

Heterogeneity of severe asthma in childhood: Confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program

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Background: Asthma in children is a heterogeneous disorder with many phenotypes. Although unsupervised cluster analysis is a useful tool for identifying phenotypes, it has not been applied to school-age children with persistent asthma across a wide range of severities.

Objectives: This study determined how children with severe asthma are distributed across a cluster analysis and how well these clusters conform to current definitions of asthma severity.

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Methods: Cluster analysis was applied to 12 continuous and composite variables from 161 children at 5 centers enrolled in the Severe Asthma Research Program.

Results: Four clusters of asthma were identified. Children in cluster 1 (n = 48) had relatively normal lung function and less atopy. Children in cluster 2 (n = 52) had slightly lower lung function, more atopy, and increased symptoms and medication use. Cluster 3 (n = 32) had greater comorbidity, increased bronchial responsiveness, and lower lung function. Cluster 4 (n = 29) had the lowest lung function and the greatest symptoms and medication use. Predictors of cluster assignment were asthma duration, the number of asthma controller medications, and baseline lung function. Children with severe asthma were present in all clusters, and no cluster corresponded to definitions of asthma severity provided in asthma treatment guidelines.

Conclusion: Severe asthma in children is highly heterogeneous. Unique phenotypic clusters previously identified in adults can also be identified in children, but with important differences. Larger validation and longitudinal studies are needed to determine the baseline and predictive validity of these phenotypic clusters in the larger clinical setting. (*J Allergy Clin Immunol* 2010;■■■■:■■■-■■■.)

Key words: Allergic sensitization, asthma, severe asthma, asthma guidelines, children, cluster analysis, lung function, phenotype

Asthma in children is a chronic, persistent disorder characterized by airway inflammation and episodic airflow obstruction in response to specific triggers.¹ Whereas some children with asthma have intermittent symptoms that are improved with short-acting bronchodilators, many have classic, persistent symptoms requiring daily treatment with inhaled corticosteroids (ICSs).^{2,3} Children with severe asthma are differentiated by ongoing symptoms and airway inflammation despite treatment with high doses of ICSs and other controller medications.⁴⁻⁶ Although the prevalence of severe asthma is low, these children have extreme morbidity^{4,5} and account for 30% to 50% of all pediatric asthma health care costs.^{7,8}

Children with severe asthma are a challenging group of patients who can be difficult to treat. Although national and international guidelines from the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) emphasize the importance of assessing asthma severity in children

Abbreviations used

ATS: American Thoracic Society
 GINA: Global Initiative for Asthma
 ICS: Inhaled corticosteroid
 LABA: Long-acting β -agonist
 NAEPP: National Asthma Education and Prevention Program
 NHLBI: National Heart, Lung, and Blood Institute
 SARP: Severe Asthma Research Program

before the initiation of therapy, severe asthma is defined primarily by lung function abnormalities, persistent symptoms, and exacerbations despite appropriate therapy.^{3,9} This approach underestimates the phenotypic heterogeneity of the disorder¹⁰ and may further lead to suboptimal asthma treatment, because the majority of children with persistent asthma have relatively normal lung function during symptom-free periods with abnormal pulmonary function only during acute exacerbations.^{11,12} Indeed, FEV₁ does not correlate well with the magnitude of asthma symptoms in children,¹³ and values less than 80% predicted have a low sensitivity (approximately 40%) for distinguishing asthma severity in this population.¹⁴ These findings suggest that more specific approaches are needed to differentiate asthma heterogeneity in children to assess better the risk and impairment associated with the disorder as well as to guide clinical asthma therapies.

Cluster analysis is an unsupervised analytical approach that is useful in the refinement of pediatric asthma diagnosis and severity assessments because of its ability to distinguish complex phenotypes without *a priori* (and therefore biased) definitions of disease severity.^{15–17} In adults with chronic obstructive pulmonary disease and asthma,^{18,19} cluster analyses have revealed distinct phenotypes of obstructive airway disease that may ultimately require modified approaches for their identification and diagnosis as well as different therapeutic interventions. Cluster analysis derived from the Severe Asthma Research Program (SARP) of the National Heart, Lung, and Blood Institute (NHLBI) has resulted in 5 novel clusters of asthma phenotypes in adults that do not correspond to the levels of asthma severity as outlined by current guidelines.¹⁹ Although that study¹⁹ and others²⁰ emphasized the importance of age of asthma onset in distinguishing the asthma clusters, no cluster analysis has been undertaken in childhood asthma. Given the significant heterogeneity in children with asthma, the purpose of this study was to apply unsupervised cluster analysis to a diverse sample of children enrolled in SARP to determine (1) whether phenotypic clusters that conform to established definitions of severe and nonsevere asthma are identifiable in children, and (2) how these clusters relate to definitions of asthma severity as proposed by the American Thoracic Society (ATS),¹⁵ the NAEPP,³ and GINA.⁹ Because children enrolled in SARP are characterized with comprehensive phenotyping similar to the adult subjects,^{4,21} we raised the question whether previously identified clusters of early-onset asthma in adults¹⁹ would also be detected in children with similar phenotypic characteristics.

METHODS

The SARP is an NHLBI-supported research program with recruitment of children 6 to 17 years of age across 5 centers in the United States. Each of the SARP centers is affiliated with a major university teaching program, and children are recruited into SARP from the outpatient clinics and inpatient hospital wards of those academic centers. As a result, children enrolled in

SARP are more likely to have difficult asthma and are representative of a referral population of children who receive care at academic versus community centers. The protocol was approved by each center's institutional review board. Informed consent was obtained from the legal guardians of each child, and verbal and written consent was obtained from participating children.

All children 6 to 17 years of age who underwent standardized characterization in SARP were eligible for inclusion. Eligible children had never smoked and had physician-diagnosed asthma and historical evidence of bronchial hyperresponsiveness or at least 12% FEV₁ bronchodilator reversibility either at baseline or during an acute exacerbation. Children were classified as having severe asthma according to ATS workshop criteria (see this article's [Table E1](#) in the Online Repository at www.jacionline.org).¹⁵ This definition assumes that comorbid conditions have been treated or addressed and that the patient is adherent with prescribed asthma treatment. Thresholds for high-dose ICS were adjusted for children and defined as ≥ 440 μ g fluticasone equivalent per day for children less than 12 years and ≥ 880 μ g of fluticasone equivalent per day for children 12 to 17 years of age (see this article's [Table E2](#) in the Online Repository at www.jacionline.org).⁴ All children enrolled received a stable dose of ICS for at least 6 months. All were stable at the time of characterization with no signs of acute respiratory illnesses. Children presenting to the SARP clinic with an acute worsening of asthma control were treated accordingly and were reassessed at a later date.

Characterization procedures

Participants underwent comprehensive phenotypic characterization consisting of questionnaires, serum IgE and eosinophil quantification, allergy skin prick testing, and bronchial responsiveness to methacholine as previously described.^{4,21} Exhaled nitric oxide was determined with both offline (Sievers NOA 280-I; Ionic Instruments, Boulder, Colo) and online (NIOX; Aerocrine, Solna, Sweden) methods in accordance with published recommendations.²² Spirometry (KoKo PDS; Ferraris, Louisville, Colo) was performed at baseline and after bronchodilator reversibility testing with 4, 6, and 8 inhalations of albuterol sulfate (90 μ g per inhalation) to determine the best response to short-acting β -agonists. Lung volumes were measured with a body plethysmograph (MedGraphics Elite Series; MEDGRAPHICS, St Paul, Minn). Spirometry predicted values were obtained by using the equations of Wang et al,²³ and plethysmographic lung volume predicted values were obtained by using the Crapo²⁴ predicted equations.

Variable reduction

The entire SARP dataset provided more than 500 variables that were reduced to 12 variables before cluster analysis. Continuous variables included the duration of asthma in months, baseline FEV₁ percent predicted, and the best postbronchodilator FEV₁ percent predicted. Categorical variables included sex, race (white, black, or other) and ICS group (none, low-dose, or high-dose). Semiquantitative variables included β -agonist use over the previous 3 months, the frequency of symptoms, the magnitude of atopic sensitization, and exhaled nitric oxide quartile. Composite variables were derived from binary or discrete questionnaire data and were developed by study physicians with experience in the study and treatment of childhood asthma to cover the broad spectrum of routine asthma assessment in the clinical setting (see this article's [Table E3](#) in the Online Repository at www.jacionline.org).¹⁹ These composite variables included the number of asthma controller medications and health care use in the previous year. For the composite variable health care use in the previous year, subjects were assigned a rank on the basis of the most severe use reported by the individual. Further description and performance of the variables for atopic sensitization and exhaled nitric oxide quartile appears in this article's [Tables E4 and E5](#) in the Online Repository at www.jacionline.org. All variables were equally weighted in the analysis. Subjects with missing data were excluded.

Statistical analysis

Cluster analysis was performed with SAS version 9.1 (SAS Institute Inc, Cary, NC) as previously described (see this article's Methods section in the

Online Repository at www.jacionline.org).¹⁹ The Ward minimum-variance hierarchical clustering method was performed by using an agglomerative (bottom-up) approach and Ward linkage (see this article's Fig E1 in the Online Repository at www.jacionline.org). At each generation of clusters, samples were merged into larger clusters to minimize and maximize with within-subjects and between-subjects sum of squares, respectively. ANOVA with Tukey *post hoc* testing and χ^2 tests were used to determine differences between groups. To determine the strongest predictors of cluster assignment, stepwise discriminant analysis of the cluster variables was performed with the Fisher²⁵ method as previously described²⁶ by using an F value entry probability of 0.05 and removal probability of 0.10. Cross-validation was performed by extracting each case and treating it as test data against the remaining cases.

RESULTS

Results from 273 children (mean age 10 years) enrolled in SARP across 4 centers in Atlanta, Ga, Winston-Salem, NC, Pittsburgh, Pa, St Louis, Mo, and Charlottesville, Va, were available for analysis. Of these, 112 were missing 1 or more of the cluster variables and were excluded. The features of excluded children did not differ from those of the final sample (see this article's Table E6 in the Online Repository at www.jacionline.org). The final sample included 161 children. Features of the sample are presented in Table I. Whereas treatment with combination ICS and long-acting β -agonist (LABA) therapy was prevalent even among children with mild-to-moderate asthma (Table I), the study sample is representative of children with difficult asthma treated at academic medical centers.

Cluster analysis

Using the agglomerative cluster approach, a dendrogram was generated and revealed 4 clusters of children with shared phenotypic characteristics (Fig E1). The presence of 4 clusters was confirmed when the cluster analysis was repeated with alternative linkage methods, including the average between groups and centroid linkage. These clusters were distinguished by age, race, asthma onset and duration, a history of sinusitis and gastroesophageal reflux, the degree of atopic sensitization, and exhaled nitric oxide (Table II). Clusters also differed according to medication and healthcare use (Table III) and lung function (Table IV). These lung function differences between clusters persisted even after stratification by age of enrollment (see this article's Tables E7 and E8 in the Online Repository at www.jacionline.org).

Cluster 1

Forty-eight children were grouped into cluster 1 (termed "late-onset symptomatic asthma"). This cluster had the lowest prevalence of severe asthma defined by ATS criteria ($n = 15$; 31%) and GINA or NAEPP criteria ($n = 1$; 2%; Fig 1; see this article's Table E9 in the Online Repository at www.jacionline.org). Ten (67%) of the children with ATS-defined severe asthma in this cluster were hospitalized within the previous year, and 6 (40%) were hospitalized for the first time. This cluster was younger with more non-Hispanic white subjects and was differentiated by an older age of symptom onset and shorter asthma duration. Although many children in this cluster had markers of atopy with positive allergy skin prick tests, the magnitude of allergic sensitization was relatively lesser compared with the other clusters, with lower exhaled nitric oxide concentrations. Eighty-eight percent ($n = 42$) of children in this cluster had an asthma exacerbation necessitating a physician encounter, and 23% ($n = 11$) were hospitalized.

TABLE I. Features of the sample

Feature	Mild-to-moderate asthma n = 72	Severe asthma n = 89	P value
Age (y)	11 $\pm$ 3	11 $\pm$ 3	.879
Male	40 (56)	49 (55)	.571
White	38 (53)	24 (27)	.001
Black	27 (38)	56 (63)	
Other			
Emergency department visit (previous year)	22 (31)	64 (72)	<.001
Hospitalization (previous year)	6 (8)	49 (55)	<.001
History of intubation (ever)	2 (3)	22 (25)	.002
Parental history of asthma	41 (58)	62 (70)	.022
History of atopic dermatitis	35 (49)	54 (61)	.114
History of pneumonia	30 (42)	57 (64)	.001
History of sinusitis	26 (31)	35 (39)	.255
History of gastroesophageal reflux	8 (11)	31 (35)	.001
Daily ICS dose (μ g fluticasone equivalent per day)	227 $\pm$ 211	893 $\pm$ 225	<.001
No ICS	18 (25)	0	<.001
Montelukast	38 (53)	88 (99)	<.001
ICS + LABA	31 (43)	77 (87)	<.001
Daily short-acting bronchodilators	17 (24)	54 (61)	<.001
Daily oral corticosteroids	0	13 (15)	<.001
Number of aeroallergen skin prick responses (out of 12), median (range)*	1 (0-9)	4 (0-12)	<.001
Serum IgE (kU/L), median (range)*	142 (2-3484)	344 (3-5458)	<.001
Blood eosinophils (%), median (range)*	3.9 (0.3-23.8)	4.4 (0.1-23.6)	.684
Baseline FEV ₁ (% predicted)	94 $\pm$ 14	85 $\pm$ 21	.002
Best FEV ₁ (% predicted)	104 $\pm$ 14	98 $\pm$ 19	.021
Methacholine (PC ₂₀), median (range)*	2.1 (0.1-24.3)	0.9 (0.1-23.1)	.047

Severe asthma was defined according to ATS criteria.^{4,14} Data represent mean $\pm$ SD or frequency (%) unless otherwise specified.

*Data were logarithmically transformed before analysis.

Despite having bronchial hyperresponsiveness to methacholine, these children had relatively normal lung function (or mild airflow limitation) with minimal hyperinflation (air trapping) and decreased airway resistance. Children in cluster 1 were treated with relatively fewer controller medications including a significantly lower daily dose of ICS. Although 21% of this cluster did report daily short-acting bronchodilator use, this finding may be related in part to prophylactic treatment of exercise-induced symptoms. Approximately 69% ($n = 33$) of the children in this group reported that sports were a primary trigger of asthma symptoms.

Cluster 2

Fifty-two children were assigned to cluster 2 (termed "early-onset atopic asthma with normal lung function"). Whereas 61% ($n = 28$) of children in this cluster had ATS-defined severe asthma, only 4% ($n = 2$) had severe asthma by GINA or NAEPP criteria (Fig 1). Children were similar in age and race to cluster 1 but had an earlier age of asthma onset, a longer duration of

TABLE II. Demographic and atopic features of subjects

Feature	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	P value*
Age (y)	11 ± 3	9 ± 3	10 ± 2	15 ± 2	12 ± 2	<.001
Male	89 (55)	22 (46)	27 (52)	21 (66)	19 (66)	.205
White	62 (39)	26 (54)	25 (48)	8 (25)	3 (10)	<.001
Black	83 (52)	15 (31)	25 (48)	19 (59)	24 (83)	
Other	14 (9)	7 (15)	2 (4)	5 (16)	2 (7)	
Age of asthma diagnosis (mo)	38 ± 39	73 ± 46	30 ± 29	14 ± 12	19 ± 17	<.001
Duration of asthma (mo)	99 ± 51	38 ± 23	95 ± 15	170 ± 15	129 ± 13	<.001
Body mass index >90th percentile	47 (29)	13 (27)	16 (31)	12 (38)	6 (21)	.522
Parental history of asthma	103 (64)	29 (60)	33 (64)	19 (59)	22 (76)	.398
History of atopic dermatitis	89 (55)	24 (50)	29 (56)	15 (47)	21 (72)	.179
History of pneumonia	87 (54)	23 (48)	27 (52)	22 (69)	15 (52)	.299
History of sinusitis	61 (38)	16 (33)	14 (27)	21 (66)	10 (35)	.003
History of gastroesophageal reflux	39 (24)	7 (15)	13 (25)	11 (34)	8 (28)	.028
Number of skin prick responses (out of 12), median (range)†	3 (0-12)	1 (0-12)	3 (0-12)	4 (0-10)	3 (0-8)	.007
Serum IgE (kU/L), median (range)†	548 (2-5458)	105 (2-3484)	405 (3-3511)	216 (25-5458)	361 (7-1800)	.005
Blood eosinophils (%), median (range)†	4.1 (0.1-23.8)	2.9 (0.4-13.2)	5.5 (0.4-23.8)	3.9 (0.2-13.9)	5.4 (0.1-23.6)	.053
Exhaled nitric oxide						
Offline (ppb, n = 80)†	9 (2-46)	7 (2-30)	9 (4-31)	12 (4-27)	14 (7-46)	.021
Online (ppb, n = 81)†	20 (3-260)	12 (3-63)	16 (4-74)	21 (6-260)	30 (4-169)	.041

Data represent mean ± SD or frequency (%) unless otherwise specified.

*P value from ANOVA or χ^2 analysis between the 4 clusters.

†Data were logarithmically transformed before analysis.

asthma symptoms, and increased markers of atopy, although exhaled nitric oxide was not significantly different from cluster 1. Health care use was again prominent; 88% (n = 46) of children in this cluster had a physician encounter for an acute asthma exacerbation within the previous year, and 33% (n = 17) were hospitalized. Although children in this group were treated more frequently with controller medications as well as higher daily doses of ICS, lung function, including spirometric and lung volume variables, and best postbronchodilator responses were similar to those observed in cluster 1. However, 52% (n = 27) reported daily short-acting bronchodilator use. Because 37% (n = 19) of children in this group also reported asthma symptoms with daily activities such as walking up stairs, it is unlikely that short-acting bronchodilator use was solely a result of prophylactic therapy before exercise.

Cluster 3

Thirty-two children were grouped into cluster 3 (termed “early-onset atopic asthma with mild airflow limitation and comorbidities”). Similar to cluster 2, 63% (n = 12) had ATS-defined severe asthma, whereas only 16% (n = 5) had severe asthma by GINA or NAEPP criteria (Fig 1). This cluster included fewer non-Hispanic white subjects with an earlier onset of asthma symptoms and the longest asthma duration. Children in cluster 3 also had elevated exhaled nitric oxide concentrations compared

with clusters 1 and 2 and significant comorbidities, including a higher prevalence of gastroesophageal reflux and chronic sinusitis requiring antibiotic treatment. Children in this cluster were also more likely to be treated with oral corticosteroids. Seventy-two percent (n = 23) had a physician encounter for an asthma exacerbation within the previous year, and 41% (n = 13) were hospitalized. This cluster was further differentiated by the degree of airflow limitation and hyperinflation. Although children in cluster 3 had an enhanced bronchodilator response, airflow limitation was not completely reversed after 6 to 8 inhalations of albuterol. Children in this cluster also had a lower total lung capacity, increased airway resistance, and greater bronchial hyperresponsiveness to methacholine. More than half of this group (n = 18; 56%) used short-acting bronchodilators on a daily basis, and 47% (n = 15) reported asthma symptoms with daily activities such as walking and climbing stairs.

Cluster 4

Twenty-nine children were assigned to cluster 4 (termed “early-onset atopic asthma with advanced airflow limitation”). Eighty-six percent (n = 24) of children in this cluster were classified as having severe asthma according to ATS criteria, whereas only 14% (n = 4) met GINA or NAEPP criteria for severe asthma (Fig 1). Cluster 4 included the highest prevalence of black subjects and was similar to cluster 3 with regard to

TABLE III. Medication use and health care use

Variable	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	P value*
No ICS	17 (11)	11 (23)	1 (2)	5 (16)	0	<.001
Low-dose to moderate-dose ICS	54 (34)	21 (44)	20 (38)	7 (22)	5 (17)	
High-dose ICS	90 (56)	16 (33)	31 (59)	20 (63)	24 (83)	
Daily ICS dose (μ g fluticasone)*	587 $\pm$ 393	399 $\pm$ 332	622 $\pm$ 354	623 $\pm$ 450	829 $\pm$ 364	<.001
Daily β -agonist use	77 (44)	10 (21)	27 (52)	18 (56)	16 (55)	.002
Controller medications						
No controller medications	14 (9)	9 (19)	2 (4)	3 (9)	0	.015
Montelukast only	6 (4)	2 (4)	0	4 (13)	0	.018
ICS only	13 (8)	6 (13)	4 (8)	1 (3)	2 (7)	.496
ICS + LABA or montelukast	31 (19)	16 (33)	9 (17)	3 (9)	3 (10)	.021
ICS + LABA + montelukast	97 (60)	15 (31)	37 (71)	21 (66)	24 (83)	<.001
Omalizumab	3 (2)	0	2 (4)	0	1 (3)	.386
Oral corticosteroids	12 (7)	0	4 (8)	5 (16)	3 (10)	.062
At least 1 oral corticosteroid burst	120 (75)	31 (65)	41 (79)	23 (72)	26 (90)	.128
No. of oral corticosteroid bursts†	2 $\pm$ 3	2 $\pm$ 2	3 $\pm$ 3	4 $\pm$ 4	3 $\pm$ 2	.018
Health care use (previous year)†						
None	22 (14)	6 (13)	6 (12)	9 (28)	1 (3)	.037
Physician visit for acute symptoms	149 (93)	42 (88)	46 (88)	23 (72)	28 (97)	.037
Emergency department visit	87 (54)	20 (42)	32 (62)	18 (56)	17 (59)	.217
Hospital admission	55 (3)	11 (23)	17 (33)	13 (41)	14 (48)	.116
ICU admission	33 (21)	8 (17)	10 (19)	7 (22)	8 (28)	.702
Intubation (ever)	19 (15)	0	9 (21)	4 (20)	6 (24)	.018

ICU, Intensive care unit.

Data represent mean $\pm$ SD or frequency (%).*P value from χ^2 analysis between the 4 clusters.

†Data are mutually exclusive (subjects were ranked by the most severe level of health care use).

asthma onset and asthma duration, although there were fewer comorbidities. This cluster was further differentiated by the highest exhaled nitric oxide values and the highest extent of health care use. Ninety-seven percent ($n = 28$) of children in this group saw a physician for an acute exacerbation within the previous year, and 48% ($n = 22$) were hospitalized, with 28% ($n = 8$) requiring intensive care. Children in cluster 4 were therefore treated with the highest daily doses of ICS, and most were receiving at least 3 asthma controller medications. This cluster was also differentiated by the lowest lung function, including baseline airflow limitation and hyperinflation that were not completely reversed with bronchodilator administration. Similar to cluster 3, children in this cluster also had increased airway resistance and greater bronchial responsiveness to methacholine. Lower total lung capacity was also observed in this cluster, although this finding was restricted to children 12 to 17 years of age (Tables E7 and E8). Daily symptoms requiring short-acting bronchodilator treatment were also common in this group ($n = 16$; 55%), and nearly one half ($n = 14$; 48%) reported asthma symptoms with activities of daily living.

Predictors of cluster assignment

Asthma duration ($P < .001$), the number of asthma controller medications ($P = .001$), and baseline FEV₁ percent predicted values ($P < .001$) were identified as the strongest predictors of cluster assignment in this sample (Wilks $\lambda = 0.071$; $\chi^2 = 401.99$; $P < .001$; see this article's Table E10 in the Online Repository at www.jacionline.org). These 3 variables alone resulted in

correct classification of 93% of the original subjects (Fig 2) and 92% of cross-validated grouped cases (see this article's Table E11 in the Online Repository at www.jacionline.org).

DISCUSSION

Asthma in children is a complicated and heterogeneous disorder with distinct phenotypes. By using an unsupervised cluster analysis in children with a wide range of asthma severity characterized in the SARP network, we have identified 4 clusters of childhood asthma with shared phenotypic features. Similar to the previous SARP report that described increased allergic sensitization in clusters of adults with early-onset asthma,^{21,27} clusters of childhood asthma were all atopic, although the magnitude of allergic sensitization differed between groups. Asthma duration, the number of asthma controller medications, and baseline lung function were also major determinants of asthma phenotype in this cluster analysis. Although children with ATS-defined severe asthma were present in all clusters, no single cluster corresponded well to the definitions of asthma severity proposed in published guidelines.^{3,9} This is likely a result of overly stringent lung function requirements (ie, FEV₁ < 60%) for childhood severe asthma,¹² which were extrapolated from adult reference norms.^{3,9} These findings highlight the complexity and unique differences of childhood asthma and emphasize the need for unbiased approaches to refine current guidelines for asthma diagnosis and treatment in children.

In a previous cluster analysis of adults enrolled in SARP, Moore et al¹⁹ observed 5 distinct clusters of asthma that differed

TABLE IV. Lung function variables

Variable	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	P value*
Baseline spirometry						
FVC (% predicted)	99 ± 14	102 ± 15	101 ± 11	93 ± 18	92 ± 12	.002
FEV ₁ (% predicted)	89 ± 19	96 ± 19	91 ± 15	84 ± 21	75 ± 16	<.001
FEV ₁ /FVC	0.78 ± 0.11	0.82 ± 0.11	0.79 ± 0.09	0.72 ± 0.10	0.73 ± 0.10	<.001
Postbronchodilator spirometry						
FVC (% predicted)	105 ± 16	109 ± 16	105 ± 13	100 ± 20	99 ± 17	.038
FEV ₁ (% predicted)	101 ± 17	109 ± 19	103 ± 13	97 ± 19	90 ± 12	<.001
FEV ₁ /FVC	0.84 ± 0.08	0.86 ± 0.08	0.86 ± 0.06	0.82 ± 0.08	0.79 ± 0.11	.003
Change in % predicted FEV ₁	15 ± 16	13 ± 15	14 ± 14	18 ± 19	20 ± 19	.220
Baseline lung volumes						
TLC (% predicted)	99 ± 13	102 ± 13	100 ± 11	92 ± 11	95 ± 16	.034
RV (% predicted)	127 ± 49	122 ± 49	126 ± 42	122 ± 53	139 ± 58	.618
RV/TLC	0.28 ± 0.11	0.26 ± 0.08	0.26 ± 0.08	0.29 ± 0.15	0.34 ± 0.15	.025
Raw (% predicted)	132 ± 68	108 ± 46	120 ± 63	185 ± 68	154 ± 84	<.001
Postbronchodilator lung volumes						
TLC (% predicted)	98 ± 12	99 ± 10	102 ± 11	91 ± 9	94 ± 14	.004
RV (% predicted)	116 ± 39	115 ± 31	116 ± 46	115 ± 49	116 ± 34	.998
RV/TLC	0.25 ± 0.08	0.26 ± 0.07	0.24 ± 0.08	0.27 ± 0.14	0.26 ± 0.07	.613
Raw (% predicted)	83 ± 33	74 ± 36	79 ± 36	99 ± 41	83 ± 33	.170
Methacholine PC ₂₀ (mg), median (range)†	1.32 (0.16-23.14)	1.20 (0.09-3.05)	1.13 (0.12-3.02)	0.43 (0.06-3.18)	0.63 (0.25-2.21)	.018

FVC, Forced vital capacity; Raw, airway resistance; RV, residual volume; TLC, total lung capacity.

Data represent mean ± SD or frequency (%) unless otherwise specified.

*P value from analysis of variance between the 4 clusters.

†Data were logarithmically transformed before analysis.

primarily in the age of asthma onset, allergic sensitization, baseline lung function, bronchodilator reversibility, medication use, and health care use. Two of these clusters were associated with early-onset atopic asthma and normal or relatively mild airflow obstruction, whereas 2 others were associated with airflow obstruction that displayed different degrees of bronchodilator reversibility.¹⁹ By using a similar characterization method, we have identified 4 similar clusters of asthma in children, although the degree of lung function impairment was significantly lesser. Whereas baseline FEV₁ percent predicted values were 75% to 84% in clusters 3 and 4, clusters of adults with early-onset atopic asthma had baseline FEV₁ percent predicted values of 43% to 57%.¹⁹ Similarly, the magnitude of FEV₁ bronchodilator administration was significantly greater in children and suggests that “fixed” airflow limitation is not a distinguishing feature of severe asthma in this age group. Interestingly, children in clusters 3 and 4 did have evidence of hyperinflation (air trapping) both at baseline and after bronchodilator administration, but to a much lesser extent than what has been previously reported in adults.^{19,21}

Although the stability of airflow obstruction and hyperinflation in childhood asthma is not entirely clear, there is increasing evidence that an important subgroup of children with persistent wheezing and asthma symptoms acquires significant baseline airflow limitation by the early adult years.²⁸⁻³⁰ In the Melbourne birth cohort study,³¹ children with severe asthma at 10 years of age had the lowest FEV₁ and FEV₁/forced vital capacity ratios throughout the first 42 years of life.³¹ Thus the magnitude of airflow limitation in childhood asthma may represent an important

marker of progressive asthma that worsens and results in more severe disease in adults over time. Even in children with mild-to-moderate asthma, approximately 30% have declines in the postbronchodilator FEV₁ percent predicted value of more than 1% per year regardless of treatment with ICS.³² This observation may be related to impaired lung growth,³³ which could result in accelerated lung function decline in the adult years. Further study is needed to understand how lung function changes and evolves in these clusters with age.

Unlike previous cluster analyses of asthma in adults,¹⁸⁻²⁰ health care use was not a robust discriminator of cluster assignment in children. Although children in cluster 4 had the highest degree of health care use, the majority of children in each cluster had physician contact for an asthma exacerbation within the previous year. Although this observation may be an artifact of the study sample because children in SARP were recruited from academic medical centers, this finding is also consistent with the episodic nature of childhood asthma. Indeed, there is an important distinction between the severity of exacerbations and overall asthma control.^{10,34} Whereas *asthma severity* refers to the required level of therapy during active treatment of asthma symptoms (ie, the magnitude of disease activity), *asthma control* refers to the extent to which asthma symptoms are alleviated by treatment.³⁵ Although asthma control often predicts the risk of future exacerbations,³⁶ children can have severe exacerbations despite limited symptoms and normal lung function before the event.³⁷ These children are difficult to evaluate because many are not symptomatic between exacerbations and medications may be

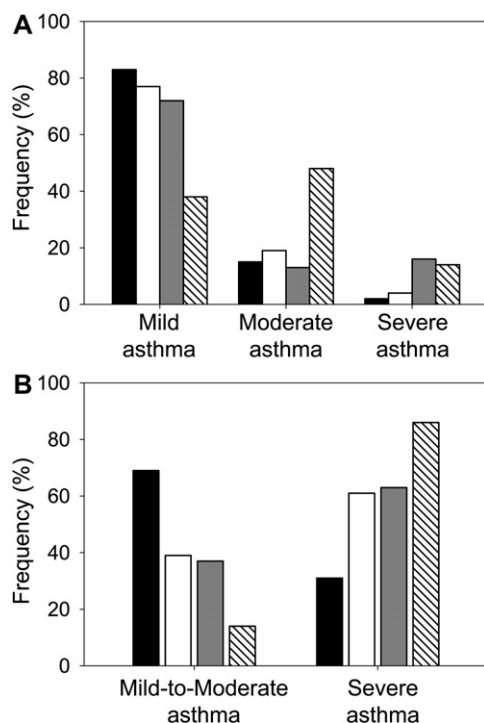


FIG 1. A, Frequency of children with mild, moderate, and severe asthma defined by NAEPP or GINA guidelines. **B**, Frequency of children with mild-to-moderate and severe asthma defined by ATS criteria in each cluster (cluster 1, black bars; cluster 2, white bars; cluster 3, gray bars; cluster 4, hatched bars).

discontinued. Future revision of definitions of asthma severity may need to take this observation into account, because the intensity of treatment in these children may not be the best indicator of impairment and future risk.

An important strength of this study is that cluster analysis, by definition, is unsupervised, and thus the identified clusters conform to shared phenotypic features and not *a priori* severity assignments. This study nonetheless does have limitations. First, it is unclear whether children enrolled in SARP differ systematically from children who refused participation. Although selection bias is a concern in all observational studies, this bias may influence the conclusions drawn and the generalization of our results, particularly because the SARP sample was enriched for children with difficult asthma who are evaluated at academic medical centers. However, the clinical characteristics associated with asthma severity in this sample, including lung function measures, markers of allergic sensitization, and exhaled nitric oxide values, are similar to what has been previously reported in other samples of children with severe asthma.^{5,6,12} Regardless, our sample may not accurately identify different phenotypes of milder asthma severity that are likely encountered in clinical practice. Thus, expansion of our study to children with more mild intermittent forms of asthma would likely have resulted in additional subjects and therefore subclustering within clusters 1 and 2. Second, although enrollment of additional non-Hispanic white subjects would have led to a more geographically representative sample, the disproportionate grouping of black subjects in clusters 3 and 4 likely reflects important ethnic differences in asthma phenotypes. Because health care use was highly prevalent in each cluster, the disproportionate racial distributions are not solely

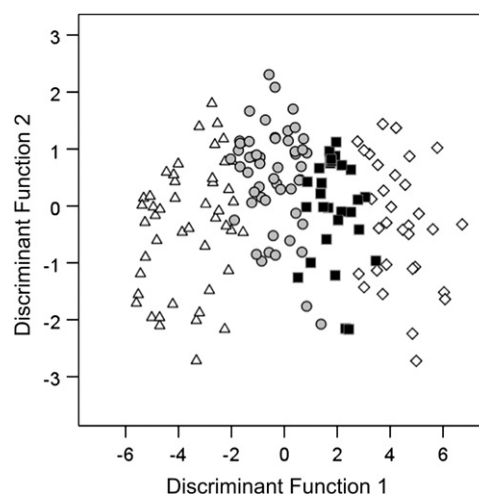


FIG 2. Scatterplot of the discriminant functions generated from discriminant analysis of asthma duration, the extent of asthma controller therapy, and baseline FEV₁ percent predicted values. Each data point represents a single subject. The plot depicts clustering and separation of cluster 1 (white triangles), cluster 2 (gray circles), cluster 3 (black squares), and cluster 4 (white diamonds) using these 3 variables.

attributable to health care access. Indeed, other genetic-based studies have shown that black subjects with asthma have the earliest age of asthma onset, the strongest family history of asthma, and the lowest baseline FEV₁ percent predicted values compared with white and Hispanic subjects.³⁸ Third, it is also important to note that the results obtained from cluster analysis may be dependent on the cluster technique used. Because a cluster analysis will always find patterns in data, regardless of the organization of the dataset, there is not a single best method for performing the analysis. Thus, the inclusion of more children would likely have resulted in further subclustering within our 4 identified clusters. For this reason, these results must be interpreted within the larger clinical context. Although all children in this study were stable at the time of assessment, the stability of these clusters over time and in response to different or novel asthma interventions (including pharmacologic therapies) is unknown. Thus, the predictive aspects of these clusters are also unclear and will require validation in future longitudinal studies of childhood asthma. A separate validation in a different and perhaps larger sample of children with severe asthma would also be useful to understand better the heterogeneity of the disorder.

In conclusion, we have identified 4 clusters of childhood asthma in the NIH/NHLBI SARP. Foremost, these data emphasize that asthma, particularly severe asthma, is a highly heterogeneous disorder. Importantly, no identified cluster corresponded entirely to definitions of severe asthma proposed by national and international guidelines or the ATS. Although this may reflect our variable selection, the consensus-based definitions of severe asthma may also require further validation in children. Whereas the GINA and NAEPP criteria for severe asthma are based primarily on symptoms and lung function, our pediatric asthma clusters were determined as much by the magnitude of atopy and duration of asthma as by airflow limitation and hyperinflation. Exhaled nitric oxide concentrations and the age of asthma symptom onset were also differentiating features of the clusters, whereas health care use was a lesser determinant. These data highlight the complexity and heterogeneity of childhood asthma

and support the need for additional studies, including validation of these clusters in other samples of children with severe asthma. If these clusters are indeed clinically meaningful, then cluster analysis and other unsupervised approaches may ultimately assist with the refinement of current guidelines for asthma diagnosis and treatment in children.

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Clinical implications: Cluster analysis identifies distinct phenotypes of asthma in children that do not correspond to definitions of asthma severity proposed by current guidelines. Clusters of asthma in adults can also be identified in children, but with important differences.

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METHODS

Cluster analysis was performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). The Ward minimum-variance hierarchical clustering method was performed by using an agglomerative (bottom-up) approach and Ward linkage. At each generation of clusters, samples were merged into larger clusters to minimize and maximize with within-subjects and between-subjects sum of squares, respectively. ANOVA with Tukey *post hoc* testing and χ^2 tests were used to determine differences between groups. To determine the strongest predictors of cluster assignment, stepwise discriminant analysis of the 12 cluster variables was performed with the Fisher method, which is robust against departures from normality. This method yields a set of discriminant functions on the basis of the linear combinations of variables that provide the best discrimination between groups. Previous probabilities for group assignment were adjusted for the number of cases included in the analysis. Covariance of the predictor variables was assessed by using pooled within-groups matrices and Box M tests. The ability of the canonical discriminant functions

to distinguish between groups was further evaluated by Wilks λ and χ^2 tests. All variables were entered simultaneously using the Wilks λ method. Entry and removal probabilities for the F statistic were set at 0.05 and 0.10, respectively. Cross-validation was performed by classifying each case by the functions derived from all other cases.

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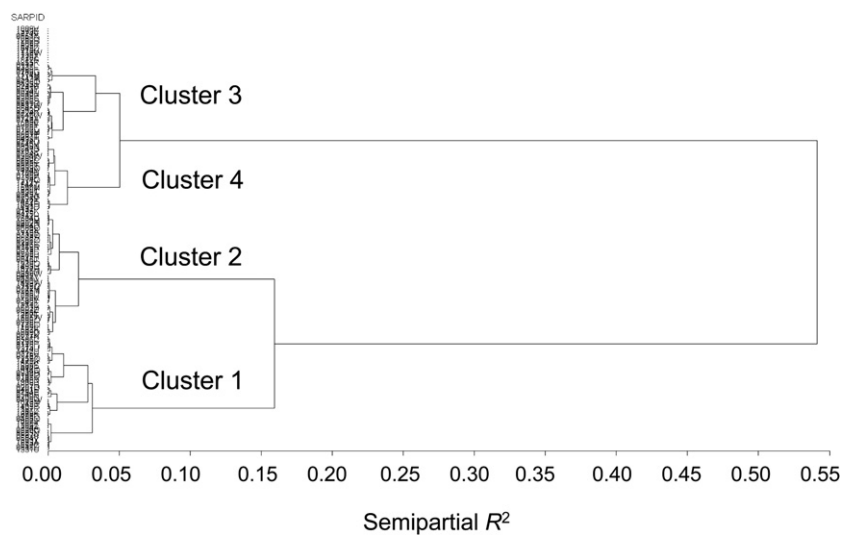


FIG E1. Dendrogram. Using the Wald minimum-variance hierarchical clustering method and an agglomerative (bottom-up approach), 161 subjects from the NIH/NHLBI SARP were clustered into a single final group. At each generation of clusters, samples were merged into larger clusters to minimize the within-cluster sum of squares or maximize the between-subjects sum of squares. With successive clustering, 4 groups were apparent.

TABLE E1. The NIH/NHLBI SARP definition of severe asthma

Major criteria for severe asthma (must have at least 1 to achieve asthma control):

- Treatment with high-dose ICSs
- Treatment with continuous oral corticosteroids (at least 50% of the year)

Minor criteria for severe asthma (must have at least 2):

- Treatment with additional controller medications to maintain asthma control
- Daily use of short-acting bronchodilators (5 of 7 days)
- Persistent airflow obstruction, with baseline FEV₁ <80% predicted
- One or more urgent care visits for asthma in the previous year
- Three or more oral corticosteroid bursts in the previous year
- A history of prompt deterioration in asthma symptoms with a reduction in the dose of ICS or oral corticosteroids
- A near-fatal asthma event requiring intubation in the past

The SARP definition of severe asthma was adopted from the ATS's Workshop on Refractory Asthma.^{E1} According to this definition, for subjects to have severe asthma, they must have at least 1 (of 2) major criteria and at least 2 (of 7) minor criteria. This definition further assumes that subjects are adherent with their prescribed asthma therapy and that all relevant comorbidities have been addressed and treated accordingly.

TABLE E2. Thresholds of high-dose ICS in adults and children

Inhaled corticosteroid	Adults (12 y and older) Minimum $\mu\text{g}/\text{d}$	Children (less than 12 y) Minimum $\mu\text{g}/\text{d}$
Fluticasone	880 μg (Flovent)	440 μg (Flovent)
Fluticasone/salmeterol	1000 μg (Advair discus) 920 μg (Advair)	500 μg (Advair discus) 460 μg (Advair)
Budesonide	1600 μg (Pulmicort Turbuhaler) 1440 μg (Pulmicort Flexhaler)	600 μg (Pulmicort Turbuhaler) 450 μg (Pulmicort Flexhaler) 2000 μg (Pulmicort Respules)
Budesonide/formoterol	640 μg (Symbicort)	480 μg (Symbicort)
Flunisolide	800 μg (Aerospan) 2500 μg (Aerobid)	1250 μg (Aerobid)
Beclomethasone	640 μg (Qvar)	160 μg (Qvar)
Triamcinolone	2500 μg (Azmecort)	1200 μg (Azmecort)
Mometasone	880 μg (Asmanex Twisthaler)	440 μg (Asmanex Twisthaler)

TABLE E3. Variables included in the cluster analysis

Variable	Variable type	Variable name	Key
1	Continuous	Asthma duration	In months
2	Continuous	Baseline FEV ₁	% predicted before bronchodilation
3	Continuous	Maximum FEV ₁	% predicted after maximal bronchodilation
4	Categoric	Race	White, black, other
5	Categoric	Sex	Male, female
6	Categoric	ICS group	None, low-dose ICS, high-dose ICS
7	Semiquantitative	β-Agonist use	0: Never 1: Once per month 2: Weekly 3: Daily
8	Composite	Asthma controller medications	0: None 1: Montelukast or ICS monotherapy 2: ICS plus montelukast or LABA 3: ICS plus montelukast and LABA 4: Oral corticosteroids or omalizumab
9	Composite	Health care use in the previous year	0: None 1: Emergency visit for asthma (physician/emergency department) 2: ≥3 oral corticosteroid bursts 3: Hospital admission 4: Intensive care unit admission
10	Semiquantitative	Frequency of symptoms	0: Once a month or less 1: Weekly, but less than twice per week 2: Weekly, but less than once per day 3: Daily
11	Semiquantitative	Atopic sensitization	0: Ln IgE <5.53, ≤2 positive skin tests 1: Ln IgE >5.53, ≤2 positive skin tests 2: Ln IgE <5.53, ≥3 positive skin tests 3: Ln IgE >5.53, ≥3 positive skin tests
12	Semiquantitative	Exhaled nitric oxide quartile	0: Lowest (offline <6.4, online <6.7 ppb) 1: First (offline <9.1, online <18.1 ppb) 2: Second (offline <14.5, online <38 ppb) 3: Highest (offline >14.5, online >38 ppb)

Ln, Natural logarithm.

TABLE E4. Generation and performance of the composite variable atopic sensitization

Atopic sensitization composite variable responses	n	High-dose ICS (%)	Hospitalized previous year (%)	Baseline FEV ₁ (%)	Asthma duration (mo)
Ln IgE <5.53, ≤2 positive skin tests	57	39	26	98.34	79.86
Ln IgE >5.53, ≤2 positive skin tests	24	71	46	89.27	100.83
Ln IgE <5.53, ≥3 positive skin tests	34	66	41	92.10	109.71
Ln IgE >5.53, ≥3 positive skin tests	59	74	41	85.93	111.39

Ln, Natural logarithm.

This composite variable was generated from a median split of serum IgE (ln IgE cut point of 5.53, which corresponds to a serum IgE of 252 kU/L) data and a median split of the number of positive skin prick responses (cut point of 2). The 5 columns on the right verify that the variable effectively discriminates between ICS dose, health care use, lung function, and duration of asthma.

TABLE E5. Generation and performance of the composite variable exhaled nitric oxide quartile

Exhaled nitric oxide composite variable responses	n	High-dose ICS (%)	Hospitalized previous year (%)	Baseline FEV ₁ (%)	Log eosinophils	Log IgE
Lowest (offline <6.4, online <6.7 ppb)	36	41	22	94.44	0.40	4.40
First (offline <9.1, online <18.1 ppb)	42	51	26	95.91	0.51	5.00
Second (offline <14.5, online <38 ppb)	38	67	47	88.39	0.62	5.75
Highest (offline >14.5, online >38 ppb)	51	65	41	86.09	0.66	6.08

Because exhaled nitric oxide was measured in some children by using offline methods and in others by using online methods, quartiles of exhaled nitric oxide were assigned to offline values and online values separately. Cut points for offline exhaled nitric oxide quartiles were 6.4 ppb (25th percentile), 9.1 ppb (50th percentile), and 14.5 ppb (75th percentile). Cut points for online exhaled nitric oxide quartiles were 6.7 ppb (25th percentile), 18.1 ppb (50th percentile), and 38 ppb (75th percentile). The separate quartile assignments were then merged to create 1 variable. The 4 columns on the right verify that the variable effectively discriminates between ICS dose, health care use, lung function, blood eosinophils, and IgE.

TABLE E6. Features of children excluded from cluster analysis because of missing data

Feature	Excluded children n = 112	Included children n = 161	P value
Age (y)	12 ± 2	11 ± 3	.762
Male/female	60/40	55/45	.464
White/black/other	30/60/10	39/52/9	.422
ATS-defined severe asthma	67	55	.431
Asthma duration (mo)	106 ± 25	99 ± 50	.607
Controller medications			
ICS only	7	8	.661
ICS + LABA or montelukast	20	19	.584
ICS + LABA + montelukast	67	60	.423
Baseline FEV ₁ (% predicted)	94 ± 13	89 ± 19	.221

Data represent mean ± SD or percentage.

TABLE E7. Lung function variables in children 6 to 11 years of age

	Total sample (n = 85)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 38)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 37)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 0)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 10)	P value*
Baseline spirometry						
FVC (% predicted)	102 ± 14	104 ± 15	102 ± 11	—	93 ± 13	.063
FEV ₁ (% predicted)	94 ± 18	100 ± 18	91 ± 15	—	76 ± 15	<.001
FEV ₁ /FVC	0.80 ± 0.10	0.83 ± 0.09	0.79 ± 0.09	—	0.70 ± 0.09	.001
Postbronchodilator spirometry						
FVC (% predicted)	108 ± 15	113 ± 16	107 ± 13	—	97 ± 12	.017
FEV ₁ (% predicted)	106 ± 18	113 ± 19	104 ± 13	—	85 ± 11	<.001
FEV ₁ /FVC	0.85 ± 0.08	0.87 ± 0.08	0.86 ± 0.06	—	0.74 ± 0.10	<.001
Change in % predicted FEV ₁ (%)	13 ± 12	13 ± 11	14 ± 14	—	13 ± 13	.938
Baseline lung volumes						
TLC (% predicted)	101 ± 14	103 ± 14	99 ± 11	—	99 ± 19	.488
RV (% predicted)	130 ± 47	122 ± 41	128 ± 43	—	162 ± 67	.098
RV/TLC	0.29 ± 0.11	0.26 ± 0.06	0.27 ± 0.08	—	0.44 ± 0.18	<.001
Raw (% predicted)	114 ± 57	100 ± 42	118 ± 65	—	144 ± 61	.127
Postbronchodilator lung volumes						
TLC (% predicted)	100 ± 12	101 ± 10	101 ± 11	—	95 ± 17	.399
RV (% predicted)	119 ± 37	117 ± 32	114 ± 41	—	140 ± 33	.206
RV/TLC	0.26 ± 0.07	0.26 ± 0.07	0.24 ± 0.07	—	0.32 ± 0.06	.039
Raw (% predicted)	75 ± 35	66 ± 32	81 ± 36	—	83 ± 43	.280
Methacholine PC ₂₀ (mg), median (range)†	1.88 (0.09-20.10)	2.25 (0.09-20.10)	1.66 (0.14-16.16)	—	1.07 (0.88-1.25)	.408

FVC, Forced vital capacity; Raw, airway resistance; RV, residual volume; TLC, total lung capacity.

Data represent mean ± SD or frequency (%) unless otherwise specified.

*P value from ANOVA between the 4 clusters.

†Data were logarithmically transformed before analysis.

TABLE E8. Lung function variables in children 12 to 17 years of age

Variable	Total sample (n = 76)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 10)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 15)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 19)	P value*
Baseline spirometry						
FVC (% predicted)	94 ± 14	97 ± 9	99 ± 9	93 ± 18	91 ± 11	.450
FEV ₁ (% predicted)	83 ± 18	92 ± 8	91 ± 10	84 ± 21	70 ± 15	.001
FEV ₁ /FVC	0.75 ± 0.11	0.80 ± 0.10	0.80 ± 0.10	0.72 ± 0.10	0.72 ± 0.12	.043
Postbronchodilator spirometry						
FVC (% predicted)	99 ± 16	98 ± 9	99 ± 9	101 ± 19	99 ± 20	.947
FEV ₁ (% predicted)	97 ± 15	102 ± 5	101 ± 11	98 ± 18	89 ± 13	.028
FEV ₁ /FVC	0.84 ± 0.08	0.86 ± 0.08	0.86 ± 0.06	0.82 ± 0.08	0.79 ± 0.11	.003
Change in % predicted FEV ₁ (%)	18 ± 20	7 ± 4	9 ± 12	17 ± 19	32 ± 25	.002
Baseline lung volumes						
TLC (% predicted)	99 ± 13	103 ± 13	100 ± 11	92 ± 11	95 ± 16	.034
RV (% predicted)	127 ± 49	122 ± 49	126 ± 42	122 ± 53	139 ± 58	.618
RV/TLC	0.28 ± 0.11	0.26 ± 0.08	0.26 ± 0.08	0.29 ± 0.15	0.34 ± 0.15	.025
Raw (% predicted)	132 ± 68	108 ± 46	120 ± 63	185 ± 68	154 ± 84	<.001
Postbronchodilator lung volumes						
TLC (% predicted)	98 ± 12	99 ± 10	102 ± 11	91 ± 9	94 ± 14	.032
RV (% predicted)	116 ± 39	115 ± 31	116 ± 46	115 ± 49	116 ± 34	.702
RV/TLC	0.25 ± 0.08	0.26 ± 0.07	0.24 ± 0.08	0.27 ± 0.13	0.26 ± 0.07	.721
Raw (% predicted)	81 ± 36	74 ± 36	79 ± 36	99 ± 41	83 ± 33	.335
Methacholine PC ₂₀ (mg), median (range)†	0.84 (0.06-3.18)	1.20 (0.09-3.05)	1.13 (0.12-3.02)	0.43 (0.06-3.18)	0.63 (0.25-2.21)	.066

Data represent mean ± SD or frequency (%) unless otherwise specified.

*P value from ANOVA between the 4 clusters.

†Data were logarithmically transformed before analysis.

TABLE E9. GINA and NAEPP criteria for severe persistent asthma^{E2,E3}

Feature of severe asthma	GINA guidelines	NAEPP guidelines (children 5-11 y)	NAEPP guidelines (children ≥12 y)
Daytime asthma Symptoms	Daily	Throughout the day	Throughout the day
Nocturnal asthma symptoms	Frequent	Often (7 times/wk)	Often (7 times/wk)
Exacerbations	Frequent	≥2 times/y	≥2 times/y
Activities	Limited	Extremely limited	Extremely limited
FEV ₁	<60% predicted FEV ₁ variability >30%	<60% predicted FEV ₁ /FVC <75%	<60% predicted FEV ₁ /FVC reduced >5%

FVC, Forced vital capacity.

TABLE E10. Results of stepwise linear discriminant analysis of the 12 variables used in cluster analysis

Step	Variables included	Tolerance	Significance of F to remove	Wilks λ	F value	P value
1	Asthma duration	1.000	403.03	0.115	403.03	<.001
2	Asthma duration	0.958	389.74	0.103	110.01	<.001
	No. of controller medications	0.958	6.01			
3	Asthma duration	0.935	372.76	0.089	71.59	<.001
	No. of controller medications	0.832	8.67			
	Baseline FEV ₁ % predicted	0.864	8.423			

Asthma duration, the number of asthma controller medications, and baseline FEV₁ percent predicted values were identified as the strongest predictors of cluster assignment.

TABLE E11. Cluster assignment classification results according to asthma duration, the number of asthma controller medications, and baseline FEV₁ percent predicted values

Model	Cluster	Predicted cluster membership				Total
		Cluster 1	Cluster 2	Cluster 3	Cluster 4	
Original model	Cluster 1	43	5	0	0	48
	Cluster 2	0	50	0	2	52
	Cluster 3	0	0	31	1	32
	Cluster 4	0	1	2	26	29
Cross-validated model*	Cluster 1	43	5	0	0	48
	Cluster 2	0	50	0	2	52
	Cluster 3	0	0	30	2	32
	Cluster 4	0	1	3	25	29

Data were generated from stepwise linear discriminant analysis and represent the number of subjects.

*Cross-validation was performed by classifying each case by the functions derived from all other cases (excluding the case of interest).