Journal of Asthma, 49:158–169, 2012
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ISSN: 0277-0903 print/1532-4303 online
DOI: 10.3109/02770903.2011.649872

informa
healthcare

ASTHMA CONTROL

Characterization of Asthma Exacerbations in Primary Care Using Cluster Analysis

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Rationale. Patients with a history of asthma exacerbations are at a higher risk for future episodes of severe asthma exacerbations. Characterization of asthma phenotypes could help improve asthma management, including reducing exacerbations. *Aim.* The aim of this study is to identify distinctive patient characteristics associated with a history of asthma exacerbations using cluster analysis. *Methods.* We used data assessing asthma control from two cross-sectional surveys of adult and pediatric patients in the primary care setting. A supervised cluster analysis with recursive partitioning approach was applied to identify characteristics that maximized the differences across subgroups. *Results.* The sample comprised 2205 adults and 2435 children and adolescents with asthma. Key predictors were identified in seven adult clusters including visiting an asthma specialist, number of hours worked, and excessive use of rescue medication. The rate ratio (RR) for having an exacerbation was significantly higher (2.88; 95% confidence interval (CI), 2.46–3.36) in Cluster 7, with more female patients reporting severe disease, high body mass index, sinus infections, gastroesophageal reflux disease, skin allergies, and lower asthma control score. Features identified in the six pediatric clusters included visiting an asthma specialist, missed school days, race/ethnicity, and age. The RR for having an exacerbation was higher in Cluster 6 (2.36; 95% CI, 2.11–2.64), with patients reporting more severe disease, sinus and skin allergies, and lower asthma control score. *Conclusions.* Identification of specific risk factors can be enhanced by using supervised cluster analysis. This approach allows grouping of patients with unique characteristics to help identify patients at higher risk of exacerbations.

Keywords asthma exacerbations, cluster analysis, primary care, survey

INTRODUCTION

Despite advances in asthma care and management, asthma remains an unpredictable chronic disease with profound public health implications. In both adult and pediatric populations, asthma exacerbations exert a toll on the health-care system and are responsible for significant loss of patient or caregiver productivity (1). Specifically, asthma exacerbations can lead to urgent care and emergency department visits, hospitalizations, discomfort, school and work absenteeism, dissatisfaction with care, and death (1, 2). Asthma exacerbations range in severity from mild transient events (previously called mild exacerbations) to severe life-threatening events. Mild exacerbations are now accepted to be part of poor current asthma control and have different therapeutic approaches to severe events (3). Mild exacerbations present with moderate wheeze and peak expiratory flow (PEF) over 80% predictive or personal best. Moderate exacerbations present with loud wheeze and PEF between 60% and 80% predictive. Severe exacerbations present with usually loud wheeze and PEF <60% predictive or personal best (4).

Asthma treatment guidelines emphasize severity and control within the domains of *impairment and risk.* Assessment of impairment is based on asthma symptoms, quality of life, and functional limitations, while risk is based on the long-term effect of asthma exacerbations, progressive decline in lung function, and medication side effects (4, 5). This paradigm shift in the overall approach with more focus on asthma control addresses the highly variable nature of asthma and highlights the challenge for defining asthma subtypes.

Recently there has been considerable interest in defining asthma phenotypes (6). Asthma subtypes have historically been defined as intrinsic and extrinsic asthma, evolving to atopic and nonatopic asthma, often defined on the basis of positive skin tests to common allergens (7). However, these categorizations are not sufficiently precise for defining specific asthma subtypes, as they tend to focus on one marker or characteristic.

There is an urgent need for novel methodologies to identify asthma subtypes more prone to exacerbations and its associated predictive factors. Cluster analysis is a useful technique for identifying new relevant factors or patterns. Similar or dissimilar patterns within a data set can be partitioned based on cluster algorithms. With this approach, patterns within an identified cluster are more similar to each other than they are to a pattern belonging to a different cluster. The "clustering" can be accomplished

The results of the adult cluster analysis were presented at the Annual Meeting of the American Thoracic Society, May 14–19, 2010, New Orleans, LA (late breaking poster presentation).

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using an unsupervised or supervised method. Unsupervised cluster algorithms do not use predefined class labels that would indicate grouping properties in the data set (8). In contrast, supervised cluster analysis uses prior knowledge and constraints to facilitate and guide the grouping of the data in a relevant pattern. There have been recent reports of unsupervised cluster analyses to classify asthma subtypes (9–12). In the current analysis we used a supervised approach to maximize the difference of variables associated with the exacerbations. The resultant grouping allowed for the classification of data subsets with diverse characteristics and identified patterns that were associated with varying rates of exacerbation. In this analysis, we used data from two cross-sectional surveys in primary care settings across the United States in adults (13) and children (14). Given the importance of asthma exacerbations and the associated risks for increased morbidity and mortality, it is critical to understand the factors leading to these events and their associated phenotypes in a population seen in primary care. The overall objective of the analysis was to identify specific phenotypes based on medical history and personal characteristics in patients with a history of exacerbations and also to highlight the utility of supervised cluster analysis for identifying key risk factors.

Materials and Methods

Patient Population

Characteristics of the adult patient population and the pediatric patient population are reported in more detail in previous publications (GlaxoSmithKline studies ADA111118 and ADA111119, respectively) (13, 14). Briefly, these

Table 1.—Demographic characteristics of the pediatric cohort by cluster.

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	*p*-Value*
Demographic characteristics, *N* (%)	*N* = 2435	*N* = 1269	*N* = 447	*N* = 103	*N* = 169	*N* = 130	*N* = 317	
Gender, *n* (%)								
Male	1356 (56.2)	705 (56.2)	234 (52.6)	63 (62.4)	101 (60.1)	73 (56.2)	180 (57.1)	.4050
Age (years), median (IQR)	9 (6–12)	9 (6–12)	11 (9–14)	5 (5–6)	5 (5–6)	7 (5–10)	9 (6–12)	NC
Race/ethnicity, *n* (%)								
White	941 (39.3)	558 (44.8)	149 (33.9)	0 (0.0)	63 (38.4)	41 (31.5)	130 (41.8)	NC
African American	524 (21.9)	220 (17.7)	103 (23.4)	0 (0.0)	76 (46.3)	36 (27.7)	89 (28.6)	
Hispanic	723 (30.2)	354 (28.4)	152 (34.5)	103 (100.0)	0 (0.0)	45 (34.6)	69 (22.2)	
Other	206 (8.6)	114 (9.1)	36 (8.2)	0 (0.0)	25 (15.2)	8 (6.2)	23 (7.4)	
BMI (kg/m^2), median (IQR)	19 (16–23)	19 (16–23)	22 (18–27)	17 (16–19)	16 (15–19)	19 (16–24)	20 (16–24)	<.0001
Obese (BMI > 95 percentile), *n* (%)	100 (5.0)	43 (4.1)	31 (7.9)	0	2 (1.6)	8 (7.7)	16 (6.0)	0.0025
Education status (caregiver), *n* (%)								
No high school	346 (14.5)	149 (12.0)	82 (18.7)	45 (43.7)	19 (11.2)	18 (14.2)	33 (10.7)	<.0001
High school	1040 (43.5)	499 (40.1)	207 (47.2)	44 (42.7)	90 (53.3)	78 (61.4)	122 (39.5)	
Associate or bachelor's degree	684 (28.6)	388 (31.2)	113 (25.7)	10 (9.7)	42 (24.9)	29 (22.8)	102 (33.0)	
Master's, professional, or doctorate	322 (13.5)	209 (16.8)	37 (8.4)	4 (3.9)	18 (10.7)	2 (1.6)	52 (16.8)	
Household income (2007), *n* (%)								
Less than $34,999	886 (37.4)	402 (32.7)	180 (41.2)	62 (60.8)	75 (45.5)	70 (55.1)	97 (31.5)	<.0001
$35,000– $89,999	577 (24.4)	311 (25.3)	103 (23.6)	9 (8.8)	41 (24.8)	19 (15.0)	94 (30.5)	
$90,000 or higher	424 (17.9)	270 (22.0)	53 (12.1)	5 (4.9)	22 (13.3)	15 (11.8)	59 (19.2)	
Did not answer	481 (20.3)	246 (20.0)	101 (23.1)	26 (25.5)	27 (16.4)	23 (18.1)	58 (18.8)	
Health insurance coverage, *n* (%)								
Private	1085 (45.1)	649 (51.7)	166 (37.6)	16 (16.0)	66 (39.3)	32 (25.0)	156 (50.2)	<.0001
Medicaid	1114 (46.3)	516 (41.1)	233 (52.7)	71 (71.0)	86 (51.2)	81 (63.3)	127 (40.8)	<.0001
Military health	25 (1.0)	9 (0.7)	5 (1.1)	1 (1.0)	4 (2.4)	1 (0.8)	5 (1.6)	.3802
Other insurance	172 (7.2)	82 (6.5)	29 (6.6)	13 (13.0)	14 (8.3)	13 (10.2)	21 (6.8)	.1420
No insurance coverage	35 (1.5)	15 (1.2)	10 (2.3)	0 (0.0)	3 (1.8)	4 (3.1)	3 (1.0)	.2054
Drugs covered by insurance	2306 (96.8)	1209 (97.2)	419 (96.1)	99 (97.1)	157 (95.7)	123 (97.6)	299 (96.1)	.2334
Child missed school time, *n* (%)[a]								
1–3 days	804 (33.6)	324 (26.0)	215 (48.8)	49 (47.6)	84 (50.9)	0 (0.0)	132 (43.3)	NC
≥4 days	232 (9.7)	58 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	125 (96.2)	49 (16.1)	
Not in school	240 (10.0)	135 (10.8)	20 (4.5)	21 (20.4)	35 (21.2)	0 (0.0)	29 (9.5)	
Did not miss school	1093 (45.7)	718 (57.5)	206 (46.7)	33 (32.0)	46 (27.9)	0 (0.0)	90 (29.5)	
Do not know	23 (1.0)	13 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.8)	5 (1.6)	
Parent missed work days, *n* (%)[a]								
Missed 1–3 days	415 (17.6)	155 (12.6)	90 (20.7)	22 (21.6)	46 (27.7)	27 (21.4)	75 (25.0)	<.0001
Missed ≥4 days	61 (2.6)	11 (0.9)	6 (1.4)	3 (2.9)	7 (4.2)	20 (15.9)	14 (4.7)	
Works, but no missed days	1020 (43.3)	618 (50.3)	198 (45.5)	34 (33.3)	60 (36.1)	15 (11.9)	95 (31.7)	
Does not work	862 (36.6)	445 (36.2)	141 (32.4)	43 (42.2)	53 (31.9)	64 (50.8)	116 (38.7)	

Notes: The full analysis included all the variables included in the table.
IQR, interquartile range; BMI, body mass index; NC, not calculated since corresponds to a variable used to split patients into mutually exclusive subgroups.
[a]In the past 4 weeks.
**P*-value for overall comparison across clusters.

studies were multi-site, cross-sectional surveys of patients with asthma visiting their primary health-care provider. Patients completed a brief self-administered (or caregiver-administered) questionnaire collecting demographic and baseline characteristics, including the childhood asthma control test (C-ACT) or the asthma control test (ACT™; QualityMetric Inc., Lincoln, RI, USA). The primary study was approved by a central institutional review board.

Patients coming into the office for a scheduled appointment provided consent prior to any procedures. Eligible pediatric and adolescent patients met the following criteria: (1) aged 4–17 years; (2) reported (self or caregiver) to have asthma diagnosed by a health-care provider; and (3) reported (self or caregiver) no history of cystic fibrosis or chronic bronchitis. To better reflect general practice health care, sites were included if they (1) did not specialize in asthma treatment or did not have an asthma specialist on staff; (2) did not participate in a respiratory-related clinical research study in the previous 3 years; (3) did not use the ACT regularly; and (4) had at least one physician on staff serving as the site's principal investigator and were able to generate a list of all patients with asthma seen in the office during the study period. Eligible adult patients met the following criteria: (1) aged $\geq$18 years; (2) reported asthma diagnosed by a health-care provider; (3) reported no history of chronic obstructive pulmonary disease, chronic bronchitis, or emphysema; and (4) reported use of at least one asthma medication in the previous year.

Questionnaires were used to collect demographic, medical history, and other relevant information (Tables 1–4). For the pediatric survey, caregivers completed all or part of the questionnaire, depending on the patient's age. Asthma impact assessment is a standardized question often used in clinical trials based on a 10-point scale (from 0 or no effect on daily activities, to 10 or complete effect for performing daily activities) for routine activities (e.g., shopping, exercising, or studying). Asthma severity was self-reported. History of asthma exacerbation was defined as the use of oral corticosteroids for asthma, visit to an emergency department or urgent care center because of asthma, or hospitalized overnight because of asthma in the past 12 months.

TABLE 2.—Medical history characteristics of the pediatric cohort by cluster.

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	*p*-Value*
Medical history characteristics, *N* (%)	*N* = 2435	*N* = 1269	*N* = 447	*N* = 103	*N* = 169	*N* = 130	*N* = 317	
Asthma severity, *n* (%)								
Mild	1238 (51.5)	1238 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NC
Moderate	1014 (42.2)	0 (0.0)	417 (93.3)	95 (92.2)	149 (88.2)	99 (76.2)	254 (80.1)	
Severe	152 (6.3)	0 (0.0)	30 (6.7)	8 (7.8)	20 (11.8)	31 (23.8)	63 (19.9)	
Exacerbations, *n* (%)[a]	972 (39.9)	373 (29.4)	153 (34.2)	40 (38.8)	100 (59.2)	86 (66.2)	220 (69.4)	<.0001
C-ACT (score)[b], median (IQR)	19 (16–22)	21 (19–23)	18 (15–21)	19 (16–22)	17 (15–19)	15 (11–18)	17 (14–21)	<.0001
Visited a specialist in the past 12 months, *n* (%)	522 (21.7)	215 (17.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	307 (100)	NC
Reason for visit, *n* (%)								
Annual physical or well visit	380 (16.6)	237 (19.8)	59 (13.9)	19 (20.4)	24 (14.8)	12 (10.6)	29 (9.8)	<.0001
Asthma—routine visit	233 (10.2)	93 (7.8)	49 (11.6)	15 (16.1)	27 (16.7)	18 (15.9)	31 (10.4)	
Asthma—related to attack	278 (12.2)	83 (6.9)	69 (16.3)	13 (14.0)	25 (15.4)	33 (29.2)	55 (18.5)	
Other breathing conditions	512 (22.4)	289 (24.2)	98 (23.1)	17 (18.3)	34 (21.0)	21 (18.6)	53 (17.8)	
Possible ear/sinus infection	195 (8.5)	113 (9.4)	27 (6.4)	3 (3.2)	15 (9.3)	7 (6.2)	30 (10.1)	
Other medical conditions	687 (30.1)	381 (31.9)	122 (28.8)	26 (28.0)	37 (22.8)	22 (19.5)	99 (33.3)	
Allergy and other respiratory conditions, *n* (%)								
Cold or flu in the past 4 weeks	1386 (57.8)	699 (55.9)	235 (52.8)	76 (76.0)	104 (63.4)	90 (69.8)	182 (58.3)	<.0001
Sinus infection in the past 4 weeks	535 (22.3)	237 (19.0)	115 (25.8)	25 (25.0)	33 (20.1)	41 (31.8)	84 (26.9)	.0004
Ear infection or strep in the past 12 months	1021 (42.4)	516 (41.3)	180 (40.4)	57 (57.0)	68 (40.2)	72 (55.4)	128 (40.6)	.0014
Nasal allergy in the past 12 months	1553 (64.5)	768 (61.5)	304 (68.3)	62 (62.0)	118 (69.8)	85 (65.4)	216 (68.6)	.0290
Skin allergies in the past 12 months	589 (24.5)	267 (21.4)	97 (21.8)	23 (23.0)	56 (33.1)	36 (27.7)	110 (34.9)	<.0001
Time of year asthma bothers, *n* (%)								
Spring	1490 (62.0)	695 (56.0)	299 (67.0)	57 (55.9)	132 (78.1)	97 (74.6)	210 (66.7)	<.0001
Summer	1559 (64.9)	336 (27.1)	190 (42.6)	39 (38.2)	79 (46.7)	65 (50.0)	135 (42.9)	<.0001
Fall	844 (35.1)	548 (44.2)	252 (56.5)	58 (56.9)	96 (56.8)	76 (58.5)	173 (54.9)	<.0001
Winter	1203 (50.1)	753 (60.7)	277 (62.1)	84 (82.4)	118 (69.8)	107 (82.3)	238 (75.6)	<.0001
Used asthma medications in the past 4 weeks, *n* (%)	1946 (80.6)	897 (71.8)	390 (87.4)	89 (86.4)	152 (89.9)	125 (96.2)	293 (92.4)	<.0001
Used rescue inhaler in the past 4 weeks, *n* (%)	1732 (71.1)	776 (61.2)	349 (78.1)	84 (81.6)	137 (81.1)	117 (90.0)	269 (84.9)	<.0001
Passive smoke exposure, *n* (%)	358 (14.8)	177 (14.1)	69 (15.5)	14 (13.6)	28 (16.6)	30 (23.1)	40 (12.8)	.1011

Notes: The full analysis included all the variables included in the table. IQR, interquartile range; C-ACT, childhood asthma control test; NC, not calculated since corresponds to a variable used to split patients into mutually exclusive subgroups.

[a]Asthma exacerbation was defined as the use of oral steroids, emergency room or urgent care visit because of asthma, or hospitalization because of asthma in the past 12 months.

[b]C-ACT score: $\geq$20 (well controlled); 13–19 (not well controlled); $\leq$12 (very poorly controlled).

**P*-value for overall comparison across clusters.

TABLE 3.—Demographic and other characteristics of the adult cohort by cluster.

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	*p*-Value*
Demographic characteristics, *N* (%)	*N* = 2205	*N* = 1223	*N* = 107	*N* = 105	*N* = 295	*N* = 106	*N* = 196	*N* = 173	
Gender, *n* (%)									
Female	1580 (72.1)	827 (69.0)	90 (76.9)	68 (63.6)	226 (77.9)	78 (73.6)	152 (77.6)	139 (78.5)	.0009
Age (years), median (IQR)	47 (35–57)	47 (34–57)	57 (42–69)	44 (33–52)	45 (32–57)	45 (35–57)	47 (37–58)	48 (37–59)	<.0001
Race/ethnicity, *n* (%)									
White	1471 (67.8)	828 (69.7)	82 (71.3)	73 (68.2)	177 (61.2)	74 (69.8)	125 (64.8)	112 (64.7)	.0108
African American	258 (11.9)	129 (10.9)	12 (10.4)	13 (12.1)	46 (15.9)	11 (10.4)	24 (12.4)	23 (13.3)	
Hispanic	241 (11.1)	110 (9.3)	14 (12.2)	9 (8.4)	43 (14.9)	7 (6.6)	31 (16.1)	27 (15.6)	
Other	201 (9.3)	121 (10.2)	7 (6.1)	12 (11.2)	23 (8.0)	14 (13.2)	13 (6.7)	11 (6.4)	
BMI (kg/m^2), median (IQR)	30 (26–35)	29 (26–34)	27 (24–33)	29 (26–35)	31 (26–36)	31 (26–37)	32 (28–38)	31 (27–37)	<.0001
Education status, *n* (%)									
No high school	139 (6.4)	65 (5.4)	6 (5.1)	2 (1.9)	19 (6.6)	13 (12.3)	18 (9.3)	16 (9.3)	<.0001
High school	940 (43.1)	487 (40.7)	50 (42.7)	29 (26.9)	124 (43.2)	67 (63.2)	96 (49.5)	87 (50.6)	
Associate or bachelor's degree	760 (34.9)	431 (36.0)	38 (32.5)	56 (51.9)	109 (38.0)	22 (20.8)	60 (30.9)	44 (25.6)	
Master's, professional, or doctorate	341 (15.6)	213 (17.8)	23 (19.7)	21 (19.4)	35 (12.2)	4 (3.8)	20 (10.3)	25 (14.5)	
Household income (2007), *n* (%)									
Less than $34,999	608 (28.1)	278 (23.4)	33 (28.9)	10 (9.4)	84 (29.6)	54 (51.4)	76 (39.8)	73 (41.5)	<.0001
$35,000–$89,999	796 (36.8)	445 (37.5)	43 (37.7)	54 (50.9)	109 (38.4)	28 (26.7)	61 (31.9)	56 (31.8)	
$90,000 or higher	395 (18.3)	249 (21.0)	18 (15.8)	30 (28.3)	41 (14.4)	9 (8.6)	30 (15.7)	18 (10.2)	
Did not answer	365 (16.9)	216 (18.2)	20 (17.5)	12 (11.3)	50 (17.6)	14 (13.3)	24 (12.6)	29 (16.5)	
Health insurance coverage, *n* (%)									
Private	1606 (73.7)	927 (77.8)	81 (69.8)	99 (92.5)	208 (72.0)	57 (53.8)	126 (64.9)	108 (61.4)	<.0001
Medicare	403 (18.5)	174 (14.6)	49 (42.2)	7 (6.5)	56 (19.4)	28 (26.4)	41 (21.1)	48 (27.3)	<.0001
Medicaid	168 (7.7)	62 (5.2)	5 (4.3)	0 (0.0)	21 (7.3)	25 (23.6)	28 (14.4)	27 (15.3)	<.0001
Military health	45 (2.1)	20 (1.7)	7 (6.0)	1 (0.9)	5 (1.7)	1 (0.9)	4 (2.1)	7 (4.0)	.0237
Other insurance	109 (5.0)	50 (4.2)	5 (4.3)	2 (1.9)	19 (6.6)	6 (5.7)	16 (8.2)	11 (6.3)	.1079
No insurance coverage	89 (4.1)	54 (4.5)	1 (0.9)	1 (0.9)	14 (4.8)	2 (1.9)	12 (6.2)	5 (2.8)	.0880
Patient work time (hours per week), median (IQR)[a]	35 (0–40)	40 (0–40)	0 (0–15)	42 (40–50)	30 (0–40)	0 (0–40)	16 (0–40)	7 (0–40)	NC
Patient missed work or school days, *n* (%)									
Missed work/school in the past 4 weeks	232 (16.5)	63 (7.5)	6 (15.8)	10 (9.3)	49 (28.2)	7 (14.9)	62 (56.9)	35 (38.0)	<.0001

Notes: The full analysis included all the variables included in the table. IQR, interquartile range; BMI, body mass index; NC, not calculated since corresponds to a variable used to split patients into mutually exclusive subgroups.
[a]Patient work time/hours per week ranged from 0 to 50 hours per week.
**P*-value for overall comparison across clusters.

Statistical Methods

Descriptive statistics were used to present demographic and medical history data, proportions were used for categorical variables, and medians with interquartile ranges (IQRs) were used for continuous variables. A supervised cluster analysis with recursive partitioning approach was used to identify subgroups that maximized the difference among patients with a history of past exacerbations, where the minimum size of each subgroup leaf or terminal node was set as 100. The complexity parameter was used to control the size of the tree by minimizing the cross-validation error (15, 16). A subgroup membership was assigned to each patient based on the selected tree representing the pediatric and adult cohort. Baseline differences among the subgroups were tested using a nonparametric Kruskal–Wallis test for continuous variables and the χ^2-test for categorical variables. Generalized linear models with multiple contrasts were used to compare the likelihood of having an exacerbation between subgroups of patients. The rate ratio (RR) and 95% confidence intervals were used to estimate the differences in exacerbations for each cluster using Cluster 1 as the control. All tests were two sided; $p \leq .05$ was considered statistically significant. The analyses were performed using R version 2.10.1 and SAS version 9.2 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

A total of 4640 patients with asthma were included in the two cohorts. Of these, 2205 were adults and 2435 were children and adolescents.

Pediatric Population

Demographic characteristics and medical history information of the overall pediatric cohort are shown in Tables 1 and 2. Fifty-six percent of the subjects were male; race/ethnic distribution included 39% Whites, 22% African Americans, and 30% Hispanics. Regarding health insurance coverage, 45% had private insurance and 46% had Medicaid. Subjects/caregivers self-reported asthma severity as mild (52%), moderate (42%), or severe (6%). Passive smoking was reported in 15%. The median C-ACT was 19 (not well controlled). Forty percent reported a history of

TABLE 4.—Medical history characteristics of the adult cohort by cluster.

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	*p*-Value*
Medical history characteristics, *N* (%)	*N* = 2205	*N* = 1223	*N* = 107	*N* = 105	*N* = 295	*N* = 106	*N* = 196	*N* = 173	
Asthma severity, *n* (%)									
Mild	1047 (48.9)	738 (62.6)	65 (56.5)	70 (66.7)	94 (33.2)	17 (16.5)	28 (15.1)	35 (20.5)	<.0001
Moderate	958 (44.8)	411 (34.9)	41 (35.7)	32 (30.5)	171 (60.4)	77 (74.8)	125 (67.6)	101 (59.1)	
Severe	135 (6.3)	29 (2.5)	9 (7.8)	3 (2.9)	18 (6.4)	9 (8.7)	32 (17.3)	35 (20.5)	
Exacerbations, *n* (%)[a]	727 (33.0)	262 (21.8)	44 (35.2)	55 (50.9)	97 (33.3)	43 (40.6)	115 (58.7)	111 (62.7)	<.0001
Asthma control test (score), median (IQR)[b]	18 (14–22)	20 (17–23)	19 (16–22)	20 (18–22)	16 (14–19)	12 (10–15)	11 (9–13)	13 (10–16)	<.0001
Visited a specialist in the past 12 months, *n* (%)	385 (17.7)	0 (0)	107 (100)	105 (100)	0 (0)	0 (0)	0 (0)	173 (100)	NC
Reason for visit, *n* (%)									
Annual physical or well visit	300 (14.1)	194 (16.6)	22 (18.2)	15 (14.2)	31 (11.2)	20 (18.9)	0 (0.0)	18 (10.5)	NC
Asthma—routine visit	216 (10.2)	100 (8.6)	15 (12.4)	9 (8.5)	36 (13.0)	0 (0.0)	34 (19.1)	22 (12.9)	
Asthma—related to attack	155 (7.3)	42 (3.6)	4 (3.3)	3 (2.8)	25 (9.0)	0 (0.0)	62 (34.8)	19 (11.1)	
Other breathing conditions	479 (22.5)	231 (19.8)	21 (17.4)	25 (23.6)	76 (27.4)	0 (0.0)	82 (46.1)	44 (25.7)	
Other medical conditions	976 (45.9)	600 (51.4)	59 (48.8)	54 (50.9)	109 (39.4)	86 (81.1)	0 (0.0)	68 (39.8)	
Allergy and other conditions									
Cold or flu in the past 4 weeks	885 (40.3)	434 (36.2)	33 (26.8)	40 (37.4)	141 (48.5)	48 (45.3)	108 (55.1)	81 (46.0)	<.0001
Sinus infection in the past 4 weeks	611 (27.8)	267 (22.3)	48 (39.0)	23 (21.5)	97 (33.3)	34 (32.1)	72 (36.7)	70 (39.8)	<.0001
GERD in the past 12 months	770 (35.1)	385 (32.2)	42 (34.1)	29 (26.9)	113 (39.0)	43 (40.6)	84 (43.1)	74 (41.8)	.0030
Nasal allergy in the past 12 months	1422 (64.8)	730 (61.1)	91 (74.0)	76 (70.4)	201 (69.3)	70 (66.0)	128 (65.6)	126 (71.2)	.0043
Skin allergies in the past 12 months	433 (19.7)	212 (17.8)	25 (20.3)	21 (19.4)	69 (23.8)	22 (20.8)	34 (17.4)	50 (28.2)	.0217
Time of year asthma worsens, *n* (%)									
Spring	1580 (73.7)	806 (69.2)	81 (71.1)	82 (78.8)	222 (76.6)	84 (80.0)	166 (86.5)	139 (79.9)	<.0001
Summer	993 (46.3)	478 (41.0)	58 (50.9)	47 (45.2)	143 (49.3)	66 (62.9)	103 (53.6)	98 (56.3)	<.0001
Fall	1229 (57.3)	627 (53.8)	67 (58.8)	69 (66.3)	179 (61.7)	64 (61.0)	118 (61.5)	105 (60.3)	.0269
Winter	1326 (61.8)	679 (58.3)	58 (50.9)	58 (55.8)	187 (64.5)	76 (72.4)	137 (71.4)	131 (75.3)	<.0001
Used asthma medications in the past 4 weeks, *n* (%)	1824 (83.5)	915 (76.6)	103 (88.8)	92 (85.2)	248 (85.8)	103 (97.2)	193 (98.5)	170 (96.6)	<.0001
Used rescue inhaler in the past 4 weeks, *n* (%)[c]									
3 or more times a day	184 (8.3)	49 (4.1)	5 (4.0)	3 (2.8)	0 (0.0)	25 (23.8)	68 (34.7)	34 (19.2)	NC
1–2 times per day	477 (21.6)	181 (15.1)	25 (20.0)	10 (9.3)	0 (0.0)	80 (76.2)	128 (65.3)	53 (29.9)	
2–3 times per week	480 (21.8)	244 (20.3)	26 (20.8)	22 (20.4)	146 (50.2)	0 (0.0)	0 (0.0)	42 (23.7)	
Once a week or less	513 (23.3)	331 (27.5)	37 (29.6)	39 (36.1)	75 (25.8)	0 (0.0)	0 (0.0)	31 (17.5)	
Not at all	550 (25.0)	397 (33.0)	32 (25.6)	34 (31.5)	70 (24.1)	0 (0.0)	0 (0.0)	17 (9.6)	
Smoking status, *n* (%)									
Current smoker	622 (28.7)	334 (28.2)	35 (30.2)	31 (29.0)	74 (26.0)	31 (29.8)	68 (35.1)	49 (28.3)	
Former smoker	298 (13.8)	154 (13.0)	8 (6.9)	4 (3.7)	48 (16.8)	29 (27.9)	31 (16.0)	24 (13.9)	
Nonsmoker	1245 (57.5)	698 (58.9)	73 (62.9)	72 (67.3)	163 (57.2)	44 (42.3)	95 (49.0)	100 (57.8)	<.0001

Notes: The full analysis included all the variables included in the table. IQR, interquartile range; GERD, gastroesophageal reflux disease; NC, not calculated since corresponds to a variable used to split patients into mutually exclusive subgroups.
[a]Asthma exacerbation was defined as the use of oral steroids, emergency room or urgent care visit because of asthma, or hospitalization because of asthma in the past 12 months.
[b]Asthma control test score: ≥20 (well controlled); 16–19 (not well controlled); ≤15 (very poorly controlled).
[c]Derived from the asthma control test.
**P*-value for overall comparison across clusters.

exacerbations in the past 12 months, 22% had visited a specialist in the past 12 months, and one-third had missed 1–2 days of school time in the past 4 weeks.

Figure 1 depicts the most distinguishing features of each cluster. Figure 3 illustrates the distribution of variables/characteristics based on importance to predict exacerbations. The top three characteristics were C-ACT, visit to the office due to a respiratory infection, and age. The six clusters identified through the analysis are presented in Figure 5.

Adult Population

Demographic characteristics and medical history information of the overall adult cohort are shown in Tables 3 and 4. The majority of adult subjects were female (72%), and the mean body mass index (BMI) was 30 kg/m^2. Regarding health insurance coverage, 74% had private insurance and 19% had Medicare. Subjects self-reported asthma severity as mild (49%), moderate (45%), or severe (6%). Current smoking was reported in 28.7% and nonsmoking in 57%. The median ACT was 18 (not well controlled). One-third of the subjects reported a history of exacerbations in the past 12 months, 18% had visited a specialist in the past 12 months, and 17% reported missing work or school in the past 4 weeks.

Figure 2 depicts the most distinguishing features of each cluster. Figure 4 illustrates the distribution of variables/characteristics based on importance to predict exacerbations. The top three characteristics were BMI, age, and ACT score. The seven clusters identified through the analysis are presented in Figure 6.

Distinguishing features of each pediatric asthma

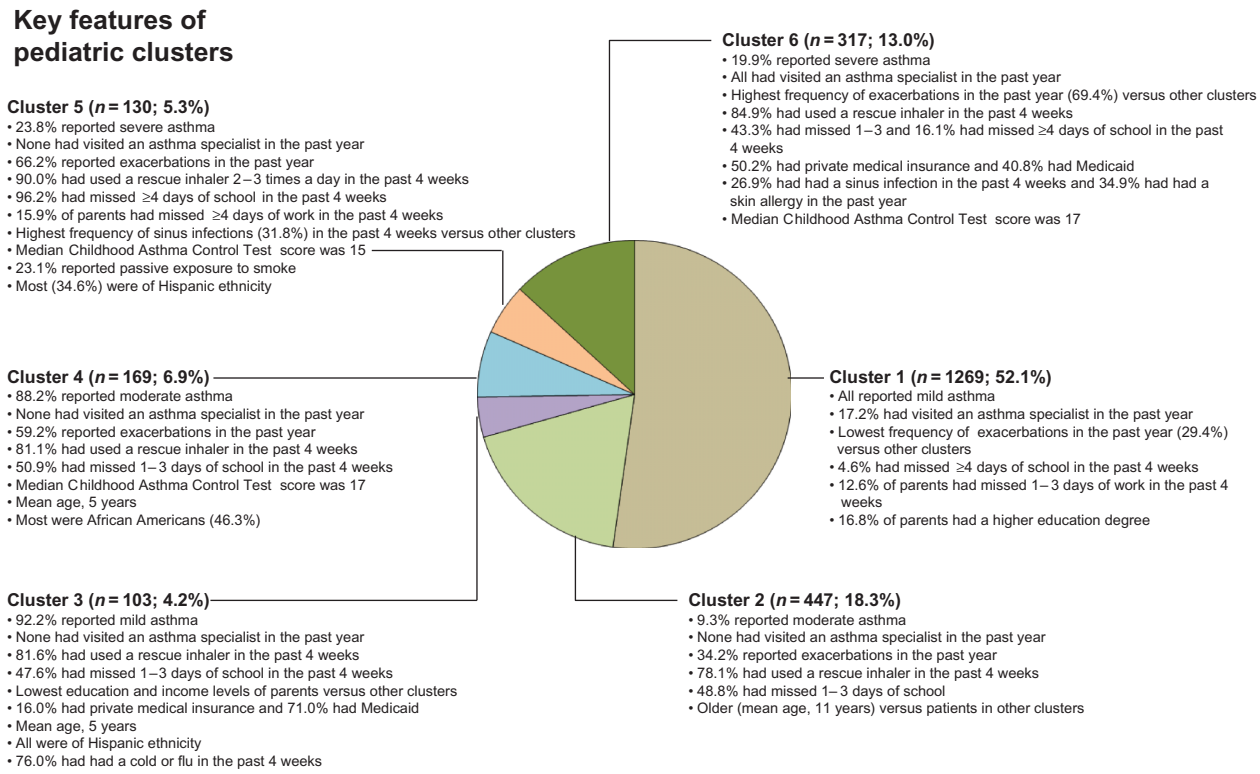

FIGURE 1.—Distinguishing features of each pediatric asthma cluster.

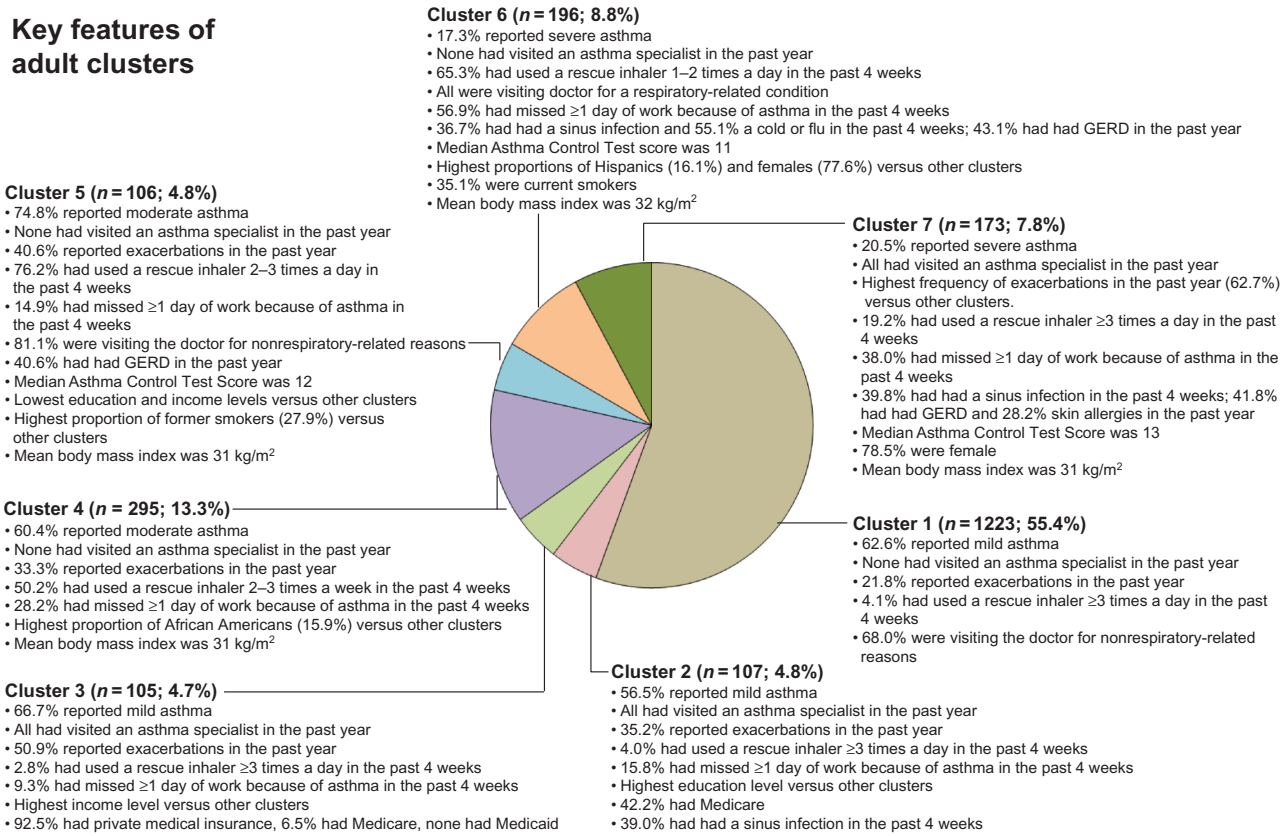

FIGURE 2.—Distinguishing features of each adult asthma cluster.

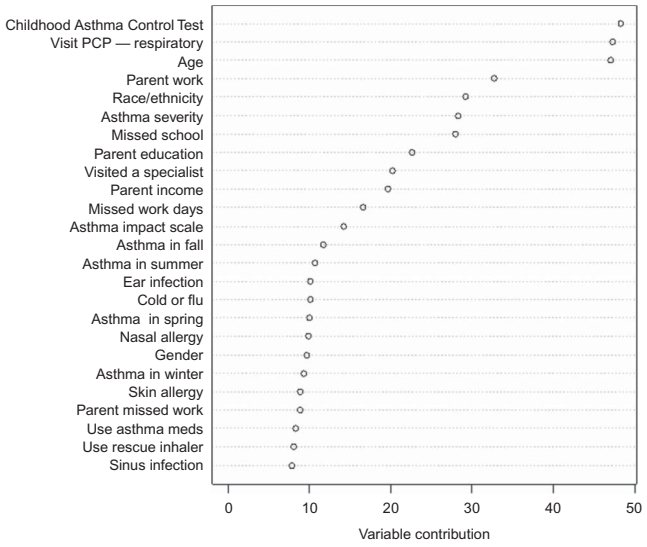

FIGURE 3.—Variable importance to classify exacerbations in the pediatric cohort.
This figure represents the importance of a variable in terms of the contribution each variable has for classifying the level of pediatric exacerbations. Each dot indicates the value of the increase in the contribution of a given variable.

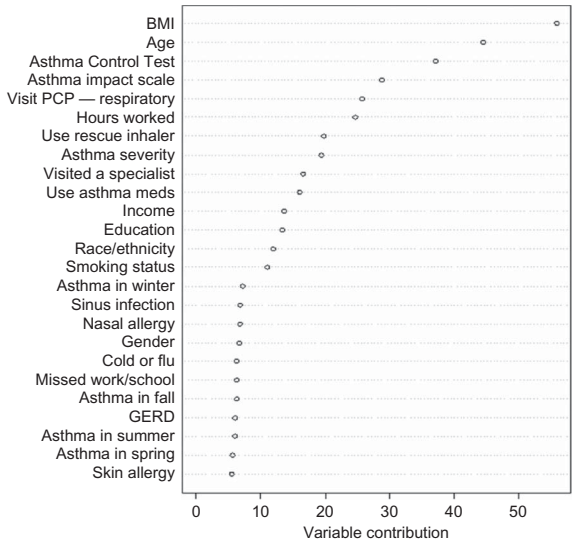

FIGURE 4.—Variable importance to classify exacerbations in the adult cohort.
This figure represents the importance of a variable in terms of the contribution each variable has for classifying the level of adult exacerbations. Each dot indicates the value of the increase in the contribution of a given variable.

DISCUSSION

This is the largest cluster analysis completed to date in the adult and pediatric primary care setting incorporating a novel approach to study asthma exacerbations. The morbidity and mortality associated with asthma exacerbations are often caused by a failure to appreciate the severity of the episode and factors related to uncontrolled disease (17). In the current analysis exacerbations met the criteria for severe asthma exacerbations defined as events that require urgent action on the part of the patient and physician (use of systemic steroids) to prevent a serious outcome, such as hospitalization or death from asthma (3).

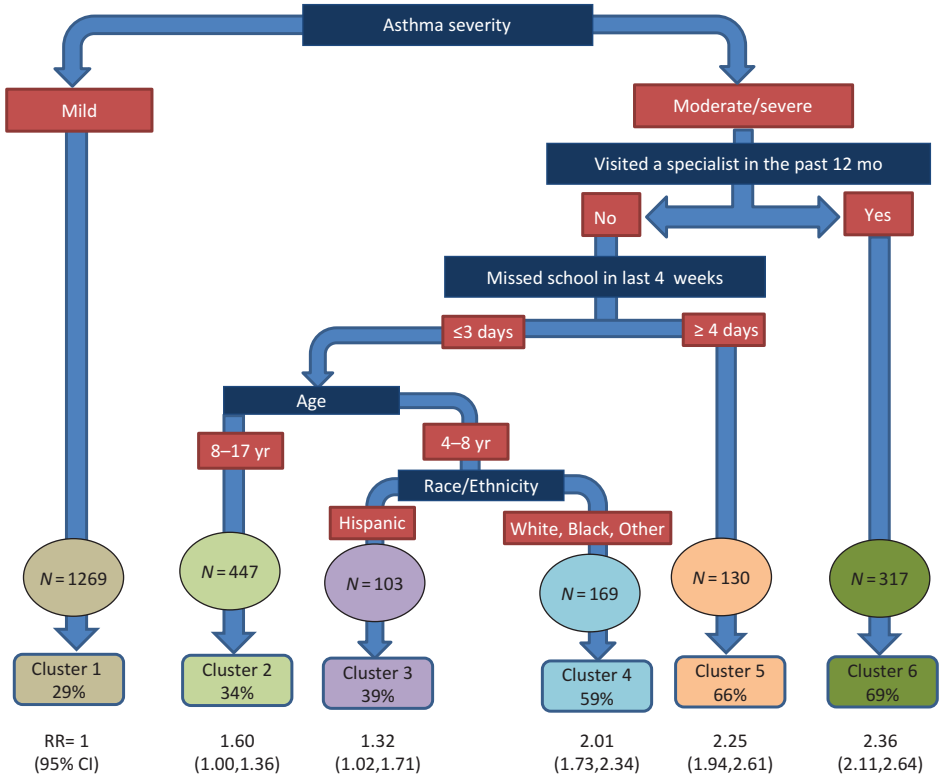

FIGURE 5.—Tree analysis defining clusters in the pediatric cohort in relation to exacerbations.
The sample size for each cluster is presented in the circles (over the arrows). The rate of exacerbations for each cluster is presented in the rectangles. RR, rate ratio.

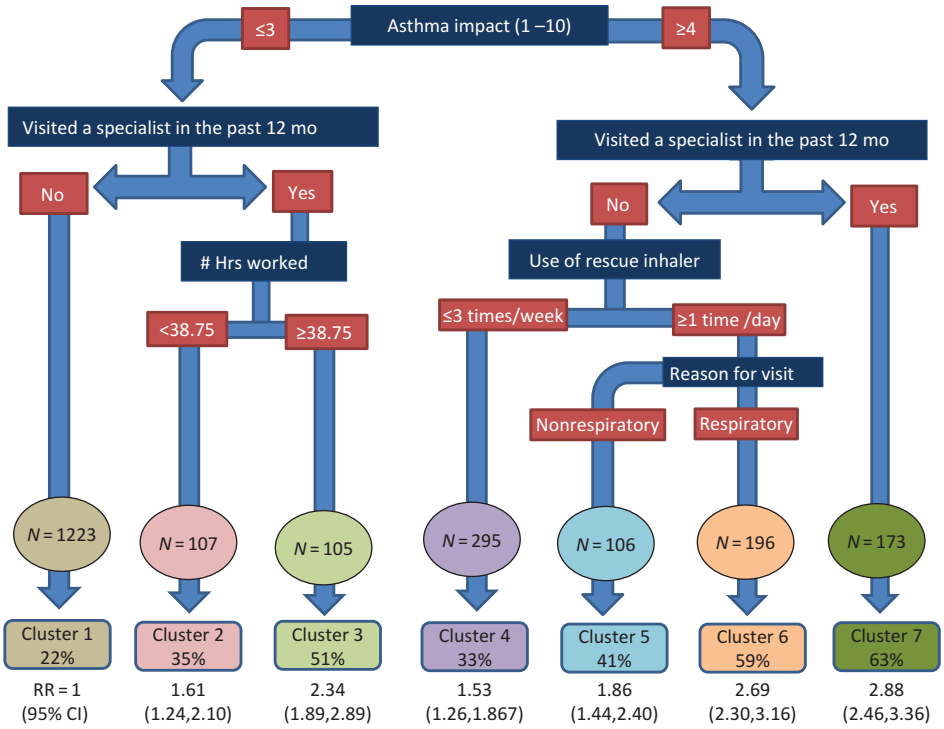

FIGURE 6.—Tree analysis defining clusters in the adult cohort in relation to exacerbations.
The sample size for each cluster is presented in the circles (over the arrows). The percent rate of exacerbations for each cluster is presented in the rectangles. RR, rate ratio.

Severe asthma exacerbations can occur in patients with all degrees of asthma severity. Although their frequency can be increased in patients with difficult-to-control asthma, even patients considered to have mild, easy-to-treat asthma can experience severe asthma exacerbations (3). The analysis focused on patient-reported data and did not include clinical measures or biomarkers, offering a practical opportunity for understanding risk factors in settings where specialized assessments such as spirometry or exhaled nitric oxide are not always available (18).

In general, the level of asthma control and the frequency of exacerbations are linked, with poor control resulting in more frequent exacerbations. Not surprisingly, in the current analysis an association between the level of uncontrolled disease and clusters with higher frequency of exacerbations was identified. This highlights the importance of assessing regularly both impairment (control) and risk (exacerbations) (4, 5). In the pediatric cohort, Clusters 2, 4, 5, and 6 fell in the not well-controlled range (C-ACT score 19–13). Asthma control is a good marker, but not sufficient, to predict exacerbations with precision. This is consistent with recent findings of a long-term clinical trial in children highlighting the challenges of predicting asthma exacerbations, even when multiple measures are used (19). Similarly, in the adult cohort, the level of asthma control in Clusters 5, 6, and 7 fell in the very poorly controlled range (ACT score < 15).

In the pediatric Clusters 5 and 6, sinus infection and skin allergies were associated with more exacerbations. The difference in reported history of sinus infection was not consistent across other pediatric clusters (with less risk for exacerbations). Hispanic children (4–8 years of age) in Cluster 3 were less likely to have exacerbations than non-Hispanic children in Cluster 4. Interestingly, the percent of parents with higher education in Cluster 1 (mild disease) was similar to Cluster 6 (severe disease). In contrast, Clusters 3 and 5 had the lowest level of education, with RRs of 1.32 and 2.25, respectively, highlighting the fact that single measures are difficult to interpret as predictors of exacerbations. Fitzpatrick and colleagues (11) recently reported the results of an unsupervised cluster analysis using 12 continuous and composite variables among 161 children. Although direct comparisons cannot be established with our study, the four reported clusters were distinguished by age, race, asthma duration and onset, history of sinusitis, gastroesophageal reflux, atopic sensitization, and exhaled nitric oxide. Clusters also differed based on medication, health-care use, and lung function (11).

In school-age children, uncontrolled asthma has led to an estimated annual loss of 12.8 million school days, or approximately 3.2 missed days of school for each student with asthma in the United States (20, 21). In our analysis, children who missed ≥4 days of school were in the clusters with the highest percentage of severe asthma, had a low asthma control, reported sinus infections, cold, or flu, had high passive smoke exposure, and had high use of rescue medication. Caregivers of children with uncontrolled asthma also missed more days of work because of their

child's asthma. Of note, these children reported visiting a specialist in the past 12 months, but were not followed by a specialist on a regular basis.

Schatz et al. (22) identified that poor asthma control in adult patients was associated with low income, absence of regular specialist care, African Americans and Hispanics, and gastroesophageal reflux disease (GERD) among other factors. Likewise Peters et al. (23) reported that poor control was associated with low education and income, chronic sinusitis, and GERD, among other factors. In our analysis, we identified females, Hispanic ethnicity, having Medicaid, obesity, cold, or flu, sinusitis, GERD, and increased use of rescue medication as factors associated with exacerbations predominantly in adult Clusters 6 and 7.

Recent reports using unsupervised cluster analysis have focused on objective parameters including markers of lung function and inflammation (9–12). Haldar and colleagues identified three clusters in primary care from a cohort of 184 patients in the United Kingdom (9). The clusters were represented by early-onset atopic, obese noneosinophilic, and benign asthma. Consistent with our observations, some clusters reported in the primary care population had milder disease with significantly fewer symptoms and other unique characteristics such as increased BMI, exacerbation rate, and female gender. However, it is not possible to establish direct comparisons because of differences in methodology and end points. Similarly, Moore et al. (10) identified different phenotypes overlapping across adult asthma severities. The characteristics of patients seen by specialists ranged from early onset of atopic asthma with normal lung function and minimal health-care utilization to patients with severe airflow obstruction. Sinusitis and GERD were associated with more severe disease, as in our study. Cluster 3 and 4 in the adult cohort show some important discordance between impairment and risk. Cluster 3 appears to be high risk and low impairment and Cluster 4 appears to be average risk and high impairment (although without much rescue inhaler use).

In the current study, responder bias must be considered when evaluating these results, since the information was self-reported through questionnaires completed by the patient and/or caregiver and thus is limited by the quality of respondent recall and respondents' ability to comprehend the intent of the questions. In addition, these results characterize patients with asthma who were seeking medical care (respiratory and nonrespiratory) for any reason at primary care settings and, therefore, may not be generalizable to patients who may receive asthma care from a specialist or in the ED. Because this study excluded sites that specialize in asthma or had an asthma specialist on staff, the estimate of severity and uncontrolled asthma may be overestimated. However, to minimize some of these limitations, we conducted a chart review of participants and nonparticipants in the study and confirmed that the demographic and general characteristics of the participant and nonparticipant subsamples were similar, providing further confidence that those included in the study indeed had asthma. In addition, assessment of self-reported asthma was characterized in a similar fashion as in other previous reports (20, 21). Another limitation in the methodology is the node size of 100 which could be restrictive, since changing the node size may alter the profile of the clusters. Finally, this analysis requires prospective validation to confirm these findings.

CONCLUSIONS

Overall, this study showed that there are marked differences in characteristics between the adult and pediatric cohorts (Table 5). The only characteristic common in both cohorts was history of visiting an asthma specialist in the previous year. Other clinical factors such as asthma impact score and asthma severity were independently associated with the pediatric cohort and adult cohort, respectively (Figures 7 and 8). The main individual factors predicting exacerbations across the clusters, regardless of grouping, were asthma control and age. In addition, visiting the office due to a respiratory infection and BMI were associated with the pediatric cluster and adult cluster, respectively.

Approximately two-thirds of patients with asthma receive care from primary care clinicians, such as internists, family practitioners, pediatricians, or nurse practitioners. The other third is under the care of specialists, including allergists or pulmonologists (18). This information underscores the importance of having a good understanding of the characteristics of patients seen in primary care. Identification of modifiable risk factors in relation to asthma exacerbations may offer the opportunity to implement tailored interventions to improve asthma quality of life and control. In this analysis, about half of the patient population in both cohorts reported having mild

TABLE 5.—Comparison of characteristics defining grouping between pediatric and adult cohorts.

Characteristics	Pediatric cohort	Adult cohort
Clinical		
Asthma severity (mild vs. moderate/severe)	√	
Asthma impact score (≤3 vs. ≥4)		√
Use of rescue inhaler (≤3 times/week vs. ≥1 time/day)		√
Demographic		
Age (4–8 years vs. >8–17 years)	√	
Race/ethnicity (White, African American, Other, vs. Hispanic)	√	
Other		
Visit a specialist in the past 12 months (yes vs. no)	√	√
Reason for office visit (nonrespiratory vs. respiratory)		√
Number of hours worked (<38.75 vs. ≥38.75)		√
Missed school in the last 4 weeks (≤3 days vs. ≥4 days)	√	

Notes: The table illustrates "visiting a specialist in the past 12 months" as a similarity between both the adult and pediatric cohorts. In the adult cohort, asthma score and rescue medication use were key clinical characteristics distinguishing the population, whereas in the pediatric cohort, asthma severity, age, and race/ethnicity were more important. Other characteristics related to the adult cohort were reason for office visit and number of hours worked. In the pediatric cohort missed school in the previous month was a key variable to further distinguish the cohort into unique clusters.

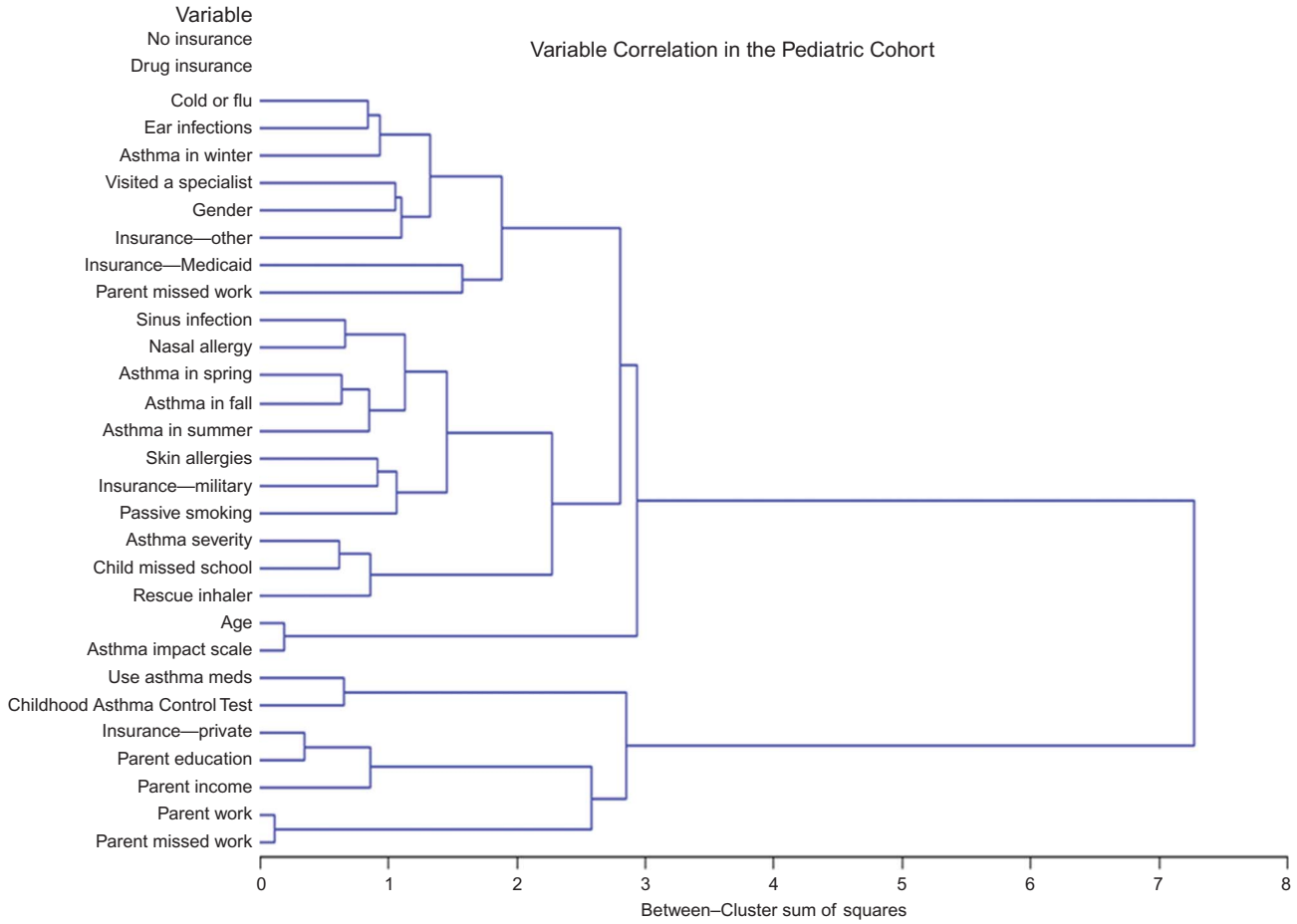

FIGURE 7.—Variable correlation in the pediatric cohort.
Correlated predictors of exacerbation in the pediatric cohort were grouped together based on the pair-wise correlation coefficients.

disease and, consequently, their asthma was well controlled. However, the other half can be divided into subgroups with different characteristics associated with an increased risk for exacerbations. In the more severe pediatric clusters (Clusters 5 and 6), the RR for exacerbations was 2.25 and 2.36, respectively. In the more severe adult clusters (Clusters 6 and 7), the RR for exacerbations was 2.69 and 2.88, respectively. Preventing asthma exacerbations is preferable to managing them. Treating comorbid conditions, maintaining weight control, timely referrals to specialists, avoidance of triggers (i.e., smoking), and regular assessment of asthma control are some of the ways to prevent such exacerbations. The characterization of asthma phenotypes using this type of approach, which maximizes the differences across subgroups, represents a new opportunity to enhance the detection of uncovered risk factors. Future studies should consist of a multidimensional approach involving patient-reported characteristics and objective measurements of the disease.

ACKNOWLEDGMENTS

The authors acknowledge Alicia Gilsenan, Ryan Ziemiecki, Abenah Vanderpuije, Xiaolei Zhou, and Christine Bui from RTI Health Solutions as well as Richard Stanford, William Lincourt, and Amanda Emmett from GlaxoSmithKline for their contribution to data collection for the primary studies. The authors are most appreciative of Drs Lynn Katz and Charlene Prazma for their helpful comments regarding the manuscript. Editorial support in the form of figure generation, grammatical editing, and referencing was provided by Dr Elaine F. Griffin at Evidence Scientific Solutions and was funded by GlaxoSmithKline.

DECLARATION OF INTEREST

All authors were employees of GlaxoSmithKline at the time of the study. Dr Miller is currently an employee of UCB, Inc.

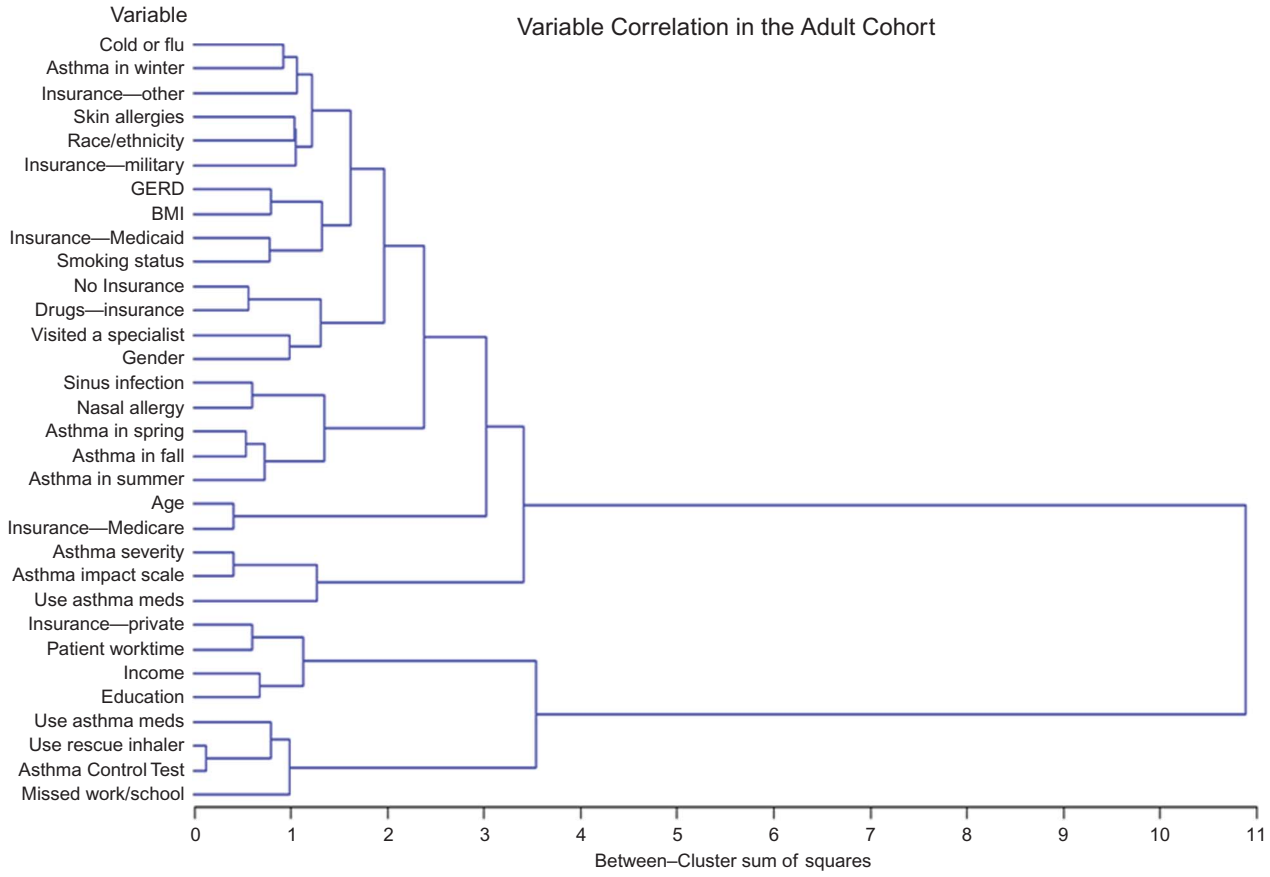

FIGURE 8.—Variable correlation in the adult cohort.
Correlated predictors of exacerbation in the adult cohort were grouped together based on the pair-wise correlation coefficients.

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