

Original Article

Latent Class Analysis of School-Age Children at Risk for Asthma Exacerbation

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What is already known about this topic? Children at risk for asthma exacerbations are a heterogeneous group, with clinical features and pathophysiologic mechanisms that may differ from those that drive asthma severity. There are few studies of children at risk for exacerbation.

What does this article add to our knowledge? Latent class analysis identified 4 groups that differed in demographic features, sensitization/type 2 markers, lung function variables, and future exacerbation occurrence. Exacerbations were most prevalent in latent classes with multiple sensitization and airflow limitation.

How does this study impact current management guidelines? Multiple sensitization, in addition to previous exacerbations and lung function, may be a useful predictor of future exacerbations. However, exacerbations were common in each latent class and highlight the heterogeneity of asthma in school-age children.

BACKGROUND: Factors responsible for asthma exacerbations in children are complex and may differ from those that drive asthma severity.

OBJECTIVE: To identify latent classes of children at risk for asthma exacerbation and determine whether latent class assignment is useful in the prediction of future exacerbation.

METHODS: Latent class analysis was performed on 513 children aged 6 to 17 years at risk for asthma exacerbation, with 31 variables encompassing demographics, medical history, treatment, symptoms, lung function, sensitization, and type 2 inflammation. Primary and secondary outcomes included exacerbation occurrence by 12 months and time to first exacerbation, respectively.

RESULTS: Four latent classes were identified with differing demographic features, sensitization and type 2 inflammatory markers, prior exacerbation severity and health care utilization,

and lung function. Exacerbations occurred in 22.4% of class 1 (“lesser sensitization with normal lung function”), 27.9% of class 2 (“lesser sensitization with prior severe exacerbation and normal lung function”), 45.3% of class 3 (“multiple sensitization with reversible airflow limitation”), and 64.3% of class 4 (“multiple sensitization with partially reversible airflow limitation”) ($P < .001$). Time to exacerbation also followed similar trends and was shortest in the latent classes with multiple sensitization and airflow limitation ($P < .001$). Outcomes were driven largely by children with exacerbation-prone asthma (defined as ≥ 3 exacerbations in the prior year), who were present in each class but most strongly represented in classes 3 and 4. **CONCLUSIONS:** Children at risk for asthma exacerbation are a heterogeneous group. Sensitization, prior exacerbation severity, and lung function variables may be particularly useful in identifying children at greatest risk for future exacerbation. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma in children; Phenotype; Asthma exacerbation; Asthma control; Asthma outcomes; Latent class analysis; Lung function; Type 2 inflammation; Aeroallergen sensitization

Asthma control is suboptimal in the majority of children in the United States,¹⁻³ despite widespread availability of asthma controller medications such as inhaled corticosteroids (ICS) and standardized treatment guidelines.^{4,5} Although deaths from asthma have declined,⁶ more than half of children with asthma continue to experience an exacerbation each year.⁷ National surveillance data in children also highlight disturbing trends of decreased primary care visits for asthma and increased emergency department (ED) visits for asthma exacerbations⁸ that also contribute to school absenteeism,^{9,10} decreased productivity in working parents,¹¹ and rising asthma costs.¹¹⁻¹⁴

Although the factors responsible for asthma exacerbations in children are complex, it is also recognized that children at risk for

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Conflicts of interest: C. R. Morris is the inventor or co-inventor of several UCSF-Benioff Children's Hospital Oakland patents/patent-pending applications that include nutritional supplements, and biomarkers of cardiovascular disease; is an inventor of an Emory University School of Medicine patent application for a nutritional supplement; is a consultant for Pfizer; and has received research support from MAST Therapeutics unrelated to the present work. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

ACQ- Asthma Control Questionnaire

BMI- Body mass index

CI- Confidence interval

ED- Emergency department

FEV₁- Forced expiratory volume in 1 second

FVC- Forced vital capacity

ICS- Inhaled corticosteroid

LCA- Latent class analysis

MARS- Medication Adherence Report Scale

asthma exacerbations are heterogeneous, with clinical features and pathophysiologic mechanisms that may differ from those that drive asthma severity.¹⁵ However, there are very few phenotypic and longitudinal outcome studies of populations of children enriched for high exacerbation risk. Given these knowledge gaps, we applied latent class analysis (LCA) to a dataset of well-characterized children 6 to 17 years of age with physician-diagnosed and -confirmed asthma at risk for asthma exacerbation. The purposes of this study were to: (1) identify latent classes of children at risk for asthma exacerbation and (2) determine whether latent class assignment is useful in the prediction of future exacerbation. We hypothesized that a latent class of children with exacerbation-prone asthma (defined as having ≥ 3 exacerbations in the previous year) would be identified and would be associated with greater symptom burden, lower lung function, poorer quality of life, and higher odds of subsequent exacerbation within 12 months of follow-up.

METHODS

Children 6 to 17 years of age at risk for exacerbation recruited into outpatient asthma clinical research studies at Emory University and Children's Healthcare of Atlanta between January 1, 2004, and December 31, 2015, were included in the analysis. Criteria for inclusion were: (1) physician-diagnosed asthma with historical evidence of either $\geq 12\%$ reversibility in forced expiratory volume in 1 second (FEV₁) relative to baseline or airway hyperresponsiveness evidenced by a provocative concentration of methacholine causing a 20% drop in FEV₁ ≤ 16 mg/mL, and (2) prior asthma exacerbation necessitating treatment with systemic corticosteroids within the preceding 12 months or uncontrolled asthma per treatment guidelines,⁵ evidenced by daytime symptoms more than 2 times per week, nocturnal awakenings 2 or more times per month, or self-reported activity interference. Other exclusions included premature birth before 35 weeks of gestation, current smoking >5 pack years, or other chronic airway disorders such as cystic fibrosis, pulmonary aspiration, or vocal cord dysfunction. Permission to proceed with this study was granted by the Emory University and Children's Healthcare of Atlanta Institutional Review Boards. Informed written consent was obtained from legal guardians. Verbal assent was also obtained from children aged 6 to 10 years and written assent was obtained from children and adolescents aged 11 to 17 years.

Participant recruitment and characterization

Participants were recruited from the ED, hospital wards, and asthma clinics of Children's Healthcare of Atlanta at Eggleston hospital and through community-based advertisements. Participants completed an outpatient study visit during which questionnaires and clinical phenotyping procedures were performed. All participants were stable at the time of the study visit with no self-reported acute

illness and no exacerbation treated with systemic corticosteroids within the preceding 4 weeks. A subset of participants also received a single injection of intramuscular triamcinolone acetonide (1 mg/kg, up to 60 mg maximum dose) for the purpose of systemic corticosteroid responsiveness testing; these patients returned for additional clinical phenotyping procedures at 14 (+7) days.¹⁶

Community (ie, zip code) characteristics were obtained from Tables S101 (Age and Sex), S1501 (Educational Attainment), and DP03 (Selected Economic Characteristics) of the 2010-2014 American Community Survey 5-year estimates.¹⁷ Asthma-related quality of life over the preceding 2 weeks was assessed with the Pediatric Asthma Quality of Life Questionnaire that excludes assessment of the environmental domain.¹⁸ A subset of participants also completed the Asthma Control Test,¹⁹ the 7-item Asthma Control Questionnaire (ACQ),²⁰ and the 5-item Medication Adherence Report Scale (MARS).^{21,22} Exhaled nitric oxide concentrations were measured with a commercial device (NIOX, Aerocrine, Solna, Sweden, or NIOX MINO, Circassia Pharmaceuticals, Chicago, Ill) according to technical standards.²³ Aeroallergen sensitization was assessed by specific IgE testing (Children's Healthcare of Atlanta, Atlanta, Ga) or skin prick testing with 12 extracts: tree mix, grass mix, weed mix, *Ambrosia artemisiifolia*, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, dog dander, cat dander, *Blattella germanica*, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus* (Greer Laboratories, Lenoir, NC). Venipuncture was also performed for quantification of blood eosinophils (Children's Healthcare of Atlanta).

Spirometry (KoKo PDS, Ferraris, Louisville, Colo) was performed after a bronchodilator withhold of ≥ 4 hours for short-acting β -agonists and ≥ 12 hours for long-acting β -agonists. Best FEV₁ and forced vital capacity (FVC) values from 3 reproducible maneuvers²⁴ were recorded at baseline and after 360 mcg albuterol sulfate delivered by a metered dose inhaler. Spirometry data were interpreted according to Global Lung Function Initiative prediction equations.²⁵ A subset of participants, on separate days, also underwent lung volume measurement with a body plethysmograph (MedGraphics Elite Series; Medical Graphics Corporation, St Paul, Minn) for quantification of residual volume and total lung capacity and bronchoprovocation testing with methacholine concentrations of 0 to 16 mg/mL (Provocholine; Methapharm Inc., Coral Springs, Fla) delivered by a Rosenthal dosimeter (Pulmonary Data Service Instrumentation, Louisville, Colo). Bronchoprovocation was limited to participants with baseline FEV₁ $> 70\%$ predicted. After the study procedures were completed, treatment was adjusted in accordance with treatment guidelines.⁵

Statistical analyses

LCA was performed using Mplus software v.8 (Muthen & Muthen, Los Angeles, Calif) that allows for the use of both continuous and categorical latent variables. The LCA analysis input consisted of 31 variables to determine the optimal number of latent classes, including 10 dichotomous variables, 2 categorical variables, and 19 continuous variables. Dichotomous variables included: (1) sex, (2) Hispanic ethnicity, (3) tobacco smoke exposure (defined as any smoker in any household in which the subject regularly spends time), (4) history of eczema (ever), (5) history of sinusitis (ever), (6) history of pneumonia (ever), (7) indoor pet exposure (defined as a cat or dog inside the home), (8) parent with asthma (ever in lifetime), (9) ED visit for asthma in the past 12 months, and (10) hospitalization for asthma in the past 12 months. Categorical variables included race (black, white, other) and body mass index (BMI)

TABLE I. Demographic, exposure, and medical history characteristics of the 4 latent classes

Characteristics	Lesser sensitization with normal lung function (n = 180)	Lesser sensitization with prior severe exacerbation and normal lung function (n = 143)	Multiple sensitization with reversible airflow limitation (n = 147)	Multiple sensitization with partially reversible airflow limitation (n = 43)
Latent class assignment	1	2	3	4
Age (y)	11.0 (9.1, 13.4)	9.42 (7.4, 11.6)	12.2 (10.0, 14.5)	13.2 (10.9, 15.6)
Asthma duration (y)	7.7 (5.0, 10.3)	6.8 (4.0, 8.8)	10.5 (7.9, 12.9)	11.0 (8.7, 13.3)
Males	100 (55.6)	75 (52.4)	95 (64.6)	30 (69.8)
Race				
Non-Hispanic white	74 (41.1)	45 (31.5)	18 (12.2)	4 (9.3)
Non-Hispanic black	90 (50.0)	80 (55.9)	108 (73.5)	35 (81.4)
Other	16 (8.9)	18 (12.6)	21 (14.3)	4 (9.3)
Hispanic	14 (7.8)	3 (2.1)	8 (5.4)	4 (9.3)
Body mass index percentile				
Overweight (85%-95%)	30 (16.7)	28 (19.6)	39 (26.5)	10 (23.3)
Obese ($\geq 95\%$)	26 (14.4)	47 (32.9)	52 (35.4)	12 (27.9)
Medical history (ever)				
Eczema	90 (50.0)	86 (60.1)	105 (71.4)	30 (69.8)
Sinusitis	54 (30.0)	32 (22.4)	52 (35.4)	15 (34.9)
Pneumonia	71 (39.4)	61 (42.7)	81 (55.1)	28 (65.1)
Current exposures				
Indoor dog or cat	77 (42.8)	62 (43.4)	55 (37.4)	17 (39.5)
Indoor smoking	13 (7.2)	16 (11.2)	36 (24.5)	10 (23.3)
Parent with asthma	85 (47.2)	72 (50.3)	96 (65.3)	30 (69.8)
Highest household education*				
Did not complete high school	6 (4.4)	2 (1.6)	12 (9.4)	2 (5.7)
High school degree	19 (14.0)	19 (14.8)	26 (20.5)	6 (17.1)
Some college	45 (33.1)	41 (32.0)	43 (33.9)	15 (42.9)
College degree	66 (48.5)	66 (51.6)	46 (36.2)	12 (34.3)
Zip code features				
Population (thousands)	34.8 (20.2, 44.5)	32.5 (20.7, 48.4)	34.7 (26.4, 48.4)	31.3 (21.4, 40.1)
Unemployment (%)	11 (8.2, 15.3)	9.8 (7.6, 12.9)	13.9 (8.8, 19.5)	13.8 (8.8, 18.9)
Bachelor's degree (%)	28.2 (19.5, 38.7)	31.3 (21.6, 46.5)	24.4 (16.8, 35.5)	24.0 (18.5, 33.2)
Families below poverty (%)	19.0 (14.5, 25.6)	19.1 (12.6, 24.6)	24.5 (18.3, 31.0)	23.4 (16.4, 31.2)

Data represent the number of participants (%) or the median (25th, 75th percentile).

*Class 1, n = 136; class 2, n = 128; class 3, n = 127; class 4, n = 35.

percentile (<85%, 85%-95%, $\geq 95\%$). Continuous variables included: (1) age, (2) asthma duration, (3) number of asthma controller medications, (4) symptom score over the previous 4 weeks (sum of daytime cough, daytime wheeze, and nighttime symptoms each coded as 0 = never, 1 = monthly, 2 = once weekly, 3 = at least twice weekly, 4 = daily), (5) baseline FEV₁ (% predicted), (6) baseline FVC (% predicted), (7) baseline FEV₁/FVC (% predicted), (8) postbronchodilator FEV₁ (% predicted), (9) postbronchodilator FVC (% predicted), (10) postbronchodilator FEV₁/FVC (% predicted), (11) absolute FEV₁ change (defined as postbronchodilator %predicted – baseline %predicted), (12) exhaled nitric oxide concentration (ppb), (13) serum IgE level (kU/L), (14) blood eosinophil percentage, (15) percentage of positive allergens (out of 12), (16) zip code population, (17) zip code unemployment (%), (18) zip code educational attainment (% with bachelor's degree), and (19) zip code families below the poverty threshold (%). Models of 1 to 5 latent classes were repeatedly fitted with the number of latent classes in a stepwise fashion. Best fit was assessed via model fit statistics (log-likelihood, Akaike information criterion, adjusted Bayesian information criterion), entropy, the Lo-Mendell-Rubin adjusted ratio test, and clinical judgment. Each participant was assigned to the

latent class with the highest membership probability. Features of latent classes were compared with χ^2 tests and analysis of variance with Tukey's *post hoc* tests.

Outcome analyses

The primary outcome was the proportion of participants within each latent class with any exacerbation necessitating treatment with systemic corticosteroids within 12 months after the study visit,²⁶ assessed by χ^2 tests. Logistic regression was used to obtain odds ratios and 95% confidence intervals (CIs). The secondary outcome was time to first exacerbation assessed with proportional-hazards regression models. Exploratory outcomes included any exacerbation necessitating hospitalization for asthma and ACQ scores after systemic triamcinolone administration in the subset of participants who underwent corticosteroid responsiveness testing. Analyses used a .05 significance level without correction for multiple testing given the exploratory nature of the work.

RESULTS

A total of 513 children with complete data were included in the LCA. The distribution of study participants by the inclusion

TABLE II. Symptoms, medications, health care utilization, and type 2 inflammatory markers in the 4 latent classes

Feature	Lesser sensitization with normal lung function (n = 180)	Lesser sensitization with prior severe exacerbation and normal lung function (n = 143)	Multiple sensitization with reversible airflow limitation (n = 147)	Multiple sensitization with partially reversible airflow limitation (n = 43)
Latent class assignment	1	2	3	4
Symptoms (past 4 wk)				
Symptom score	3.0 (1.0, 6.0)	2.0 (1.0, 5.0)	5.0 (2.0, 8.0)	6.0 (3.5, 10.5)
Daily cough	12 (6.7)	12 (8.3)	32 (21.7)	8 (18.6)
Daily wheeze	4 (2.2)	5 (3.5)	15 (10.2)	8 (18.6)
Daily shortness of breath	11 (6.1)	9 (6.3)	18 (12.2)	9 (20.9)
Daily nighttime awakenings	8 (5.0)	8 (5.6)	24 (16.3)	10 (23.3)
Activity limitation	47 (26.1)	26 (18.2)	61 (41.5)	22 (51.2)
Asthma control				
ACT score (past month)*	19.0 (11.0, 22.0)	20.0 (15.0, 22.0)	18.0 (15.0, 21.0)	17.5 (15.0, 19.0)
ACQ7 score (past week) [†]	1.1 (0.39, 1.8)	0.4 (0.3, 1.1)	1.3 (0.7, 1.7)	1.9 (1.4, 2.7)
Controller medications				
No. of controller medications	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (2.0, 3.0)	3.0 (3.0, 3.0)
Medication adherence score [‡]	25 (23, 25)	24 (23, 25)	21 (18, 24)	24 (23, 25)
ICS	143 (79.4)	114 (80.3)	140 (95.2)	40 (93.0)
ICS + LABA	88 (48.9)	60 (42.0)	120 (81.6)	38 (88.4)
Montelukast	110 (61.1)	71 (49.7)	120 (81.6)	36 (83.7)
Omalizumab	3 (1.7)	2 (1.4)	7 (4.8)	5 (11.6)
Oral corticosteroids	7 (3.9)	4 (2.8)	14 (9.5)	6 (14.0)
Exacerbations (past year)				
Any exacerbation	124 (68.9)	89 (62.2)	119 (81.0)	34 (79.1)
≥3 exacerbations	38 (21.1)	30 (21.0)	50 (34.0)	20 (46.5)
Exacerbation rate	0 (0, 2.0)	0 (0, 1.0)	1.0 (0, 2.0)	1.5 (0.25, 3.0)
Health care utilization				
ED (past year)	69 (38.5)	64 (44.8)	105 (71.4)	33 (76.7)
Hospitalization (past year)	21 (11.7)	34 (23.8)	62 (42.2)	24 (55.8)
Intensive care admission (ever)	32 (17.8)	27 (18.9)	68 (46.3)	24 (55.8)
Intubation (ever)	19 (10.6)	11 (7.7)	35 (23.8)	11 (25.6)
Type 2 inflammatory markers				
Serum IgE (kU/L)	248 (56.0, 632)	293 (121, 696)	588 (219, 1410)	407 (213, 1058)
Eosinophils (%)	3.4 (1.7, 6.0)	3.7 (1.9, 6.7)	6.4 (4.0, 10.1)	4.5 (3.0, 9.1)
Eosinophils (cells/μL)	203 (106, 319)	203 (145, 354)	396 (230, 551)	247 (131, 581)
Exhaled nitric oxide (ppb)	19.0 (10.0, 39.6)	17.0 (8.5, 37.0)	35.6 (20.7, 62.1)	31.8 (20.5, 47.0)
Aeroallergen sensitization				
Positive allergens (% of 12)	16.7 (8.3, 41.7)	20.8 (8.33, 41.7)	50.0 (25.0, 83.3)	45.8 (25.0, 66.7)
No sensitization	40 (24.2)	28 (21.2)	7 (5.5)	1 (2.8)
Monosensitization	25 (15.2)	16 (12.1)	4 (3.1)	3 (8.3)
Dust sensitization	83 (46.1)	63 (44.1)	102 (69.4)	28 (65.1)
Cat or dog sensitization	50 (27.8)	56 (39.2)	75 (51.0)	21 (48.8)
Cockroach sensitization	29 (17.8)	26 (19.7)	57 (44.9)	15 (41.7)
Mold sensitization	53 (29.4)	43 (30.1)	75 (51.0)	23 (53.5)
Pollen sensitization	68 (37.8)	67 (46.9)	96 (65.3)	26 (60.5)

Data represent the number of participants (%) or the median (25th, 75th percentile).

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β -agonists; MARS, Medication Adherence Report Scale.

*Class 1, n = 92; class 2, n = 89; class 3, n = 78; class 4, n = 20.

[†]Class 1, n = 67; class 2, n = 74; class 3, n = 85; class 4, n = 19.

[‡]MARS5 score, range 5-25, where higher values reflect greater adherence. Class 1, n = 44; class 2, n = 41; class 3, n = 36; class 4, n = 10.

criterion is shown in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). For the LCA, 2-, 3-, 4-, and 5-class solutions were evaluated. Although the 5-class solution had the best model fits (as indicated by the smallest fit-value) and highest entropy (Table E2, available in this article's

Online Repository at www.jaci-inpractice.org), this solution yielded an unacceptable sample size (N = 3) in one of the resultant latent classes (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Therefore, the 4-class solution was chosen as the best fit; this solution also yielded a

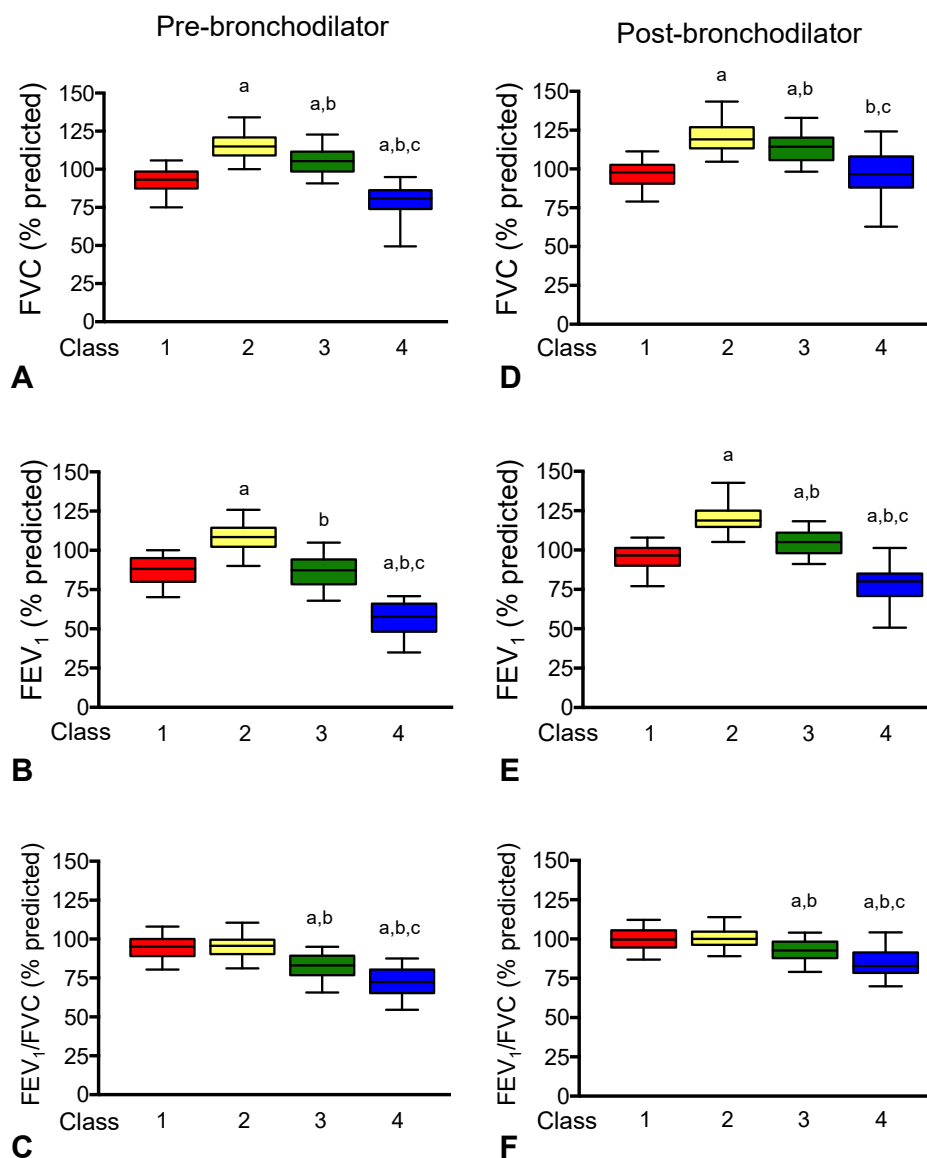


FIGURE 1. Pre- and postbronchodilator (A, D) FVC, (B, E) FEV₁, and (C, F) FEV₁/FVC in class 1 (lesser sensitization with normal lung function), class 2 (lesser sensitization with prior severe exacerbation and normal lung function), class 3 (multiple sensitization with reversible airflow limitation), and class 4 (multiple sensitization with partially reversible airflow limitation). ^a*P* < .05 versus class 1, ^b*P* < .05 versus class 2, ^c*P* < .05 versus class 3. FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity.

high-class membership probability for all participants (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Individual variables are shown in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org) and represented by *z*-scores. Demographic, exposure, and medical history characteristics of the 4 latent classes are shown in Table I, and symptoms, medications, prior exacerbations, health care utilization, and type 2 inflammatory markers are shown in Table II. Lung function values are shown in Figure 1, air trapping and airway hyperresponsiveness data are shown in Figure 2, and asthma-related quality of life scores are shown in Figure 3. To simplify the discussion, latent classes were assigned a summary label. Key features of the 4 latent classes are detailed below.

Lesser sensitization with normal lung function (latent class 1)

One hundred eighty children (35.1%) were included in this latent class, termed "lesser sensitization with normal lung function." This class had the lowest prevalence of comorbidity and family history of asthma. Children in this class overall had uncontrolled asthma with the fewest controller medications. Twenty-one percent of children in this class (*n* = 38) had exacerbation-prone asthma with ≥3 exacerbations in the prior year, but had lesser health care utilization. Although the majority of these children (approximately 75%) had sensitization to at least 1 aeroallergen, type 2 inflammatory features tended to be lower in this group. Lung function was largely preserved in this

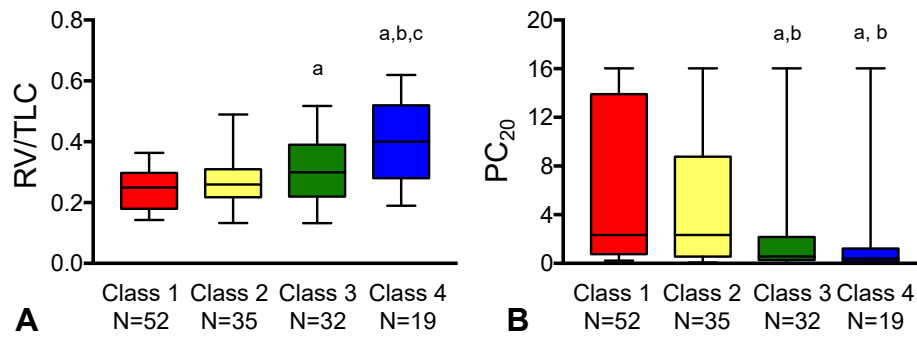


FIGURE 2. (A) RV/TLC and (B) methacholine PC₂₀ concentration in class 1 (lesser sensitization with normal lung function), class 2 (lesser sensitization with prior severe exacerbation and normal lung function), class 3 (multiple sensitization with reversible airflow limitation), and class 4 (multiple sensitization with partially reversible airflow limitation). ^a*P* < .05 versus class 1, ^b*P* < .05 versus class 2, ^c*P* < .05 versus class 3. PC₂₀, Provocative concentration of methacholine causing a 20% decline in forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity.

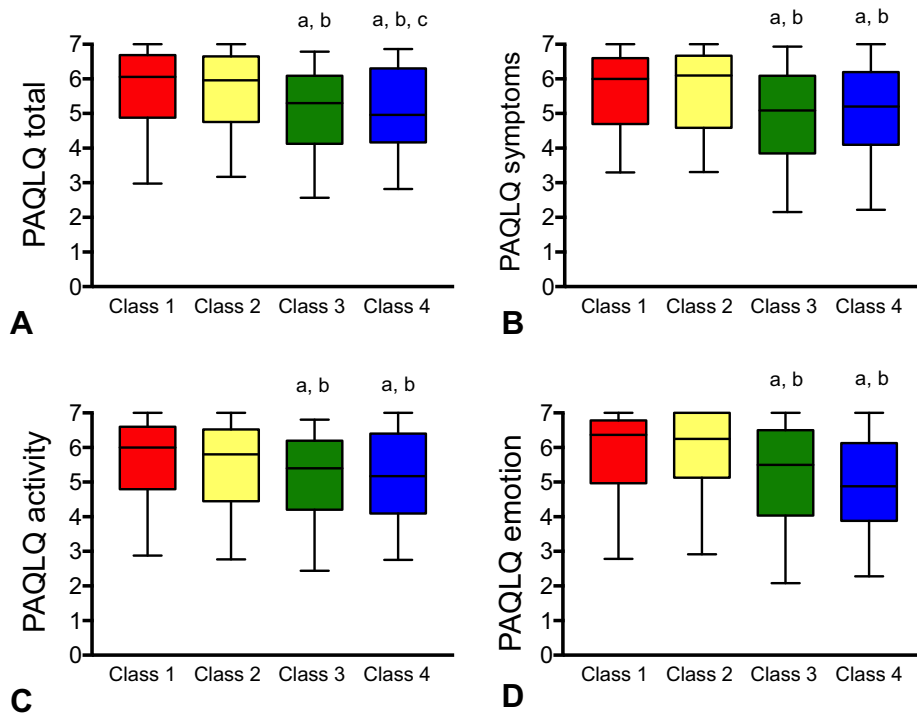


FIGURE 3. Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (A) total, (B) symptom, (C) activity, and (D) emotional domain scores in class 1 (lesser sensitization with normal lung function), class 2 (lesser sensitization with prior severe exacerbation and normal lung function), class 3 (multiple sensitization with reversible airflow limitation), and class 4 (multiple sensitization with partially reversible airflow limitation). ^a*P* < .05 versus class 1, ^b*P* < .05 versus class 2, ^c*P* < .05 versus class 3.

latent class. This latent class also had minimal air trapping, lesser airway hyperresponsiveness to methacholine, and the greatest quality of life.

Lesser sensitization with prior severe exacerbation and normal lung function (latent class 2)

One hundred forty-three children (27.9%) were included in this latent class, termed “lesser sensitization with prior severe exacerbation and normal function.” Children in this latent class

were younger and tended to be more obese. Symptoms, controller medications, prior exacerbations, sensitization patterns, and type 2 inflammatory features were similar to those of children with lesser sensitization and normal lung function. Twenty-one percent (*n* = 30) of children in this class had ≥3 exacerbations in the prior year, but unlike children with lesser sensitization and normal lung function, these children had more unscheduled visits and hospitalizations for asthma. Baseline FVC and FEV₁ values were also higher in this group, but FEV₁/FVC

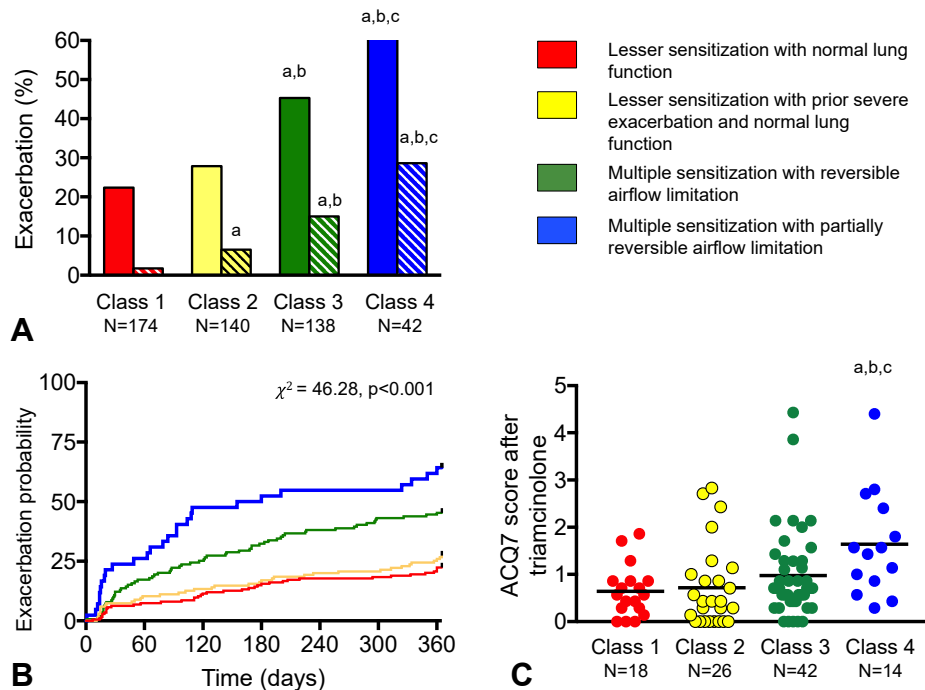


FIGURE 4. (A) Exacerbation (solid bar) and exacerbation with hospitalization (dashed bar) occurrence by 12 months, (B) time to first exacerbation, and (C) Asthma Control Questionnaire (ACQ) scores after triamcinolone administration, by latent class assignment. ^a $P < .05$ versus class 1, ^b $P < .05$ versus class 2, ^c $P < .05$ versus class 3.

ratios and quality of life measures were similar to those of children with lesser sensitization and normal lung function.

Multiple sensitization with reversible airflow limitation (latent class 3)

One hundred forty-seven children (28.7%) were included in this latent class, termed “multiple sensitization and reversible airflow limitation.” Children in this latent class were predominantly black males with a higher prevalence of parental asthma and comorbidity. These children also resided in more disadvantaged neighborhoods and had uncontrolled asthma with frequent symptoms, more prior exacerbations, indoor tobacco smoke exposure, multiple sensitization, and the highest magnitude of type 2 inflammatory markers despite more controller medications. However, medication adherence scores were also lowest suggesting lesser adherence to ICS. Thirty-four percent of children in this latent class ($n = 50$) met criteria for exacerbation-prone asthma, with ≥ 3 exacerbations in the prior year. This latent class was also distinguished by a high prevalence of near-fatal asthma necessitating intubation, frequent health care utilization in the prior year, and mild yet reversible airflow limitation accompanied by mild air trapping, greater airway hyperresponsiveness to methacholine, and more impaired quality of life.

Multiple sensitization with partially reversible airflow limitation (latent class 4)

Forty-three children (8.3%) were included in this latent class, termed “multiple sensitization with partially reversible airflow limitation.” Children in this latent class were older, mostly black males with a higher prevalence of parental asthma and

comorbidity such as pneumonia. Children in this latent class also resided in more disadvantaged neighborhoods and had the poorest asthma control, highest exacerbation rate before study enrollment, more prevalent indoor tobacco smoke exposure, and most frequent health care utilization in the prior year. Forty-seven percent of children in this latent class ($n = 20$) met criteria for exacerbation-prone asthma, with ≥ 3 exacerbations in the prior year. Children in this latent class also had a high prevalence of lifetime intubation for asthma, multiple sensitization, and elevated type 2 inflammatory markers despite more controller medications. Baseline lung function was lowest in this group and was accompanied by significant air trapping and the greatest airway hyperresponsiveness to methacholine. Airflow limitation was only partially reversible with bronchodilation and was also accompanied by more impaired quality of life.

Exacerbation outcomes

The primary outcome, any exacerbation occurrence within 12 months after the study visit, was assessed from 494 participants (96.3%). Exacerbations occurred in 22.4% of class 1 (“lesser sensitization with normal lung function”), 27.9% of class 2 (“lesser sensitization with prior severe exacerbation and normal lung function”), 45.3% of class 3 (“multiple sensitization with reversible airflow limitation”), and 64.3% of class 4 (“multiple sensitization with partially reversible airflow limitation”) ($P < .001$) (Figure 4, A, Table III). Outcomes were almost completely driven by children with exacerbation-prone asthma, defined as ≥ 3 exacerbations in the previous year (Table III).

Time to exacerbation, adjusted for season of enrollment, was also shorter for children with multiple sensitization and reversible airflow limitation (latent class 3, adjusted hazard ratio 2.51, 95%

TABLE III. Odds of exacerbation by 12 months according to latent class assignment

Exacerbation outcome*		N with outcome data	N (%) with exacerbation	Odds ratio (95% confidence interval)
<i>All participants</i>				
Class 1	Lesser sensitization with normal lung function	174	39 (22.4)	—
Class 2	Lesser sensitization with prior severe exacerbation and normal lung function	136	38 (27.9)	1.34 (0.80, 2.25)
Class 3	Multiple sensitization with reversible airflow limitation	139	63 (45.3)	2.87 (1.76, 4.68)
Class 4	Multiple sensitization with partially reversible airflow limitation	42	27 (64.3)	6.23 (3.01, 12.82)
<i>Participants with exacerbation-prone asthma†</i>				
Class 1	Lesser sensitization with normal lung function	36	13 (36.1)	—
Class 2	Lesser sensitization with prior severe exacerbation and normal lung function	45	18 (64.3)	3.19 (1.14, 8.92)
Class 3	Multiple sensitization with reversible airflow limitation	28	32 (71.1)	4.36 (1.71, 11.12)
Class 4	Multiple sensitization with partially reversible airflow limitation	20	17 (85.0)	10.03 (2.46, 40.79)

*Defined as requiring treatment with systemic corticosteroids.

†Defined as ≥ 3 exacerbations in prior year.

CI: 1.68, 3.75) and children with multiple sensitization and partially reversible airflow limitation (latent class 4, adjusted hazard ratio 3.87, 95% CI: 2.36, 6.36) (Figure 4, B). In exploratory analyses, children in classes 3 and 4 also had a higher occurrence of hospitalization (15% and 29%, respectively) (Figure 4, A). However, in the subset of children who underwent systemic corticosteroid responsiveness testing with intramuscular triamcinolone, the majority of children in class 3 ($n = 17$, 65%) achieved “well-controlled” asthma with triamcinolone administration, evidenced by an ACQ score < 0.75 .²⁷ In contrast, a significant proportion of children in class 4 ($n = 8$, 57%) had “poorly controlled” asthma after triamcinolone, evidenced by an ACQ score > 1.25 ²⁸ (Figure 4, C).

DISCUSSION

In this study, we used LCA to uncover previously unobservable patterns in a well-characterized study population of children at risk for exacerbation. LCA was selected over other exploratory approaches because it is model based, allows model comparisons to be statistically tested, and is appropriate for questionnaire-derived data yet permits differing variable measurement scales and variances.²⁹ Using LCA, we identified 2 latent classes of children with a lesser magnitude of sensitization and normal lung function who differed with regard to prior exacerbation severity. Approximately 21% of children in each of these classes met criteria for exacerbation-prone asthma with ≥ 3 exacerbations in the previous year, and nearly 25% of children in each of these 2 classes had a subsequent exacerbation within 12 months. In contrast, we also identified 2 latent classes of children with multiple sensitization who differed with regard to baseline lung function and the degree of bronchodilator reversibility. These classes had a higher proportion of participants with exacerbation-prone asthma, and subsequent exacerbations were nearly 2- to 4-fold higher in these classes. These exacerbations also tended to be more severe and were accompanied by greater hospitalization for status asthmaticus.

Consistent with our hypothesis, we did identify 2 latent classes with more symptom burden and lower lung function parameters and impaired quality of life at highest risk for subsequent exacerbation. However, exacerbations did occur in all 4 latent classes. Furthermore, participants with exacerbation-prone asthma (defined as having ≥ 3 exacerbations in the previous year) were

also present in each latent class. Therefore, we cannot say with certainty that these latent classes conform to distinct “phenotypes” of exacerbation-prone asthma. Indeed, the LCA approach is considered exploratory and hypothesis-generating. Nonetheless, our findings do have clinical and biological plausibility. Other cluster analyses of children with more severe asthma (who also tend to have frequent exacerbations) have likewise identified multiple clusters differentiated by the degree of allergic sensitization, asthma duration, controller medications, BMI, and pre-bronchodilator lung function.³⁰⁻³⁵ A consistent theme across these analyses is greater severity of asthma in clusters with more prominent type 2 inflammatory features, but some type 2 features are present in nearly all the pediatric clusters that have been described. For example, in children aged 6 to 11 years with difficult-to-treat asthma, Schatz et al³⁴ identified a moderately prevalent (31%) cluster of children without allergic rhinitis or atopic dermatitis who also had significant airflow obstruction. However, mean IgE levels were also elevated in this group, suggesting that at least some children had underlying type 2 inflammation.³⁴ Similarly, a cluster analysis of inner-city children with asthma also identified a low-prevalent (15%) cluster with the lowest levels blood eosinophils and exhaled nitric oxide, but several children in this group had aeroallergen monosensitization and 28% had a positive Phadiatop allergen sensitization screen.³⁵

Our observation of increased exacerbation occurrence in the 2 latent classes of children with multiple sensitization and airflow limitation is also similar to other findings from hypothesis-directed research. Multiple regression analyses have identified several independent risk factors of subsequent asthma exacerbations in children, including race and socioeconomic variables,³⁶ the magnitude of airflow limitation and reversal with bronchodilation,³⁷ multiple-versus monosensitization to aeroallergens,³⁸ and a prior exacerbation requiring treatment with systemic corticosteroids.³⁹ BMI has also been implicated as a risk factor for exacerbation-prone asthma in children (defined as ≥ 3 exacerbation in the previous year)¹⁵ and, in meta-analyses, was associated with a small yet significant increased risk of exacerbation in children independent of sex.⁴⁰ However, very few studies have examined associations between multiple variable groupings (ie, clusters or latent classes) and exacerbation outcomes. For example, the cluster analysis of inner-city children with asthma identified a cluster with the highest degree of type 2 inflammation and multiple aeroallergen sensitization (approximately 15%

of children) that also had the highest medication requirements, greatest airflow obstruction and airway lability, and the highest proportion of exacerbations requiring treatment with systemic corticosteroids.³⁵ However, the prospective rate of exacerbations was included as a variable in that clustering algorithm and not assessed independently of cluster assignment.³⁵ A cluster analysis of the Childhood Asthma Management Research Program (which excludes severe asthma) did identify a highly atopic cluster of children with airflow limitation, the highest bronchodilator response, severe airway hyperresponsiveness, and the highest baseline exacerbation rate who also had the shortest time to systemic corticosteroids for asthma exacerbation over 4 years of follow-up.³¹ Furthermore, 64% of participants in this group received systemic corticosteroids within the first year.²⁶ However, that study was limited to children with mild-to-moderate asthma and excluded children with more severe forms of asthma and frequent exacerbations.

Strengths of the present study include the relatively large and racially diverse sample of children at risk for exacerbation who underwent extensive phenotypic characterization before longitudinal study. However, there are a number of limitations. Admittedly, the factors responsible for asthma exacerbations in children are complex and include limited access to primary care⁴¹ and exposures to environmental allergens and irritants in addition to sensitization⁴²⁻⁴⁴ that were not adequately addressed by the study design. Poor adherence to controller medications is also common in general populations and was not thoroughly addressed by the study design.^{3,45} Although MARS scores for medication adherence suggest that adherence was acceptable in classes 1, 2, and 4, this score may overestimate adherence when assessed by electronic means.⁴⁶ Although asthma controller therapies were adjusted at the completion of the baseline characterization visit, it is therefore possible that poor adherence to ICS impacted the exacerbation outcomes. Indeed, the exploratory analysis in a limited subset of participants undergoing systemic corticosteroid responsiveness testing with intramuscular triamcinolone suggests that exacerbations may be largely preventable in class 3, but less so in class 4. Similarly, in the cluster analysis performed by the National Heart Lung and Blood Institute's Severe Asthma Research Program, children with the earliest age of symptom onset and more advanced, partially reversible airflow limitation also had the greatest burden of symptoms and associated medication use at the baseline visit,³⁰ but also had best treatment responses to fluticasone/salmeterol in highly supervised, separate replication analyses.⁴⁷ However, a second cluster that also had early onset disease and airflow limitation had the least response to guideline-based asthma treatment in that same study.⁴⁷ Similarly, the cluster of children with low lung function and the highest baseline exacerbation rate identified by the Childhood Asthma Management Research Program also did not improve with daily budesonide treatment.³¹ Other limitations include the single-versus multicenter design and recruitment of children from an academic medical center, which prohibits generalization to other populations. The number of participants who underwent baseline phenotyping also limited the clustering solution to 4 groups, which may not be sufficient for detection of low-prevalent asthma phenotypes. The study design also prohibited assessment of the temporal stability of latent classes and transition over time.

In conclusion, using LCA, we identified 4 latent classes of children at risk for asthma exacerbation that differed with regard

to demographic and medical history variables, symptoms, medications, health care utilization, type 2 inflammatory markers, and lung function. Children with exacerbation-prone asthma were present in each latent class, but were most strongly represented in the latent classes with multiple sensitization and airflow limitation. These same latent classes had the greatest disease burden and poorest quality of life at baseline and the highest odds of exacerbation by 12 months. Additional studies are needed to determine whether these latent classes correspond to clinically useful phenotypes.

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TABLE E1. Distribution of study participants (N = 513) by the inclusion criterion

Inclusion criterion	N (%) of participants
Asthma exacerbation treated with systemic corticosteroids within the past 12 mo	366 (71.3)
Uncontrolled asthma	
Daytime symptoms more than 2 times per week	103 (20.1)
Nocturnal awakenings 2 or more times per month	112 (21.8)
Interference with activity	
Symptoms with daily activities (walking, stairs)	156 (30.4)
Symptoms with sports/heavy exertion	426 (83.0)

Criteria are not mutually exclusive.

TABLE E2. Measures of latent class analysis model fit

LCA solution	Log-likelihood	AIC	Adjusted BIC	Entropy	Test vs k-1 latent classes*
2 classes	−39,273	78,722	78,816	0.822	0.017
3 classes	−39,006	78,259	78,390	0.833	0.296
4 classes	−38,775	77,866	78,034	0.873	0.143
5 classes	−38,623	77,632	77,838	0.894	0.764

AIC, Akaike information criterion; BIC, Bayesian information criterion; LCA, latent class analysis.

*Based on the Lo-Mendell-Rubin adjusted likelihood ratio test.

TABLE E3. Distribution of participants in the 2-class to 5-class models

LCA solution	Class 1, N	Class 2, N	Class 3, N	Class 4, N	Class 5, N
2 classes	329	184			
3 classes	201	149	163		
4 classes	180	147	143	43	
5 classes	178	145	45	3	142

LCA, Latent class analysis.

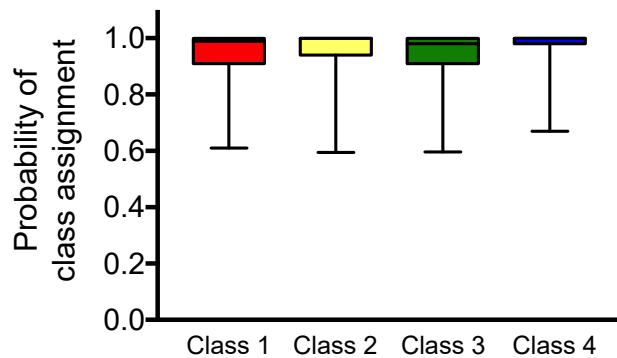


FIGURE E1. Class membership probability for class 1 (lesser sensitization with normal lung function), class 2 (lesser sensitization with prior severe exacerbation and normal lung function), class 3 (multiple sensitization with reversible airflow limitation), and class 4 (multiple sensitization with partially reversible airflow limitation). For each latent class, the probability of assignment was >0.97 on average for each participant.

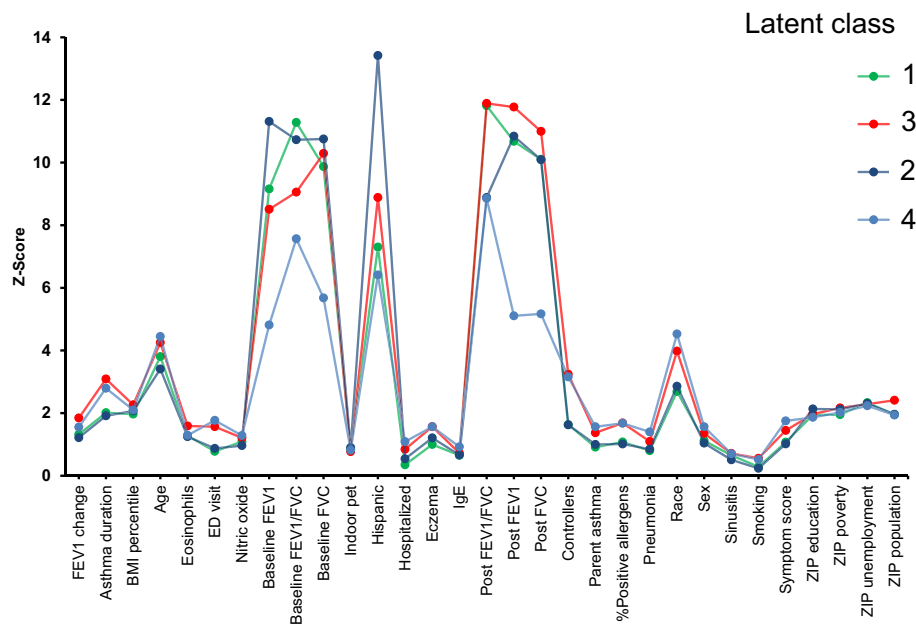


FIGURE E2. Dependent variables results by latent class assignment, shown as standardized z-scores. The z-score for each variable reflects the number of standard deviations from the mean. Differences in peak heights indicate how well the variables distinguish classes from each other. For most variables, z-scores differ by at least 1, which reflects 1 standard deviation above the mean. *BMI*, Body mass index; *ED*, emergency department; *FEV₁*, forced expiratory volume in 1 second; *FVC*, forced vital capacity.