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Heterogeneity of Mild to Moderate Persistent Asthma in Children: Confirmation by Latent Class Analysis and Association with 1-Year Outcomes

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Abstract

BACKGROUND: Compared with adults, phenotypic characterization of children with asthma is still limited and it remains difficult to predict which children with asthma are at highest risk for poor outcomes.

OBJECTIVE: To identify latent classes in a large population of treatment-adherent children with mild to moderate asthma enrolled in clinical trials and determine whether latent class assignment predicts future lung function abnormalities and exacerbation rate.

METHODS: Latent class analysis was performed on 2593 children with mild to moderate asthma aged 5 18 years, with 19 variables encompassing demographic characteristics, medical history, symptoms, lung function, allergic sensitization, and type 2 inflammation. Outcomes included lung function and the annualized exacerbation rate at 12 months of follow-up.

RESULTS: Five latent classes were identified with differing demographic features, asthma control, sensitization, type 2 inflammatory markers, and lung function. Exacerbation rates were 1.30 ± 0.12 for class 1 (multiple sensitization with partially reversible airflow limitation), 0.90 ± 0.05 for class 2 (multiple sensitization with reversible airflow limitation), 0.87 ± 0.08 for class 3 (lesser sensitization with reversible airflow limitation), 0.87 ± 0.05 for class 4 (multiple sensitization with normal lung function), and 0.71 ± 0.06 for class 5 (lesser sensitization with normal lung function). Lung function abnormalities persisted in class 1 at 12 months.

CONCLUSIONS: Children with mild to moderate asthma are a heterogeneous group. Allergic sensitization and lung function may be particularly useful in identifying children at the greatest risk for future exacerbation. Additional studies are needed to determine whether latent classes correspond to meaningful phenotypes for the purpose of personalized treatment.

Keywords

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

INTRODUCTION

Asthma currently affects 8.4% of all children in the United States.[1] Yet despite widespread availability of inhaled corticosteroids (ICSs) and standardization of asthma treatment guidelines, asthma control remains suboptimal in most children.[2,3] Consequently, more than

50% of all children with asthma experience at least 1 exacerbation each year,[1] including children with nonsevere asthma who have less troublesome day-to-day symptoms[4] and normal lung function.[5] The morbidity from exacerbations of asthma in children is significant and contributes to missed school/work days,[6–8] impaired caregiver functional status,[9] and a growing personal[10] and societal[11] economic burden estimated at more than $80 billion annually.[12]

Although the factors responsible for poor asthma control and asthma exacerbations in children are complex,[13] there is also growing recognition that children with asthma are a heterogeneous group, with many underlying biological pathways or "endotypes" that contribute to differing phenotypic disease presentations, differential responses to asthma treatments, and varied clinical outcomes.[14–21] Mandates for "personalized" versus "one size fits all" treatment of children with asthma have therefore been issued,[22] but several challenges persist. First, compared with adults, phenotypes of childhood asthma are understudied and still unclear. There are also notable differences in the clinical manifestations of asthma between adults and children such as the magnitude of lung function deficits[23] and exacerbation frequency[24] that prohibit extrapolation of phenotypic findings between age groups. Second, most previous phenotypic analyses in children have focused on difficult-to-treat or severe asthma populations,[25] which are not the predominant group encountered in most clinical practice settings. Therefore, phenotypic characterization of children with asthma is still limited and it remains difficult to predict which children with asthma are at the highest risk for poor outcomes (such as recurrent exacerbations) across the spectrum of disease severity.

Given these knowledge gaps, we applied latent class analysis (LCA) to a cohort of more than 2500 well-characterized children with mild to moderate persistent asthma aged 5 to 18 years with documented adherence to asthma controller therapies enrolled in previous National Heart, Lung and Blood Institute asthma network phase 3 clinical trials. The purpose was to (1) identify latent classes and (2) determine whether latent class assignment predicts subsequent lung function abnormalities and exacerbation rate at 12 months of follow-up. We hypothesized that a latent class distinguished by underlying type 2 eosinophilic inflammation and airflow limitation despite nonsevere disease would be identified and would have the lowest lung function and highest exacerbation rate by 1 year of follow-up.

METHODS

LCA was performed on 8 National Heart, Lung and Blood Institute clinical trials involving 2593 children with mild to moderate asthma aged 5 to 18 years: the Childhood Asthma Management Research Program (CAMP, NCT00000575),[26,27] Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (no NCT),[28–30] Pediatric Asthma Controller Trial (NCT00272506),[31,32] Best Add-On Therapy Giving Effective Response (NCT00395304),[20,33] Treating Children to Prevent Exacerbations of Asthma (NCT00394329),[34] Step-Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (NCT02066129),[35] Best African American Response to Asthma Drugs (NCT01967173),[21] and Steroids in Eosinophil Negative Asthma (NCT02066298).[36] Details

of these studies are presented in Table E1 in this article's Online Repository at www.jaci-inpractice. org. All studies were overseen by dedicated quality control committees and data coordinating centers and used similar intake questionnaires. Paper case report forms were entered electronically and mailed to the data coordinating center for review and accuracy upon completion. Each center maintained staff and site certification and used the same manual of procedures for characterization. Written informed consent was obtained from all caregivers, and written or verbal assent was obtained from all participants for trial participation and secondary analyses. CAMP data were obtained from BioLINCC through a material transfer agreement (A.M.F.). Other study data were used with the permission of network principal investigators (coauthors).

Participants

All participants with persistent asthma with documented adherence to paper or electronic diaries were included in this analysis (N = 2593). Thresholds for acceptable adherence were defined as more than 75% to 80% of expected diaries completed during the study run-in periods. In each study, asthma was physician-diagnosed and was confirmed by symptom thresholds (ie, symptoms more than twice weekly off therapy or well controlled with daily asthma therapy). Most of the studies also had 12% or more absolute reversibility in the FEV_1 after bronchodilator administration or airway hyper-reponsiveness to methacholine (ie, provocative concentration causing a 20% decline in FEV_1 [PC_{20}] <12.5 or <16 mg/mL) as criteria for study entry.

Participant characterization procedures

Participants completed questionnaires pertaining to demographic characteristics, family history, child allergy and respiratory symptoms, and treatment of symptoms including medications and health care utilization. A subset of participants (n = 1551 [59.8%]) also completed the Asthma Control Test (ACT)[37,38] and the 6-question Asthma Control Questionnaire (ACQ).[39] Peripheral blood eosinophils and total serum IgE were quantified in clinical laboratories. Spirometry with bronchodilator reversibility was performed at baseline and after receipt of 2 to 4 inhalations of albuterol sulfate (90 mg per actuation) delivered by metered-dose inhaler. Spirometry was conducted according to published standards at the time of the test.[40] FEV_1, forced vital capacity (FVC), and the ratio of FEV_1/FVC were recorded from the best of 3 attempts. Sensitization was assessed by skin testing or specific IgE testing for the following aeroallergens common to each study: dust mite (mix), cockroach (mix), cat dander, dog dander, mold (mix), grass (mix), tree (mix), and weed (mix). Skin testing was performed using the Multi-test II (Lincoln Diagnostics, Decatur, Ill) prick technique. Test results were considered positive if the prick resulted in a wheal with a mean diameter (mean of maximum and 90° midpoint diameters) that was at least 3 mm greater than that produced by the saline control. Specific IgE levels were quantified at centralized laboratories. Tests with levels more than 0.34 IU/mL were considered positive. Exhaled nitric oxide was also measured by online methods in a subset of participants.[41]

Variable selection and handling

Variable selection is detailed in the Online Repository and in Table E2 in this article's Online Repository at www.jaci-inpractice. org. Dichotomous variables included (1) age

group (6–11 vs >11 years), (2) sex, (3) hospitalization in the past year, (4) intensive care unit admission for asthma (ever), (5) blood eosinophil group (<4% or ≥4%), (6) sibling with asthma, (7) parent with asthma, (8) sensitization to pets, (9) sensitization to other aeroallergens, (10) indoor pet, and (11) tobacco smoke exposure. Categorical variables included (1) race (white/Caucasian, black/African American, and other/mixed), (2) number of unscheduled visits for asthma in the past year (0, 1, ≥ ≥2), (3) prebronchodilator FEV_1 *z* score (< −1.64, −1.64 to 0, >0), (4) prebronchodilator FEV_1/FVC *z* score (< −1.64, −1.64 to 0, >0), (5) postbronchodilator FEV_1 *z* score (< −1.64, −1.64 to 0, >0), (6) IgE level in kU/L (<100, 100–500, 500–1000, >1000), (7) body mass index (BMI) percentile (<60%, 60% −90%, >90%), and (8) asthma control quartile (lowest = worst control; highest = control) obtained from either the ACT or the best ACQ score. Lung function data were expressed as *z* scores and interpreted according to lower limit of normal (LLN) values established by the Global Lung Function Initiative prediction equations.[42]

Outcomes

Outcomes included lung function (pre- and postbronchodilator FEV_1, FVC, FEV_1/FVC) and the annualized rate of exacerbation at the end of follow-up. For the CAMP study, outcomes were assessed over the first year only. The definition of exacerbation used was proposed by a National Institutes of Health Working Group[43] and was defined as escalation of symptoms resulting in treatment with systemic corticosteroids (ie, dexamethasone, prednisone, or prednisolone equivalent to 2 mg/kg/d for 2 days followed by 1 mg/kg/d for 2 days). Two courses of systemic corticosteroids had to be separated by at least 1 week to count as 2 exacerbations.

Latent class analyses

LCA was performed with SAS software version 9.4 (SAS Institute, Cary, NC) using the PROC LCA procedure[44] and a maximum likelihood model algorithm that allows missing data under the missing completely at random assumption, which was tested and evaluated. Models of 1 to 8 latent classes were repeatedly fitted with the number of latent classes in a stepwise fashion. Models were freely estimated with no specified parameter restrictions. Conditional probabilities (probability of selected characteristics within a class) and posterior probabilities (probability of latent class membership for each participant) were calculated. Best fit was assessed by comparison of the bootstrapped *P* values for the likelihood ratio test and the Bayesian information criterion test. Each participant was assigned to the latent class with the highest membership probability.

Outcome analyses

End of follow-up lung function and the annualized rate of exacerbations were assessed in each latent class irrespective of treatment assignment with generalized linear models with adjustment for study. Exploratory analyses were performed on parallel-arm treatment studies (CAMP, Pediatric Asthma Controller Trial, Treating Children to Prevent Exacerbations of Asthma, and Step-Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations) with asthma treatment assignment as follows: (1) placebo, (2) other asthma medication (leukotriene receptor antagonist), nedocromil, or rescue ICS), or (3) daily ICS. Analyses used a significance level of .05 without adjustment for multiple testing.

RESULTS

A total of 2593 children were included in the LCA. Evaluations were done for 4-, 5-, and 6-class solutions; the 5-class solution was chosen as best fit and yielded a high class membership probability for all participants with acceptable fit statistics (adjusted Bayesian information criterion: 26,930.16; entropy: 0.88). The distribution of study variables by latent class assignment is presented in Table I. By design, each LCA variable was significantly different between latent classes. The distribution of studies within each latent class is shown in Figure 1. Other features of the study participants are presented in Table II. To simplify the discussion, latent classes were assigned a summary label. Key features of the 5 latent classes are detailed herein.

Latent class 1: Multiple sensitization with partially reversible airflow limitation

Latent class 1, titled “multiple sensitization with partially reversible airflow limitation,” included 244 children (9.4%). Children in this latent class were predominantly white/Caucasian males and had the poorest overall asthma control. This class also had the highest proportion of Hispanics. In addition, this class was characterized by multiple sensitization to pets and other aeroallergens, the highest blood eosinophils, and high total serum IgE concentrations, with 36% of children having concentrations more than 1000 kU/L. Forty-one percent of children in this latent class were not receiving controller therapy at study enrollment and 11.5% had been hospitalized for asthma in the previous year. Lung function values were also the lowest in this group, and 100% of children in this class had prebronchodilator FEV_1 *z* scores below the LLN (ie, < −1.64), respectively. Lung function values remained the lowest in this latent class after bronchodilation and 16% of children had postbronchodilator FEV_1 *z* scores below the LLN. Airway hyperresponsiveness to methacholine was also the greatest in this latent class.

Latent class 2: Multiple sensitization with reversible airflow limitation

This was the largest latent class, with 926 children (35.7%), and was titled “multiple sensitization with reversible airflow limitation.” Children in this latent class were similar to those in latent class 1 with regard to demographic characteristics, sensitization patterns, and markers of type 2 inflammation, but had fewer historical severe exacerbations requiring hospitalization and lesser exposure to tobacco smoke. All children in this latent class had baseline FEV_1 *z* scores above the LLN (ie, > −1.64). Lung function values improved further with albuterol in nearly all children and only 0.8% of children had postbronchodilator FEV_1 *z* scores below the LLN.

Latent class 3: Lesser sensitization with reversible airflow limitation

Latent class 3 included 315 children (12.1%) and was titled “lesser sensitization with reversible airflow limitation.” This latent class included more females and more obese children with fewer historical severe exacerbations requiring hospitalization than classes 1 and 2. Tobacco smoke exposure was also the greatest in this latent class, and most of the children had either no sensitization (66%) or monosensitization (22%). Blood eosinophil percentages and total serum IgE concentrations were also low in this group compared with those in classes 1 and 2. Approximately 13% of children in this class had prebronchodilator

FEV_1 *z* scores below the LLN, respectively. Lung function values improved significantly with albuterol in most of the children and only 4.2% of children had postbronchodilator FEV_1 *z* scores below the LLN.

Latent class 4: Multiple sensitization with normal lung function

Latent class 4 included 718 children (27.6%) and was titled "multiple sensitization with normal lung function." This class was similar to classes 1 and 2 but included more nonwhite/non-Caucasian children with higher BMI percentiles. Like classes 1 and 2, this class was characterized by multiple sensitization, elevated blood eosinophils, and elevated IgE, but had a higher proportion of children (71.2%) who were treated with asthma controller medications. Lung function values were also higher in this class compared with those in classes 1 and 2, and 100% of children had baseline FEV_1 *z* scores above the LLN.

Latent class 5: Lesser sensitization with normal lung function

Latent class 5 included 390 children (15.0%) and was titled "lesser sensitization with normal lung function." This latent class was younger and included the highest proportion of females and obese children with BMI percentiles of 95% or higher. Asthma control was also the greatest in this group, although 18.6% of children still had asthma control values in the lowest (ie, poorest) quartile. Sensitization patterns were similar to those in latent class 3, with most of the children having either no sensitization (63%) or monosensitization (18%) to allergens. Blood eosinophils and total serum IgE concentrations were also low and were similar to concentrations observed in latent class 3. However, lung function was higher than in class 3, and FEV_1 *z* scores were above the LLN in 100% of children in this class. Airway hyperresponsiveness to methacholine was still noted in this class, but methacholine PC_{20} values were higher than in the other classes.

Sensitivity analyses

Given that the asthma control variable had a relatively large amount of missing data, sensitivity analyses were performed excluding this variable from the LCA. As presented in Table E3 in this article's Online Repository at www.jaci-inpractice.org, exclusion of the asthma control variable did not significantly change the results.

Outcome analyses

Days to end of follow-up were 316 ± 95 for all participants (class 1, 328 ± 97; class 2, 322 ± 91; class 3, 308 ± 104; class 4, 316 ± 91; class 5, 302 ± 103). Pre- and postbronchodilator lung function outcomes are presented in Table III. At the end of follow-up, prebronchodilator lung function values improved in each latent class compared with study entry, although children in latent class 1 still had the highest proportion of values below the LLN. After bronchodilator administration, lung function values remained the lowest in class 1. In exploratory analyses, the change in FEV_1 at the end of follow-up was not due to asthma treatment (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Study treatment assignment also did not change the proportion of participants with prebronchodilator FEV_1 or FEV_1/FVC *z* scores below the LLN in class 1 or 3 (Figure 2). However, children in class 2 had a greater lung function response with any

asthma medication (ie, ICS or other asthma controller treatments such as leukotriene receptor antagonist, nedocromil, or rescue ICS), whereas children in classes 4 and 5 had greater lung function responses with ICSs (Figure 2).

Exacerbations occurred by the end of follow-up in 41.3% of participants (class 1, 52.5%; class 2, 41.6%; class 3, 36.8%; class 4, 43.0%; class 5, 34.1%; $P < .001$). Latent class 1, compared with the other classes, had more cumulative exacerbations and a significantly higher annualized exacerbation rate (class 1, 1.30 ± 0.12; class 2, 0.90 ± 0.05; class 3, 0.87 ± 0.08; class 4,0.87 ± 0.05; class 5, 0.71 ± 0.07; $P < .001$) (Figure 3). In exploratory analyses, ICS treatment significantly reduced exacerbation occurrence and the annualized exacerbation rate by the end of follow-up in classes 1, 2, and 4 but not in classes 3 and 5 (Figure 4).

DISCUSSION

Although it is well recognized that children with asthma are a heterogeneous group, personalized medicine for these children is not common practice. Instead, treatment guidelines for children with asthma are still based on a “one size fits all” approach, with ICS as the cornerstone of therapy, in part due to limited understanding of pediatric phenotypes and their association with clinical outcomes. We therefore used LCA to uncover previously unobservable patterns in a well-characterized, large study population of children with mild to moderate persistent asthma enrolled in clinical trials. LCA has foundations in the social sciences and is particularly useful for identifying class membership among participants with multivariate categorical data. Although multivariable regression analyses could have been used to identify factors associated with 1-year asthma outcomes in this population, the present study sought to extend the existing body of hypothesis-directed literature through consideration of multiple variables simultaneously. However, we recognize that this approach is exploratory and hypothesis-generating; thus, the results should be interpreted in the context of clinical and biological plausibility.

Using LCA, we identified 5 latent classes of children with mild to moderate asthma who differed primarily in sensitization and lung function patterns. Consistent with our hypothesis, we identified a latent class with markers of type 2 inflammation and persistent airflow limitation (despite having mild to moderate disease) who also had the highest exacerbation rate by 1 year of follow-up. However, exacerbations were noted in each of the identified latent classes, albeit to a lesser extent. We therefore cannot conclude that our latent classes reflect distinct phenotypes of mild to moderate asthma in children, but these latent classes do provide some insight into potential (and differing) mechanisms of asthma in children that could be probed in future analyses.

Our findings also have plausibility and are supported by the results of other studies. Previous unsupervised analyses of children with severe asthma have also identified “clusters” with more prominent type 2 inflammatory markers (ie, sensitization and eosinophils) and features of greater asthma severity, including greater airflow limitation.[45–48] Other independent cluster analyses of children with nonsevere asthma or children across the severity spectrum have noted similar results.[49–53] However, few studies have attempted to validate the utility of

the identified groupings with prospective outcomes. Although 1 study of predominantly African American, inner-city children across the asthma severity spectrum identified a cluster with prominent type 2 inflammation, multiple aeroallergen sensitization, significant airflow limitation, and the highest proportion of exacerbations requiring treatment with systemic corticosteroids, exacerbations were included as a variable in the clustering algorithm and were not assessed independently of cluster assignment.[52] Schatz et al[46] attempted to validate their cluster assignments in children aged 6 to 11 years with difficult-to-treat or severe asthma enrolled in the Natural History of Asthma: Outcomes and Treatment Regimens study, but found no association with exacerbation occurrence, asthma control, or quality of life at month 12. However, the clustering algorithm used in that study included only 8 variables, which may have been inadequate to discriminate subtle differences between groups. Furthermore, the percentage of children with exacerbations by 12 months was also relatively high in each cluster given the difficult-to-treat nature of the patients and ranged from 37% to 53%.[46] Most relevant to the present study, a previous cluster analysis of the CAMP study (which excludes severe asthma) involving 18 variables identified a highly atopic cluster of children with airflow limitation that also had the shortest time to systemic corticosteroids for asthma exacerbation over 4 years of follow-up.[50] However, in contrast to the present study, exacerbation rates and follow-up lung function data were not reported in that analysis.[43]

Although our observed associations between multiple sensitization, greater airflow limitation, and exacerbations are not particularly novel, the magnitude of airflow limitation and previous health care utilization observed in this population of children with mild to moderate asthma is somewhat surprising. However, a recent review of asthma-related deaths in the United Kingdom found that only 39% of asthma deaths occurred in patients with severe asthma.[54] Instead, 9% and 46% of deaths occurred in patients treated for mild and moderate asthma, respectively, although that report also concluded that most of these nonsevere patients likely had poorly controlled under-treated asthma as opposed to truly mild or moderate disease.[54] Although it is certainly possible that the inclusion criteria for our included studies were insufficient in capturing mild to moderate asthma, it is also recognized that, as a construct, asthma severity reflects the level of treatment required to control symptoms and exacerbations at the present time[55] and is not a static feature.[56] Indeed, other analyses of children with mild to moderate asthma in the CAMP study noted abnormal patterns of lung function growth in 75% of children, including markedly impaired lung function growth in 11% of participants who subsequently met criteria for advanced chronic obstructive pulmonary disease.[23]

This study has several strengths, including the large sample size of diverse and representative children across the United States. Because variable prescription of (and adherence to) asthma controller medications such as ICS can complicate outcome assessment, our focus on clinical trials with criteria for protocol adherence also increases the likelihood that children were compliant with prescribed therapies. The close follow-up and standardization of care in these clinical trials also helped to mitigate the impact of limited access to primary care, which is an important determinant of asthma outcomes in general populations.[57] The clinical trials included in this analysis also assessed asthma exacerbations in a standardized way and each used a consistent definition of exacerbation in accordance

with current recommendations for asthma outcomes research.[43] This is also one of the few studies intent on asthma phenotype discovery in children that attempted to validate outcomes prospectively.

Nonetheless, there are some limitations with our approach. First, we acknowledge that model selection for LCA can be subjective. Although LCA models do allow for statistical comparisons of model fit, the outputs (and patient groupings) are ultimately dependent on the variables that are entered and the study population. Indeed, a study of different unsupervised statistical learning methods found that different variable sets led to inconsistent groupings of asthma that were not necessarily associated with severity.[58] There are also no criterion standard variables for the purpose of phenotype discovery. For example, one study affirmed the importance of medication usage, current symptoms, lung function, parental asthma, BMI, and age of asthma onset in the prediction asthma outcomes,[58] whereas another found that only 4 features identified by clinical experts (ie, age of onset, allergic sensitization, severity, and recent exacerbations) were meaningful.[49] Because many of the variables used in our LCA model were assessed only at study entry, we were also unable to assess the temporal stability of the identified latent classes and transition over time. The relatively short, 1-year follow-up period and the inclusion of both school-age and adolescent participants were also insufficient for examination of the role of puberty and sex hormones, which have been shown to impact airway responsiveness and asthma prevalence on a population level.[59] The study interventions may have also impacted the outcome measures selected for this analysis. For example, it is possible that the 12-month observations reflect suboptimal treatment of certain subsets of participants. Furthermore, the CAMP cohort may have impacted the findings because it represented most of the study population. There are also potential limitations with the generalization of our findings. Although most of the children in the present study were adherent, poor adherence to controller medications is prevalent in general populations.[13,60] Furthermore, economic hardships, limited access to primary care,[57] and ongoing exposures to environmental allergens and irritants[61–63] are known factors associated with poorer asthma outcomes in general populations of children that may not have been well represented in this study.

CONCLUSIONS

Using LCA, we identified 5 latent classes of children with mild to moderate asthma that differed with regard to multiple variables, most notably allergic sensitization and other features of type 2 inflammation and lung function patterns. Although exacerbations were noted in each latent class, exacerbation rates were the highest in children with multiple sensitization and partially reversible airflow limitation, suggestive of more advanced disease. These lung function deficits persisted at 1 year despite intervention with asthma controller medications. Sensitization and lung function measures in children with mild to moderate asthma may therefore be useful for predicting future risk in clinical settings. However, additional studies are needed to determine whether our identified latent classes correspond to meaningful phenotypes for the purpose of personalized treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
BMI	Body mass index
CAMP	Childhood Asthma Management Research Program
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
LCA	Latent class analysis
LLN	Lower limit of normal

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What is already known about this topic?

In contrast to children with difficult-to-treat or severe asthma, phenotypic characterization of children with mild to moderate persistent asthma is still limited and it remains unclear which of these children are at the highest risk for poor outcomes.

What does this article add to our knowledge?

Five latent classes were identified. At 1 year, lung function deficits and exacerbations were the greatest in the latent class with multiple sensitization and partially reversible airflow limitation despite intervention with asthma controller therapy.

How does this study impact current management guidelines?

Latent class analysis is useful for identifying risk factors in children with mild to moderate asthma. Children with multiple sensitization and partially reversible airflow limitation are a particularly vulnerable group that may warrant more aggressive treatment.

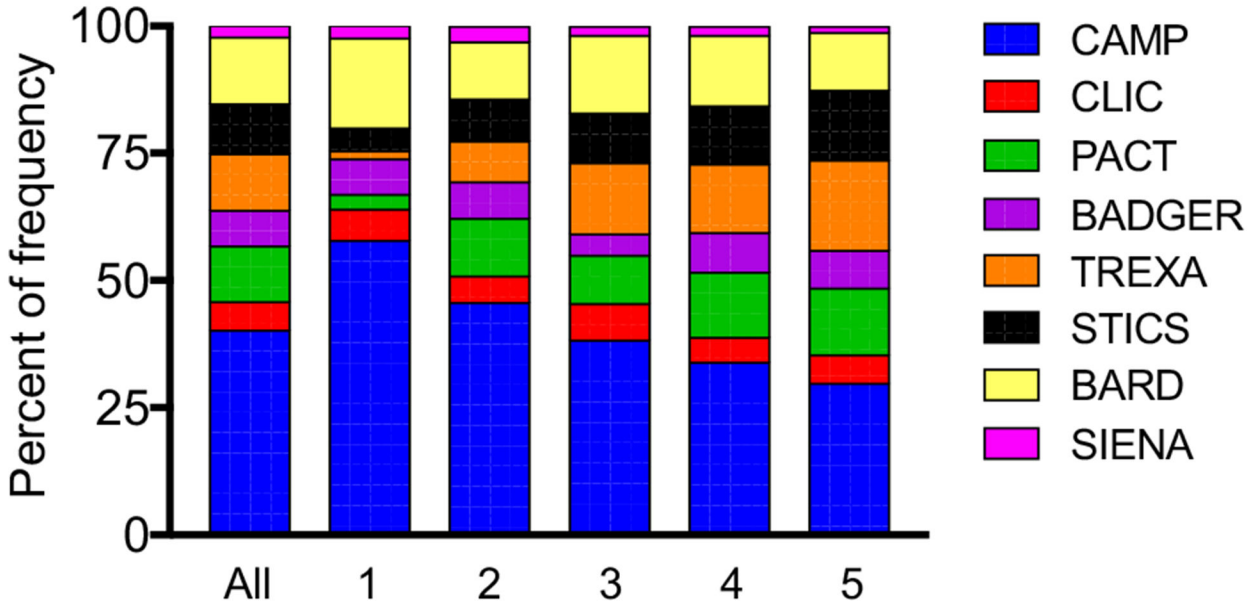

FIGURE 1.

Distribution of studies within each latent class. *BADGER*, Best Add-On Therapy Giving Effective Response; *BARD*, Best African American Response to Asthma Drugs; *CAMP*, Childhood Asthma Management Research Program; *CLIC*, Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid; *PACT*, Pediatric Asthma Controller Trial; *SIENA*, Steroids in Eosinophil Negative Asthma; *STICS*, Step-Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations; *TREXA*, Treating Children to Prevent Exacerbations of Asthma.

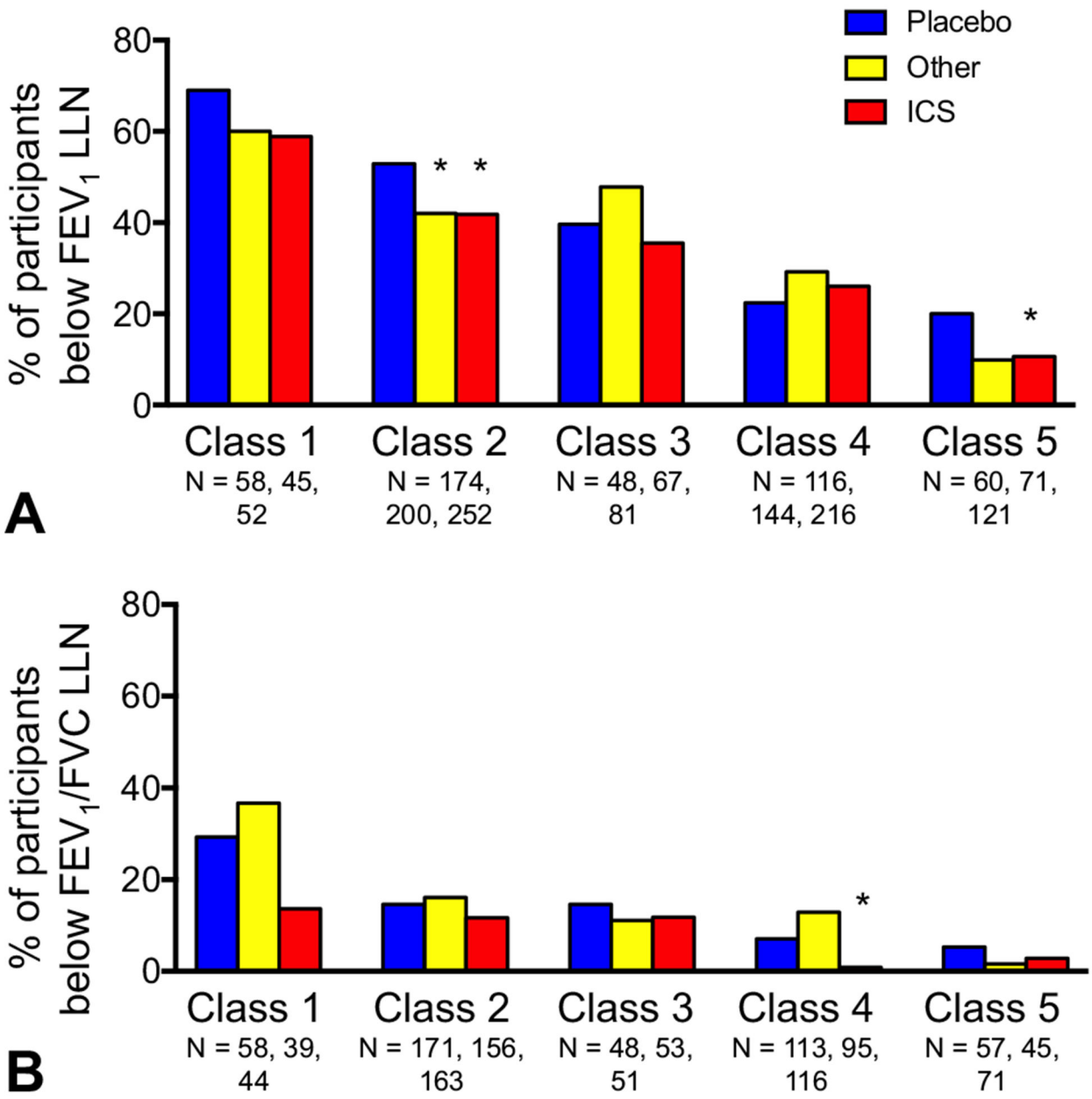

FIGURE 2.

Participants with (**A**) FEV_1 and (**B**) FEV_1/FVC below the LLN at the end of follow-up, stratified by treatment assignment and latent class 1 (multiple sensitization with partially reversible airflow limitation), 2 (multiple sensitization with reversible airflow limitation), 3 (lesser sensitization with reversible airflow limitation), 4 (multiple sensitization with normal lung function), and 5 (lesser sensitization with normal lung function). $*P<.05$ vs placebo.

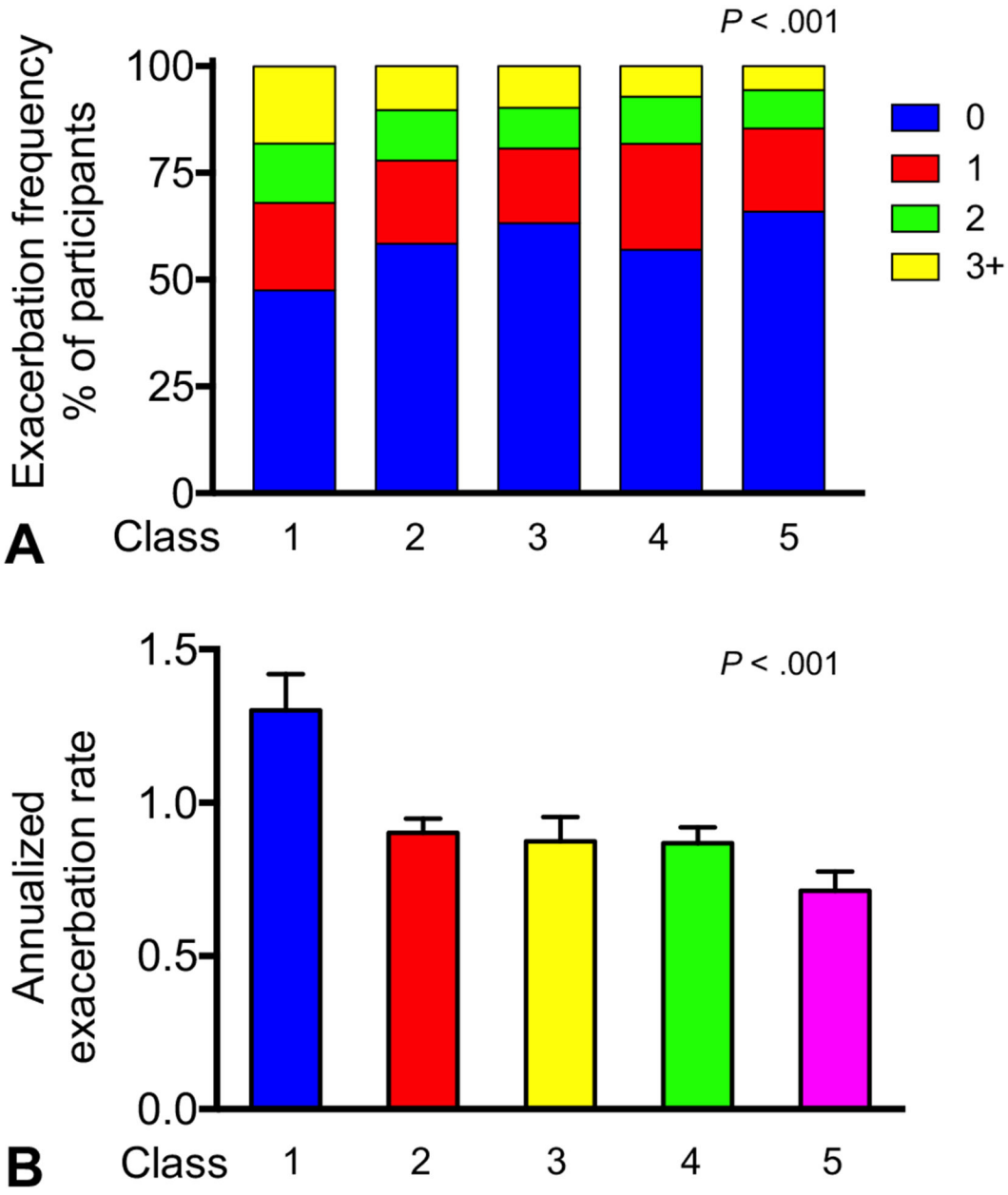

FIGURE 3.

(**A**) Exacerbation frequency and (**B**) annualized rate of exacerbations (mean ± SEM) at the end of follow-up in latent classes 1 (multiple sensitization with partially reversible airflow limitation), 2 (multiple sensitization with reversible airflow limitation), 3 (lesser sensitization with reversible airflow limitation), 4 (multiple sensitization with normal lung function), and 5 (lesser sensitization with normal lung function).

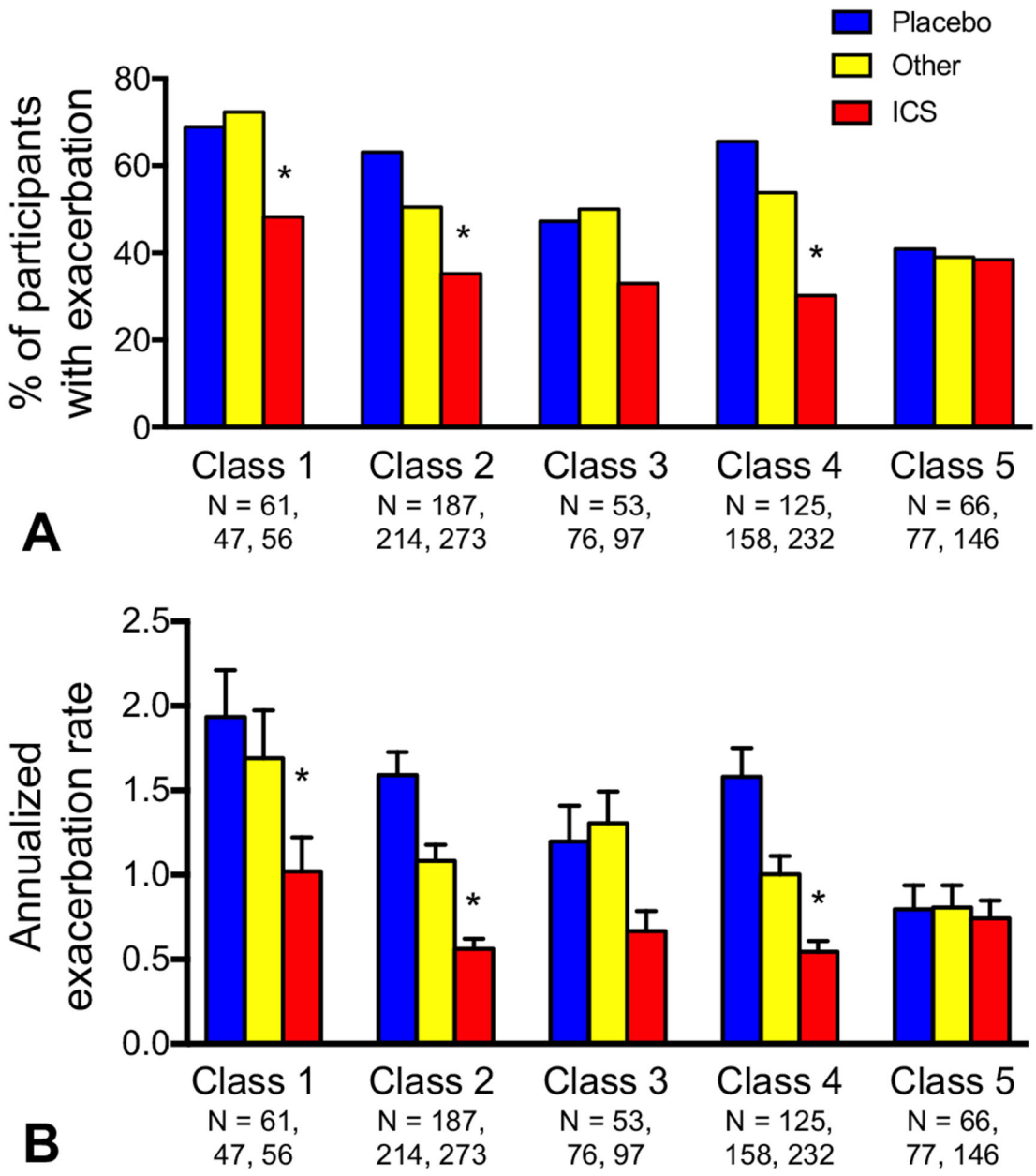

FIGURE 4.

(**A**) Exacerbation occurrence and (**B**) annualized exacerbation rate at the end of follow-up, stratified by treatment assignment and latent class 1 (multiple sensitization with partially reversible airflow limitation), 2 (multiple sensitization with reversible airflow limitation), 3 (lesser sensitization with reversible airflow limitation), 4 (multiple sensitization with normal lung function), and 5 (lesser sensitization with normal lung function). **P* < .05 vs placebo.

TABLE I.

Distribution of study variables by latent class assignment

Feature	All participants	Class 1 (multiple sensitization with partially reversible airflow limitation)	Class 2 (multiple sensitization with reversible airflow limitation)	Class 3 (lesser sensitization with reversible airflow limitation)	Class 4 (multiple sensitization with normal lung function)	Class 5 (lesser sensitization with normal lung function)
N	2593	244	926	315	718	390
Age group	9.3 (7.4, 11.4)	10.3 (8.0, 11.8)	9.9 (8.0, 11.9)	8.9 (7.0, 11.1)	8.9 (7.4, 10.9)	8.2 (7.0, 10.2)
6–11 y	2108 (81.3)	189 (77.5)	708 (76.5)	257 (81.6)	610 (85.0)	344 (88.2)
>11 y	485 (18.7)	55 (22.5)	218 (23.5)	58 (18.4)	108 (15.0)	46 (11.8)
Sex						
Male	1554 (59.9)	156 (63.9)	587 (63.4)	168 (53.3)	459 (63.9)	184 (47.2)
Female	1039 (40.1)	88 (36.1)	339 (36.6)	147 (46.7)	259 (36.1)	206 (52.8)
Race						
White/Caucasian	1637 (63.1)	164 (67.2)	600 (64.8)	203 (64.4)	399 (55.6)	271 (69.5)
Black/African American	692 (26.7)	72 (29.5)	238 (25.7)	90 (28.6)	216 (30.1)	76 (19.5)
Other/mixed	264 (10.2)	8 (3.3)	88 (9.5)	22 (7)	103 (14.3)	43 (11.0)
BMI percentile	74 (47, 92)	58 (34, 86)	71 (44, 91)	76 (46, 94)	77 (53, 94)	79 (54, 94)
<60%	917 (35.6)	125 (51.2)	348 (38.1)	110 (34.9)	221 (30.9)	113 (29.4)
60%−90%	893 (34.7)	70 (28.7)	325 (35.6)	95 (30.2)	261 (36.5)	142 (37.0)
>90%	763 (29.7)	49 (20.1)	241 (26.4)	110 (34.9)	234 (32.7)	129 (33.6)
Parent with asthma	1220 (47.0)	134 (54.9)	425 (45.9)	134 (42.5)	337 (46.9)	190 (48.7)
Sibling with asthma	1080 (41.7)	85 (34.8)	376 (40.6)	155 (49.2)	294 (40.9)	170 (43.6)
Unscheduled asthma visits						
0 visits (past year)	493 (19.0)	41 (16.8)	175 (18.9)	72 (22.9)	134 (18.7)	71 (18.2)
1 visit (past year)	422 (16.3)	42 (17.2)	148 (16.0)	37 (11.7)	137 (19.1)	58 (14.9)
≥2 visits (past year)	1678 (64.7)	161 (66.0)	603 (65.1)	206 (65.4)	447 (62.3)	261 (66.9)
Hospitalization for asthma (ever)	173 (6.7)	28 (11.5)	64 (6.9)	7 (2.2)	68 (9.5)	6 (1.5)
Intensive care unit admission for asthma (ever)	156 (6.0)	21 (8.6)	60 (6.5)	14 (4.4)	47 (6.5)	14 (3.6)
Indoor pet	1208 (46.6)	109 (44.7)	411 (44.4)	163 (51.7)	305 (42.5)	22 (56.4)
Indoor cat	479 (18.5)	60 (24.6)	158 (17.1)	71 (22.5)	114 (15.9)	76 (19.5)
Indoor dog	952 (36.7)	74 (30.3)	329 (25.5)	120 (38.1)	238 (33.1)	191 (49.0)

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Feature	All participants	Class 1 (multiple sensitization with partially reversible airflow limitation)	Class 2 (multiple sensitization with reversible airflow limitation)	Class 3 (lesser sensitization with reversible airflow limitation)	Class 4 (multiple sensitization with normal lung function)	Class 5 (lesser sensitization with normal lung function)
Tobacco smoke exposure	789 (30.4)	81 (33.2)	243 (26.2)	121 (38.4)	232 (32.3)	112 (28.7)
Blood eosinophils (%)	5.0 (2.4, 8.0)	7.0 (4.6, 10.0)	6.0 (4.0, 9.0)	2.0 (1.1, 3.8)	5.3 (3.4, 8.1)	2.0 (1.0, 3.0)
Missing	54 (2.1)	6 (2.5)	16 (1.7)	6 (1.9)	20 (2.8)	6 (1.5)
<4%	993 (39.1)	36 (15.1)	216 (23.7)	234 (75.7)	185 (26.5)	322 (83.9)
≥4%	1546 (60.9)	202 (84.9)	694 (76.3)	75 (24.3)	513 (73.5)	62 (16.1)
IgE (kU/L)	210 (66, 516)	347 (208, 556)	363 (182, 779)	41 (17, 70)	371 (190, 744)	45 (15, 83)
Missing	469 (18.1)	26 (10.7)	168 (18.1)	57 (18.1)	143 (7.9)	75 (19.2)
<100	508 (23.9)	6 (2.8)	24 (3.2)	194 (75.2)	29 (5.0)	255 (81.0)
100–500	820 (38.6)	87 (39.9)	349 (46.0)	61 (23.6)	266 (46.3)	57 (18.1)
500–1000	345 (16.2)	46 (21.1)	162 (21.4)	3 (1.2)	131 (22.8)	3 (1.0)
>1000	451 (21.2)	79 (36.2)	223 (29.4)	—	149 (25.9)	—
Sensitization to pets	1409 (54.3)	180 (74.4)	663 (72.4)	21 (6.7)	509 (72.6)	36 (9.4)
Missing	38 (1.5)	2 (0.8)	10(1.1)	1 (0.3)	17 (2.4)	8 (2.1)
Sensitization to cat	1263 (48.7)	163 (66.8)	595 (64.3)	17 (5.4)	455 (63.4)	33 (8.5)
Sensitization to dog	738 (28.5)	104 (42.6)	346 (37.4)	7 (2.2)	270 (37.6)	11 (2.8)
Sensitization to other aeroallergens	1888 (72.8)	223 (92.1)	840 (91.6)	79 (25.2)	645 (92.0)	101 (26.4)
Missing	37 (1.4)	2 (0.8)	9 (1.0)	1 (0.3)	17 (2.4)	8 (2.1)
Prebronchodilator FEV_1 *z* score	−0.2 (−1.0, 0.5)	−2.1 (−2.7, −1.8)	−0.7 (−1.1, −0.3)	−0.8 (−1.3, −0.4)	0.7 (0.3, 1.2)	0.6 (0.2, 1.1)
Missing	21 (0.8)	—	13 (1.4)	—	2 (0.3)	6 (1.5)
<−1.64	284 (11.0)	244 (100)	—	40 (12.7)	—	—
−1.64 to 0	1216 (46.9)	—	913 (100)	273 (86.7)	—	30 (7.8)
>0	1072 (41.3)	—	—	2 (0.6)	716 (100)	354 (92.2)
Prebronchodilator FEV_1/FVC *z* score	−0.2 (−1.9, −0.4)	−0.4 (−2.9, −1.8)	−0.5 (−2.1, −0.8)	−1.4 (−2.0, −0.8)	−0.8 (−1.4, −0.2)	−0.4 (−1.0, −0.2)
Missing	21 (0.8)	—	13 (1.4)	—	2 (0.3)	6 (1.5)
<−1.64	866 (33.4)	197 (80.7)	399 (43.7)	134 (42.5)	119 (16.6)	17 (4.4)
−1.64 to 0	1346 (51.9)	40 (16.4)	444 (48.6)	156 (49.5)	445 (62.2)	261 (68)
>0	360 (13.9)	7 (2.9)	70 (7.7)	25 (7.9)	152 (21.2)	106 (27.6)
Postbronchodilator FEV_1 *z* score	0.5 (−0.3, 1.2)	−1.0 (−1.5, −0.4)	0.1 (−0.4, 0.6)	−0.3 (−0.8, 0.1)	1.3 (0.9, 1.8)	1.1 (0.7, 1.6)

Feature	All participants	Class 1 (multiple sensitization with partially reversible airflow limitation)	Class 2 (multiple sensitization with reversible airflow limitation)	Class 3 (lesser sensitization with reversible airflow limitation)	Class 4 (multiple sensitization with normal lung function)	Class 5 (lesser sensitization with normal lung function)
Missing	52 (2.0)	3 (1.2)	23 (2.4)	7 (2.2)	9 (1.3)	10 (2.6)
<−1.64	58 (2.2)	38 (15.8)	7 (0.8)	13 (4.2)	—	—
−1.64 to 0	756 (29.2)	176 (73.0)	361 (40.0)	207 (67.2)	8 (1.1)	4 (1.1)
>0	1727 (66.6)	27 (11.2)	535 (59.2)	88 (28.6)	701 (98.9)	376 (98.9)
Asthma control quartile						
Missing	1042 (40.2)	141 (57.8)	422 (45.6)	120 (38.1)	243 (33.8)	116 (29.7)
Lowest (worst control)	404 (15.6)	36 (35.0)	138 (27.4)	42 (21.5)	137 (28.8)	51 (18.6)
Low	371 (14.3)	31 (30.1)	130 (25.8)	39 (20.0)	111 (23.4)	60 (21.9)
Higher	377 (14.5)	21 (20.4)	116 (23.0)	58 (29.7)	100 (21.1)	82 (29.9)
Highest (best control)	399 (15.4)	15 (14.6)	120 (23.8)	56 (28.7)	127 (26.7)	81 (29.6)

Note. By design, all variables were significantly different between latent classes, so *P* values are not shown. Data represent the median (25th, 95th percentile) or the number of participants (%).

TABLE II.

Other features of the participants

Feature	Class 1 (multiple sensitization with partially reversible airflow limitation)	Class 2 (multiple sensitization with reversible airflow limitation)	Class 3 (lesser sensitization with reversible airflow limitation)	Class 4 (multiple sensitization with normal lung function)	Class 5 (lesser sensitization with normal lung function)	*P* value
N	244	926	315	718	390	
Asthma symptom duration (y)	6.9 (4.9, 9.7)	6.7 (4.5, 9.2)	6.4 (4.6, 8.5)	6.2 (4.1, 8.1)	6.1 (4.1, 7.8)	<.001
Hispanic ethnicity	52 (21.3)	155 (16.7)	38 (12.1)	81 (11.3)	39 (10.0)	<.001
Obesity (BMI ≥95%)	244 (13.5)	926 (17.7)	315 (23.8)	718 (23.4)	390 (24.9)	<.001
Parent with allergies	149 (61.1)	571 (61.7)	181 (57.5)	446 (62.1)	235 (60.3)	.681
Sibling with allergies	86 (35.2)	396 (42.8)	135 (42.9)	322 (44.8)	160 (41.0)	.123
Physician-diagnosed eczema	80 (32.8)	366 (39.5)	90 (28.6)	323 (45.0)	139 (35.6)	<.001
Asthma controller medications						<.001
None	101 (41.4)	367 (39.6)	117 (37.1)	207 (28.8)	114 (29.2)	
Non-ICS	11 (4.5)	29 (3.1)	18 (5.7)	31 (4.3)	19 (4.9)	
ICS monotherapy	81 (33.2)	359 (38.8)	111 (35.2)	324 (45.1)	166 (42.6)	
ICS plus additional	51 (20.9)	171 (18.5)	69 (21.9)	156 (21.7)	91 (23.3)	
Oral corticosteroid bursts, n (past year)						<.001
0	137 (56.1)	556 (60.0)	197 (62.5)	375 (52.2)	231 (59.2)	
1	28 (11.5)	136 (14.7)	54 (17.1)	159 (22.1)	76 (19.5)	
2	46 (18.9)	126 (13.6)	24 (7.6)	106 (14.8)	45 (11.5)	
≥3	33 (13.5)	108 (11.7)	40 (12.7)	78 (10.9)	38 (9.7)	
Sensitization *						<.001
No sensitization	2 (0.8)	14 (1.5)	206 (65.6)		241 (63.1)	
Monosensitization	24 (9.9)	120 (13.1)	69 (22.0)	12 (1.7)	70 (18.3)	
Multiple sensitization	216 (89.3)	783 (85.4)	39 (12.4)	71 (10.1)	71 (18.6)	
Percentage of positive aeroallergens (of 8)	50 (28.6, 75.0)	42.9 (28.6, 71.4)	0 (0, 12.5)	618 (88.2)42.9 (25.0, 62.5)	0 (0, 12.5)	
Blood eosinophils (per microliter) †	476 (305, 722)	425 (260, 637)	151 (89, 248)	426 (230, 594)	146 (82, 229)	<.001
Exhaled nitric oxide (ppb) ‡	13.7 (9.5, 31.5)	15.9 (9.0, 27.7)	9.3 (6.4, 12.9)	13.0 (7.0, 22.5)	7.4 (5.8, 11.0)	<.001
Prebronchodilator §						

Feature	Class 1 (multiple sensitization with partially reversible airflow limitation)	Class 2 (multiple sensitization with reversible airflow limitation)	Class 3 (lesser sensitization with reversible airflow limitation)	Class 4 (multiple sensitization with normal lung function)	Class 5 (lesser sensitization with normal lung function)	*P* value
FVC (% predicted)	89 (83, 96)	103 (96, 109)	99 (93, 105)	116 (109, 123)	111 (105, 118)	<.001
FEV_1 (% predicted)	74 (67, 77)	92 (87, 96)	90 (84, 95)	108 (104, 114)	107 (103, 114)	<.001
FEV_1/FVC (% predicted)	80 (74, 86)	89 (83, 95)	90 (84, 95)	94 (90, 99)	97 (93, 100)	<.001
Postbronchodilator						
FVC (% predicted)[‖]	97 (88, 105)	105 (98, 113)	100 (93, 107)	117 (110, 123)	113 (106, 119)	<.001
FEV_1 (% predicted)[¶]	88 (92, 95)	102 (96, 107)	96 (90, 102)	116 (111, 123)	113 (108, 119)	<.001
FEV_1/FVC (% predicted)[‖]	91 (86, 96)	96 (92, 101)	96 (90, 100)	100 (96, 103)	101 (97, 104)	<.001
Methacholine PC_{20}[#]	0.5 (0.2, 1.0)	0.8 (0.4, 2.3)	1.6 (0.6, 3.0)	1.4 (0.6, 3.9)	2.8 (1.2, 6.3)	<.001

Note. Data represent the median (25th, 95th percentile) or the number of participants (%).

[*] Class 1, n = 242; class 2, n = 917; class 3, n = 314; class 4, n = 701; class 5, n = 382.

[†] Class 1, n = 236; class 2, n = 910; class 3, n = 309; class 4, n = 698; class 5, n = 385.

[‡] Class 1, n = 55; class 2, n = 391; class 3, n = 144; class 4, n = 370; class 5, n = 224.

[§] Class 1, n = 244; class 2, n = 913; class 3, n = 315; class 4, n = 716; class 5, n = 384.

[‖] Class 1, n = 219; class 2, n = 751; class 3, n = 255; class 4, n = 584; class 5, n = 309.

[¶] Class 1, n = 241; class 2, n = 903; class 3, n = 308; class 4, n = 709; class 5, n = 380.

[#] Class 1, n = 205; class 2, n = 821; class 3, n = 258; class 4, n = 636; class 5, n = 322.

TABLE III.

Lung function values in the 5 latent classes at the end of follow-up

Feature	Class 1 (multiple sensitization with partially reversible airflow limitation)	Class 2 (multiple sensitization with reversible airflow limitation)	Class 3 (lesser sensitization with reversible airflow limitation)	Class 4 (multiple sensitization with normal lung function)	Class 5 (lesser sensitization with normal lung function)	*P* value
N (pre-, postbronchodilator)	211, 190	803, 639	258, 206	622, 456	318, 234	
Prebronchodilator						
FVC (% predicted)	111 (102, 121)	116 (107, 124)	115 (106, 122)	127 (119, 137)	124 (116, 134)	<.001
FEV_1 (% predicted)	94 (84, 107)	104 (96, 112)	102 (94, 110)	119 (111, 127)	119 (112, 127)	<.001
z score	−0.4 (−1.3, 0.5)	0.3 (−0.3, 1.0)	0.2 (−0.4, 0.8)	1.6 (0.9, 2.2)	1.6 (1.0, 2.2)	<.001
z score <LLN *	37 (17.5)	36 (4.5)	8 (3.1)	8 (1.3)	—	<.001
FEV_1/FVC (% predicted)	85 (78, 92)	90 (83, 95)	90 (85, 96)	94 (88, 98)	96 (92, 100)	<.001
z score	−1.9 (−2.5, −1.0)	−1.4 (−2.1, −0.8)	−1.3 (−1.9, −0.6)	−0.9 (−1.6, −0.3)	−0.7 (−1.2, −0.1)	<.001
z score <LLN	126 (59.7)	321 (40.0)	101 (39.1)	143 (23.0)	35 (11.0)	<.001
Postbronchodilator						
FVC (% predicted)	115 (107, 125)	118 (109, 127)	115 (107, 123)	128 (119, 137)	125 (117, 133)	<.001
FEV_1 (% predicted)	107 (96, 116)	113 (106, 121)	109 (102, 118)	126 (118, 135)	124 (116, 133)	<.001
z score	0.6 (−0.3, 1.3)	1.1 (0.5, 1.7)	0.7 (0.1, 1.5)	2.1 (1.5, 2.8)	2.0 (1.4, 2.7)	<.001
z score <LLN	10 (5.2)	7 (1.1)	2 (1.0)	3 (0.7)	—	<.001
FEV_1/FVC (% predicted)	93 (87, 99)	96 (91, 100)	96 (91, 99)	99 (94, 102)	99 (96, 103)	<.001
z score	−1.0 (−1.7, −0.2)	−0.6 (−1.3, 0.1)	−0.6 (−1.2, −0.1)	−0.2 (−0.8, 0.4)	−0.1 (−0.6, 0.5)	<.001
z score <LLN	52 (27.4)	85 (13.3)	30 (14.6)	29 (6.4)	7 (3.0)	<.001

Note. Data represent the median (25th, 95th percentile) or the number of participants (%).

* LLN equivalent to a *z* score of ≤1.64.