and adolescents with asthma remains to be established.

The purpose of the present study was to determine how low-income children with asthma in Brazil are distributed across a cluster analysis.

METHODS

This was a retrospective study involving 306 children and adolescents (6-18 years of age) with a clinical diagnosis of asthma who were outpatients at *Pinheiros* Primary Care Unit or at *Hospital Infantil Darcy Vargas*—both of which take part in the public health care system and are located in the city of São Paulo, Brazil—for at least one year of follow-up, between September of 2010 and December of 2014. Eligibility criteria were being between 6 and 18 years of age, a nonsmoker, and a representative of the community health care center. At enrollment, the participants were clinically stable with no signs of asthma exacerbation (30 days with no changes regarding symptoms or medication use). The severity of asthma was classified according to the revised 2014 GINA report,⁽⁹⁾ whereas asthma phenotypes were based on clinical data obtained from the medical records of the patients. The study was approved by the Research Ethics Committee of *Hospital Infantil Darcy Vargas* (Protocol no. 1.540.338). Since the present study was retrospective, the authors signed a confidentiality agreement which precluded the need to obtain written informed consent from the patients.

Selection of variables for analysis

The variables selected for the cluster analysis were considered important to define the disease phenotype and are commonly measured in clinical practice.⁽³⁻⁵⁾ Variables with high multicollinearity or that were similar for more than 95% of the patients were not included

in the cluster analysis. Twenty variables were included in the cluster analysis: gender (male or female); obesity (body mass index [BMI] ≥ 30 kg/m²); race (white, brown, or black); asthma severity based on prescribed treatment step (from 1 to 5)⁽⁹⁾; age at the onset of asthma (≤ 2 years, 3-6 years, or ≥ 7 years); asthma triggers (upper respiratory tract infection, exercise, or multiple triggers); blood eosinophils (absolute values and blood eosinophil levels $> 5\%$); number of previous asthma hospitalizations (none, 1-3, or ≥ 4); tendency toward exacerbation—more than 3 exacerbations in the previous year—(yes or no); history of ICU admission (yes or no); specific serum IgE levels (via ImmunoCAP Specific IgE; Phadia, Uppsala, Sweden)—atopy identified to most common allergens—(none, dust mite allergens, or multiple allergens); gastroesophageal reflux (yes or no); sinus infection (yes or no); baseline FEV₁ (% predicted); FEV₁/FVC ratio; labile FEV₁—defined as a variation in pre-bronchodilator FEV₁ $> 20\%$ between visits in the previous year—(yes or no); presence of fixed airway obstruction—persistence of post-bronchodilator airway obstruction or FEV₁/FVC ratio lower than the lower limit of normality⁽¹⁴⁾ despite the use of high doses of ICS and a 7-day course of prednisone—(yes or no); and best response to bronchodilator in the previous year.

Spirometric criteria were in accordance with Pellegrino et al.,⁽¹⁵⁾ and the tests were performed with a Koko[®] spirometer (PDS Instrumentation Inc., Louisville, CO, USA). Bronchodilator reversibility tests were performed using 400 μ g of albuterol. Predictive values were in accordance with those proposed by Quanjer et al.⁽¹⁴⁾ Fixed airway obstruction was defined by lower limit of normal, which was based on the proportion of subjects in the groups whose test results fell below the fifth percentile, in accordance with the multiethnic reference values proposed by Quanjer et al.⁽¹⁴⁾

Statistical analysis

A uniform cluster analysis methodology was applied using an agglomerative two-step test and log-likelihood distance measure. The lowest Schwarz Bayesian information criterion was used to determine the number of clusters. This analytical technique identifies subgroups of a sample according to their similarities, which subsequently enables the determination of the variables that best discriminate such subgroups of the group a priori.⁽³⁾ To compare differences between the clusters, one-way ANOVA and chi-square tests were used for parametric continuous and categorical variables, respectively. A forward stepwise discriminant analysis using Wilks' lambda and Fisher's linear discriminant function was performed. A discriminant analysis was applied to identify factors that independently discriminate pre-specified groups and determined whether the subjects assigned to one group were different from the subjects assigned to another group. The dependent variable included cluster classification; the independent variables included the same 20 variables used in the cluster

analysis. A second discriminant analysis was conducted for asthma severity based on prescribed treatment step (from 1 to 5) as the dependent variable and the 20 variables included in the initial analysis as the independent variables. The present study included 15 subjects per variable, which is three times higher than the minimum recommendation for discriminant analysis (five subjects per variable).⁽¹⁶⁾ The statistical significance level was set at 5% for all tests. The IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA), was used for statistical analyses.

RESULTS

The clinical data regarding the 306 children and adolescents with asthma included in the study were available for the cluster analysis. Seventeen subjects were excluded due to incomplete data. The baseline characteristics of the remaining 289 subjects are presented in Table 1. In the sample studied, 177 subjects (61%) were male, the mean age was 12 years, and the vast majority exhibited atopic asthma (92%). The age at the onset of asthma in most subjects was < 2 years (68%); in addition, most were White (66%). Rhinitis and topic eczema were detected in 281

(97%) and in 13 (5%) of the patients, respectively. The sample was representative of the children and adolescents in the community who attended the public health care facilities. As for the severity of asthma, 107 subjects (35%) were classified as having mild asthma (steps 1 and 2), whereas 88 (29%) and 110 (36%) as having moderate asthma (step 3) and severe asthma (steps 4 and 5), respectively. Mean pulmonary function test results showed normal values; FEV₁ in % of predicted was 97.2% ± 12.3%, and FEV₁/FVC ratio was 0.86 ± 0.08.

Phenotypic characterization of asthma clusters

Table 2 shows the distribution of patients and the variables studied among the clusters. Cluster 1 (normal pulmonary function test results, mild eosinophilic inflammation, low tendency toward exacerbation, asthma onset at a later age, and mild atopy) included 94 (33%) of the subjects; they were equally distributed by gender (53%), and most were identified as having mild asthma (64% in steps 1 or 2) and mild eosinophilic inflammation (blood eosinophil levels > 5% in 37% of the subjects). Cluster 1 exhibited the lowest tendency toward exacerbation—66% had had no hospitalizations due to asthma in the previous year,

Table 1. Baseline characteristics of the children and adolescents with asthma stratified by asthma severity.^a

Characteristic	Asthma severity			Total	p
	Mild (steps 1-2)	Moderate (step 3)	Severe (steps 4-5)		
Number of subjects	100	84	105	289	
Anthropometric data					
Male	60 (60)	44 (52)	73 (70)	177 (61)	0.05
Age, years	12 ± 3	13 ± 4	12 ± 3	12 ± 3	0.44
BMI, kg/m ²	19.9 ± 4.1	20.2 ± 4.2	19.8 ± 4.2	19.9 ± 4.2	0.81
Obesity	13 (13)	10 (12)	9 (9)	32 (11)	0.57
Race					
White	66 (66)	57 (68)	66 (63)	190 (66)	
Brown	30 (30)	25 (30)	35 (33)	90 (31)	0.93
Black	4 (4)	2 (2)	4 (4)	10 (3)	
Age at asthma onset, years					
≤ 2	67 (67)	59 (70)	72 (69)	199 (69)	
3-6	21 (21)	17 (20)	21 (20)	59 (20)	0.18
≥ 7	12 (12)	8 (9)	12 (11)	32 (11)	
Atopy	89 (89)	76 (89)	100 (95)	265 (92)	0.41
Pulmonary function					
FEV ₁ , % predicted	100.2 ± 12.0	97.5 ± 11.6	94.5 ± 13.1	97.2 ± 12.3	0.32
FEV ₁ /FVC	0.88 ± 0.06	0.85 ± 0.08	0.85 ± 0.09	0.86 ± 0.08	0.03
Fixed airway obstruction	8 (8)	12 (14)	18 (17)	38 (13)	0.14
Bronchodilator response	17.5 ± 9.3	20.1 ± 11.4	22.9 ± 16.6	20.2 ± 13.1	0.01
Hospitalization due to asthma in the previous year					
None	56 (56)	48 (57)	57 (45)	151 (52)	
1-3	24 (24)	21 (25)	28 (27)	73 (25)	0.31
≥ 4	20 (20)	15 (18)	30 (27)	66 (23)	
Exacerbation tendency	36 (36)	40 (48)	43 (41)	119 (41)	0.28
Hospitalization in an ICU	7 (7)	6 (7)	13 (12)	26 (9)	0.31

BMI: body mass index. ^aValues expressed as n (%) or mean ± SD.

30% showed a tendency toward exacerbation, and 5% had a history of ICU admission. Atopy was less common in cluster 1 subjects than in those in the other clusters (negative tests for specific serum IgE in 16% and mean total IgE = 721.1 ± 682.3 IU/mL). The pulmonary function was characterized by showing the highest values for pre- and post-bronchodilator FEV₁ (% of predicted) and for the FEV₁/FVC ratio. Labile bronchodilator response (mean FEV₁ = $16.5\% \pm 9.5\%$ of predicted) and fixed airway obstruction were the lowest among the clusters, whereas the age at asthma onset was the highest (≥ 7 years of age in 19%).

Cluster 2 (normal pulmonary function test results, severe eosinophilic inflammation, severe atopy, high tendency for exacerbation, and early age at asthma onset) comprised the smallest number of subjects ($n = 87$; 30%). It primarily comprised male subjects (56%) with moderate asthma (step 3; 47%), increased blood eosinophilic inflammation (blood eosinophil levels $> 5\%$ in 98%), and increased IgE (mean = $1,361.6 \pm 1,137.8$ IU/mL). The specific serum IgE test was primarily positive for mites (37%), and upper respiratory tract infection was the most relevant asthma trigger (70%). Health care utilization in the previous year ranged between that in clusters 1 and 3; however, the tendency toward exacerbation was the highest (58%). Pulmonary function was predominantly normal; only 4 (5%) of the patients were diagnosed with fixed airway obstruction. Moreover, most of the subjects in cluster 2 had an early age at asthma onset (< 2 years in 77%).

Cluster 3 (poor pulmonary function test results, severe eosinophilic inflammation, severe atopy, and high tendency for exacerbation) comprised the largest group ($n = 108$; 37%). This cluster exhibited the highest proportion of male subjects (72%), with predominately severe asthma (step 4 or 5 in 54%), increased eosinophilic inflammation (eosinophil levels $> 5\%$ in 86%), and high IgE levels (mean = $1,222.6 \pm 973.0$ IU/mL). The specific serum IgE test was predominantly positive for multiple factors (90%), and the majority presented multiple asthma triggers (74%). The subjects in cluster 3 exhibited a greater number of exacerbations than did those in the other clusters (hospitalizations due to asthma in the previous year in 64% and history of ICU admission in 16%). The subjects in cluster 3 had the worst pulmonary function test results (the lowest pre- and post-bronchodilator FEV₁ in % of predicted and FEV₁/FVC ratio). Moreover, those subjects most often showed fixed airway obstruction, labile VEF₁, and poor bronchodilator responses than did those in the other clusters.

Discriminant analysis

The multiple discriminant analysis using the same 20 variables included in the cluster analysis indicated that 10 variables strongly discriminated the cluster:

atopic burden (blood eosinophil levels and specific serum IgE test), pulmonary function (fixed airway obstruction, labile FEV₁, and poor bronchodilator response), health care utilization (tendency toward exacerbation and hospitalization in the previous year), asthma triggers, asthma severity, and age at onset of asthma. The discriminant function model exhibited good accuracy and predicted 90% of the case allocations correctly. The second discriminant analysis, in which asthma severity (prescribed treatment step 1, 2, 3, 4, or 5) was used as a dependent variable exhibited poor accuracy and predicted only 31% of the case allocations correctly.

DISCUSSION

Asthma in children and adolescents is a complicated and heterogeneous disorder with distinct phenotypes. We identified three clusters by using an unsupervised cluster analysis in low-income children and adolescents with a wide range of levels of asthma severity. In cluster 1, there were less frequent health care utilization, milder atopy, older age at asthma onset, milder asthma, and normal lung function. The patients in cluster 2 showed normal pulmonary function test results, more severe eosinophilic inflammation, more severe atopy status, a moderate number of exacerbations, and asthma onset at an earlier age. Finally, the patients in cluster 3 presented with poor pulmonary function, severe eosinophilic inflammation, severe atopy status, and high number of exacerbations.

The demographic characteristics of our patients are consistent with childhood asthma, the characteristics of which include a higher proportion of boys, early age at asthma onset, and there are presence of atopy and a high prevalence of rhinitis. The coexistence of atopy, rhinitis, and asthma has also been previously observed in a cross-sectional study including children with asthma.⁽⁴⁷⁾ The authors suggested that asthma, rhinitis, and eczema can be classified altogether as an allergic comorbidity.

The cluster analysis indicated only three clusters of children and adolescents with shared phenotypic characteristics, whereas Fitzpatrick et al.⁽⁶⁾ described four clusters, and Howrylak et al.⁽⁷⁾ described five clusters. The characteristics that differentiated each cluster were similar to the characteristics reported in previous studies^(6,7,18); the common characteristics among the current and the previous studies included atopic burden, lung function, and health care utilization. However, the age at the onset of asthma in our study was a distinguishing feature when we compare it with the study by Fitzpatrick et al.⁽⁶⁾ The clusters previously reported exhibited more heterogeneous clinical features when compared with those in the present study, which was grouped into only three clusters. We also observed that there was an association of a high proportion of patients with allergy due to multiple factors with poorer pulmonary function, severe asthma, more severe eosinophilic

Table 2. Characteristics of the children and adolescents with asthma stratified by cluster analysis.^a

Characteristic	All	Cluster 1	Cluster 2	Cluster 3	p
Number of subjects	289	94	87	108	
Anthropometric data					
Male	177 (61)	50 (53)	49 (56)	78 (72)	0.01
Age, years	12 (3)	11 (4)	12 (3)	13 (3)	0.04
BMI, kg/m ²	19.9 ± 4.2	19.4 ± 3.5	19.6 ± 4.0	20.6 ± 4.0	0.10
Obesity	32 (11)	11 (12)	8 (9)	13 (12)	0.79
Race					
White	190 (66)	59 (63)	54 (62)	76 (70)	0.06
Brown	90 (31)	35 (37)	27 (31)	28 (25)	
Black	10 (3)	0 (0)	6 (7)	4 (4)	
Asthma severity, step					
1	74 (25)	47 (50)	2 (2)	25 (23)	< 0.001
2	26 (9)	13 (14)	12 (14)	1 (1)	
3	84 (29)	19 (20)	41 (47)	24 (22)	
4	98 (34)	13 (14)	31 (36)	53 (49)	
5	8 (3)	2 (2)	1 (1)	5 (5)	
Age at asthma onset, years					
≤ 2	199 (69)	52 (55)	67 (77)	79 (73)	< 0.001
3-6	59 (20)	24 (25)	20 (23)	15 (14)	
≥ 7	32 (11)	18 (19)	0 (0)	14 (13)	
Asthma triggers					
URTI	138 (48)	53 (56)	61 (70)	24 (22)	< 0.001
Exercise	23 (8)	8 (8)	11 (12)	4 (4)	
Multiple	129 (44)	33 (35)	15 (17)	80 (74)	
Hospitalization due to asthma in the previous year					
None	151 (52)	62 (66)	50 (57)	39 (36)	< 0.001
1-3	73 (25)	19 (20)	22 (25)	32 (30)	
≥ 4	66 (23)	13 (14)	15 (17)	37 (34)	
Exacerbation tendency					
Hospitalization in an ICU	119 (41)	28 (30)	51 (58)	40 (37)	< 0.001
	26 (9)	5 (5)	4 (5)	17 (16)	< 0.01
Atopic status					
IgE, IU/mL	1101.3 ± 980.7	721.1 ± 682.3	1361.6 ± 1137.8	1222.6 ± 973.0	< 0.001
Specific serum IgE test results					
Negative	25 (9)	15 (16)	9 (10)	1 (1)	< 0.001
Mites	61 (21)	18 (19)	32 (37)	11 (10)	
Multiple	204 (70)	61 (65)	46 (53)	96 (89)	
Blood eosinophils					
Blood eosinophils > 5%	8.1 ± 5.0	4.3 ± 3.1	10.6 ± 4.7	9.4 ± 4.8	< 0.001
	214 (74)	35 (37)	85 (98)	93 (86)	< 0.001
Reported comorbidities					
Allergic rhinitis	281 (97)	91 (97)	86 (99)	103 (95)	0.38
Topic eczema	13 (5)	4 (4)	3 (3)	6 (6)	0.77
Reflux	18 (6)	5 (5)	3 (3)	10 (9)	0.22
Bronchiectasis	6 (2)	2 (2)	2 (2)	2 (2)	0.97
Sinus infection	19 (7)	7 (7)	4 (5)	8 (7)	0.67
Pulmonary function					
Pre-BD FEV ₁ , % predicted	97.2 ± 12.3	102.1 ± 9.7	97.7 ± 13.9	92.9 ± 12.3	< 0.05
Post-BD FEV ₁ , % predicted	104.3 ± 13.3	108.8 ± 10.5	106.1 ± 15.4	98.5 ± 10.2	< 0.05
FEV ₁ /FVC	0.86 ± 0.08	0.90 ± 0.05	0.86 ± 0.06	0.82 ± 0.09	< 0.001
FEV ₁ lability ^b	160 (55)	31 (33)	40 (46)	89 (82)	< 0.001
Fixed airway obstruction	38 (13)	1 (1)	4 (5)	33 (31)	< 0.001
Bronchodilator response	20.2 ± 13.1	14.3 ± 8.2	18.0 ± 9.7	27.2 ± 15.6	< 0.001

BMI: body mass index; URTI: upper respiratory tract infection; and BD: bronchodilator. ^aValues expressed as n (%) or mean ± SD. ^bVariation > 20% in pre-BD FEV₁ in one year.

inflammation, and a higher number of exacerbations. These findings are supported by a previous study demonstrating that patients presenting multiple allergy sensitizations also had a higher level of severity (moderate to severe asthma), a greater proportion of asthma exacerbations, and a significantly greater proportion of inflammatory markers.⁽⁸⁾

In our study, the discriminant analysis that used asthma severity as the dependent variable exhibited poor accuracy and predicted only 31% of the case allocations correctly. Moreover, only the FEV₁/FVC ratio and the response to bronchodilators were significantly different among the groups. Health care utilization and fixed airway obstruction were not distinguishing features of asthma severity. Similarly to other studies involving children⁽⁶⁻⁸⁾ or adults,⁽²⁻⁴⁾ the asthma phenotypes did not correspond to the levels of asthma severity proposed by the GINA guidelines.⁽⁹⁾ Moreover, asthma exacerbations and different levels of asthma severity were identified in all of the clusters, a finding that corroborates the study by Fitzpatrick et al.⁽⁶⁾ Despite few asthma symptoms and normal lung function, children with asthma also had severe exacerbations. For example, even children and adolescents with mild asthma reported ICU admissions. These findings might have occurred because of the poor socioeconomic conditions in our population; sometimes it is difficult for them to receive proper medical treatment during their infrequent asthma

exacerbations, which might worsen their respiratory status and lead them to an ICU.

The degree of pulmonary function impairment in children and adolescents is significantly lower than that previously observed in adults. Although fixed airway obstruction was more frequently found in the patients in cluster 3, it was also identified in those in the other two clusters (13% of the subjects). Therefore, spirometry alone is not a good parameter to determine asthma severity, and the use of spirometry for the management of childhood asthma seems not to improve, by itself, the quality of life of the patients.⁽¹⁹⁾ Most patients (87%) had no fixed airway obstruction, and this fact may present a window of opportunity for proper treatment.

In our population, we did not identify an association between obesity and asthma severity, as previously reported in adults.⁽²⁰⁾

In summary, childhood asthma is characterized by the presence of atopy, a high rate of exacerbations, and fairly preserved lung function. We identified various similarities with the previous clusters that had been described in children and adolescents, and this indicates that this approach has good generalizability. Our study might contribute to a better understanding of asthma phenotypes due to the lack of studies investigating asthma phenotypes in low-income children and adolescents.

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