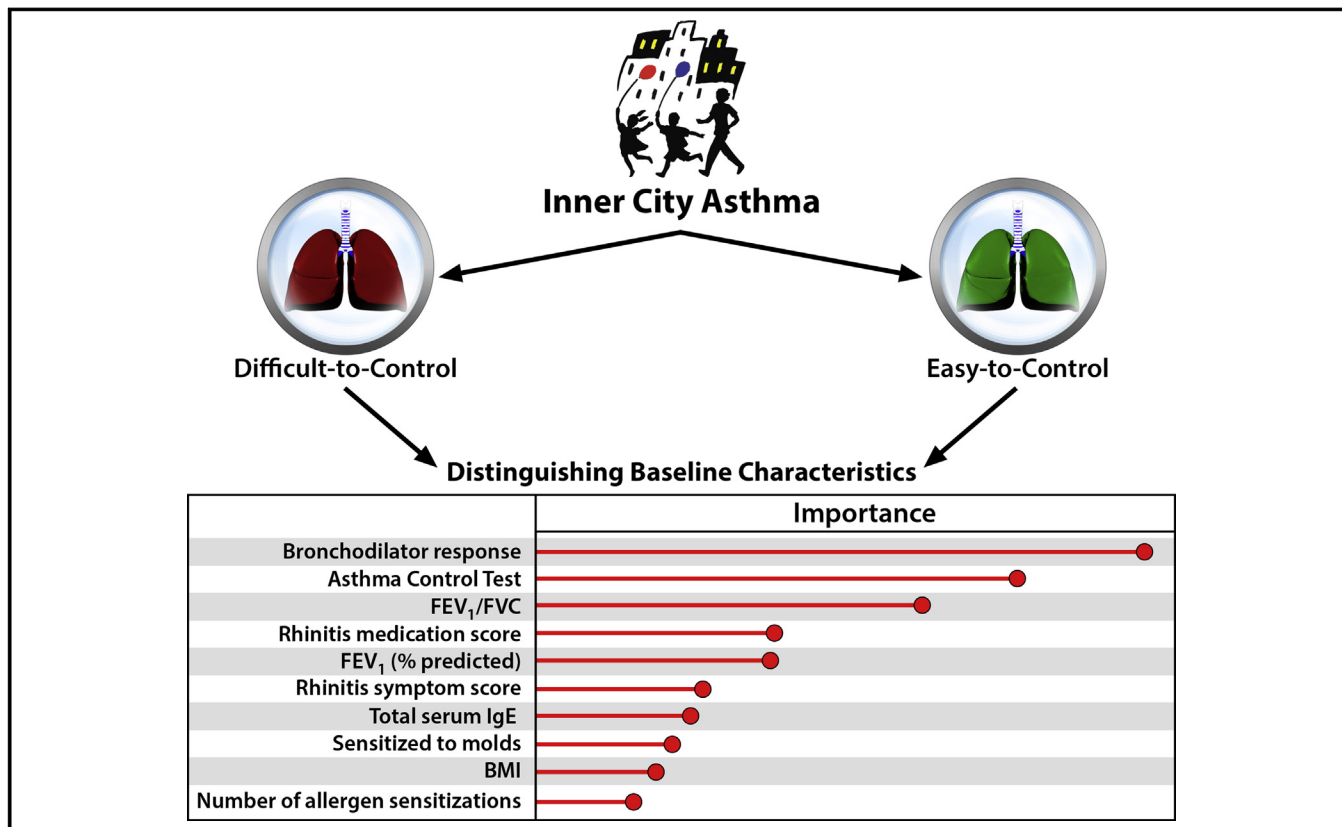


Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents



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GRAPHICAL ABSTRACT



Background: Treatment levels required to control asthma vary greatly across a population with asthma. The factors that contribute to variability in treatment requirements of inner-city children have not been fully elucidated.

Objective: We sought to identify the clinical characteristics that distinguish difficult-to-control asthma from easy-to-control asthma.

Methods: Asthmatic children aged 6 to 17 years underwent baseline assessment and bimonthly guideline-based

management visits over 1 year. Difficult-to-control and easy-to-control asthma were defined as daily therapy with 500 µg of fluticasone or greater with or without a long-acting β-agonist versus 100 µg or less assigned on at least 4 visits. Forty-four baseline variables were used to compare the 2 groups by using univariate analyses and to identify the most relevant features of difficult-to-control asthma by using a variable selection algorithm. Nonlinear seasonal variation in longitudinal measures (symptoms, pulmonary physiology, and

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University School of Medicine and Health Sciences, Washington; ^jSt Louis Children's Hospital; ^kthe University of Wisconsin School of Medicine and Public Health, Madison; ^lthe National Institute of Allergy and Infectious Diseases, Bethesda; and ^mNational Jewish Health, Denver, and Children's Hospital Colorado and University of Colorado School of Medicine, Aurora.

exacerbations) was examined by using generalized additive mixed-effects models.

Results: Among 619 recruited participants, 40.9% had difficult-to-control asthma, 37.5% had easy-to-control asthma, and 21.6% fell into neither group. At baseline, FEV₁ bronchodilator responsiveness was the most important characteristic distinguishing difficult-to-control asthma from easy-to-control asthma. Markers of rhinitis severity and atopy were among the other major discriminating features. Over time, difficult-to-control asthma was characterized by high exacerbation rates, particularly in spring and fall; greater daytime and nighttime symptoms, especially in fall and winter; and compromised pulmonary physiology despite ongoing high-dose controller therapy. **Conclusions:** Despite good adherence, difficult-to-control asthma showed little improvement in symptoms, exacerbations, or pulmonary physiology over the year. In addition to pulmonary physiology measures, rhinitis severity and atopy were associated with high-dose asthma controller therapy requirement. (*J Allergy Clin Immunol* 2016;138:1030-41.)

Key words: Child, asthma, inner-city asthma, asthma phenotype, asthma morbidity, asthma severity, asthma exacerbations, pulmonary function, rhinitis, allergen sensitization, IgE

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The concept of asthma as a heterogeneous disease is supported by several observations, particularly the variation in clinical parameters, such as symptoms, pulmonary function,

Abbreviations used

ACT: Asthma Control Test
APIC: Asthma Phenotypes in the Inner City
ARIA: Allergic Rhinitis and its Impact on Asthma
BMI: Body mass index
cACT: Childhood Asthma Control Test
FVC: Forced vital capacity
ICAC: Inner City Asthma Consortium
sIgE: Allergen-specific IgE

bronchial hyperresponsiveness, and treatment responses, among patients. In addition, heterogeneity of the response to treatment has become of increasing interest and importance with the development of new therapies and a movement toward precision medical approaches for asthma. The extent to which treatment response heterogeneity and associated phenotypes exist in inner-city children with asthma has yet to be defined. In an earlier 46-week study in which guideline-based care was provided in the context of a randomized, double-blind design testing the use of fraction of exhaled nitric oxide values to guide therapy, inner-city children required a broad range of asthma controller treatment steps, suggesting that easy-to-control and difficult-to-control asthma might represent different disease phenotypes.¹

A considerable problem with studies that attempt to identify asthma phenotypes is that patient characterization occurs as a single evaluation and does not include a measure of phenotype stability over time in the majority of cases. Furthermore, in most of these studies, it is not clear whether therapy has been optimized

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based on guidelines and that adherence to treatment has been carefully assessed.

The National Institutes of Allergy and Infectious Diseases–funded Inner City Asthma Consortium (ICAC) designed this multicenter study with the primary objective to determine distinct characteristics that would discriminate difficult-to-control from easy-to-control asthma in inner-city children. To achieve this goal, the study sought to enroll and evaluate children with a broad range of asthma severity. The design also aimed at addressing the above-identified deficiencies: the study involved prospective, multiple-visit evaluations of its participants for an entire year during which a standardized algorithm was used to optimize asthma management based on National Asthma Education and Prevention Program Guidelines. In addition, given the known relationship between rhinitis and asthma,² this study included careful evaluation of rhinitis and an integrated rhinitis treatment plan also based on a standardized algorithm. Finally, substantial effort was devoted to participant adherence to both asthma and rhinitis treatments.

METHODS

Study design

Asthma Phenotypes in the Inner City (APIC) was a prospective longitudinal study of 6- to 17-year-old children with asthma living in 9 urban areas. Participant selection criteria included residence in an area with greater than 20% of residents below the poverty level, a physician's diagnosis of asthma, at least 2 episodes of short-acting β -agonist administration within the past 12 months (exclusive of use associated with exercise-induced symptoms), and 50% or greater adherence to controller medication between the screening and enrollment visits, as described below. Exclusion of those participants who did not achieve 50% adherence was done to limit the effect of poor adherence, so that response to treatment, rather than variation related to lack of treatment, could be studied. The study was approved by each clinical site's institutional review board, and written informed consent was obtained from the parent or legal guardian of the child. The study design is illustrated in Fig 1.

Study evaluation and management

Participants received a comprehensive assessment at screening and had their asthma and rhinitis managed based on National Asthma Education and Prevention Program Expert Panel Report-3³ and Allergic Rhinitis and its Impact on Asthma (ARIA) 2008⁴ guidelines–derived treatment algorithms with assessment and medication adjustments every 2 months for 1 year (V0, V1, V2, V3, V4, V5, and V6). Clinical data about asthma and rhinitis were entered into a computer program that determined the treatment to standardize evaluation and treatment across sites. Clinicians could override the computer-generated treatment recommendations if they were deemed necessary. For asthma management, a predefined Expert Panel Report-3–based treatment algorithm (see Table E1 in this article's Online Repository at www.jacionline.org) was used by the study clinicians to determine each participant's controller regimen (see Table E2 in this article's Online Repository at www.jacionline.org) based on asthma symptoms, spirometric results, and exacerbation history (see Table E3 in this article's Online Repository at www.jacionline.org). Asthma morbidity was assessed and scored by using 3 domains from the Composite Asthma Severity Index.⁵ These domains were assessed at each study visit and included daytime symptoms and albuterol use in the past 2 weeks, nighttime symptoms and albuterol use in the past 2 weeks, and exacerbations in the past 2 months. Detailed scoring information related to these domains is shown in Table E4 in this article's Online Repository at www.jacionline.org. For rhinitis management, an ARIA-derived algorithm was used to adjust medications based on the reported severity (level of bother) and frequency of nasal symptoms, as well as allergy status (see Table E5 in this article's Online

Repository at www.jacionline.org). All study participants also received albuterol as rescue therapy and a supply of prednisone that could be used for relief of acute symptoms on consultation with a study clinician. All asthma and rhinitis medications (except montelukast) were provided free of charge to the study participants.

Adherence to asthma therapy was assessed at each study visit for all participants requiring daily controller therapy (ie, greater than step 0). Calculation of used doses was performed after review of built-in dose counters at the visit or after receipt of devices in the mail if they were not brought to the visit. Percentage adherence was determined based on the number of doses taken divided by the number prescribed. A standardized questionnaire about adherence that was previously used in other ICAC studies was also administered at each visit. If the medications were not returned to the study site, percentage adherence was calculated based on questionnaire data. Questionnaire data were used to determine adherence in approximately 20% of study visits.

Study assessments

The visit schedule of study assessments used in this analysis is presented in Table E6 in this article's Online Repository at www.jacionline.org. Skin prick tests were performed at screening (unless results within 1 year from a prior ICAC study were available) for 12 common indoor and outdoor allergens (mouse epithelium, dog epithelium [mixed breeds], mite mix standardized [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* mix], cat hair standardized, rat epithelium, American cockroach, German cockroach, *Alternaria tenuis*, *Aspergillus fumigatus*, ragweed mix [giant/short], Eastern 8 tree mix, and Kentucky blue/June, orchard, and timothy grass mix), with juniper and Bermuda grass being additionally tested at sites (Dallas and Denver) at which those allergens are common. All allergen extracts were obtained from Greer Laboratories (Lenoir, NC). Total serum IgE measurement, Phadiatop inhalant allergy screening, fx5 food allergy screening, and measurement of allergen-specific IgE (sIgE; ImmunoCAP, Phadia, Uppsala Sweden) to a panel of 20 allergens (egg white, milk, peanut, German cockroach, American cockroach, *D farinae*, *D pteronyssinus*, cat dander, dog dander, mouse urine proteins, rat urine proteins, *Alternaria alternata*, *A fumigatus*, oak, pecan, birch, maple/box elder, *Cladosporium herbarum*, giant ragweed, and timothy grass) were also measured from blood drawn at V0. Allergen sensitization was defined by a wheal 3 mm or more larger than that elicited by the saline control in the presence of a positive histamine control wheal of at least 3 mm on skin prick testing (a smaller histamine wheal invalidated skin tests from being used in the analysis) or a specific IgE level of 0.35 kU/L or greater for environmental and food allergens. Variables representing a positive skin prick test response or positive sIgE measurement were grouped together by using a hierarchical clustering algorithm based on Pearson correlations.⁶ By using the result of this cluster analysis as a guide, the 20 sIgEs and the 12 skin test allergens were grouped into one of the following 7 categories: roaches, pets, rodents, trees, foods, molds, and dust mites.

A complete blood count with differential was performed at V0 for blood eosinophil and neutrophil counts. The blood sample was also tested for total 25-hydroxyvitamin D.

By using a Jaeger spirometer (BD, Franklin Lakes, NJ), spirometry was performed at every management visit, and bronchodilator responsiveness was assessed at screening and V6. Bronchodilator responsiveness was defined as the percentage change in FEV₁ as measured before and 15 minutes after 4 inhalations of albuterol. Training and supervision of the clinical site technicians was performed by pulmonary function specialists from the University of Wisconsin–Madison. Acceptability was based on the American Thoracic Society/European Respiratory Society guidelines.⁷ For children less than 8 years of age, the American Thoracic Society Preschool Guidelines were used.⁸

Fraction of exhaled nitric oxide values were measured at V0 and V6 by using the NIOX MINO device (Aerocrine, Stockholm, Sweden). Two maneuvers were performed, and if the results agreed within 5%, they were averaged. If they did not agree, a third maneuver was performed, and the 2 closest results were averaged.

The Asthma Control Test (ACT) or Childhood Asthma Control Test (cACT) was administered at Screening and V6.^{9–12}

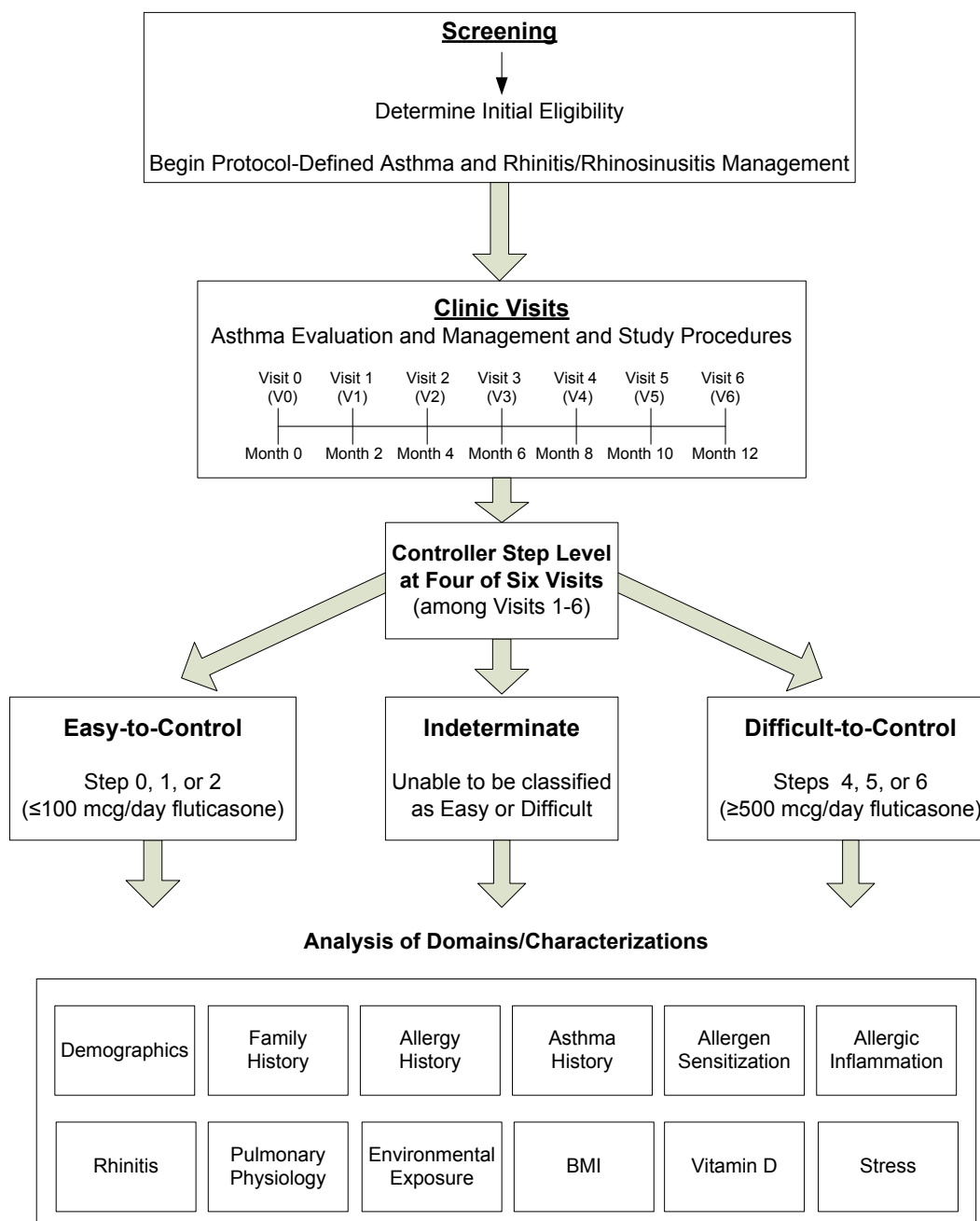


FIG 1. Schematic of APIC study design: flow diagram illustrating (1) screening visit; (2) clinic visits; (3) definition of the easy-to-control, indeterminate, and difficult-to-control groups based on controller treatment step throughout the study; and (4) domains used to group characteristics measured on each participant throughout the study.

As a measure of household stress, perceived stress was assessed by administering the Perceived Stress Scale to the child's primary caretaker at V0. The Perceived Stress Scale is a 10-item scale that measures the degree to which respondents believe their lives were unpredictable, uncontrollable, and overwhelming in the preceding month (reliability = 0.85).¹³

Obesity was measured at screening based on body mass index (BMI) *z* scores based on US Centers for Disease Control and Prevention guidelines.¹⁴ Environmental tobacco exposure was evaluated at screening and V6 based on the reported number of smokers in the home and urinary cotinine levels, which were measured by using the NicAlert test (Nymox Pharmaceutical, Hasbrouck Heights, NJ).

Variables used in the analyses were identified in a literature review performed during protocol development to identify clinical and mechanistic

factors that contribute to asthma severity. The study assessments served as a source of variables for analysis, which were subsequently grouped into a number of clinical domains, as shown in Table E7 in this article's Online Repository at www.jacionline.org.

Outcome definition

We defined the study groups *a priori* based on asthma step level controller requirement. Difficult-to-control asthma was defined as requiring 500 μ g/d or more of fluticasone with or without a long-acting β -agonist at 4 or more of the 6 postbaseline study visits. Of note, difficult-to-control asthma was not defined as uncontrolled or poorly controlled asthma. Participants requiring 100 μ g/d or less of fluticasone or montelukast only or needing no controller medication at

4 of the 6 postbaseline study visits were classified as having easy-to-control asthma. Those participants who did not fall into the difficult-to-control or easy-to-control groups were considered to have “indeterminate” asthma. The decision to limit the analyses to participants who completed 4, 5, or 6 visits was prespecified in the protocol to allow us to accurately classify participants with difficult-to-control, easy-to-control, and indeterminate asthma over a 12-month period. All group assignments were made after study completion.

Statistical methods

A consensus process was used to determine 44 variables measured at screening or V0 that were representative of the following domains (also shown in Table E7): demographics, family history, personal allergy history, asthma history, rhinitis, BMI, vitamin D, environmental exposures, allergen sensitization, pulmonary physiology (FEV₁ bronchodilator responsiveness, percent predicted FEV₁, and FEV₁/forced vital capacity [FVC]), allergic inflammation, and psychological stress. R version 3.2.2 was used for all analyses.

For each study group (difficult-to-control, easy-to-control, and indeterminate asthma), generalized additive mixed models were used to estimate the longitudinal pattern of treatment step throughout the study, as well as seasonal variations in symptoms, exacerbations, and pulmonary function.

ANOVA and Kruskal-Wallis tests were used for continuous variables (normally distributed and nonnormal, respectively) and χ^2 or Fisher exact tests were used for categorical variables to compare the 44 identified variables between study groups. FEV₁ bronchodilator responsiveness, FEV₁ percent predicted, and FEV₁/FVC ratios were analyzed as continuous variables. Although not originally identified in the list of 44 variables, BMI percentile at screening, controller treatment step at screening, and rhinitis medication score at screening (categorized) were also compared. No adjustment was made to account for multiple comparisons arising from comparisons between groups or multiple variables.

By using the 44 identified variables, the Boruta variable selection algorithm was then used to determine the most relevant features distinguishing difficult-to-control from easy-to-control asthma.¹⁵ Boruta, which adjusts for multiple comparisons and accounts for collinearity and potential interactions between variables, measures the contribution of each variable in accurately classifying an outcome by examining the effect of omitting it from the overall model. As a result, each variable is classified by the algorithm as confirmed, tentative, or rejected with regard to its relevance in distinguishing difficult-to-control from easy-to-control asthma. Before performing this analysis, a single imputation based on a fully conditional specification approach was performed on all variables to account for missing data.

Among participants with difficult-to-control asthma, a similar analysis was conducted to identify characteristics relevant to distinguishing participants with controlled asthma at V6 from participants with uncontrolled asthma. In this analysis control status was defined as having an ACT/cACT score of 20 or greater at the last study visit.

RESULTS

Between August 2011 and September 2013, 1195 children were recruited, 845 were eligible for screening, and 717 became part of the longitudinal cohort (Fig 2). Of these, 619 (86.3%) completed at least 4 of the 6 bimonthly visits for evaluation and management of asthma and rhinitis and were included in this analysis. Two hundred fifty-three (40.9%) participants met the criteria for difficult-to-control asthma, 232 (37.5%) had easy-to-control asthma, and 134 (21.6%) had indeterminate asthma. Characteristics of the 485 participants in the difficult-to-control and easy-to-control groups are presented in Table I. Male subjects comprised 57.7% of the study population. Black non-Hispanic participants represented 64.3% of the total, followed by Hispanic participants (28.3%). The average age at screening was 10.9 years.

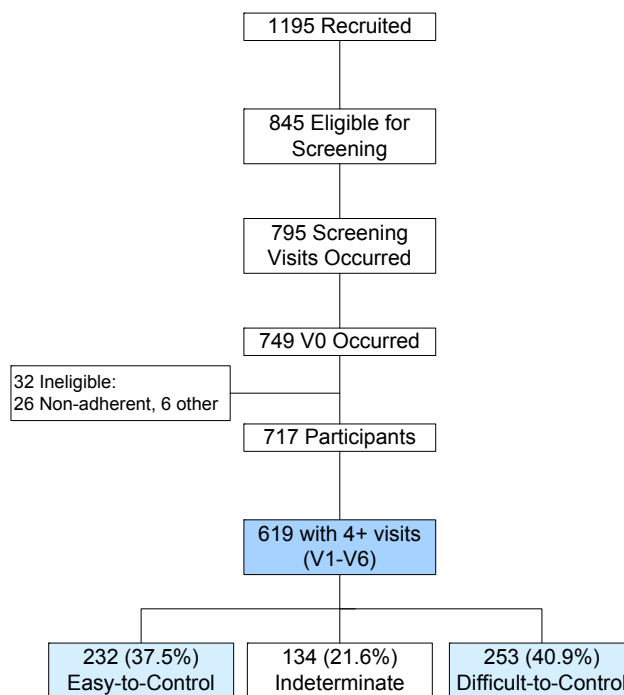


FIG 2. CONSORT diagram: flow diagram illustrating the number of subjects screened, as well as the number of participants in the full APIC cohort and included in the analytic sample.

Characteristics of all 619 participants in the 3 groups (ie, including the indeterminate group) are presented in Table E8 in this article's Online Repository at www.jacionline.org. The majority of participants classified as having indeterminate asthma required variable treatment step levels during the year; only 18 participants consistently remained on the “intermediate” level of therapy of 200 μ g/d fluticasone for 4 or more visits.

The guidelines-directed asthma treatment step level of the difficult-to-control and easy-to-control groups during the 1-year follow-up period is shown in Fig 3. The assigned controller treatment step of the difficult-to-control group as a whole remained persistently increased during the study, such that the mean controller treatment step was 4.72 (95% CI, 4.59-4.85) at screening and 5.00 (95% CI, 4.86-5.13) at V6. In contrast, the assigned controller treatment step for the easy-to-control group decreased, such that the mean controller treatment step was 1.81 (95% CI, 1.67-1.94) at screening and 0.76 (95% CI, 0.62-0.91) at V6. This indicates that, in the context of the guideline-based management, the easy-to-control group can improve over time because they required gradually lower controller step level therapy while maintaining good control. In contrast, an important feature of the difficult-to-control group was the inability to taper controller therapy below step 4 over the year. Of note, adherence to controller therapy was comparable between groups, with a median adherence of 78.4% in the difficult-to-control group, 76.2% in the easy-to-control group, and 77.8% in the indeterminate group ($P = .26$). Although the phenotypes of difficult-to-control and easy-to-control asthma were stable over time, they also appeared to be distinctly evident from the start of the study. Of the 253 participants in the difficult-to-control group, 203 (80.2%) were at steps 4 to 6 at screening. Of 212 participants in the easy-to-control group, 153 (65.9%) were at steps 0 to 2 at

TABLE I. Participants' characteristics and demographics

Characteristic	No.	All participants	Difficult	Easy	P value
Demographics					
Male sex	485	280 (57.7%)	138 (54.5%)	142 (61.2%)	.16
Race*	484				.07
Black (non-Hispanic)		311 (64.3%)	173 (68.7%)	138 (59.5%)	
Hispanic		137 (28.3%)	67 (26.6%)	70 (30.2%)	
Other/mixed		26 (5.4%)	9 (3.6%)	17 (7.3%)	
White (non-Hispanic)		10 (2.1%)	3 (1.2%)	7 (3.0%)	
Age at screening (y)	485	10.9 (3.0)	10.7 (3.0)	11.1 (3.1)	.15
Family history					
Family history of asthma	472	346 (73.3%)	186 (74.7%)	160 (71.7%)	.54
Family history of hay fever/rhinitis/allergies	460	259 (56.3%)	133 (55.9%)	126 (56.8%)	.92
Family history of eczema	465	263 (56.6%)	146 (60.1%)	117 (52.7%)	.13
Allergy history					
Self-report of food allergies	485	144 (29.7%)	77 (30.4%)	67 (28.9%)	.78
History of anaphylaxis	485	35 (7.2%)	23 (9.1%)	12 (5.2%)	.14
Eczema diagnosis	485	267 (55.1%)	150 (59.3%)	117 (50.4%)	.06
Asthma history					
Age asthma first diagnosed (y)	483	3.3 (3.2)	2.8 (2.9)	3.9 (3.4)	<.001
Age asthma symptoms started (y)	483	1.4 (2.6)	1.6 (2.7)	1.1 (2.4)	.02
ACT/cACT† at screening	484				<.001
Very poorly controlled		35 (7.2%)	28 (11.1%)	7 (3.0%)	
Not well controlled		140 (28.9%)	103 (40.9%)	37 (15.9%)	
Well controlled		309 (63.8%)	121 (48.0%)	188 (81.0%)	
Controller treatment step at screening‡	485				<.001
Steps 0-2		176 (36.3%)	23 (9.1%)	153 (65.9%)	
Step 3		64 (13.2%)	27 (10.7%)	37 (15.9%)	
Steps 4-6		245 (50.5%)	203 (80.2%)	42 (18.1%)	
BMI					
BMI z score at screening	485	1.0 (1.2)	1.1 (1.2)	0.9 (1.1)	.14
BMI percentile at screening‡	485	87.3 (58.0-97.6)	88.3 (61.7-98.2)	85.5 (54.9-96.7)	.06
Vitamin D					
Total 25-hydroxyvitamin D at V0 (ng/mL)	475	19.1 (7.2)	18.7 (7.4)	19.5 (7.0)	.25
Environmental exposure					
Any smokers in the home at screening	482	195 (40.5%)	109 (43.4%)	86 (37.2%)	.20
NicAlert result at screening	476	1.3 (1.1)	1.3 (1.1)	1.3 (1.0)	.90
Gas stove in home	475	311 (65.5%)	160 (64.3%)	151 (66.8%)	.63
Dampness in home	473	168 (35.5%)	94 (37.8%)	74 (33.0%)	.33
AC unit in child's bedroom	475	319 (67.2%)	170 (68.3%)	149 (65.9%)	.66
Forced air for heat in home	476	288 (60.5%)	152 (60.8%)	136 (60.2%)	.96
Rodents in home	475	142 (29.9%)	75 (30.1%)	67 (29.6%)	.99
Roaches in home	473	82 (17.3%)	49 (19.8%)	33 (14.7%)	.18
Pets in home	475	178 (37.5%)	99 (39.8%)	79 (35.0%)	.33
Stress					
Caretaker Perceived Stress Scale at V0	482	14.4 (7.5)	15.1 (7.6)	13.7 (7.3)	.05
Allergen sensitization					
Total serum IgE at V0 (kU/L)§	478	248.0 (91.0-765.2)	405.0 (101.0-1087.0)	197.0 (72.0-529.0)	<.001
No. of allergen sensitizations (panel of 22) at V0	485	8.7 (6.2)	9.9 (6.3)	7.5 (5.9)	<.001
Positive Phadiatop screen	476	374 (78.6%)	202 (81.5%)	172 (75.4%)	.14
Positive fx5 food allergy screen result	477	270 (56.6%)	154 (61.8%)	116 (50.9%)	.02
Sensitized to molds¶ at V0	485	240 (49.5%)	149 (58.9%)	91 (39.2%)	<.001
Sensitized to dust mites# at V0	485	287 (59.2%)	159 (62.8%)	128 (55.2%)	.10
Sensitized to roaches** at V0	485	272 (56.1%)	151 (59.7%)	121 (52.2%)	.12
Sensitized to rodents†† at V0	485	208 (42.9%)	127 (50.2%)	81 (34.9%)	.001
Sensitized to pets‡‡ at V0	485	315 (64.9%)	176 (69.6%)	139 (59.9%)	.03
Sensitized to pollen/peanut§§ at V0	485	344 (70.9%)	197 (77.9%)	147 (63.4%)	.001
Sensitized to foods at V0	479	143 (29.9%)	77 (30.7%)	66 (28.9%)	.75
Inflammation					
FENO at V0 (ppb)§	448	19.0 (11.0-35.5)	20.5 (12.0-38.2)	17.4 (10.7-32.0)	.05
Blood eosinophil count at V0 (cells/mm ³)§	476	270.0 (168.0-440.0)	300.0 (190.0-500.0)	200.0 (115.0-400.0)	.004
Blood neutrophil count at V0 (cells/mm ³)§	476	2900.0 (2000.0-3900.0)	3000.0 (2100.0-4100.0)	2700.0 (2000.0-3736.0)	.03
Pulmonary physiology					
Bronchodilator response at screening	480	13.6 (14.1)	18.3 (15.9)	8.6 (9.6)	<.001

(Continued)

TABLE I. (Continued)

Characteristic	No.	All participants	Difficult	Easy	P value
FEV ₁ (% predicted) at screening	485	91.4 (17.4)	86.7 (17.7)	96.6 (15.4)	<.001
FEV ₁ /FVC ratio (×100) at screening	475	77.5 (9.8)	74.2 (10.3)	81.0 (8.0)	<.001
Rhinitis					
Rhinitis classification at screening	485				.006
Allergic		333 (68.7%)	189 (74.7%)	144 (62.1%)	
Nonallergic		102 (21.0%)	46 (18.2%)	56 (24.1%)	
No rhinitis		50 (10.3%)	18 (7.1%)	32 (13.8%)	
Rhinitis medication score¶¶ at screening	485	9.5 (6.2)	11.1 (5.6)	7.9 (6.3)	<.001
Rhinitis medications at screening‡	485				<.001
None		108 (22.3%)	37 (14.6%)	71 (30.6%)	
Antihistamine only		67 (13.8%)	24 (9.5%)	43 (18.5%)	
Nasal steroids only		72 (14.8%)	40 (15.8%)	32 (13.8%)	
Antihistamine and nasal steroids		238 (49.1%)	152 (60.1%)	86 (37.1%)	
Rhinitis symptom score## at screening	485	8.8 (6.0)	10.1 (6.2)	7.3 (5.3)	<.001

Unless otherwise noted, characteristics are compared by using χ^2 or Fisher exact tests for categorical variables and ANOVA or *t* tests for continuous variables. Unless otherwise noted, summary statistics are frequencies (percentages) for categorical variables and means and SDs for continuous variables.

FENO, Fraction of exhaled nitric oxide.

*Race is dichotomized (black vs other) when establishing variable importance in distinguishing patients with difficult-to-control from those with easy-to-control asthma.

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

‡Not included in the list of variables to establish variable importance in distinguishing difficult-to-control from easy-to-control asthma.

§Summarized by using medians and interquartile ranges and tested with a Kruskal-Wallis test.

||Sensitization is based on a positive skin prick test response, positive specific IgE level, or both to at least 2 of the following allergens: *A tenuis* (skin prick test) or *A alternata* (specific IgE); *A fumigatus* (both skin prick test and specific IgE); *C herbarum* (specific IgE only); *D farinae*; *D 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 grass mix; peanut; egg; and milk.

¶Sensitization is based on a positive skin test response, positive specific IgE level, or both to at least 1 of the following allergens: *A tenuis* (skin prick test) or *A alternata* (specific IgE measurement), *A fumigatus*, and *C herbarum*.

‡Sensitization is based on a positive skin prick test response, positive specific IgE level, or both to at least 1 of the following allergens: *D farinae* and *D pteronyssinus*.

**Sensitization is based on a positive skin prick test response, positive specific IgE level, or both to at least 1 of the following allergens: German cockroach and American cockroach.

††Sensitization is based on a positive skin prick test response, positive specific IgE level, or both to at least 1 of the following allergens: mouse and rat.

‡‡Sensitization is based on a positive skin prick test response, positive specific IgE level, or both to at least 1 of the following allergens: cat and dog.

§§Sensitization is based on a positive skin prick test response, positive specific IgE level, or both 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 grass mix; and peanut.

|||Sensitization is based on a positive skin prick test response, positive specific IgE level, or both to at least 1 of the following allergens: egg and milk.

¶¶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 (see Table E5).

screening, as shown in Table I. The guidelines-directed asthma treatment step level of all 3 groups is presented in Fig E1 in this article's Online Repository at www.jacionline.org.

The seasonal severity and patterns of conventionally assessed clinical parameters (daytime symptoms and albuterol use, nighttime symptoms and albuterol use, FEV₁/FVC ratio, and frequency of asthma exacerbations) are presented in Fig 4. Compared with the easy-to-control group, the difficult-to-control group was characterized by relatively high and striking seasonally varying levels of asthma symptoms (fall and winter peaks; summer low) and exacerbations (fall and spring peaks; summer low). Persistent but variable airflow obstruction was also noted in the difficult-to-control group over the course of the study. Indeed, over the study's 12 months, difficult-to-control participants had more impaired and more variable lung function than easy-to-control participants. In the difficult-to-control group the average within-participant mean of FEV₁ (percent predicted) over 12 months was 88.9 (SD, 14.8), whereas in the easy-to-control group it was 97.7 (SD, 12.7; *P* < .001). Alternatively, the average within-participant SD of FEV₁ (percent predicted) was 9.7 (SD, 4.8) in the difficult-to-control group and 6.0 (SD, 3.0) in the easy-to-control group (*P* < .001). Similarly, in the difficult-to-control group the average

within-participant mean of the FEV₁/FVC ratio (×100) over 12 months was 76.3% (SD, 8.6), whereas in the easy-to-control group it was 82.1% (SD, 6.4; *P* < .001). Alternatively, the average within-participant SD was 5.4 (SD, 2.7) in the difficult-to-control group, whereas in the easy-to-control group it was 3.1 (SD, 1.6; *P* < .001). Notably, the clinical pattern of greater asthma severity in the difficult-to-control group occurred despite sustained use of the highest step levels of guideline-based asthma controller medication management over the course of the year. In contrast, the easy-to-control group demonstrated low levels of symptoms and exacerbations and normal airflow by using spirometry, without significant seasonal variation in symptoms or pulmonary physiology. Although it appears that the easy-to-control group also exhibited spring and fall variation in asthma exacerbations, the rate of exacerbations was very low, fluctuating from 1% to 2%. The seasonal clinical data for all 3 groups can be found in Fig E2 in this article's Online Repository at www.jacionline.org.

Univariate comparisons (Table I) between the difficult-to-control and easy-to-control groups found that 22 of 47 baseline variables differed. Specifically, participants with difficult-to-control asthma tended to have worse asthma control and lung function than participants with easy-to-control asthma, as well

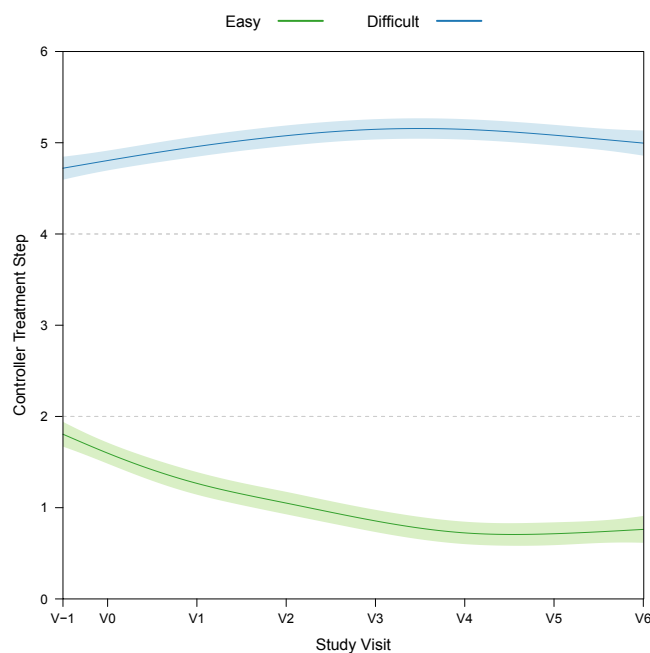


FIG 3. Controller treatment step for the easy-to-control and difficult-to-control groups over 12 months. Green and blue lines (shaded areas) indicate means (95% CIs) of controller treatment step for the easy-to-control and difficult-to-control groups, respectively, over 12 months.

as higher levels of controller treatment, caretaker perceived stress, atopy, rhinitis severity, and inflammatory markers. To account for multiple comparisons, collinearity among variables and potential interactions, a variable importance analysis applied to 44 of the 47 baseline variables (shown in the left panel of Fig 5), found FEV₁ bronchodilator responsiveness to be the most relevant variable that distinguished difficult-to-control from easy-to-control asthma. Several additional variables obtained at screening or V0 were confirmed as being relevant in distinguishing difficult-to-control from easy-to-control asthma, including ACT/cACT score, FEV₁/FVC ratio, rhinitis medication score, FEV₁ (percent predicted), rhinitis symptom score, total serum IgE level, sensitization to mold, BMI z score, total number of allergen sensitizations, and blood neutrophil count. Because lung function was one of the determinants of the treatment step level, which in turn was the basis for a participant to be categorized into one of 3 *a priori*-defined groups, we repeated the variable importance analysis after removing the pulmonary physiology variables. As seen in the right panel of Fig 5, the variables identified as relevant in the first analysis remained relevant after removal of pulmonary function, except for blood neutrophil counts. Additionally, the age at which asthma was first diagnosed and the age of asthma symptom onset emerged as relevant distinguishing variables.

Using an ACT/cACT score at V6 of 20 or higher as a cut point for well-controlled asthma,^{9,12} univariate analysis of the same 47 variables was performed to determine whether there were any statistically significant differences at screening or V0 between the subgroups with controlled and uncontrolled asthma within the difficult-to-control group. Of the 253 participants in the difficult-to-control group, 239 had V6 ACT/cACT data for analysis; 178 (74.5%) had controlled asthma, and 61 (25.5%) did not. Among 44 of the 47 variables, only the ACT/cACT score

at screening was confirmed as being relevant to distinguishing these 2 subgroups.

DISCUSSION

This is the first study to date of a large population of children characterized prospectively while receiving guideline-based management for asthma and rhinitis. The unique and novel aspects of the study are its longitudinal assessment of participants to help characterize and establish the stability of the groups over time; inclusion of standardized, guideline-based asthma and rhinitis assessments and computerized management algorithms; and collection of variables in a broad range of domains, as reflected by the literature at the time of protocol development.

Clear clinical parameter differences were found at study entry between inner-city children with difficult-to-control asthma versus those with easy-to-control asthma. Of the 44 baseline variables used to establish variable importance in distinguishing difficult-to-control from easy-to-control asthma, FEV₁ bronchodilator responsiveness was the most distinguishing characteristic. The Asthma Outcomes Workshop Report¹⁶ has recommended that assessment of bronchodilator responsiveness be used to characterize populations in clinical trials and to classify patients into clinically meaningful groups; our work provides important information that supports this endorsement. Because bronchodilator responsiveness is strongly related to baseline pulmonary function, it was not surprising that FEV₁/FVC ratio and FEV₁ (percent predicted) values also differentiated these 2 groups.¹⁷⁻²⁰

A retrospective cross-sectional study of low-income, mainly Hispanic children in Los Angeles found that bronchodilator responsiveness of at least 10% was significantly related to poor asthma control in controller-naïve children.²¹ Children with this degree of bronchodilator responsiveness, even in the face of normal spirometric results, had more nocturnal symptoms, increased β -agonist use, and exercise limitation while also having a greater number of allergen sensitizations. Given the fact that pulmonary function was one of the determinants of our decision-making algorithm for increasing or decreasing the level of asthma controller treatment at each visit, which, in turn, determined whether a participant would be categorized as having difficult-to-control or easy-to-control asthma, the variable importance analysis was also performed after removing pulmonary physiology measures. Except for the blood neutrophil count, all of the other parameters remained relevant in their ability to distinguish difficult-to-control asthma, with only 2 emerging characteristics: age at asthma diagnosis and age at which asthma symptoms started.

The observation of the important contribution of rhinitis in the difficult-to-control asthma phenotype is noteworthy, highlighting the relevance of the upper airway in the heterogeneity of response to asthma therapy. Other studies have identified associations between severe asthma and rhinitis in both adults and children,²²⁻²⁴ and some have suggested that treatment of allergic rhinitis with intranasal corticosteroids is associated with improved asthma control.²⁵ Our findings are consistent with the hypothesis that asthma and rhinitis constitute manifestations of the same disease in 2 parts of the respiratory tract² and reinforce the ARIA guidelines that rhinitis management should be incorporated as part of asthma management.^{26,27}

Markers of atopy, particularly total serum IgE levels, mold sensitization, and the total number of allergen sensitizations, also distinguished patients with difficult-to-control asthma. Like

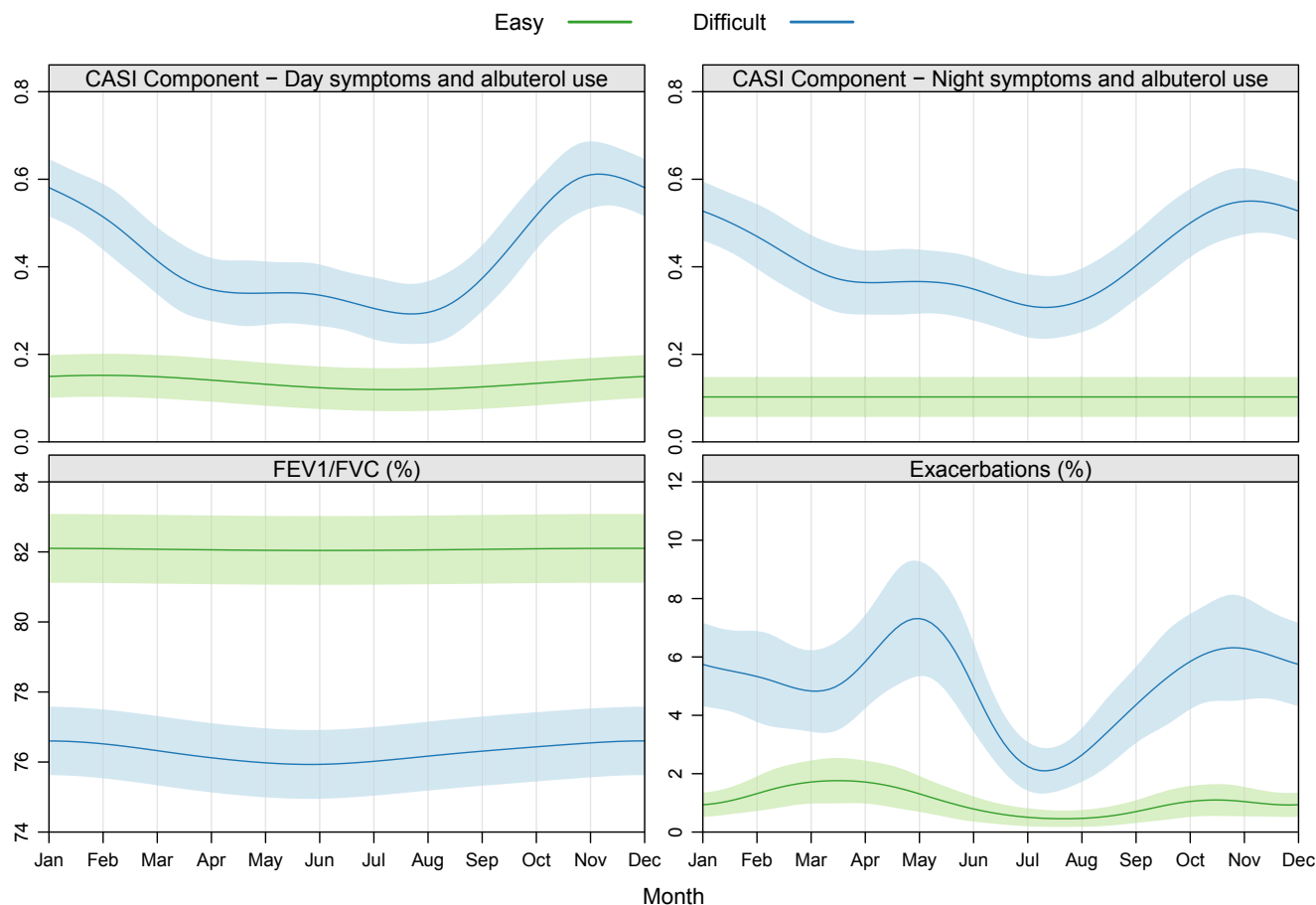


FIG 4. Seasonal variation in clinical severity measures in the easy-to-control, indeterminate, and difficult-to-control groups. Green and blue lines (shaded areas) indicate means or probabilities (95% CIs) of clinical severity measures for the easy-to-control and difficult-to-control groups, respectively, over 12 months. Clinical severity measures are the Composite Asthma Severity Index (CASI) component measuring day symptoms and albuterol use in the last 2 weeks (0-3 points), the CASI component measuring nighttime symptoms and albuterol use in the last 2 weeks (0-3 points), the FEV₁/FVC ratio ($\times 100$), and the monthly incidence of exacerbations, as defined by prednisone use.

rhinitis, atopy was not among the criteria on the basis of which asthma step therapy and, consequently, group assignment were determined. Although atopy and rhinitis outcomes had already emerged as relevant in the original variable importance analysis we conducted, they remained relevant when pulmonary function was removed (Fig 5). Other studies have shown strong inverse associations between total IgE levels and asthma control,^{28,29} and our previous work has demonstrated an association between mold sensitization and increased asthma morbidity in inner-city children.³⁰ Interestingly, other established inner-city allergens, including cockroach³¹ and mouse,³² were not found to be relevant in this study. Most likely, this is because their relevance in disease is strongly linked to both sensitization and exposure. Allergen exposure outcomes were not included in this analysis because they were obtained only from a subgroup of participants.

BMI also emerged as a relevant characteristic distinguishing difficult-to-control from easy-to-control groups. This finding is consistent with previous work that showed an association between obesity and increased morbidity and worsening pulmonary function in children with asthma,^{33,34} as well as an adverse effect of obesity on corticosteroid responsiveness.^{35,36}

Age at asthma diagnosis and age at which asthma symptoms started both emerged as distinguishing factors between difficult-to-control and easy-to-control asthma. These factors have not been reported to be associated with the heterogeneity of response to asthma treatment.

Finally, our finding of blood neutrophil counts as a factor that could differentiate difficult-to-control from easy-to-control asthma was unexpected, and its significance is unclear. This finding was no longer relevant when the variable importance analysis was performed without pulmonary measures. Notably, the blood eosinophil count did not prove to be a relevant discriminating characteristic.

During the 12-month longitudinal part of the study, the 2 groups (difficult-to-control and easy-to-control) exhibited similarities and differences in clinical parameters measured over time. The major differences were that (1) the difficult-to-control group did not show any trend for improvement over 1 year despite guideline-based treatment, whereas the easy-to-control group did, and (2) the difficult-to-control group had higher peaks in exacerbation rates in the spring and fall and more daytime and nighttime symptoms in the fall and winter. Notable similarities

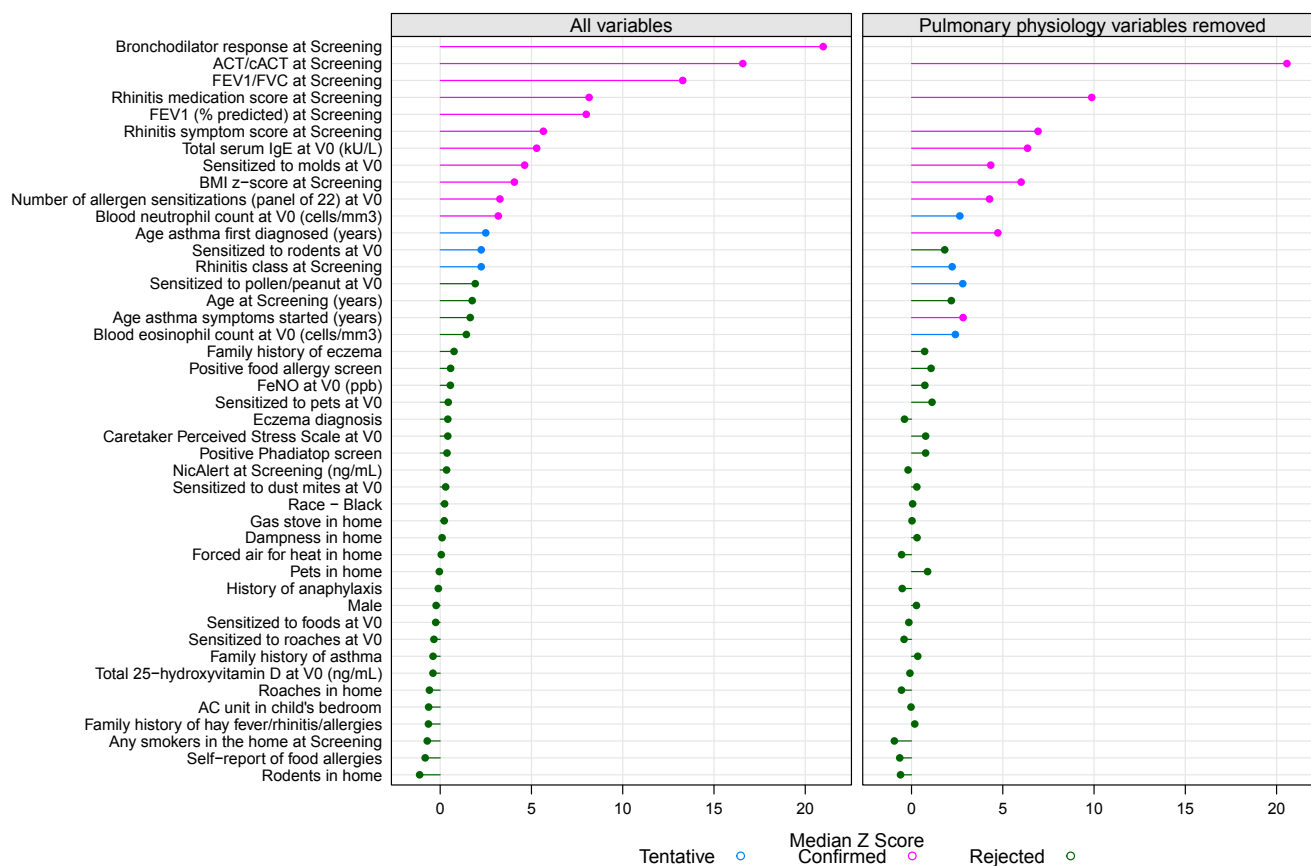


FIG 5. Variable importance plot of characteristics (with and without pulmonary physiology variables) distinguishing the difficult-to-control from easy-to-control groups. Circles plot median z scores for each variable, a measure of importance obtained from Boruta, a feature selection algorithm in which higher values indicate a higher level of importance. Solid blue circles indicate variables confirmed as being relevant to distinguishing the difficult-to-control from easy-to-control groups. Pink and green circles indicate variables that are tentative or rejected, respectively, and are not relevant to distinguishing between the difficult-to-control from easy-to-control groups.

between the difficult-to-control and easy-to-control groups included comparable adherence rates to asthma therapy, lowest incidence of exacerbations in the summer, and relatively constant pulmonary function, although at different levels, over the year.

The prospective nature of this study allowed us to partially examine the phenotypic stability of inner-city children with asthma. Given that the definition of our study groups included a stability criterion (to be within a specific range of therapy step levels in 4/6 study visits), the results presented in Fig 3 are not surprising. However, the fact that the easy-to-control group showed a progressive decrease in medication requirements over the course of the study whereas the difficult-to-control group did not emphasizes the unique nature of these children's asthma. In support of this notion is the lack of any improvement in lung function that this group has exhibited, as well as the increased rate of nocturnal symptoms over the fall and winter months, which also constitutes a unique characteristic. The concept of nocturnal asthma as an indicator of poor asthma control was endorsed in the Global Initiative for Asthma report,³⁷ and other investigators have previously demonstrated that nocturnal asthma is associated with more severe disease and greater bronchodilator responsiveness.²⁹ Although the greater frequency of symptoms and exacerbations in the difficult-to-control group was expected, the disparity of

seasonal variability in daytime and nighttime symptoms and asthma exacerbations between the 2 groups was a surprising finding. A large retrospective study of children found similar seasonal variability, such that there were fewer symptoms in the summer and more symptoms from fall through spring, but did not link this variability with a specific asthma phenotype.³⁸

Our study has potential limitations. Adherence measurements might not accurately reflect actual use because they were based on calculation of used doses from returned inhalers and/or a standardized questionnaire, which has not been validated. We acknowledge that pulmonary function was used in the determination of treatment step level, and this could have enhanced the relative importance of spirometry in our findings. As a result, we performed 2 analyses: when pulmonary physiology measures were removed, rhinitis, atopy, and BMI continued to be relevant factors, and age of asthma diagnosis and age of asthma symptom onset both emerged as new relevant variables. Other factors determining treatment level requirements might exist. For the most part, APIC assessed variables that have been traditionally studied. The method used to measure stress might lack precision, which could potentially affect our findings. The domains of stress and environmental exposure were lacking comprehensive measurements that could more fully describe them. For example, we

TABLE II. Potential prioritization of assessments to identify difficult-to-control asthma

FEV ₁ before/after albuterol
ACT/cACT
Spirometry
Rhinitis severity*
Total serum IgE measurement
Assessment of IgE to environmental allergens
BMI

*See Table E5.

addressed caregiver-perceived stress, but not other potential sources of stress, such as neighborhood violence.

New markers, particularly markers of immune cell, epithelial cell, and airway smooth muscle cell biology, might be necessary to develop predictors of the response to treatment, as well as predictors of achieving asthma control. In a *post hoc* analysis conventional baseline outcomes aside from ACT/cACT did not appear to influence asthma control among participants with difficult-to-control asthma in this study.

In this large prospective study we found that heterogeneity of treatment response in children with asthma is associated with clinical characteristics that can be identified early in the course of treatment. In addition to bronchodilator responsiveness, pulmonary physiology, rhinitis, and atopy were major features that distinguished children requiring high-dose asthma controller therapy. Assessments for clinicians and researchers to consider at initial evaluation are presented in Table II. Our observations point to the importance of allergen sensitization and its sequelae in children with asthma. These findings also put into perspective how various domains can link together to describe patient phenotypes, as well as potential pathways of disease.

We thank APIC study participants and their families, who gave of themselves to be our investigational partners; our study staff personnel, who are dedicated to our inner-city asthma mission and clinical research excellence; and Christine Sorkness and Patrick Heinritz in the ICAC Administrative Center (Madison, Wis) and Samuel Arbes, Michelle Walter, and Herman Mitchell at Rho for their leadership, commitment to excellence despite all of the challenges, and their legacies in inner-city asthma research.

Clinical implications: Clinical baseline characteristics related to pulmonary physiology, rhinitis severity, and atopy prospectively distinguish difficult-to-control from easy-to-control asthma.

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Distinguishing Characteristics of Difficult-to-Control Asthma in Inner-City Children and Adolescents

Online Repository

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Table E1: Asthma treatment adjustment based on control levels and adherence.

Control Level	Treatment Algorithm for Participants with Unacceptable Adherence	Treatment Algorithm for Participants with Acceptable Adherence
1	Continue same controller regimen	If on Step 0, maintain at Step 0. If on Steps 1-6, decrease controller regimen by 1 step.
2	Continue same controller regimen or place on Step 2 therapy, whichever is higher	Increase controller regimen by 1 step, or continue Step 6 therapy if already on Step 6.
3	Continue same controller regimen or place on Step 2 therapy, whichever is higher	No systemic glucocorticosteroid since the last visit* If on Steps 0-5, increase controller regimen by 1 step. If on Step 6, continue Step 6 or treat with Step 6 <u>and</u> a 4 day burst of prednisone. ≥1 course(s) of systemic glucocorticosteroids since the last visit* If on Steps 0-4, increase controller regimen by 2 steps. If on Step 5, increase controller regimen to Step 6 or treat with Step 6 <u>and</u> a 4 day burst of prednisone. If on Step 6, continue Step 6 or treat with Step 6 <u>and</u> a 4 day burst of prednisone.
4	Continue same controller regimen or place on Step 3 therapy, whichever is higher or treat with 4-day prednisone burst and continue same controller regimen or place on Step 3 therapy, whichever is higher	If on Steps 0-4 increase controller regimen by 2 steps. If on Step 5, increase to Step 6 or treat with Step 6 <u>and</u> a 4-day prednisone burst. If already on Step 6, continue on Step 6 or treat with Step 6 <u>and</u> a 4-day burst of prednisone.

*Defined as a prescription of a course of systemic glucocorticosteroid by a clinician or initiation of a course of systemic steroids by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic glucocorticosteroid without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Table E2: Asthma controller treatment steps.

Step	Medication
0	No controller medication; Ventolin® HFA prn
1	Singulair® 5 mg PO once per day 6 to 14 years of age 10 mg PO once per day ≥ 15 years of age
2	Flovent® Diskus® 50 mcg bid
3	Flovent® Diskus® 100 mcg bid
4	Flovent® Diskus® 250 mcg bid
5	Advair™ Diskus® 250/50 mcg bid
6	Advair™ Diskus® 500/50 mcg bid

Table E3: Control levels of symptoms, bronchodilator usage, and FEV₁ (% personal best).

Control Level	Maximum of 1) # days with asthma symptoms/ two weeks and 2) # days with rescue albuterol use/ two weeks*	Maximum of 1) # nights of sleep disruption due to asthma/ two weeks and 2) # nights use of albuterol for awakening/ two weeks*	FEV₁ (% personal best)	Courses of Systemic Glucocorticosteroids since the last Visit†
1	0-3 days	0-1 night	≥ 85	No
2	4-9 days	2 nights	80-84	Yes
3	10-13 days	3-4 nights	70-79	-
4	14 days	5-14 nights	< 70	-

* Determined from participant recall, based on the 2-week interval directly preceding the study visit.

† Defined as a prescription of a course of systemic glucocorticosteroid by a clinician or initiation of a course of systemic glucocorticosteroid by a participant to prevent a serious asthma outcome. If a participant initiates and completes a course of systemic glucocorticosteroid without clinician involvement, this course will be counted only if it meets the following minimum dosage: prednisone, prednisolone, or methylprednisolone at ≥ 20mg per day for 3 of any 5 consecutive days; or dexamethasone at ≥ 10mg per day for ≥ 1 day.

Table E4. CASI component scores.

	Score
Day Symptoms and Albuterol in the last 2 weeks (maximum days)	
0-3	0
4-9	1
10-13	2
14	3
Night Symptoms and Albuterol in the last 2 weeks (maximum nights)	
0-1	0
2	1
3-4	2
5-14	3
Exacerbations	
Prednisone Burst	2
Prednisone Burst + Hospitalization	4

Table E5. Rhinitis Treatment Adjustment Based on Frequency and Severity Outcomes from the Modified Rhinitis Symptom Utility Index (MRSUI)*

Adjustment Based on Frequency and Severity Outcomes**

Days in past 2 weeks having any symptoms (Frequency)	“Not Bothered” (Severity)	“Somewhat Bothered” (Severity)	“Bothered a Lot” (Severity)
0 Days	Decrease to the next lower step		
1-3 Days	No change	No change	Increase to the next higher step
4-7 Days	No change	Increase to the next higher step	Increase to the next higher step
>7 Days	Increase to the next higher step	Increase to the next higher step	Increase to the next higher step

Rhinitis Treatment Steps

Step	Allergic Rhinitis	Non-Allergic Rhinitis
0	No medication	No medication
1	cetirizine 10 mg PRN or Singulair® 5 mg PO QD 6 to 14 years of age; 10 mg PO QD ≥15 years of age (treatment option only if this is a pre-study medication)	N/A
2	Flonase® Nasal Spray 200 mcg QD (2 sprays per nostril) plus cetirizine 10 mg PRN or Singulair® 5 mg PO QD 6 to 14 years of age; 10 mg PO QD ≥15 years of age (treatment option only if this is a pre-study medication)	Flonase® Nasal Spray 200 mcg QD (2 sprays per nostril)

* Scoring was modified slightly for the APIC study, but is based on the Rhinitis Symptom Utility Index.¹

** The study clinician could modify the treatment plan based on a report of a sinus infection treated with antibiotics, evidence of a viral infection, findings on nasal exam, or other circumstance where the clinician felt changes in the treatment plan were required.

Table E6. Relevant study assessments by visit.

Visit	Screening	Baseline 0	Month 2 1	Month 4 2	Month 6 3	Month 8 4	Month 10 5	Month 12 6
Demographics	X							
Asthma and Allergy History	X							
Allergen Skin Test	X							
Rhinitis/Rhinosinusitis Diagnostic Questionnaire	X							
Pre-bronchodilator Spirometry	X	X	X	X	X	X	X	X
Asthma Symptoms and Utilization	X	X	X	X	X	X	X	X
Rhinitis Symptom Assessment	X	X	X	X	X	X	X	X
Nasal Exam ¹	X	X	X	X	X	X	X	X
Physical Exam	X							X
Post-bronchodilator Spirometry	X							X
Asthma Control Test	X							X
Smoking – Caretaker & Participant	X							X
Targeted Pulmonary Exam		X	X	X	X	X	X	
Adherence Review		X	X	X	X	X	X	X
Urine Collection - Cotinine		X						
Blood Sample Collection		X						
Perceived Stress Scale - Caretaker		X						X
FeNO		X						X

¹ The nasal exam is required at Screening and Month 12 (Visit 6); it is optional for all other study visits.

Table E7. Variables used in univariate and variable importance analyses. Unless otherwise specified, all variables were used in the variable importance analysis.

Domain	Variables
Demographics	Male
	Race Black Other
	Race ¹ Black (non-Hispanic) Hispanic Other/Mixed White (non-Hispanic)
	Age at Screening (years)
	Family history of asthma
Family history	Family history of hay fever/rhinitis/allergies
	Family history of eczema
	Self-report of food allergies
Allergy history	History of anaphylaxis
	Eczema diagnosis
	Age asthma first diagnosed (years)
Asthma history	Age asthma symptoms started (years)
	ACT/cACT ² at Screening
	Controller treatment step at Screening ¹
	BMI z-score at Screening
BMI	BMI percentile at Screening ¹
	Total 25-hydroxyvitamin D at V0 (ng/mL)
Vitamin D	Any smokers in the home at Screening
Environmental exposures	NicAlert result at Screening
	Gas stove in home
	Dampness in home
	AC unit in child's bedroom
	Forced air for heat in home
	Rodents in home
	Roaches in home
	Pets in home
	Caretaker Perceived Stress Scale at V0
Stress	Total serum IgE at V0 (kU/L) ³
	Number of allergen sensitizations (panel of 22) ⁵ at V0
	Positive Phadiatop screen at V0
	Positive fx5 food allergy screen at V0
	Sensitized to molds ⁶ at V0
	Sensitized to dust mites ⁷ at V0
	Sensitized to roaches ⁸ at V0

	Sensitized to rodents ⁹ at V0
	Sensitized to pets ¹⁰ at V0
	Sensitized to pollen/peanut ¹¹ at V0
	Sensitized to foods ¹² at V0
Inflammation	FeNO at V0 (ppb) ³
	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
	FEV ₁ /FVC (x100) at Screening
Rhinitis	Rhinitis classification at Screening No rhinitis Non-allergic rhinitis Allergic rhinitis
	Rhinitis medication score ¹³ at Screening
	Rhinitis medications at Screening ¹ None Antihistamine only Nasal steroids only Antihistamine & nasal steroids
	Rhinitis symptom score ¹⁴ at Screening

- Variable is included in univariate analysis but not used to establish variable importance in distinguishing difficult- from easy-to-control asthma.
- 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).
- Variable is log10 transformed when establishing variable importance in distinguishing difficult- from easy-to-control asthma.
- Positive skin prick test and/or a positive specific IgE.
- 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.
- 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* and *Dermatophagoides pteronyssinus*.
- German cockroach and American cockroach.
- Mouse and rat.
- Cat and dog.
- Oak, pecan, birch, maple, Eastern 8 tree mix, ragweed, Timothy grass, K-O-T grass mix and peanut.
- Egg and milk.
- 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 (see Table E5).

- 1 Table E8. Participant characteristics and demographics: Unless otherwise noted, characteristics are compared using chi-square or
 2 Fisher's exact test for categorical variables, and ANOVA or t-test for continuous variables. Unless otherwise noted, summary
 3 statistics are frequency (%) for categorical variables and mean and standard deviation for continuous variables.

Characteristic	N	All participants	Difficult	Easy	Indeterminate	P-value			
						Overall	Difficult vs Easy	Difficult vs Indetermi- nate	Easy vs Indetermi- nate
Demographics									
Male	619	361 (58.3%)	138 (54.5%)	142 (61.2%)	81 (60.4%)	0.28	0.16	0.31	0.97
Race ¹	616					0.21	0.07	0.52	0.57
Black (non-Hispanic)		394 (64.0%)	173 (68.7%)	138 (59.5%)	83 (62.9%)				
Hispanic		177 (28.7%)	67 (26.6%)	70 (30.2%)	40 (30.3%)				
Other/Mixed		34 (5.5%)	9 (3.6%)	17 (7.3%)	8 (6.1%)				
White (non-Hispanic)		11 (1.8%)	3 (1.2%)	7 (3.0%)	1 (0.8%)				
Age at Screening (years)	619	10.8 (3.0)	10.7 (3.0)	11.1 (3.1)	10.2 (2.9)	0.02	0.15	0.09	0.004
Family history									
Family history of asthma	604	445 (73.7%)	186 (74.7%)	160 (71.7%)	99 (75.0%)	0.71	0.54	>0.99	0.59
Family history of hay fever/rhinitis/allergies	586	334 (57.0%)	133 (55.9%)	126 (56.8%)	75 (59.5%)	0.80	0.92	0.58	0.70
Family history of eczema	590	334 (56.6%)	146 (60.1%)	117 (52.7%)	71 (56.8%)	0.28	0.13	0.62	0.53
Allergy history									
Self-report of food allergies	619	191 (30.9%)	77 (30.4%)	67 (28.9%)	47 (35.1%)	0.46	0.78	0.41	0.27
History of anaphylaxis	619	46 (7.4%)	23 (9.1%)	12 (5.2%)	11 (8.2%)	0.24	0.14	0.92	0.35
Eczema diagnosis	619	338 (54.6%)	150 (59.3%)	117 (50.4%)	71 (53.0%)	0.14	0.06	0.28	0.72
Asthma history									
Age asthma first diagnosed (years)	617	3.3 (3.2)	2.8 (2.9)	3.9 (3.4)	3.3 (3.3)	0.002	<0.001	0.12	0.15
Age asthma symptoms started - (years)	617	1.4 (2.7)	1.6 (2.7)	1.1 (2.4)	1.7 (3.1)	0.03	0.02	0.81	0.04

Characteristic	N	All participants	Difficult	Easy	Indeterminate	P-value			
						Overall	Difficult vs Easy	Difficult vs Indeterminate	Easy vs Indeterminate
ACT/cACT ² at Screening	618					<0.001	<0.001	0.07	<0.001
Very poorly controlled		52 (8.4%)	28 (11.1%)	7 (3.0%)	17 (12.7%)				
Not well controlled		179 (29.0%)	103 (40.9%)	37 (15.9%)	39 (29.1%)				
Well controlled		387 (62.6%)	121 (48.0%)	188 (81.0%)	78 (58.2%)				
Controller treatment step at Screening ³	619					<0.001	<0.001	<0.001	<0.001
Steps 0-2		212 (34.2%)	23 (9.1%)	153 (65.9%)	36 (26.9%)				
Step 3		91 (14.7%)	27 (10.7%)	37 (15.9%)	27 (20.1%)				
Steps 4-6		316 (51.1%)	203 (80.2%)	42 (18.1%)	71 (53.0%)				
BMI									
BMI z-score at Screening	619	1.0 (1.2)	1.1 (1.2)	0.9 (1.1)	1.0 (1.1)	0.32	0.14	0.51	0.53
BMI percentile at Screening ³	619	87.0 [58.2;97.6]	88.3 [61.7;98.2]	85.5 [54.9;96.7]	82.9 [58.7;97.6]	0.17	0.06	0.31	0.63
Vitamin D									
Total 25-hydroxyvitamin D at V0 (ng/mL)	606	19.3 (7.3)	18.7 (7.4)	19.5 (7.0)	20.0 (7.8)	0.23	0.25	0.12	0.52
Environmental exposure									
Any smokers in the home at Screening	616	248 (40.3%)	109 (43.4%)	86 (37.2%)	53 (39.6%)	0.38	0.20	0.53	0.74
NicAlert result at Screening	610	1.3 (1.1)	1.3 (1.1)	1.3 (1.0)	1.2 (1.1)	0.85	0.90	0.58	0.66
Gas stove in home	606	404 (66.7%)	160 (64.3%)	151 (66.8%)	93 (71.0%)	0.42	0.63	0.23	0.48
Dampness in home	603	222 (36.8%)	94 (37.8%)	74 (33.0%)	54 (41.5%)	0.26	0.33	0.54	0.14
AC unit in child's bedroom	606	414 (68.3%)	170 (68.3%)	149 (65.9%)	95 (72.5%)	0.44	0.66	0.46	0.24
Forced air for heat in home	607	371 (61.1%)	152 (60.8%)	136 (60.2%)	83 (63.4%)	0.83	0.96	0.71	0.63
Rodents in home	606	183 (30.2%)	75 (30.1%)	67 (29.6%)	41 (31.3%)	0.95	0.99	0.91	0.84
Roaches in home	603	115 (19.1%)	49 (19.8%)	33 (14.7%)	33 (25.4%)	0.04	0.18	0.26	0.02
Pets in home	606	228 (37.6%)	99 (39.8%)	79 (35.0%)	50 (38.2%)	0.55	0.33	0.85	0.62

Characteristic	N	All participants	Difficult	Easy	Indeterminate	P-value			
						Overall	Difficult vs Easy	Difficult vs Indetermi- nate	Easy vs Indetermi- nate
Stress									
Caretaker Perceived Stress Scale at V0	616	14.8 (7.5)	15.1 (7.6)	13.7 (7.3)	16.0 (7.5)	0.01	0.05	0.24	0.005
Allergen sensitization									
Total serum IgE at V0 (kU/L) ⁴	610	253.0 [85.5;778.2]	405.0 [101.0;1087.0]	197.0 [72.0;529.0]	306.0 [76.0;846.7]	<0.001	<0.001	0.11	0.09
Number of allergen sensitizations (panel of 22) ⁵ at V0	619	8.7 (6.2)	9.9 (6.3)	7.5 (5.9)	8.6 (6.2)	<0.001	<0.001	0.07	0.09
Positive Phadiatop screen	607	478 (78.7%)	202 (81.5%)	172 (75.4%)	104 (79.4%)	0.27	0.14	0.73	0.47
Positive fx5 food allergy screen	608	340 (55.9%)	154 (61.8%)	116 (50.9%)	70 (53.4%)	0.04	0.02	0.14	0.72
Sensitized to molds ⁶ at V0	619	308 (49.8%)	149 (58.9%)	91 (39.2%)	68 (50.7%)	<0.001	<0.001	0.15	0.04
Sensitized to dust mites ⁷ at V0	619	364 (58.8%)	159 (62.8%)	128 (55.2%)	77 (57.5%)	0.22	0.10	0.36	0.75
Sensitized to roaches ⁸ at V0	619	346 (55.9%)	151 (59.7%)	121 (52.2%)	74 (55.2%)	0.25	0.12	0.46	0.65
Sensitized to rodents ⁹ at V0	619	261 (42.2%)	127 (50.2%)	81 (34.9%)	53 (39.6%)	0.002	0.001	0.06	0.44
Sensitized to pets ¹⁰ at V0	619	401 (64.8%)	176 (69.6%)	139 (59.9%)	86 (64.2%)	0.08	0.03	0.34	0.49
Sensitized to pollen/peanut ¹¹ at V0	619	437 (70.6%)	197 (77.9%)	147 (63.4%)	93 (69.4%)	0.002	0.001	0.09	0.29
Sensitized to foods ¹² at V0	611	181 (29.6%)	77 (30.7%)	66 (28.9%)	38 (28.8%)	0.89	0.75	0.79	>0.99
Inflammation									
FeNO at V0 (ppb) ⁴	569	19.0 [11.5;37.9]	20.5 [12.0;38.2]	17.4 [10.7;32.0]	19.5 [13.0;40.5]	0.08	0.05	0.82	0.07
Blood eosinophil count at V0 (cells/mm3) ⁴	610	300.0 [168.5;487.8]	300.0 [190.0;500.0]	200.0 [115.0;400.0]	303.0 [190.0;507.5]	0.004	0.004	0.63	0.006
Blood neutrophil	610	2880.0	3000.0	2700.0	2700.0	0.09	0.03	0.27	0.43

Characteristic	N	All participants	Difficult	Easy	Indeterminate	P-value			
						Overall	Difficult vs Easy	Difficult vs Indeterminate	Easy vs Indeterminate
count at V0 (cells/mm ³) ⁴		[2000.0;3900.0]	[2100.0;4100.0]	[2000.0;3736.0]	[2045.5;3741.2]				
Pulmonary physiology									
Bronchodilator response at Screening	610	13.3 (13.9)	18.3 (15.9)	8.6 (9.6)	11.9 (13.0)	<0.001	<0.001	<0.001	0.01
FEV ₁ (% predicted) at Screening	619	91.8 (17.2)	86.7 (17.7)	96.6 (15.4)	93.3 (16.5)	<0.001	<0.001	<0.001	0.06
FEV ₁ /FVC (x100) at Screening	609	77.9 (9.7)	74.2 (10.3)	81.0 (8.0)	79.4 (9.1)	<0.001	<0.001	<0.001	0.08
Rhinitis									
Rhinitis classification at Screening	619					0.02	0.006	0.67	0.10
Allergic		431 (69.6%)	189 (74.7%)	144 (62.1%)	98 (73.1%)				
Non-Allergic		125 (20.2%)	46 (18.2%)	56 (24.1%)	23 (17.2%)				
No Rhinitis		63 (10.2%)	18 (7.1%)	32 (13.8%)	13 (9.7%)				
Rhinitis medication score ¹³ at Screening	619	9.7 (6.1)	11.1 (5.6)	7.9 (6.3)	10.4 (5.9)	<0.001	<0.001	0.29	<0.001
Rhinitis medications at Screening ³	619					<0.001	<0.001	0.35	0.002
None		130 (21.0%)	37 (14.6%)	71 (30.6%)	22 (16.4%)				
Antihistamine only		87 (14.1%)	24 (9.5%)	43 (18.5%)	20 (14.9%)				
Nasal steroids only		89 (14.4%)	40 (15.8%)	32 (13.8%)	17 (12.7%)				
Antihistamine & nasal steroids		313 (50.6%)	152 (60.1%)	86 (37.1%)	75 (56.0%)				
Rhinitis symptom score ¹⁴ at Screening	619	9.0 (6.0)	10.1 (6.2)	7.3 (5.3)	9.8 (6.1)	<0.001	<0.001	0.63	<0.001

1. Race is dichotomized (black vs. other) when establishing variable importance in distinguishing difficult- from easy-to-control asthma.

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. Not included in list of variables to establish variable importance in distinguishing difficult- from easy-to-control asthma.

4. Summarized using the median and inter-quartile range and tested using a Kruskal-Wallis test.

5. 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.
6. Sensitization is based on a positive prick skin 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*, and *Cladosporium herbarum*.
 7. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.
 8. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: German cockroach and American cockroach.
 9. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: mouse and rat.
 10. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: cat and dog.
 11. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one 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.
 12. Sensitization is based on a positive skin prick test and/or positive specific IgE to at least one of the following allergens: egg and milk.
 13. 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.
 14. Rhinitis symptom score is based on the Modified Rhinitis Symptom Utility Index (see Table E5 in the Online Repository).

REFERENCE

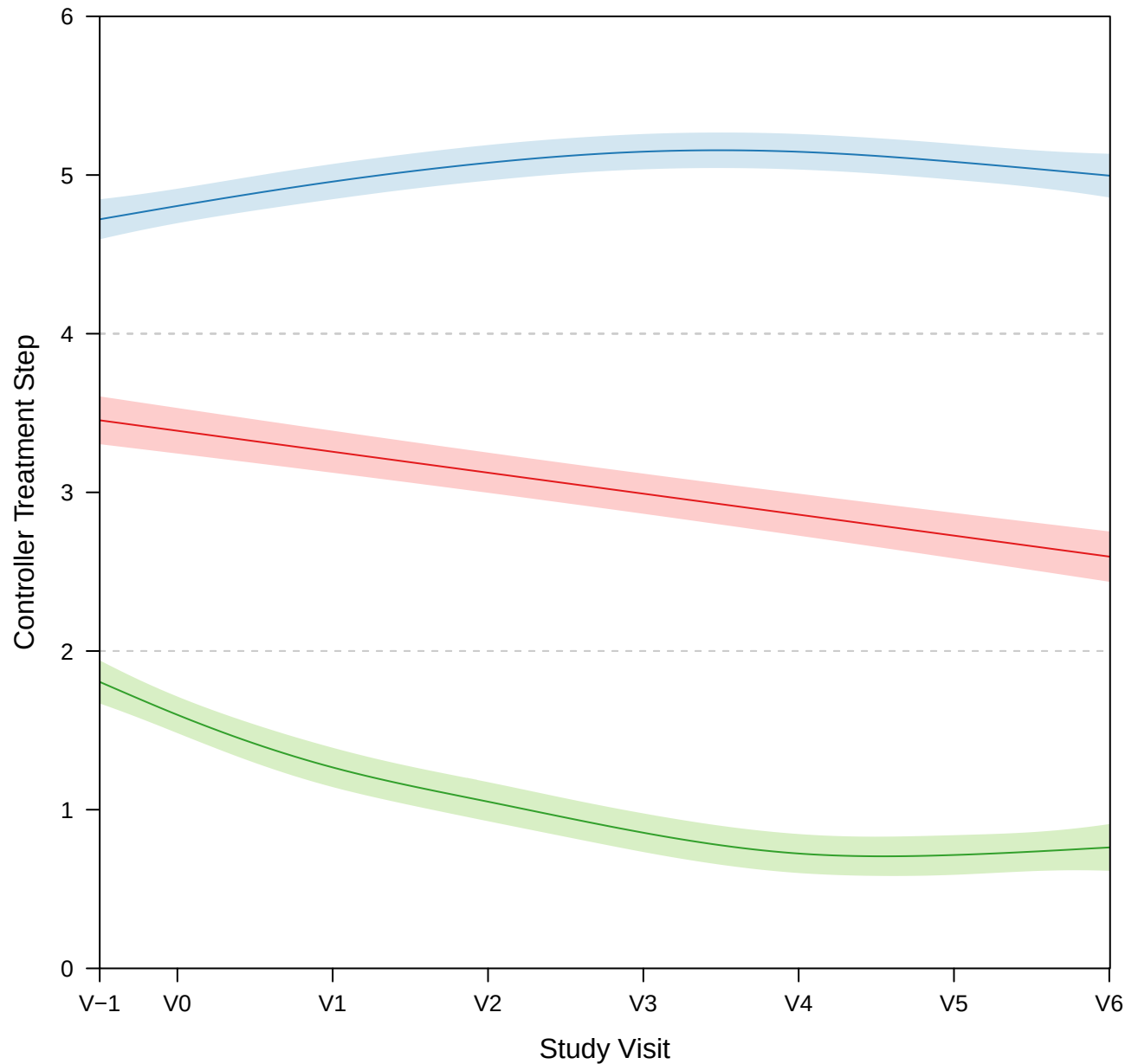
1. Revicki DA, Leidy NK, Brennan-Diemer F, Thompson C, Togias A. Development and preliminary validation of the multiattribute Rhinitis Symptom Utility Index. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 1998;7:693-702.

FIGURE LEGENDS

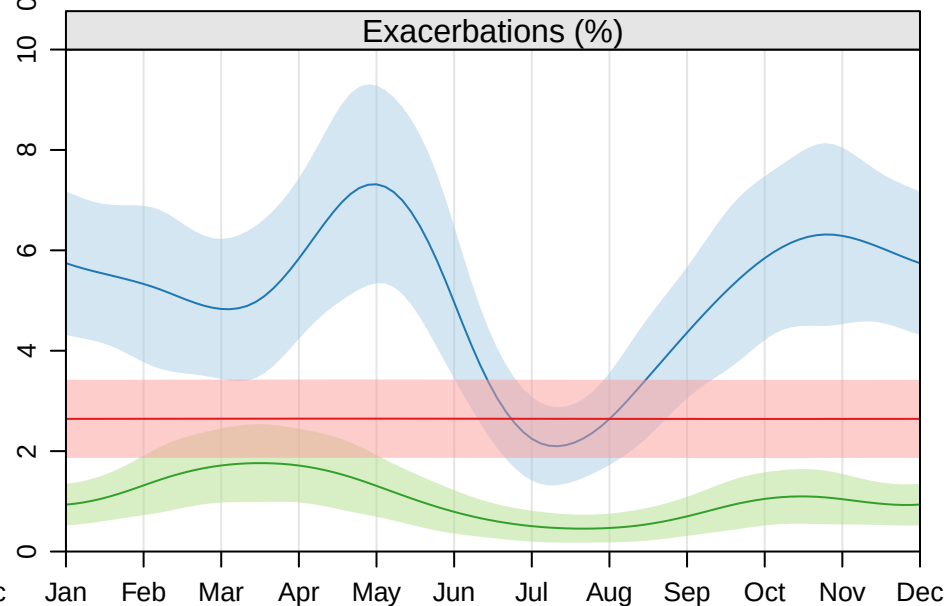
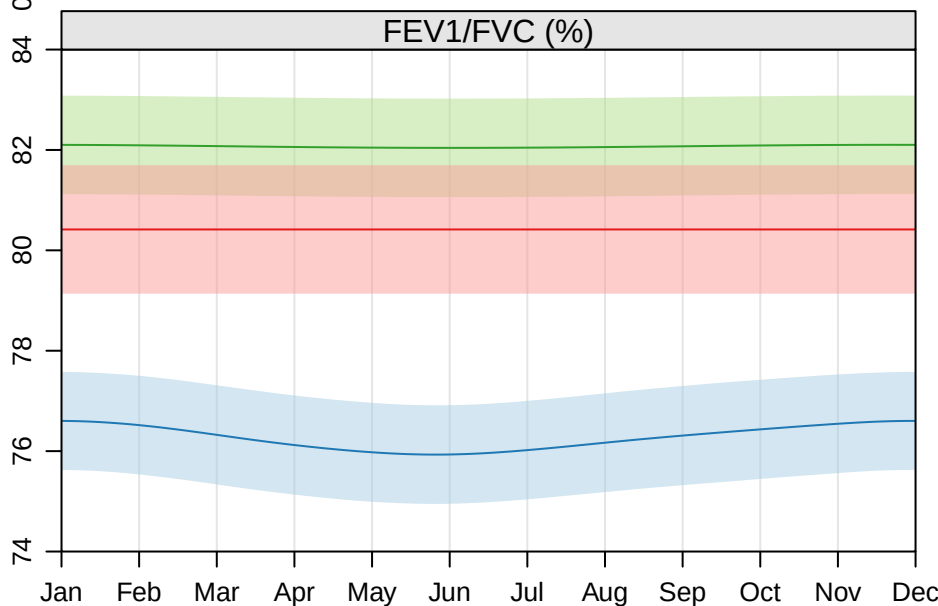
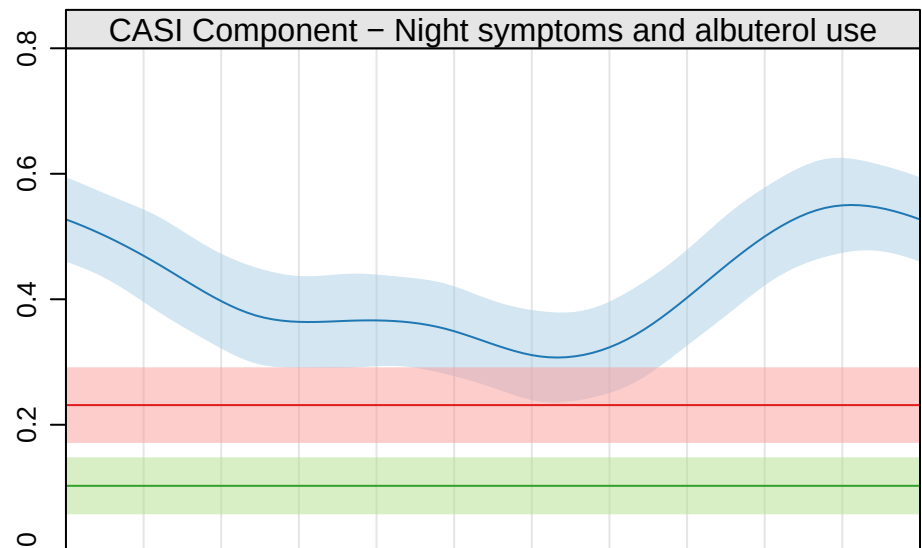
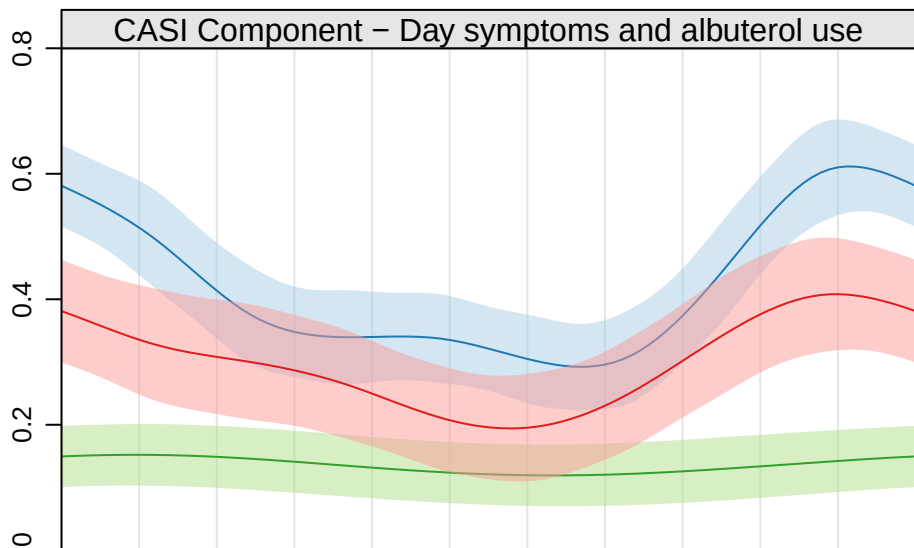
Figure E1: Controller treatment step for easy-to-control, indeterminate and difficult-to-control groups over 12 months. Green, red and blue lines (shaded areas) indicate mean (95% CI) of controller treatment step for easy-to-control, indeterminate and difficult-to-control groups respectively over 12 months.

Figure E2: Seasonal variation in clinical severity measures in easy-to-control, indeterminate and difficult-to-control groups. Green, red and blue lines (shaded areas) indicate mean or probability (95% CI) of clinical severity measure for easy-to-control, indeterminate and difficult-to-control groups respectively over 12 months. Clinical severity measures are: A) CASI component measuring day symptoms and albuterol use in the last two weeks (0 to 3 points); B) CASI component measuring night symptoms and albuterol use in the last two weeks (0 to 3 points); C) FEV_1/FVC (x100); and D) Monthly incidence of exacerbations, as defined by prednisone use.

Easy Indeterminate Difficult



Easy — Indeterminate — Difficult —



Month