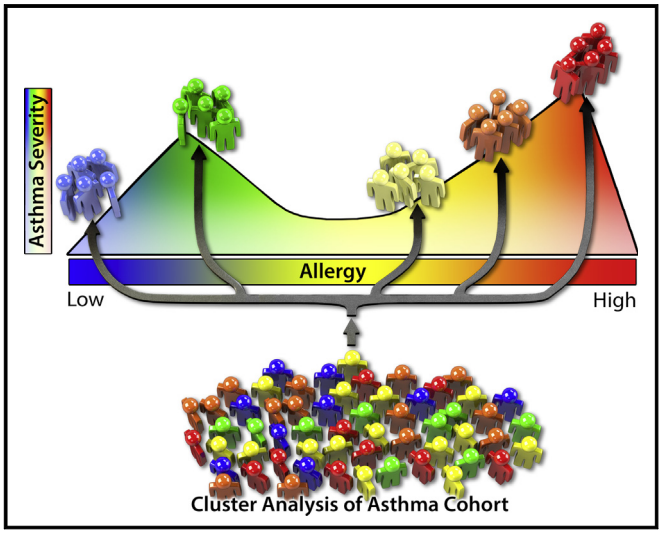
Asthma phenotypes in inner-city children

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GRAPHICAL ABSTRACT



Background: Children with asthma in low-income urban areas have high morbidity. Phenotypic analysis in these children is lacking, but may identify characteristics to inform successful tailored management approaches.

Objective: We sought to identify distinct asthma phenotypes among inner-city children receiving guidelines-based management.

Methods: Nine inner-city asthma consortium centers enrolled 717 children aged 6 to 17 years. Data were collected at baseline and prospectively every 2 months for 1 year. Participants' asthma and rhinitis were optimally managed by study physicians on the basis of guidelines. Cluster analysis using 50 baseline and 12 longitudinal variables was performed in 616 participants completing 4 or more follow-up visits.

Results: Five clusters (designated A through E) were distinguished by indicators of asthma and rhinitis severity, pulmonary physiology, allergy (sensitization and total serum

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IgE), and allergic inflammation. In comparison to other clusters, cluster A was distinguished by lower allergy/inflammation, minimally symptomatic asthma and rhinitis, and normal pulmonary physiology. Cluster B had highly symptomatic asthma despite high step-level treatment, lower allergy and inflammation, and mildly altered pulmonary physiology. Cluster C had minimally symptomatic asthma and rhinitis, intermediate allergy and inflammation, and mildly impaired pulmonary physiology. Clusters D and E exhibited progressively higher asthma and rhinitis symptoms and allergy/inflammation. Cluster E had the most symptomatic asthma while receiving high step-level treatment and had the highest total serum IgE level (median, 733 kU/L), blood eosinophil count (median, 400 cells/mm^3), and allergen sensitizations (15 of 22 tested). Conclusions: Allergy distinguishes asthma phenotypes in urban children. Severe asthma often coclusters with highly allergic children. However, a symptomatic phenotype with little allergy or allergic inflammation was identified. (J Allergy Clin Immunol 2016;138:1016-29.)

Key words: *Allergen sensitization, allergy, airway inflammation, bronchial hyperresponsiveness, asthma phenotypes, asthma severity, IgE, hierarchical cluster, inner-city asthma, rhinitis*

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Hallmarks of asthma include varying degrees of episodic dyspnea, wheezing, or coughing, in association with airway obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation. Considering the heterogeneity of features, severity, and therapeutic responses inherent in asthma, characterizing discrete phenotypes is essential to improving and personalizing asthma care. Unsupervised cluster analysis, a statistical method commonly applied in clinical studies to group participants with similar characteristics, has been used to identify discrete asthma phenotypes in several cohorts of varying ages, demographic characteristics, and underlying asthma severity.[1-8]

Children living in low-income urban regions of the United States have high morbidity and asthma severity.[9] Little is known about the asthma phenotypes in these at-risk children and whether there are phenotypes that are less likely to respond to specific interventions, including standard guidelines-based therapy. To meet this need, we designed and conducted the National Institutes of Health/National Institute of Allergy and Infectious Diseases–sponsored Inner-City Asthma Consortium Asthma Phenotypes in the Inner City (APIC) study. In this report, we present our findings from an unsupervised cluster analysis.

Abbreviations used
APIC: Asthma Phenotypes in the Inner City
BHR: Bronchial hyperresponsiveness
CAMP: Childhood Asthma Management Program
FENO: Fractional exhaled nitric oxide
FVC: Forced vital capacity
HCA: Hierarchical clustering algorithm
PC_{20}: Provocative concentration to induce a 20% decline in FEV_1

METHODS

Study population

The APIC study was designed as a prospective, epidemiological investigation of 6- to 17-year-old children with asthma from low-income areas of 9 US cities (Baltimore, Md; Boston, Mass; Chicago, Ill; Cincinnati, Ohio; Dallas, Tex; Denver, Colo; Detroit, Mich, New York, NY, and Washington, DC). The protocol was approved by institutional review boards from each center, and written informed consent was obtained from the legal guardians of participating children. Assent was obtained from 561 children according to institutional review board requirements. Between August 2011 and September 2013, 845 children were screened, 795 met eligibility criteria, and 717 completed the study entry visit (V0). These children were scheduled for bimonthly visits for 1 year (V1-V6) and received guidelines-based management of their asthma and rhinitis as well as additional evaluations. Completion of 4 or more postenrollment visits was required for inclusion in this cluster analysis. For asthma, a predefined, computerized National Asthma Education and Prevention Program Expert Panel Report-3–based treatment algorithm was used by the study clinicians to adjust the participant's controller regimen at each visit on the basis of asthma symptoms, spirometry results, and recent exacerbations.[10] For rhinitis, medications were prescribed in accordance with the Allergic Rhinitis and its Impact on Asthma recommendations.[11] The frequency and degree of bothering of nasal symptoms were captured and an algorithm was used to adjust treatment. Detailed descriptions of asthma and rhinitis management algorithms, data collection, and scoring systems for the APIC study are included in Pongracic et al.[12]

Study assessments

Each participant was characterized using a set of 50 baseline variables measured at screening or V0 as well as the within-participant mean and variance of 6 asthma severity variables measured at every visit between V0 and V6 (12 variables). These variables were selected for inclusion on the basis of a review of previous asthma cluster analyses in the literature and a consensus among APIC investigators.

A complete list of the variables entered into the hierarchical clustering algorithm (HCA) is provided in Table E1 in this article's Online Repository at www.jacionline.org. The variables were representative of several domains that were designated solely for descriptive purposes: demographic characteristics, family history, allergy history, asthma history, environmental exposures, body mass index, serum vitamin D level, stress, allergen sensitization, allergic inflammation, pulmonary physiology, asthma severity, and rhinitis.

Statistical methods

Variable reduction. Variables representing specific allergen sensitization through skin prick test or specific IgE were grouped together using an HCA based on Pearson correlations.[13] Using the result of the cluster analysis as a guide, allergens were grouped into the following 7 categories: molds, dust mites, cockroaches, rodents, pets, pollen/peanut, and foods. Instead of using separate variables for each individual allergen, separate variables representing sensitization in each of the 7 categories were created and used as variables in the clustering algorithm.

Hierarchical clustering analysis. R version 3.2.2 was used for analyses. Before analysis, any missing data at screening or V0 were imputed using a single imputation based on a fully conditional specification approach. Unless otherwise noted, all results were based on imputed data. To identify clusters of participants who were similar to each other based on the variables of interest, an agglomerative HCA was used. This algorithm works by measuring similarity between 2 participants, or 2 groups of participants, using a distance metric such that the distance between 2 participants who are alike is small whereas the distance between 2 participants who are dissimilar is large. In this case, distance between any 2 participants was calculated using a tree-based clustering algorithm that addresses multicollinearity among variables[14] while distance between any 2 clusters was calculated using a Ward's minimum-variance linkage clustering approach.[15] This algorithm was selected because it has been shown to have better performance than many commonly used algorithms for HCA in data sets with a large number of continuous and categorical variables that contain outliers, have skewed distribution, or are known to be highly collinear.[16]

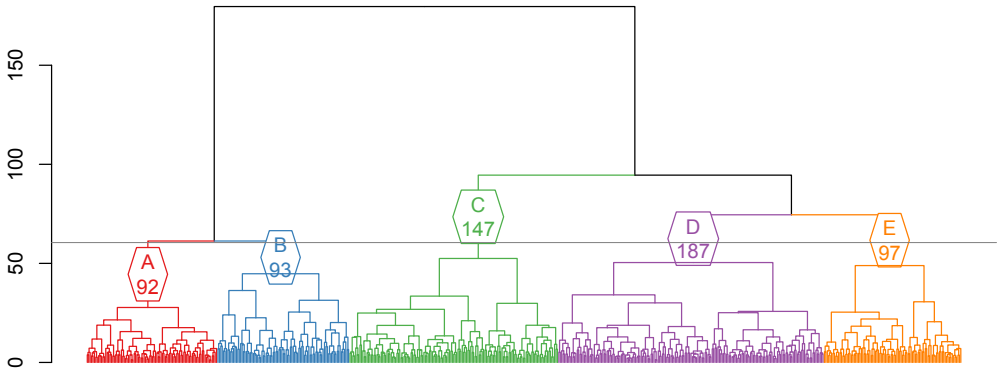


FIG 1. Dendrogram produced by the HCA. Participants in clusters A, B, C, D, and E are denoted by the colors *red, blue, green, purple,* and *orange,* respectively. The y-axis is a measure of dissimilarity between clusters such that the greater the height at which 2 clusters break off from one another, the greater the dissimilarity between the 2 clusters. The *gray line* indicates the height of the 5-cluster solution, as it cuts through 5 vertical lines, each of which represents a cluster.

Comparisons among clusters. To compare characteristics among clusters, analysis of variance and Kruskal-Wallis tests were used for continuous variables (normally distributed and non-normal, respectively), whereas chi-square and Fisher exact tests were used for categorical variables. No adjustment was made to account for multiple comparisons arising from comparisons between clusters or multiple variables. Bar charts and notched boxplots were also used to display characteristics of interest between clusters.

Characteristics relevant to distinguishing clusters. The Boruta[17] feature selection algorithm was used to identify the most relevant characteristics of cluster assignment. Boruta tests each variable's z score obtained from the random forest (a measure of loss in accuracy when a randomly permuted copy of the variable is used) to classify each variable as confirmed, tentative, or rejected with regard to its relevance in distinguishing cluster assignment. In this case, an adjustment was made to account for multiple comparisons.

RESULTS

Participant characteristics

Of 717 participants, 98 did not complete at least 4 poststudy entry evaluation visits and 3 participants were missing postentry spirometry, resulting in 616 (86%) participants included in the cluster analysis. The mean age at screening of this cohort was 10.8 years, 58.3% were male, and 63.9% were self-identified as non-Hispanic black.

Cluster analysis

The results of the HCA are demonstrated using a dendrogram in Fig 1. Five clusters were identified and arbitrarily designated by the letters A through E. Clusters contained between 92 and 187 participants.

Predictors of cluster assignment

Using the Boruta feature selection algorithm, 33 variables were confirmed to be relevant in distinguishing the 5 clusters. Fig 2 ranks these variables using the median *z* score, a measure of variable importance. To produce an overview of the 5 clusters, the confirmed variables were categorized into groups reflective of asthma severity, rhinitis severity, pulmonary physiology, allergen sensitization (production of allergen-specific and total serum IgE level), and allergic inflammation (blood eosinophilia and fractional exhaled nitric oxide [FENO]). A descriptive summary, overlaid with a graded color scheme representing quintiles of the data, was created to indicate the relative degree to which key variables of importance were present across the clusters (Fig 3). Table I provides a comprehensive description of the distribution of each variable entered into the cluster algorithm, as well as of other variables of interest, across the 5 clusters.

Bar graphs depicting the distributions of major characteristics in each cluster are provided in the following figures: Fig 4, allergy-related variables; Fig 5, variables related to pulmonary physiology and allergic inflammation; Fig 6, longitudinal summaries of asthma symptoms, medications, and exacerbations; and Fig 7, rhinitis-related variables at screening.

Cluster A

Cluster A included 92 children (14.9% of the cohort). Distinguishing features were minimally symptomatic asthma and rhinitis, normal pulmonary physiology, and comparatively the lowest levels of allergy and allergic inflammation. During the 12-month follow-up, participants received a mean within-subject asthma treatment step-level of 1.39 and few (13%) required prednisone for asthma exacerbations (Fig 3). A comparatively low proportion of participants had self-reported food allergy (17.4%) and eczema (38.0%). On average, allergic sensitization was present to only 1 of the 22 allergens tested, with a relatively low proportion (28.3%) having a positive Phadiatop allergen sensitization screen. Geometric mean total serum IgE level was 39.4 kU/L. This cluster also had comparatively low indicators of allergic inflammation, including a median blood eosinophil count of 121 cells/mm^3 and a geometric mean FENO of 14.1 ppb (Table I and Figs 4-7).

Cluster B

Cluster B included 93 children (15.1% of the cohort). Distinguishing features included comparatively lower levels of allergy and allergic inflammation (similar to cluster A), but highly symptomatic asthma despite a higher treatment step-level with an intermediate degree of rhinitis symptoms and treatment requirements (Fig 3). Participants also exhibited mildly impaired pulmonary physiology with a mean FEV_1/forced vital capacity (FVC) ($\times 100$) of 79% over 12 months and median methacholine provocative concentration to induce a 20% decline in FEV_1 (PC_{20}) of 13.3 mg/mL. Cluster B had the second highest asthma treatment

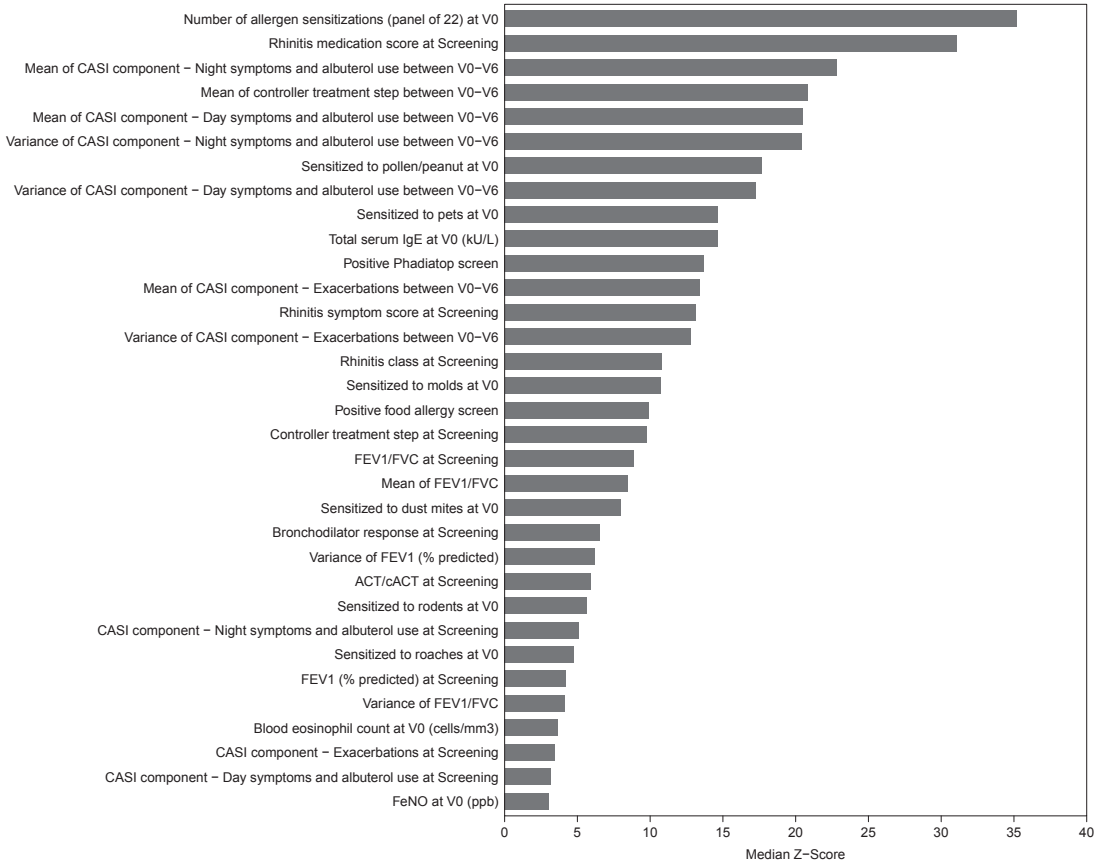


FIG 2. Variable importance plot of characteristics distinguishing the clusters. Bars plot the median *z* score for each variable, a measure of importance obtained from a feature selection algorithm called Boruta where higher values indicate a higher level of importance. Only those variables that were confirmed as relevant to distinguishing between the 5 clusters are presented in this figure. *ACT/cACT*, Asthma Control Test/Childhood Asthma Control Test; *CASI*, Composite Asthma Severity Index.

step-level (mean, 4.2) and 47.3% of the participants required prednisone for asthma exacerbations during the year. A relatively low proportion of participants had self-reported food allergy (16.8%) and eczema (38.7%), and allergic sensitization was present to 2 of the 22 allergens tested. The geometric mean total serum IgE level was 71.4 kU/L, and 45% of the participants in this cluster had a positive Phadiatop allergen sensitization screen. This cluster had comparatively low indicators of allergic inflammation, including a median blood eosinophil count of 200 cells/mm^3 and a geometric mean FENO of 14.6 ppb (Table I and Figs 4-7).

Cluster C

Cluster C included 147 children (23.9% of the population). Distinguishing features included minimally symptomatic asthma and rhinitis, low asthma medication treatment step-level, and minimally impaired pulmonary physiology. Participants had an intermediate degree of allergy and allergic inflammation (Fig 3). Detailed results include a comparatively low mean asthma treatment step-level (1.93) and a low proportion of exacerbations requiring prednisone over the 12-month follow-up (20%). Mean FEV_1/FVC (×100) over 12 months was 81% and median PC_{20} was 8.33 mg/mL. Participants exhibited an intermediate degree of allergic sensitization (an average of 8.8 out of 22 allergens) and a geometric mean total serum IgE level of 239.0 kU/L; a high proportion had a positive Phadiatop screen (93%). Inflammatory markers were intermediate compared with other clusters, with a geometric mean FENO of 20.4 ppb and median blood eosinophil count of 300 cells/mm^3. Similar to cluster A, they had a relatively high proportion of participants without rhinitis (18.4%) at screening although this decreased to 10.9% between V0 and V6 (Table I; see Table E2 in this article's Online Repository at www.jacionline.org; Figs 4-7).

Cluster D

Cluster D included 187 children (30.4% of the cohort) with relatively low symptom levels of asthma (similar to clusters A and C), but requiring an intermediate step-level of controller therapy. Cluster D had ubiquitous, symptomatic rhinitis with comparatively higher levels of allergy and allergic inflammation and an intermediate degree of pulmonary physiology impairment (Fig 3). They required an intermediate asthma treatment step-level (3.4), with 36% experiencing exacerbations over the year. Mean FEV_1/FVC (×100) was 78% over the 12-month follow-up and median PC_{20} was 4.9 mg/mL. Participants reported a high degree of food allergy and eczema (41% and 60%, respectively), were sensitized to 13 of 22 allergens, had a geometric mean total serum IgE level of 576 kU/L, and nearly all had a positive Phadiatop screen (98%).

	A	B	C	D	E	
Mean of CASI − Day symp & albuterol use[1] (V0−V6)	0.11 (0.13)	0.51 (0.36)	0.16 (0.23)	0.19 (0.25)	0.65 (0.39)	Asthma severity
Mean of CASI − Night symp & albuterol use[1] (V0−V6)	0.10 (0.19)	0.58 (0.51)	0.14 (0.22)	0.08 (0.15)	0.64 (0.44)	
Mean of CASI − Exacerbations[2] (V0−V6)	0.05 (0.12)	0.31 (0.35)	0.12 (0.24)	0.32 (0.52)	0.76 (0.73)	
Mean of controller treatment step (V0−V6)	1.39 (1.38)	4.19 (1.52)	1.93 (1.60)	3.41 (1.69)	4.68 (1.28)	
Airway obstruction[3] (V0−V6)	83.5 (5.67)	79.0 (8.81)	81.3 (6.37)	78.2 (8.14)	74.8 (8.25)	Pulmonary physiology
Bronchodilator response (%) at Screening	6.60 (8.41)	12.2 (11.6)	10.1 (9.48)	16.2 (16.1)	19.5 (16.4)	
Rhinitis medication score[4] at Screening	6.63 (6.07)	8.60 (5.53)	5.20 (5.45)	14.0 (3.04)	12.5 (5.11)	Rhinitis severity
Rhinitis symptom score[5] at Screening	7.40 (5.66)	9.03 (5.79)	6.37 (5.96)	10.5 (5.15)	11.6 (6.21)	
Number of allergen sensitizations (panel of 22)[6] at V0	1.14 (1.12)	1.98 (1.82)	8.82 (4.28)	13.0 (4.21)	14.1 (4.26)	Allergen sensitization
Total serum IgE at V0 (kU/L)[7]	39.4 (3.56)	71.4 (4.32)	259 (3.37)	576 (3.43)	616 (3.18)	
Blood eosinophil count at V0 (cells/mm3)[8]	121 [100, 210]	200 [100, 300]	300 [190, 500]	331 [200, 505]	400 [235, 570]	Allergic inflammation
FeNO at V0 (ppb)[7]	14.1 (1.78)	14.6 (2.07)	20.4 (2.14)	26.4 (2.24)	27.1 (2.20)	

Lowest — Intermediate — Highest

1. Composite Asthma Severity Index (CASI) component − Day and night symptoms includes measures of asthma symptoms and albuterol use in the last 2 weeks (scoring range between 0 and 3).
2. CASI component − Exacerbations includes hospitalizations and/or oral corticosteroid bursts in the last 2 months.
3. Airway obstruction is represented by the mean FEV1/FVC (x100) between visits 0 and 6. Color shading reflects the amount of airway obstruction, rather than the actual FEV1/FVC (x100) values.
4. Rhinitis medication score is set to 0 for no medications, 5 for antihistamines only, 10 for nasal steroids only, and 15 for antihistamines and nasal steroids.,
5. Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index.
6. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: Alternaria tenuis (skin prick test) or Alternaria alternata (specific IgE), Aspergillus fumigatus (both skin prick test and specific IgE), Cladosporium herbarum (specific IgE only), Dermatophagoides farinae, Dermatophagoides pteronyssinus, German cockroach, American cockroach, mouse, rat, cat, dog, oak, pecan, birch, maple, Eastern 8 tree mix, ragweed mix (giant/short; skin prick test) or short ragweed (specific Ige), timothy grass, Kentucky Blue/June, Orchard and Timothy (K−O−T) grass mix, peanut, egg and milk.
7. Summarized using the geometric mean and geometric mean standard deviation and tested using a Kruskal−Wallis test.
8. Summarized using the median and inter−quartile range and tested using a Kruskal−Wallis test.

FIG 3. Descriptive summary indicating the relative degree to which asthma, pulmonary physiology, rhinitis, and allergy-related variables were present in each cluster. The graded color scheme contains 5 shades of blue, representing the 20th (lightest), 40th, 60th, 80th, and 100th (darkest) percentiles of the data for each row. Overall *P* values indicating differences between the 5 clusters are $P < .0001$ for all variables.

Compared with clusters A to C, cluster D had a higher degree of allergic inflammation (geometric mean FENO of 26.4 ppb and median eosinophil count of 331 cells/mm^3). Cluster D had the most participants with allergic rhinitis (93.6% at baseline and 100% during follow-up) and experienced an intermediate level of rhinitis symptoms despite requiring the highest levels, along with cluster E, of rhinitis medication (see Table I, Table E2, and Figs 4-7).

Cluster E

Cluster E included 97 children (15.7% of the cohort) distinguished by the highest levels of symptomatic asthma and rhinitis despite receiving the highest levels of asthma and rhinitis treatment. They also had the most impaired pulmonary physiology and highest degree of allergy and allergic inflammation (Fig 3). The average asthma treatment step-level was 4.7, with the highest proportion of participants (75%) requiring prednisone for exacerbations. Day and nighttime asthma symptoms were comparatively highest at screening and during the study. Mean FEV_1/FVC (×100) over 12 months was 75% and median PC_{20} was 3.12 mg/mL. Participants also had the highest proportions with reported food allergy (42%), eczema (75%), and anaphylaxis (12%). They were sensitized to a median of 14 of 22 allergens, had a median total serum IgE level of 616 kU/L, and all had a positive Phadiatop screen. Similar to cluster D, they had higher levels of allergic inflammation, with geometric mean FENO of 27.1 ppb and median blood eosinophil count of 400 cells/mm^3. At screening and during the follow-up period, rhinitis was present in 96% (see Table I, Table E2, and Figs 4-7).

DISCUSSION

Several cluster analyses have been reported in children with asthma,[3-5,8] but none restricted to low-income, urban populations. Inner-city children may exhibit unique features of asthma, and phenotypic characterization could be informative of differential responses to asthma management strategies as previously reported in other school-age children[4,18] and adolescents.[8]

Our study's strengths include careful characterization of a large number of school-age children representing a low-income population from urban census tracts but inclusive of the full spectrum of asthma. The inclusion of variables measuring longitudinally measured outcomes while receiving standardized,

TABLE I. Characteristics of the population overall and by cluster

Characteristics	All participants (N = 616)	A (n = 92)	B (n = 93)	C (n = 147)	D (n = 187)	E (n = 97)	Overall *P* value
Demographic characteristics							
Sex: male	359 (58.3)	47 (51.1)	43 (46.2)	91 (61.9)	120 (64.2)	58 (59.8)	.03
Race: black	392 (63.9)	54 (59.3)	55 (59.8)	84 (57.5)	124 (66.3)	75 (77.3)	.02
Race*	n = 613	n = 91	n = 92	n = 146	n = 187	n = 97	.07
Black (non-Hispanic)	392 (63.9)	54 (59.3)	55 (59.8)	84 (57.5)	124 (66.3)	75 (77.3)	
Hispanic	176 (28.7)	28 (30.8)	27 (29.3)	52 (35.6)	52 (27.8)	17 (17.5)	
Other/mixed	34 (5.55)	8 (8.79)	9 (9.78)	7 (4.79)	6 (3.21)	4 (4.12)	
White (non-Hispanic)	11 (1.79)	1 (1.10)	1 (1.09)	3 (2.05)	5 (2.67)	1 (1.03)	
Age at screening (y)	10.8 ± 3.01	10.7 ± 2.84	10.3 ± 3.13	10.8 ± 3.08	11.0 ± 2.91	10.9 ± 3.15	.49
Income <$15,000	335 (54.4)	61 (66.3)	57 (61.3)	79 (53.7)	89 (47.6)	49 (50.5)	.03
Caretaker completed high school	450 (73.1)	63 (68.5)	68 (73.1)	106 (72.1)	136 (72.7)	77 (79.4)	.55
Family history							
Family history of asthma	450 (73.1)	70 (76.1)	76 (81.7)	103 (70.1)	129 (69.0)	72 (74.2)	.18
Family history of hay fever/rhinitis/allergies	355 (57.6)	55 (59.8)	66 (71.0)	71 (48.3)	109 (58.3)	54 (55.7)	.02
Family history of eczema	348 (56.5)	55 (59.8)	47 (50.5)	79 (53.7)	102 (54.5)	65 (67.0)	.14
Allergy history							
Self-report of food allergies	190 (30.8)	16 (17.4)	15 (16.1)	42 (28.6)	76 (40.6)	41 (42.3)	<.001
History of anaphylaxis	46 (7.47)	2 (2.17)	4 (4.30)	9 (6.12)	19 (10.2)	12 (12.4)	.03
Eczema diagnosis	337 (54.7)	35 (38.0)	36 (38.7)	80 (54.4)	113 (60.4)	73 (75.3)	<.001
Asthma history							
Age asthma first diagnosed (mo)	40.9 ± 37.6	42.8 ± 40.1	39.3 ± 38.5	45.8 ± 40.3	40.4 ± 35.1	34.5 ± 34.2	.22
Age asthma symptoms started (y)	1.42 ± 2.70	1.61 ± 2.88	1.60 ± 2.80	1.18 ± 2.57	1.32 ± 2.58	1.65 ± 2.85	.56
Duration of asthma (mo)*	95.0 ± 45.4 n = 614	91.3 ± 46.3 n = 92	91.1 ± 46.3 n = 93	90.0 ± 42.6 n = 146	98.4 ± 45.6 n = 186	103 ± 46.4 n = 97	.12
Controller treatment step at screening	3.40 ± 1.98	2.20 ± 1.79	3.92 ± 1.68	2.42 ± 1.94	4.05 ± 1.73	4.29 ± 1.79	<.001
Controller treatment step at screening*							<.001
Steps 0-2	212 (34.4)	56 (60.9)	22 (23.7)	80 (54.4)	38 (20.3)	16 (16.5)	
Step 3	90 (14.6)	15 (16.3)	10 (10.8)	21 (14.3)	27 (14.4)	17 (17.5)	
Steps 4-6	314 (51.0)	21 (22.8)	61 (65.6)	46 (31.3)	122 (65.2)	64 (66.0)	
Asthma Control Test/Childhood Asthma Control Test (ACT/cACT) at screening	20.1 ± 4.04	21.6 ± 3.32	19.7 ± 3.43	21.7 ± 3.48	19.9 ± 3.80	17.3 ± 4.75	<.001
ACT/cACT† at screening*	n = 615	n = 92	n = 93	n = 147	n = 187	n = 96	<.001
Very poorly controlled	52 (8.46)	2 (2.17)	5 (5.38)	6 (4.08)	18 (9.63)	21 (21.9)	
Not well controlled	178 (28.9)	17 (18.5)	36 (38.7)	27 (18.4)	54 (28.9)	44 (45.8)	
Well controlled	385 (62.6)	73 (79.3)	52 (55.9)	114 (77.6)	115 (61.5)	31 (32.3)	
CASI component—Day symptoms and albuterol use‡ at screening	0.52 ± 0.86	0.32 ± 0.73	0.58 ± 0.84	0.27 ± 0.59	0.56 ± 0.87	0.98 ± 1.11	<.001
CASI component—Night symptoms and albuterol use§ at screening	0.54 ± 0.95	0.36 ± 0.82	0.85 ± 1.02	0.30 ± 0.73	0.37 ± 0.82	1.12 ± 1.19	<.001
CASI component—Exacerbations‖ at screening	0.56 ± 1.28	0.11 ± 0.46	0.47 ± 1.08	0.30 ± 0.89	0.73 ± 1.50	1.11 ± 1.73	<.001
BMI							
BMI *z* score at screening	1.00 ± 1.16	0.92 ± 1.03	1.06 ± 1.34	1.04 ± 1.06	0.90 ± 1.21	1.16 ± 1.15	.40
BMI percentile at screening*¶	86.9 (57.7-97.6)	86.3 (59.1-95.3)	90.1 (65.4-98.3)	88.2 (58.2-97.2)	83.9 (53.8-97.3)	89.9 (55.7-98.6)	.28
Serum vitamin D							
Total 25-hydroxyvitamin D at V0 (ng/mL)	19.2 ± 7.30	19.0 ± 7.13	19.5 ± 8.73	19.8 ± 6.95	19.3 ± 7.08	18.1 ± 6.93	.54
Environmental exposures							
Any smokers in the home at screening	248 (40.3)	36 (39.1)	49 (52.7)	49 (33.3)	67 (35.8)	47 (48.5)	.01
NicAlert result at screening	1.26 ± 1.09	1.37 ± 1.15	1.08 ± 0.85	1.27 ± 1.06	1.21 ± 1.08	1.42 ± 1.30	.19

(Continued)

TABLE I. *(Continued)*

Characteristics	All participants (N = 616)	A (n = 92)	B (n = 93)	C (n = 147)	D (n = 187)	E (n = 97)	Overall *P* value
Gas stove in home	411 (66.7)	62 (67.4)	68 (73.1)	104 (70.7)	117 (62.6)	60 (61.9)	.26
Dampness in home	227 (36.9)	37 (40.2)	32 (34.4)	46 (31.3)	69 (36.9)	43 (44.3)	.29
AC unit in child's bedroom	425 (69.0)	61 (66.3)	64 (68.8)	99 (67.3)	133 (71.1)	68 (70.1)	.92
Forced air for heat in home	377 (61.2)	52 (56.5)	58 (62.4)	81 (55.1)	119 (63.6)	67 (69.1)	.19
Rodents in home	187 (30.4)	30 (32.6)	36 (38.7)	44 (29.9)	47 (25.1)	30 (30.9)	.22
Roaches in home	119 (19.3)	16 (17.4)	25 (26.9)	27 (18.4)	35 (18.7)	16 (16.5)	.37
Pets in home	232 (37.7)	35 (38.0)	39 (41.9)	48 (32.7)	70 (37.4)	40 (41.2)	.59
Stress							
Caretaker Perceived Stress Scale score at V0	14.8 ± 7.54	15.0 ± 7.34	15.9 ± 8.21	13.6 ± 8.01	14.2 ± 7.24	16.2 ± 6.57	.04
Allergen sensitization							
Total serum IgE level at V0 (kU/L)#	235 ± 5.11	39.4 ± 3.56	71.4 ± 4.32	259 ± 3.37	576 ± 3.43	616 ± 3.18	<.001
Number of allergen sensitizations (panel of 22)** at V0	8.74 ± 6.23	1.14 ± 1.12	1.98 ± 1.82	8.82 ± 4.28	13.0 ± 4.21	14.1 ± 4.26	<.001
Positive Phadiatop screen	485 (78.7)	26 (28.3)	42 (45.2)	137 (93.2)	183 (97.9)	97 (100)	<.001
Positive fx5 food allergy screen	347 (56.3)	18 (19.6)	17 (18.3)	85 (57.8)	147 (78.6)	80 (82.5)	<.001
Sensitized to molds†† at V0	308 (50.0)	6 (6.52)	16 (17.2)	68 (46.3)	141 (75.4)	77 (79.4)	<.001
Sensitized to dust mites‡‡ at V0	363 (58.9)	17 (18.5)	26 (28.0)	90 (61.2)	153 (81.8)	77 (79.4)	<.001
Sensitized to roaches§§ at V0	346 (56.2)	22 (23.9)	28 (30.1)	84 (57.1)	136 (72.7)	76 (78.4)	<.001
Sensitized to rodents‖‖ at V0	260 (42.2)	9 (9.78)	11 (11.8)	67 (45.6)	112 (59.9)	61 (62.9)	<.001
Sensitized to pets¶¶ at V0	400 (64.9)	13 (14.1)	20 (21.5)	107 (72.8)	172 (92.0)	88 (90.7)	<.001
Sensitized to pollen/peanut## at V0	435 (70.6)	12 (13.0)	24 (25.8)	125 (85.0)	179 (95.7)	95 (97.9)	<.001
Sensitized to foods*** at V0	183 (29.7)	13 (14.1)	13 (14.0)	39 (26.5)	75 (40.1)	43 (44.3)	<.001
Inflammation							
FENO at V0 (ppb)#	20.8 ± 2.2	14.1 ± 1.78	14.6 ± 2.07	20.4 ± 2.14	26.4 ± 2.24	27.1 ± 2.20	<.001
Blood eosinophil count at V0 (cells/mm^3)¶	300 (160-480)	121 (100-210)	200 (100-300)	300 (190-500)	331 (200-505)	400 (235-570)	<.001
Blood neutrophil count at V0 (cells/mm^3)¶	2800 (2000-3878)	2790 (2075-3825)	3200 (2500-4100)	2600 (2020-3700)	2700 (1960-3885)	2900 (2200-3580)	.24
Pulmonary physiology							
Bronchodilator response at screening	13.3 ± 13.8	6.60 ± 8.41	12.2 ± 11.6	10.1 ± 9.48	16.2 ± 16.1	19.5 ± 16.4	<.001
FEV_1 (% predicted) at screening	91.8 ± 17.2	97.6 ± 14.2	90.3 ± 17.6	95.8 ± 15.9	90.1 ± 18.2	85.3 ± 16.6	<.001
Mean of FEV_1 (% predicted) between V0 and V6	93.7 ± 14.3	97.2 ± 12.1	92.3 ± 15.1	95.9 ± 13.9	93.3 ± 14.5	89.0 ± 14.3	<.001
Variance of FEV_1 (% predicted) between V0 and V6	82.1 ± 99.0	42.6 ± 47.7	80.5 ± 103	53.4 ± 59.2	93.8 ± 99.0	142 ± 139	<.001
FEV_1/FVC (×100) at screening	77.9 ± 9.67	83.7 ± 6.88	77.6 ± 9.79	80.2 ± 7.69	76.1 ± 10.0	72.8 ± 10.2	<.001
Mean of FEV_1/FVC (×100) between V0 and V6	79.3 ± 8.00	83.5 ± 5.67	79.0 ± 8.81	81.3 ± 6.37	78.2 ± 8.14	74.8 ± 8.25	<.001
Variance of FEV_1/FVC (×100) between V0 and V6	24.3 ± 31.6	12.5 ± 17.6	23.3 ± 32.6	16.0 ± 16.6	31.1 ± 39.1	36.1 ± 35.0	<.001
Methacholine PC_{20}††† at V4/V5 (mg/mL)*¶	8.33 (2.07-25.0) n = 516	25.0 (8.46-25.0) n = 113	13.3 (2.80-25.0) n = 53	8.33 (2.16-25.0) n = 114	4.86 (1.38-19.0) n = 129	3.12 (0.89-10.4) n = 107	<.001
Asthma severity over 12 mo							
Mean of day symptoms and albuterol use‡‡‡ between V0 and V6*	2.16 ± 1.87	1.09 ± 0.94	3.39 ± 1.91	1.39 ± 1.33	1.72 ± 1.45	4.05 ± 1.95	<.001

(Continued)

TABLE I. *(Continued)*

Characteristics	All participants (N = 616)	A (n = 92)	B (n = 93)	C (n = 147)	D (n = 187)	E (n = 97)	Overall *P* value
Variance of day symptoms and albuterol use‡‡‡ between V0 and V6*	8.62 ± 11.7	3.19 ± 4.71	16.2 ± 14.1	5.13 ± 8.81	5.85 ± 9.16	17.1 ± 14.1	<.001
Mean of night symptoms and albuterol use§§§ between V0 and V6*	0.66 ± 1.04	0.26 ± 0.52	1.34 ± 1.40	0.36 ± 0.51	0.24 ± 0.31	1.65 ± 1.47	<.001
Variance of night symptoms and albuterol use§§§ between V0 and V6*	2.66 ± 6.96	0.80 ± 2.80	5.48 ± 9.13	1.08 ± 3.30	0.51 ± 1.30	8.26 ± 12.1	<.001
Mean of CASI component—Day symptoms and albuterol use‡ between V0 and V6	0.29 ± 0.34	0.11 ± 0.13	0.51 ± 0.36	0.16 ± 0.23	0.19 ± 0.25	0.65 ± 0.39	<.001
Variance of CASI component—Day symptoms and albuterol use‡ between V0 and V6	0.39 ± 0.56	0.13 ± 0.22	0.73 ± 0.63	0.22 ± 0.43	0.25 ± 0.43	0.87 ± 0.66	<.001
Mean of CASI component—Night symptoms and albuterol use§ between V0 and V6	0.26 ± 0.38	0.10 ± 0.19	0.58 ± 0.51	0.14 ± 0.22	0.08 ± 0.15	0.64 ± 0.44	<.001
Variance of CASI component—Night symptoms and albuterol use§ between V0 and V6	0.41 ± 0.60	0.19 ± 0.43	0.85 ± 0.72	0.23 ± 0.42	0.12 ± 0.27	1.04 ± 0.62	<.001
Mean of CASI component—Exacerbations‖ between V0 and V6	0.30 ± 0.50	0.05 ± 0.12	0.31 ± 0.35	0.12 ± 0.24	0.32 ± 0.52	0.76 ± 0.73	<.001
Variance of CASI component—Exacerbations‖ between V0 and V6	0.76 ± 1.43	0.11 ± 0.31	0.84 ± 1.27	0.30 ± 0.69	0.86 ± 1.51	1.84 ± 2.09	<.001
Prednisone burst between screening and V6*	225 (36.5)	12 (13.0)	44 (47.3)	29 (19.7)	67 (35.8)	73 (75.3)	<.001
Mean of controller treatment step between V0 and V6	3.07 ± 1.93	1.39 ± 1.38	4.19 ± 1.52	1.93 ± 1.60	3.41 ± 1.69	4.68 ± 1.28	<.001
Variance of controller treatment step between V0 and V6	0.95 ± 0.89	0.97 ± 1.03	0.94 ± 0.94	1.04 ± 0.93	0.94 ± 0.76	0.85 ± 0.86	.58
Final treatment classification*‖‖‖							<.001
Easy-to-control	230 (37.3)	67 (72.8)	9 (9.68)	92 (62.6)	55 (29.4)	7 (7.22)	
Indeterminate	134 (21.8)	19 (20.7)	23 (24.7)	29 (19.7)	46 (24.6)	17 (17.5)	
Difficult-to-control	252 (40.9)	6 (6.52)	61 (65.6)	26 (17.7)	86 (46.0)	73 (75.3)	
Cumulative adherence to ICS (%)*	75.3 ± 22.1 n = 584	73.5 ± 25.1 n = 79	76.5 ± 19.5 n = 93	74.9 ± 27.6 n = 132	75.7 ± 19.2 n = 183	75.2 ± 18.4 n = 97	.93
ACT/cACT at V6*	22.3 ± 3.24 n = 587	23.4 ± 2.76 n = 91	21.4 ± 3.22 n = 90	23.1 ± 2.96 n = 136	22.6 ± 2.77 n = 178	20.2 ± 3.77 n = 92	<.001
ACT/cACT† at V6*							<.001
Very poorly controlled	10 (1.70)	2 (2.20)	1 (1.11)	1 (0.74)	1 (0.56)	5 (5.43)	
Not well controlled	95 (16.2)	7 (7.69)	22 (24.4)	12 (8.82)	23 (12.9)	31 (33.7)	
Well controlled	482 (82.1)	82 (90.1)	67 (74.4)	123 (90.4)	154 (86.5)	56 (60.9)	
Rhinitis at screening							
Rhinitis classification at screening							<.001
Allergic	430 (69.8)	37 (40.2)	35 (37.6)	97 (66.0)	175 (93.6)	86 (88.7)	
Nonallergic	124 (20.1)	38 (41.3)	50 (53.8)	23 (15.6)	10 (5.35)	3 (3.09)	
No rhinitis	62 (10.1)	17 (18.5)	8 (8.60)	27 (18.4)	2 (1.07)	8 (8.25)	
Rhinitis medication score¶¶¶ at screening	9.73 ± 6.09	6.63 ± 6.07	8.60 ± 5.53	5.20 ± 5.45	14.0 ± 3.04	12.5 ± 5.11	<.001

(Continued)

TABLE I. *(Continued)*

Characteristics	All participants (N = 616)	A (n = 92)	B (n = 93)	C (n = 147)	D (n = 187)	E (n = 97)	Overall *P* value
Rhinitis medications at screening*							<.001
None	129 (20.9)	35 (38.0)	21 (22.6)	58 (39.5)	4 (2.14)	11 (11.3)	
Antihistamine only	87 (14.1)	14 (15.2)	10 (10.8)	51 (34.7)	7 (3.74)	5 (5.15)	
Nasal steroids only	88 (14.3)	21 (22.8)	36 (38.7)	12 (8.16)	13 (6.95)	6 (6.19)	
Antihistamine and nasal steroids	312 (50.6)	22 (23.9)	26 (28.0)	26 (17.7)	163 (87.2)	75 (77.3)	
Rhinitis symptom score### at screening	9.00 ± 6.00	7.40 ± 5.66	9.03 ± 5.79	6.37 ± 5.96	10.5 ± 5.15	11.6 ± 6.21	<.001
Rhinitis assessments over 12 mo							
Rhinitis reclassification in the course of the 12-mo follow-up*****							<.001
Allergic	438 (71.1)	31 (33.7)	35 (37.6)	107 (72.8)	175 (93.6)	90 (92.8)	
Nonallergic	139 (22.6)	47 (51.1)	53 (57.0)	24 (16.3)	12 (6.42)	3 (3.09)	
No rhinitis	39 (6.33)	14 (15.2)	5 (5.38)	16 (10.9)	0 (0.00)	4 (4.12)	
Mean of rhinitis medication score¶¶¶ between V0 and V6*	9.68 ± 5.30	5.77 ± 5.26	8.45 ± 4.80	7.53 ± 5.32	12.5 ± 3.51	12.5 ± 4.29	<.001
Variance of rhinitis medication¶¶¶ score between V0 and V6*	13.9 ± 15.4	14.9 ± 13.7	16.9 ± 13.9	16.5 ± 16.7	12.6 ± 15.9	8.54 ± 13.5	<.001
Mean of rhinitis symptom score### between V0 and V6*	6.13 ± 3.77	4.26 ± 3.21	7.17 ± 3.74	5.01 ± 3.37	6.20 ± 3.49	8.44 ± 3.93	<.001
Variance of rhinitis symptom score### between V0 and V6*	17.3 ± 15.5	12.0 ± 10.9	20.4 ± 17.6	17.3 ± 16.2	16.0 ± 14.6	21.7 ± 16.1	<.001

Unless otherwise noted, continuous variables are summarized using mean ± SD whereas categorical variables are summarized using frequency and percentage. Any missing data for variables included in the HCA were imputed. Unless otherwise noted, an overall test of the distribution of each characteristic across clusters was performed using an analysis of variance for continuous variables and chi-square test or Fisher exact test for categorical variables.

AC, Air conditioning; *BMI*, body mass index; *CASI*, Composite Asthma Severity Index; *ICS*, inhaled corticosteroid.

*Not included as a variable in the HCA.

†ACT is categorized as very poorly controlled (≤15), not well controlled (≥16 and ≤19), and well controlled (≥20). cACT is categorized as very poorly controlled (≤12), not well controlled (≥13 and ≤19), and well controlled (≥20).

‡CASI component—Day symptoms include measures of day asthma symptoms and albuterol use in the last 2 wk (scoring range between 0 and 3).

§CASI component—Night symptoms include measures of night asthma symptoms and albuterol use in the last 2 wk (scoring range between 0 and 3).

||CASI component—Exacerbations include hospitalizations and/or oral corticosteroid bursts in the last 2 mo.

¶Summarized using the median and interquartile range and tested using a Kruskal-Wallis test.

#Summarized using the geometric mean and geometric mean SD and tested using a Kruskal-Wallis test.

**Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: *Alternaria tenuis* (skin prick test) or *Alternaria alternata* (specific IgE), *Aspergillus fumigatus* (both skin prick test and specific IgE), *Cladosporium herbarum* (specific IgE only), *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, German cockroach, American cockroach, mouse, rat, cat, dog, oak, pecan, birch, maple, Eastern 8 tree mix, ragweed mix (giant/short; skin prick test) or short ragweed (specific IgE), timothy grass, Kentucky Blue/June, Orchard and Timothy (K-O-T) grass mix, peanut, egg, and milk.

††Sensitization is based on a positive prick skin test result and/or positive specific IgE to at least 1 of the following allergens: *Alternaria tenuis* (skin prick test) or *Alternaria alternata* (specific IgE), *Aspergillus fumigatus*, and *Cladosporium herbarum*.

‡‡Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.

§§Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: German cockroach and American cockroach.

||||Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: mouse and rat.

¶¶Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: cat and dog.

##Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: oak, pecan, birch, maple, Eastern 8 tree mix, ragweed, timothy grass, Kentucky Blue/June, Orchard and Timothy (K-O-T) grass mix, and peanut.

***Sensitization is based on a positive skin prick test result and/or positive specific IgE to at least 1 of the following allergens: egg and milk.

†††Methacholine challenge using a tidal breathing technique was completed in a subset of participants.

‡‡‡Days of symptoms and albuterol use is the maximum of the number of days with symptoms and the number of days with albuterol use in the last 2 wk.

§§§Nights of symptoms and albuterol use is the maximum of the number of nights with symptoms and the number of nights with albuterol use in the last 2 wk.

|||||Easy-to-control is defined by ≤100 μg/d fluticasone on at least 4 of the 6 study visits, difficult-to-control is defined by ≥500 μg/d fluticasone on at least 4 of the 6 study visits, and indeterminate is defined by neither easy- nor difficult-to-control.

¶¶¶Rhinitis medication score is set to 0 for no medications, 5 for antihistamines only, 10 for nasal steroids only, and 15 for antihistamines and nasal steroids.

###Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index.

****Participants who changed from no rhinitis at screening to allergic or nonallergic rhinitis at a later visit are classified using the later visit.

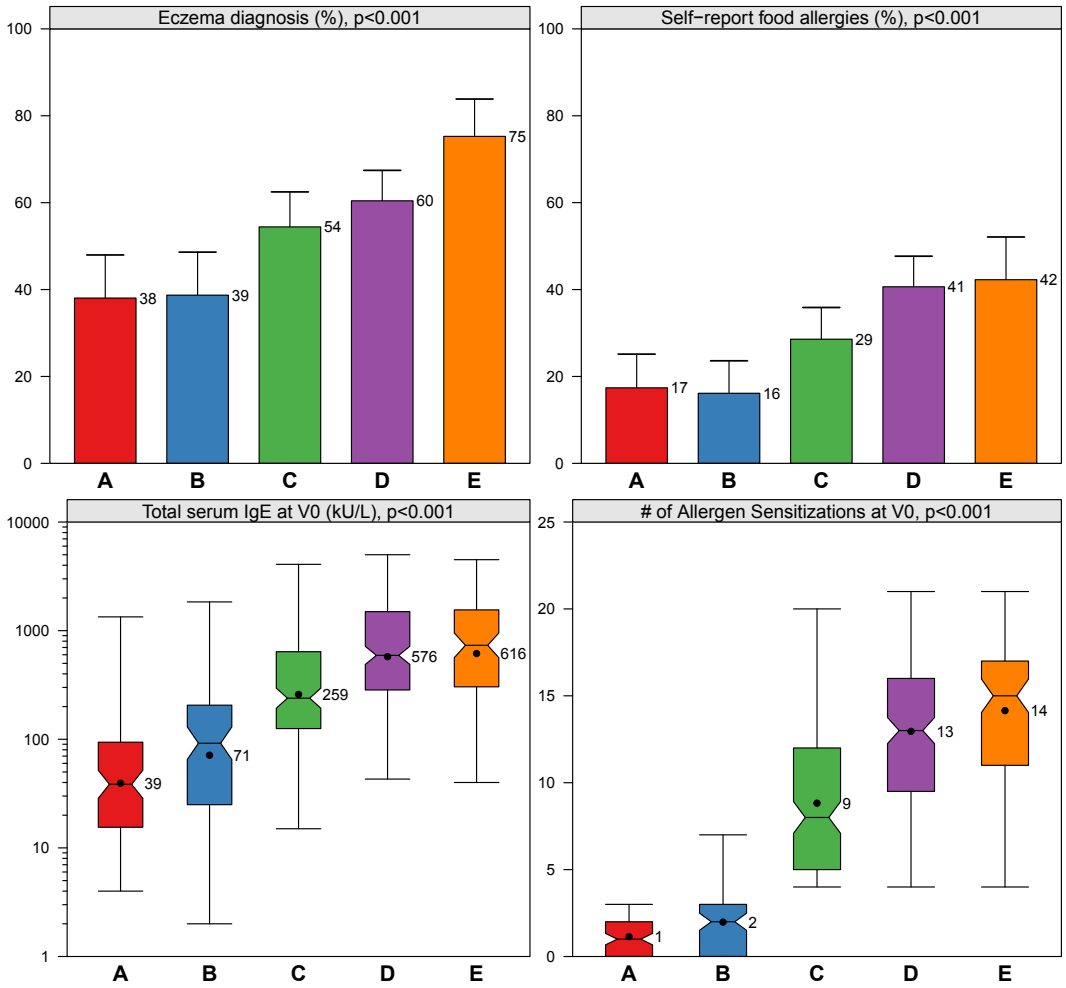


FIG 4. Characteristics related to allergy by cluster. Categorical variables are summarized by bar charts with whiskers for standard errors. Continuous variables are summarized by notched boxplots, such that the box represents the interquartile range, the whiskers add/subtract 1.5 times the 75th/25th percentiles, the line represents the median, and the notch represents the 95% CI around the median. For continuous variables, the mean number of allergen sensitizations or geometric mean of total serum IgE is represented by the *black dot*.

guidelines-based asthma and rhinitis management over a full year is another aspect of our study that addresses limitations of several other HCAs.[1,19] Another strength of this work is the use of a tree-based clustering algorithm, which has major advantages over standard clustering algorithms that use Euclidean distance metrics. In particular, this method adapts well to the inclusion of both continuous and categorical variables in the clustering algorithm, is resistant to outliers, is unaffected by linear scaling, and lessens the effect of collinearity among variables.[14,16]

We identified 5 asthma clusters with characteristics ranging from minimally symptomatic asthma and normal lung physiology with very low levels of allergy and allergic inflammation to highly symptomatic asthma characterized by substantial lung dysfunction, frequent exacerbations despite high-level asthma treatment, and high levels of allergy and inflammation along with the ubiquitous presence of highly symptomatic, difficult to manage allergic rhinitis. For 4 of the 5 clusters, we observed striking parallel relationships between allergic sensitization and indicators of asthma and rhinitis severity. However, we also identified a previously unreported cluster with comparatively low allergy and only slightly impaired pulmonary physiology that remained highly symptomatic on high levels of asthma controller therapy over the study's prospective observation year (cluster B).

Clusters C, D, and E were distinguished by progressively higher degrees of allergy, eczema, food allergy, allergic inflammation, BHR, and allergic rhinitis. We believe that these clusters represent classic T_H2-driven allergic asthma. Although BHR and asthma severity correlate with total serum IgE level[20-22] and allergen sensitization,[23-25] the strength of the association between T_H2-driven pathways and asthma severity varies among different populations and may be less prominent in adults.[6,26,27]

Cluster E was distinguished by treatment-unresponsive asthma with the most impaired lung function and the highest levels of day and night symptoms and exacerbations, despite the highest asthma controller step treatment. We consider cluster E to comprise likely candidates for emerging biological treatments targeting T_H2 pathways in patients with refractory allergic asthma.

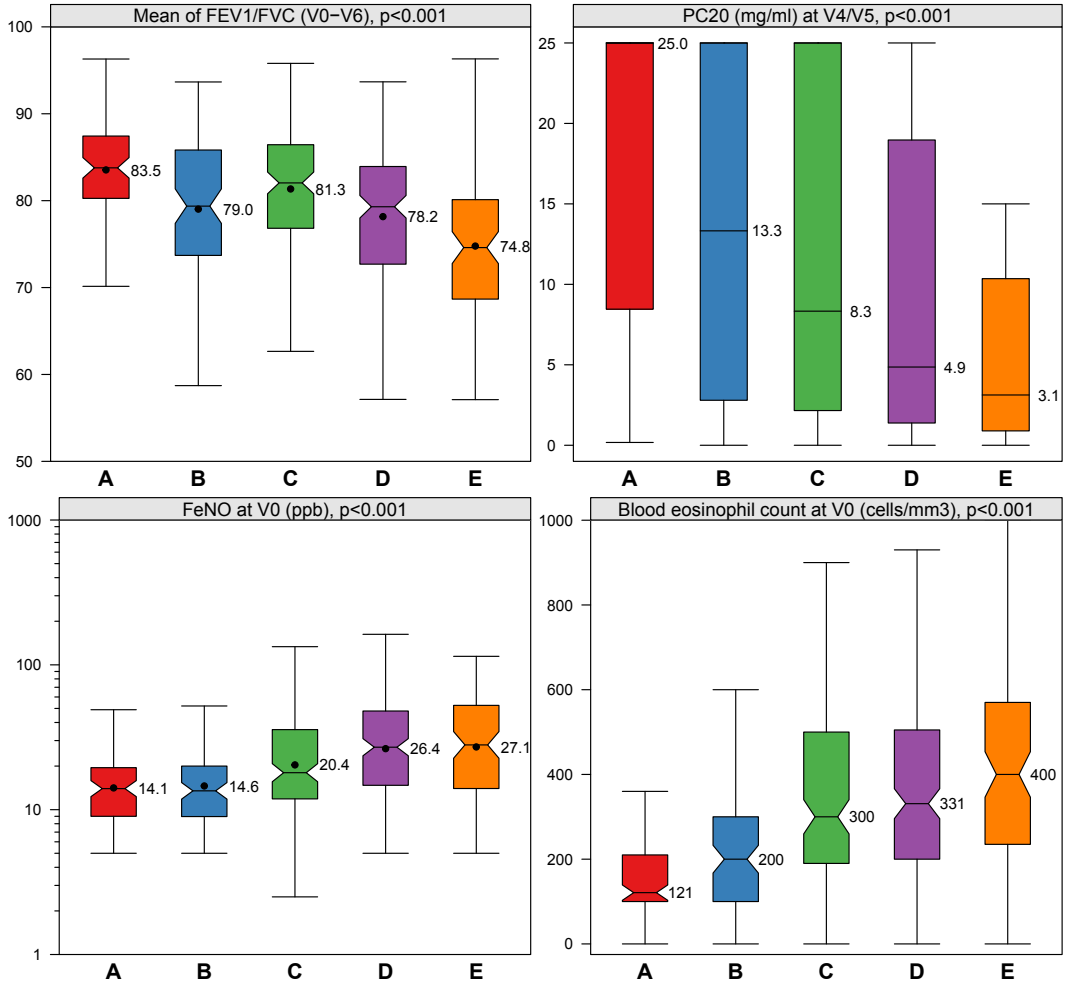


FIG 5. Characteristics of pulmonary physiology and inflammatory biomarkers by cluster. Categorical variables are summarized by barcharts with whiskers for standard errors. Continuous variables are summarized by notched boxplots, such that the box represents the interquartile range, the whiskers add/subtract 1.5 times the 75th/25th percentiles, the line represents the median, and the notch represents the 95% CI around the median. For continuous variables, mean FEV_1/FVC (×100) or geometric mean FENO is represented by the *black dot*, with the exception of blood eosinophils and PC_{20}, where median value is most appropriate. *CASI*, Composite Asthma Severity Index.

Clusters A and B exhibited relatively lower levels of allergen sensitization, total serum IgE level, and minimal allergic inflammation. However, in contrast to cluster A, cluster B had highly symptomatic asthma even while receiving higher levels of controller therapy than the other clusters (except for those with severe allergic asthma comprising cluster E). We speculate that these children may reflect a discrete phenotype of asthma whose symptoms are out of proportion to their degree of readily measurable pulmonary impairment and airway inflammation. Alternatively, these children may have uncontrolled or unrecognized comorbidities such as gastroesophageal reflux disease and rhinosinusitis triggering symptoms or perhaps even be afflicted by asthma masqueraders such as vocal cord dysfunction. Cluster B had the highest percentage of homes with a resident smoker. Although only marginally higher compared with several other clusters, we speculate that environmental tobacco smoke–triggered symptoms, such as cough and wheeze, may have contributed to this cluster's highly symptomatic profile. Additional diagnostic testing and possibly deviation from the progressive application of standard guidelines-based step therapy may need to be considered for these children.

Cluster C was intermediate for allergy or inflammatory biomarkers and had little evidence of impaired pulmonary physiology. Asthma symptoms and medication requirements were minimal and similar to cluster A. Even though allergen sensitization was present, cluster C also had a low degree of rhinitis symptoms and medication scores. Rhinitis is recognized as a potentially important contributor to asthma severity,[28] with the lower airway affected by pathophysiologic pathways responsible for rhinitis in a manner consistent with the "united airway disease" hypothesis.[29] We speculate that cluster C represents a group where allergen sensitization may be partially uncoupled from the clinical manifestations of allergy, as has been well described for some patients with food and inhalant sensitization.[30] Alternatively, compared with clusters D and E, this phenotype had relatively lower levels of allergy and may manifest asthma and rhinitis symptoms that are readily controlled with low-intensity therapy.

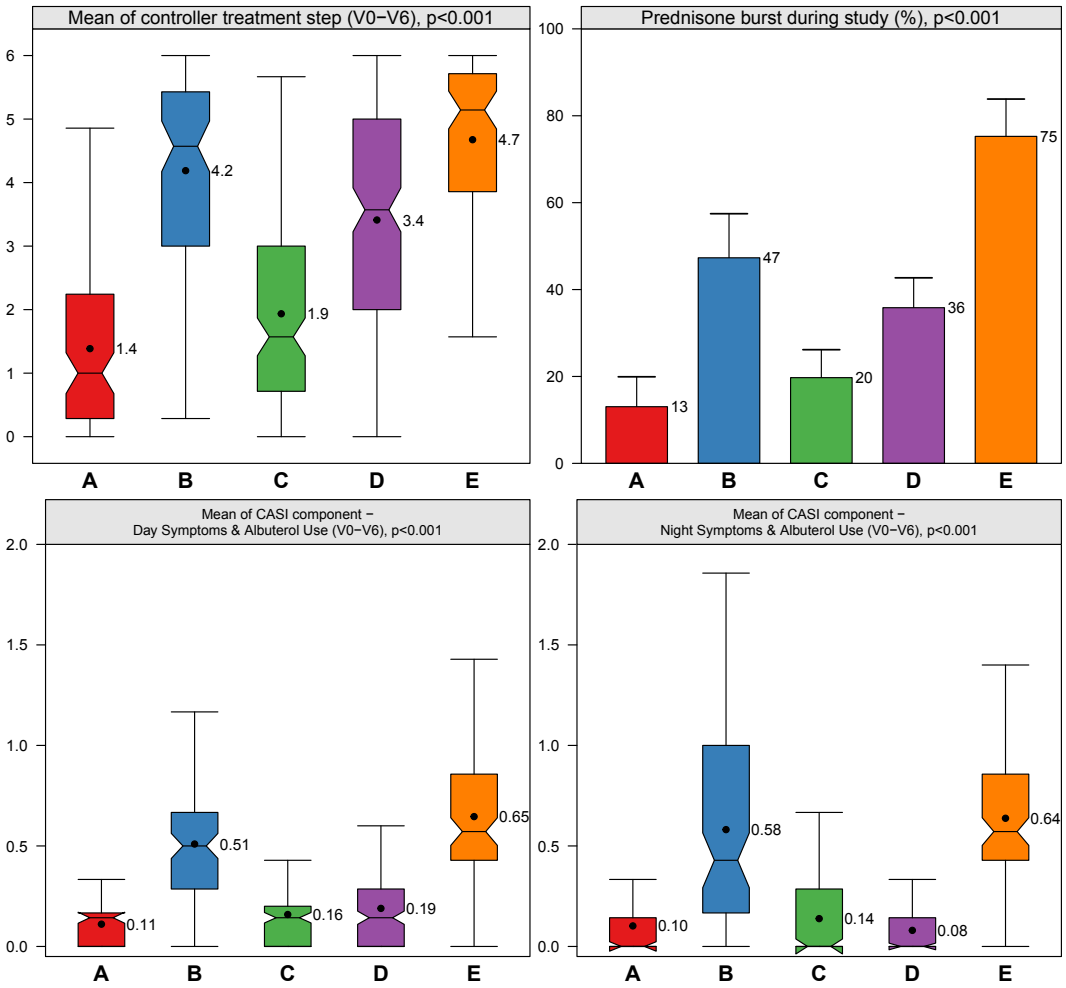


FIG 6. Characteristics of asthma symptoms, exacerbations, and treatment by cluster. Categorical variables are summarized by bar charts with whiskers for standard errors. Continuous variables are summarized by notched boxplots, such that the box represents the interquartile range, the whiskers add/subtract 1.5 times the 75th/25th percentiles, the line represents the median, and the notch represents the 95% CI around the median. For continuous variables, the *black dot* indicates the mean value.

Several HCAs have been reported among children in an age range that approximates our participants.[3-5] The results from these reports are somewhat variable regarding the strength of the association between allergy and apparent asthma severity, as determined by the degree of symptoms, exacerbations, and pulmonary physiology impairment and medication requirements. Discrepancies between these studies can be attributed to differences in study inclusion criteria and the variables selected, which greatly influence clustering patterns. However, some phenotypic characteristics of the reported populations can be compared with clusters identified in the APIC population.

Our results are most similar to an HCA of 1041 children aged 5 to 12 years who enrolled in the Childhood Asthma Management Program (CAMP).[4] These children were recruited for a clinical trial, and an important difference from our population is that enrollees were required to have persistent symptoms and BHR, but were limited to having mild to moderate disease severity. Similar to our results, 5 clusters were distinguished on the basis of degree of allergy, lung function, and asthma burden (primarily exacerbation frequency). Similar to the APIC clusters A and E, CAMP clusters 1 and 5 exhibited the least and highest degree of allergy (sensitization and total serum IgE level), respectively, with corresponding low and high risk of asthma exacerbation. In contrast to our study, a highly symptomatic, high medication requirement cluster with lower levels of allergy, inflammation, and BHR (similar to our cluster B) was not identified. Each cluster in the CAMP cohort had substantial BHR (PC_{20} in the range of 4 mg/mL or lower). It is likely that children similar to those in APIC cluster B were excluded from the CAMP cohort because of exclusion of children who lacked evidence of BHR and lung dysfunction at screening. Furthermore, in contrast to the CAMP population, APIC participants were managed using a step-care approach, which often led to treatment with long-acting beta agonists, which were not used in CAMP.

Similar to our phenotypes, clusters were also identified in a persistent asthma restricted population of 315 children, aged 6 to 12 years in France,[5] that included a highly sensitized cluster exhibiting the most severe asthma and a cluster with little evidence of sensitization exhibiting “mild asthma.”

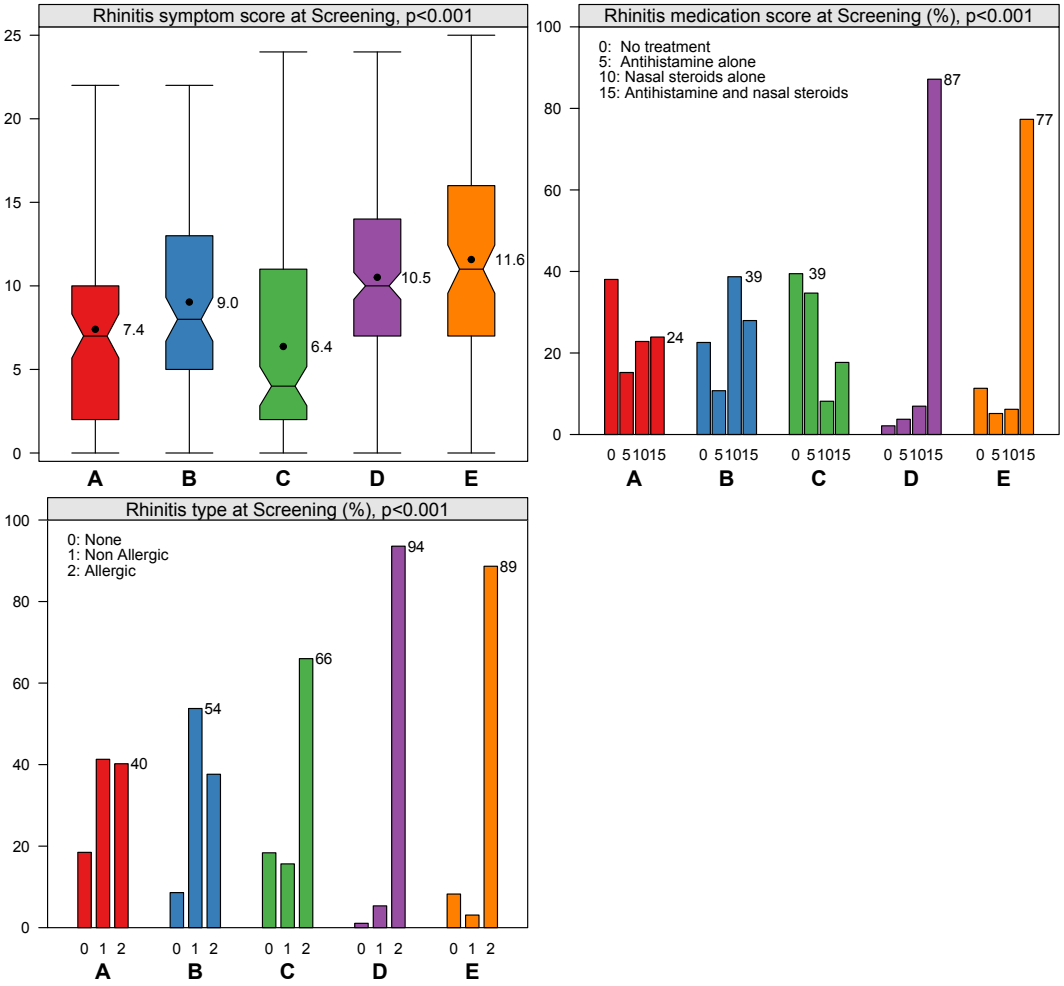


FIG 7. Characteristics of rhinitis by cluster. Categorical variables are summarized by bar charts with whiskers for standard errors. Continuous variables are summarized by notched boxplots, such that the box represents the interquartile range, the whiskers add/subtract 1.5 times the 75th/25th percentiles, the line represents the median, and the notch represents the 95% CI around the median. For rhinitis symptom score, the *black dot* indicates the mean value. A detailed algorithm describing rhinitis medication management during the APIC study can be found in Pongracic et al.[12] *ACT/cACT,* Asthma Control Test/Childhood Asthma Control Test; *CASI,* Composite Asthma Severity Index.

An HCA among 161 children aged 6 to 17 years in the Severe Asthma Research Program was less comparable to the APIC children.[3] Four clusters varied primarily by their duration of asthma and degree of lung dysfunction, with asthma severity being evenly distributed among the clusters. In contrast, the duration of asthma was not significantly different among APIC clusters but the level of symptomatic asthma, rate of asthma exacerbations, and medication requirements varied greatly across the clusters (Table I). This, and other discrepancies, may be related to the restriction of Severe Asthma Research Program enrollment to participants considered to have difficult asthma with required demonstration of BHR or FEV_1 reversibility after albuterol. Similar to our findings, the Severe Asthma Research Program cluster with the least lung dysfunction and asthma medication requirements also had the least allergen sensitization, lowest total serum IgE level, and blood eosinophil counts.

A common limitation among unsupervised HCA is the selection of variables that are somewhat arbitrary and based on the authors' opinions of which factors are likely to be discriminatory among asthma phenotypes. The variables may exclude potentially important host and environmental factors including specific dietary consumption, toxins, allergens, or other risk-modifying exposures. Furthermore, although some variables may contribute to the pathogenesis of asthma in an independent manner, others may be dependent on complex interactions with other variables that would not necessarily be uncovered by cluster analysis. For example, cockroach allergen sensitization combined with high levels of exposure has been shown to have a substantial impact on asthma severity in inner-city children,[24] whereas evaluation of sensitization alone may miss this important risk factor. Also, some variables may lack adequate precision or may not fully represent a given domain, leading to a diminished ability to implicate factors that are truly distinguishing features of asthma phenotypes. For example, the stress domain was represented in our study only by the 10-question Caretaker Perceived Stress Scale score. This tool was recommended in the National Institutes of Health/Agency for Healthcare Research and Quality-sponsored Asthma Outcomes Workshop Expert Report

as a brief, well-validated, and simply administered measure of global stress.[31] However, the Caretaker Perceived Stress Scale does not necessarily capture aspects of chronic stress or other behavioral or psychosocial mediators of asthma outcomes that are common in inner-city living and have been linked to asthma severity, such as violence and severely negative life events.[32-35] Another potential limitation is that data reduction techniques may contribute to the generation of inconsistent clusters that are more sensitive to relatively conservative shifts in the specific variables selected.[19] However, at this time, there is no standard set of variables that can be universally recommended for inclusion in HCA. Finally, our findings may be specific for asthma phenotypes restricted to low-income urban children and not generalizable to other populations.

In spite of these limitations, unsupervised clustering analyses can provide unique information related to the pathophysiology of asthma and other disorders by identifying specific disease characteristics that play a significant role in separating phenotypes. Knowledge of these characteristics can provide rationale for considering management options beyond current standardized treatment guidelines and allow potential targeted strategies to be directed toward those patients most likely to benefit.

In conclusion, there is significant asthma heterogeneity among children living in low-income areas of US inner cities. We found that most asthma in this population appears to cluster by the degree of allergy, rhinitis, allergic inflammatory markers, and impaired pulmonary physiology, with these factors worsening in parallel and correlating with more severe disease. These findings provide a solid basis for personalized care where emphasis on environmental allergen management, allergen desensitization, and anti-T_H2 therapy is more appropriate for an allergic phenotype as opposed to the somewhat less-common persistently symptomatic phenotype with little allergy and inflammation that we also identified in this population.

Clinical implications: Management strategies targeting allergy and allergic inflammation are appropriate for most inner-city allergic asthma phenotypes. This approach may be misdirected in those exhibiting frequent symptoms but little allergy or allergic inflammation.

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Asthma Phenotypes in Inner-City Children

Online Repository

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Table E1. Variables used in the univariate analysis and hierarchical clustering algorithm

	Variables
Demographics	Female
	Race Black Other
	Race[1] Black (non-Hispanic) Hispanic Other/Mixed White (non-Hispanic)
	Age at Screening (years)
	Income < $15,000
	Caretaker completed high school
Family history	Family history of asthma
	Family history of hay fever/rhinitis/allergies
	Family history of eczema
Allergy history	Self-report of food allergies
	History of anaphylaxis
	Eczema diagnosis
Asthma history	Age asthma first diagnosed (months)
	Age asthma symptoms started (years)
	Duration of asthma (months)[1]
	Controller treatment step at Screening
	Controller treatment step at Screening[1] Steps 0-2 Step 3 Steps 4-6
	Asthma Control Test/Childhood ACT (ACT/cACT) at Screening
	ACT/cACT at Screening (categorized)[1,2] Very poorly controlled Not well controlled Well controlled
	CASI component - Day symptoms and albuterol use[3] at Screening
	CASI component - Night symptoms and albuterol use[4] at Screening
	CASI component - Exacerbations[5] at Screening
Body Mass Index	BMI z-score at Screening
	BMI percentile at Screening[1]
Serum Vitamin D	Total 25-hydroxyvitamin D at V0 (ng/mL)
Environmental exposures	Any smokers in the home at Screening
	NicAlert result at Screening (continuous) 0 = 0-10 ng/mL 1 = 10-30 ng/mL 2 = 30-100 ng/mL 3 = 100-200 ng/mL 4 = 200-500 ng/mL 5 = 500-1000 ng/mL 6 = >1000 ng/mL
	Gas stove in home
	Dampness in home

	Variables
	AC unit in child's bedroom
	Forced air for heat in home
	Rodents in home
	Roaches in home
	Pets in home
Stress	Caretaker Perceived Stress Scale at V0
Allergen sensitization[7]	Total serum IgE at V0[6]
	Number of allergen sensitizations (panel of 22)[8] at V0
	Positive Phadiatop screen at V0
	Positive fx5 food allergy screen at V0
	Sensitized to molds[9] at V0
	Sensitized to dust mites[10] at V0
	Sensitized to roaches[11] at V0
	Sensitized to rodents[12] at V0
	Sensitized to pets[13] at V0
	Sensitized to pollen/peanut[14] at V0
	Sensitized to foods[15] at V0
Inflammation	FeNO at V0 (ppb)[6]
	Blood eosinophil count at V0 (cells/mm3)
	Blood neutrophil count at V0 (cells/mm3)
Pulmonary physiology	Bronchodilator response at Screening
	FEV_1 (% predicted) at Screening
	Mean of FEV_1 (% predicted) between V0 and V6
	Variance of FEV_1 (% predicted) between V0 and V6
	FEV_1/FVC at Screening
	Mean of FEV_1/FVC between V0 and V6
	Variance of FEV_1/FVC between V0 and V6
	Methacholine PC_{20}[16] at V4/V5 (mg/ml)[1]
Asthma severity over 12 months	Mean of CASI Component – Day symptoms and albuterol use[3] between V0 and V6
	Variance of CASI Component – Day symptoms and albuterol use[3] between V0 and V6
	Mean of CASI Component – Night symptoms and albuterol use[4] between V0 and V6
	Variance of CASI Component – Night symptoms and albuterol use[4] between V0 and V6
	Mean of CASI Component – Exacerbations[5] between V0 and V6
	Variance of CASI Component – Exacerbations[5] between V0 and V6
	Mean of controller treatment step between V0 and V6
	Variance of controller treatment step between V0 and V6
	Final treatment classification[1,17] Easy-to-Control Indeterminate Difficult-to-Control
	Cumulative adherence to ICS (%)[1]
	Asthma Control Test (ACT)/Childhood ACT at V6[1]
	Asthma Control Test (ACT)/Childhood ACT[2] at V6[1] Very poorly controlled Not well controlled

	Variables
	Well controlled
	Prednisone burst between Screening and V6[1]
Rhinitis at Screening	Rhinitis classification at Screening Allergic Non-Allergic No Rhinitis
	Rhinitis medication score[18] at Screening
	Rhinitis medications at Screening[1] None Antihistamine only Nasal steroids only Antihistamine & nasal steroids
	Rhinitis symptom score[19] at Screening
Rhinitis severity over 12 months	Rhinitis classification over 12 months[1,20] Allergic Non-Allergic No Rhinitis
	Mean of rhinitis medication score[18] between V0-V6[1]
	Variance of rhinitis medication score[18] between V0-V6[1]
	Mean of rhinitis symptom score[19] between V0-V6[1]
	Variance of rhinitis symptom score[19] between V0-V6[1]

1. Variable is included in univariate analysis but not included in the hierarchical clustering algorithm.
2. ACT is categorized as very poorly controlled (≤15), not well controlled (≥16 & ≤19), and well controlled (≥20). cACT is categorized as very poorly controlled (≤12), not well controlled (≥13 & ≤19), and well controlled (≥20).
3. Composite Asthma Severity Index (CASI) component – Day symptoms includes measures of day asthma symptoms and albuterol use in the last 2 weeks (scoring range between 0 and 3)
4. CASI component – Night symptoms includes measures of night asthma symptoms and albuterol use in the last 2 weeks (scoring range between 0 and 3)
5. CASI component – Exacerbations includes hospitalizations and/or oral corticosteroid bursts in the last 2 months.
6. Variable is log10 transformed when establishing variable importance in distinguishing difficult- from easy-to-control asthma.
7. Positive skin prick test and/or a positive specific IgE.
8. *Alternaria tenuis* (skin prick test) or *Alternaria alternata* (specific IgE), *Aspergillus fumigatus* (both skin prick test and specific IgE), *Cladosporium herbarum* (specific IgE only), *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, German cockroach, American cockroach, mouse, rat, cat, dog, oak, pecan, birch, maple, Eastern 8 tree mix, ragweed mix (giant/short; skin prick test) or short ragweed (specific Ige), Timothy grass, Kentucky Blue/June, Orchard and Timothy (K-O-T) grass mix, peanut, egg and milk.
9. *Alternaria tenuis* (skin prick test) or *Alternaria alternata* (specific IgE), *Aspergillus fumigatus* (both skin prick test and specific IgE), *Cladosporium herbarum* (specific IgE only).
10. *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.
11. German cockroach and American cockroach.
12. Mouse and rat.
13. Cat and dog
14. Oak, pecan, birch, maple, Eastern 8 tree mix, ragweed, Timothy grass, K-O-T grass mix and peanut.
15. Egg and milk.
16. Methacholine challenge using a tidal breathing technique was completed in a subset of participants.
17. Easy-to-control is defined by ≤ 100 mcg/day fluticasone on at least four of the six study visits, difficult-to-control is defined by ≥ 500 mcg/day fluticasone on at least four of the six study visits, and indeterminate is defined by neither easy- nor difficult-to-control
18. Rhinitis medication score is set to 0 for no medications, 5 for antihistamines only, 10 for nasal steroids only, and 15 for antihistamines and nasal steroids.
19. Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index.[1]
20. Participants that changed from no rhinitis at Screening to allergic or non-allergic rhinitis at a later visit are classified using the later visit.

Table E2. Rhinitis classifications, medication scores and symptom scores at Screening and between V0 and V6. Continuous variables are summarized using the mean and standard deviation while categorical variables are summarized using the frequency and percent.

Cluster	Timepoint	Prevalence			Disease Activity	
		No Rhinitis	Non-Allergic Rhinitis	Allergic Rhinitis	Rhinitis Symptom Scores[1]	Rhinitis Medication Scores[2]
A	Screening	17 (18.5%)	38 (41.3%)	37 (40.2%)	7.40 (5.66)	6.63 (6.07)
	Mean between V0-V6	14 (15.2%)	47 (51.1%)	31 (33.7%)	4.26 (3.21)	5.77 (5.26)
B	Screening	8 (8.60%)	50 (53.8%)	35 (37.6%)	9.03 (5.79)	8.60 (5.53)
	Mean between V0-V6	5 (5.38%)	53 (57.0%)	35 (37.6%)	7.17 (3.74)	8.45 (4.80)
C	Screening	27 (18.4%)	23 (15.6%)	97 (66.0%)	6.37 (5.96)	5.20 (5.45)
	Mean between V0-V6	16 (10.9%)	24 (16.3%)	107 (72.8%)	5.01 (3.37)	7.53 (5.32)
D	Screening	2 (1.07%)	10 (5.35%)	175 (93.6%)	10.5 (5.15)	14.0 (3.04)
	Mean between V0-V6	0 (0.00%)	12 (6.42%)	175 (93.6%)	6.20 (3.49)	12.5 (3.51)
E	Screening	8 (8.25%)	3 (3.09%)	86 (88.7%)	11.6 (6.21)	12.5 (5.11)
	Mean between V0-V6	4 (4.12%)	3 (3.09%)	90 (92.8%)	8.44 (3.93)	12.5 (4.29)

1. Rhinitis medication score is set to 0 for no medications, 5 for antihistamines only, 10 for nasal steroids only, and 15 for antihistamines and nasal steroids.
2. Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index.[1]

Reference

1. Pongracic JA, Krouse RZ, Babineau DC, et al. Distinguishing Characteristics of Difficult-to-Control Asthma in Inner-City Children. J Aller Clin Immunol Submitted simultaneously.