

Seasonal risk factors for asthma exacerbations among inner-city children

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Background: Asthma exacerbations remain common, even in children and adolescents, despite optimal medical management. Identification of host risk factors for exacerbations is incomplete, particularly for seasonal episodes.

Objective: We sought to define host risk factors for asthma exacerbations unique to their season of occurrence.

Methods: This is a retrospective analysis of patients aged 6 to 20 years who comprised the control groups of the Asthma Control Evaluation study and the Inner City Anti-IgE Therapy for Asthma study. Univariate and multivariate models were constructed to determine whether patients' demographic and historical factors, allergic sensitization, fraction of exhaled nitric oxide values, spirometric measurements, asthma control, and treatment requirements were associated with seasonal exacerbations.

Results: The analysis included 400 patients (54.5% male; 59.0% African American; median age, 13 years). Exacerbations occurred in 37.5% of participants over the periods of observation and were most common in the fall (28.8% of participants). In univariate analysis impaired pulmonary function was significantly associated with greater odds of

exacerbations for all seasons, as was an exacerbation in the previous season for all seasons except spring. In multivariate analysis exacerbation in the previous season was the strongest predictor in fall and winter, whereas a higher requirement for inhaled corticosteroids was the strongest predictor in spring and summer. The multivariate models had the best predictive power for fall exacerbations (30.5% variance attributed).

Conclusions: Among a large cohort of inner-city children with asthma, patients' risk factors for exacerbation vary by season. Thus information on individual patients might be beneficial in strategies to prevent these seasonal events. (*J Allergy Clin Immunol* 2015;■■■■:■■■-■■■.)

Key words: Asthma, seasons, biomarkers, asthma exacerbations, IgE, exhaled nitric oxide, allergy, eosinophils, pulmonary function

Asthma exacerbations remain a major factor contributing to the morbidity and even mortality of pediatric patients with asthma.¹ Moreover, asthma exacerbations account for a large proportion

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This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under contract nos. NO1-AI-25496, NO1-AI-25482, HHSN272200900052C, and HHSN272201000052I. Additional support was provided by the National Center for Research Resources, National Institutes of Health, under grants RR00052, M01RR00533, UL1 RR024982, M01RR00071, 5M01RR020359-04, 1UL1RR025771, 1UL1RR025780, 1UL1RR024156, UL1RR031988, UL1RR025741, and UL1TR000451. Lincoln Diagnostics provided the Multi-Test, and GlaxoSmithKline (GSK) provided study drug for Asthma Control Evaluation study participants. Novartis Pharmaceuticals provided study drug under a clinical trial agreement with the University of Wisconsin-Madison, Dey Pharma provided EpiPens, and SC Johnson provided household pest control for Inner City Anti-IgE Therapy for Asthma study participants. None of these companies had a role in the development or approval of the protocol, conduct of the trial, data analysis, manuscript preparation, or the decision to submit for publication.

Disclosure of potential conflict of interest: S. J. Teach has received research support from the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) and Novartis; is employed by the Children's National Health System; has received research support from the NIH/NIAID, the Kohls Foundation, the Stewart Foundation, and PCORI; and has received royalties from UpToDate. S. J. Szeffler has received research support and travel support from the NIAID Inner-City Asthma Consortium; has received consultancy fees from Merck, Boehringer

Ingelheim, GlaxoSmithKline, and Genentech; has received research support from GlaxoSmithKline; has received lecture fees from Merck; and has a patent with the National Heart, Lung, and Blood Institute (NHLBI) CARE Network. H. E. Mitchell and A. Calatroni has received research support from the NIH/NIAID. J. Wildfire and G. R. Bloomberg have received research support and travel support from the NIH/NIAID. C. M. Kercksmar has received research support from the NIH, is a board member for GlaxoSmithKline, and has received royalties from UpToDate. A. H. Liu has received lecture fees from Merck Sharp & Dohme and is a Data Safety Committee member for GlaxoSmithKline. M. M. Makhija has received travel support from the NIAID Inner-City Asthma Consortium. E. Matsui has received research support from the NIH, is a board member for the US Environmental Protection Agency Science Advisory Board, and is employed by Johns Hopkins University. W. Morgan has received research support and travel support from the NIAID/NIH and the University of Wisconsin-Madison; has received consultancy fees from Genentech and the Cystic Fibrosis Foundation; is employed by the University of Arizona; has received research support from AsthmaNet NIH/NHLBI, the Cystic Fibrosis Foundation, Mt Sinai College of Medicine, and the NIH/NHLBI; and has received lecture fees from the American Thoracic Society and the American College of Chest Physicians. G. O'Connor has received research support from the NIH. W. W. Busse has been supported by the NHLBI/NIH; is a board member for Merck; has received consultancy fees from Novartis, GlaxoSmithKline, Genentech, Roche, Pfizer, Boston Scientific, Circassia, ICON, AstraZeneca, Sanofi, Amgen, MedImmune, NeoStem, Takeda, and Boehringer Ingelheim; has received research support from the NIAID/NIH and the NHLBI/NIH; and has received royalties from Elsevier. P. J. Gergen declares that he has no relevant conflicts of interest.

Received for publication August 21, 2014; revised December 17, 2014; accepted for publication December 19, 2014.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2014.12.1942>

Abbreviations

ACE: Asthma Control Evaluation
 BMI: Body mass index
 FENO: Fraction of exhaled nitric oxide
 FVC: Forced vital capacity
 ICATA: Inner City Anti-IgE Therapy for Asthma study
 ICS: Inhaled corticosteroid
 OR: Odds ratio

of the direct and indirect medical costs associated with the disease.^{2,3} Although guideline-directed care reduces the frequency of asthma exacerbations among children, these events continue to occur in many patients.⁴ Given the importance of exacerbations to the overall burden of asthma, attention has focused on the causes of these events, including viral respiratory tract infections, airborne allergens, pollutants, and stress.⁵ Although asthma exacerbations can occur at any time during the year, seasonal patterns exist, and in children exacerbation rates are highest in the fall and lowest in the summer.⁶⁻⁸ The seasonal increase in fall exacerbations is highly consistent and, based on studies from Canada, has been referred to as the “September epidemic.”⁹ Fall exacerbations have been attributed to an increased frequency of rhinovirus respiratory tract infections among children when they return to school.^{10,11} However, other factors, such as allergic sensitization and an increase in exposure to environmental allergens, have also been proposed to work in combination with viral respiratory tract infections to trigger fall asthma exacerbations.¹² Although the environmental contributors to asthma exacerbations are well recognized and appreciated, patients’ characteristics associated with a susceptibility to these events on a seasonal basis have not been completely defined nor has the importance of these factors in determining possible differences in the timing of exacerbations.

An achievement of optimal asthma control includes efforts to reduce the frequency of exacerbations.¹³ Understanding which characteristics are associated with an increased risk for asthma exacerbation is a critical step to prevent these events and might include seasonal modification of treatment. Toward that goal, a predominant finding in predicting who is at risk for asthma exacerbation has been the observation that prior exacerbations are the best predictor of future exacerbations.¹⁴⁻¹⁷ Although this finding has important utility, its tautological nature suggests that incompletely defined additional factors might also predict exacerbations. Furthermore, there has been little research that explores risk factors for exacerbations in individual seasons other than the fall or whether these risk factors can be predicted and, as a consequence, whether this information might improve approaches to prevent seasonal exacerbations. Consequently, we hypothesized that specific patients’ characteristics might be associated with seasonal asthma exacerbations. Such characteristics could act to identify which patients are at high risk for seasonal asthma exacerbations and therefore might serve as a framework to identify more effective treatment strategies to prevent these events.

METHODS**Overview**

This analysis examines risk factors for asthma exacerbations in 400 control group participants from 2 recent studies from the Inner-City Asthma Consortium: the Asthma Control Evaluation (ACE) study (n = 253)⁴ and

the Inner City Anti-IgE Therapy for Asthma (ICATA) study (n = 147).¹⁸ Seasonal and year-round predictors are considered by using both univariate and multivariate analytic techniques. Of note, in both the ACE and ICATA studies, all participants (including control subjects) were given guideline-based treatment by asthma specialists before randomization and throughout the year-long follow-up. In the ACE study fraction of exhaled nitric oxide (FENO) was added to the evaluation regimen to determine treatment for the intervention group. For the ICATA study, omalizumab was added to guideline treatment for the intervention group. In both studies the guideline-treated control and intervention groups were closely monitored for symptoms and exacerbations during the follow-up year. Both studies were approved by each institution’s institutional review board. Study details, including study sites and inclusion and exclusion criteria, are included in Table E1 in this article’s Online Repository at www.jacionline.org. Both studies enrolled largely minority participants with persistent asthma from urban neighborhoods. Important differences between the trials include the ages of enrolled participants (12-20 years for the ACE study and 6-20 years for the ICATA study), the proportion of Hispanics enrolled (22.9% for the ACE study and 42.2% for the ICATA study), and the requirement that patients in the ICATA study have a combined body weight and total serum IgE level suitable for omalizumab dosing and a positive skin prick test response to at least 1 perennial allergen; however, 85% of patients in the ACE study also met this requirement.

ACE population and study design

A total of 546 participants aged 12 to 20 years with asthma were enrolled in the ACE study at 10 large urban research centers in the United States.⁴ The ACE study had a randomized, double-blind, parallel-group design. At screening visits, each participant was assessed for asthma symptoms, previous treatment, pulmonary function, allergen skin prick test sensitivity, total serum IgE levels, and allergen-specific IgE levels. Participants were evaluated at 7 additional visits at 6- to 8-week intervals, with symptom assessments and pulmonary function testing at each visit. Treatment was adjusted according to guideline-based algorithms¹³ with or without taking into consideration FENO values. All study drugs were provided. Exacerbations were defined as a need for systemic corticosteroids, hospitalization, or both.

ICATA population and study design

The ICATA study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial that compared omalizumab with placebo added to guideline-based therapy in 419 inner-city children, adolescents, and young adults (aged 6-20 years) with persistent allergic asthma.¹⁸ Similar to the ACE study, at screening visits, each participant was assessed for asthma symptoms, previous treatment, pulmonary function, allergen skin prick test sensitivity, total serum IgE levels, and allergen-specific IgE levels. Asthma medications covered by the participants’ insurance plans were prescribed but were not supplied, with the exception of omalizumab or placebo study injections and oral prednisone for exacerbations. Like the ACE study, exacerbations were defined by the need for systemic corticosteroids, hospitalization, or both.

Statistical analyses

Participants from the ACE and ICATA studies were pooled for all analyses to increase sample size and to improve generalizability. Exacerbation predictors are described as either “baseline” or “previous season.” Baseline predictors were measured at or before study randomization, whereas previous season predictors were postrandomization measures collected before the start of the season of interest. For example, the FEV₁/forced vital capacity (FVC) ratio from the summer was used to predict exacerbations in the fall. The exacerbation outcome was binary (≥ 1 exacerbation vs no exacerbations in a given season). The initial 90 days of follow-up exacerbation data were not included as outcomes because there was no prior season prediction data; however, data from this period were used as predictors for the following season. A minimum of 45 days of follow-up for exacerbations in a given season was required for inclusion in the analysis. All participants with at least 5

months of follow-up were included. A random effect for participant was added to account for within-participant correlation in models looking across multiple seasons.

Univariate associations for each season were calculated by using logistic regression models and reported as odds ratios (ORs) and 95% CIs. Mixed models were constructed to obtain overall associations accounting for repeated measurements and to calculate appropriate interaction *P* values. Multivariate models were calculated by using the R package “hier.part.”¹⁹ Hierarchical partitioning was performed on the variables that had any significant seasonal association, calculating the independent contribution of each factor in predicting exacerbations. This technique, rather than seeking a best fit, uses all possible models in a logistic regression to distinguish the predictor variables with the highest independent contribution.

We scored participant risk using a simple algorithm. We started with 18 risk factors that were significant univariate predictors of exacerbation and then removed 10 of the items that were collinear, leaving 8 measures. Skin test results and total IgE levels were combined and presented as a single measure for “allergy,” leaving the following 7 items, which were scored by using tertiles: age, exacerbation history in the previous season, inhaled corticosteroid (ICS) treatment step, FEV₁/FVC ratio, FENO values, blood eosinophil counts, and allergy (see Table E2 in this article’s Online Repository at www.jacionline.org).

Log transformations of skewed data (FENO values, total IgE levels, allergen-specific IgE levels, and sum of the 5 allergen-specific IgE levels) were used for univariate analyses. A *P* value of less than .05 was considered statistically significant. All statistical analyses were performed with SAS statistical software, version 9.3 (SAS Institute, Cary, NC), and the R system for statistical computing, version 3.0.2. The calculation of relative importance was conducted by using the R add-on package hier.part.

RESULTS

Participants’ characteristics

For more information on participants’ characteristics, see Table I. The 400 participants from the ACE and ICATA study control treatment groups included in these analyses were typically low income (55.5% with income <\$15,000), minority (59% black and 30% Hispanic), and overweight (median body mass index [BMI] percentile at screening, 88.8%). Their median age was 13 years. In the 6 months before study entry, 16.8% were hospitalized for asthma. At study screening, the mean Asthma Control Test score was low (18.6 ± 4.2) but increased after 3 to 4 weeks of guideline-based treatment before randomization (mean, 20.9 ± 3.5).

Frequency of exacerbations

During the follow-up periods after randomization in the individual clinical trials, 149 (37.5%) of the 400 participants experienced an asthma exacerbation that required systemic corticosteroid use (Table II).¹³ The highest frequency of exacerbations (28.8% of participants) occurred during the fall months (September–November). Spring was the second highest season for exacerbations, with 19.9% of the children having an exacerbations, followed by winter (15.9% of participants) and, finally, summer (14.5% of participants).

Univariate associations with exacerbations

Full year. When examining exacerbations over the course of the year without regard to season, the univariate factors most associated with exacerbations included an exacerbation during the prior year (OR, 2.61 [95% CI, 1.85–3.68]), decreased pulmonary function (FEV₁: OR, 0.98 [95% CI, 0.97–0.99]; FEV₁/FVC [x100]: OR [for a 1-point change], 0.96 [95% CI, 0.93–0.97]),

increased total IgE level (OR, 1.66 [95% CI, 1.14–2.48]), higher requirement for ICS (OR, 1.15 [95% CI, 1.04–1.27]), increased Composite Asthma Severity Index score (OR, 1.08 [95% CI, 1.00–1.16]),²⁰ and increased blood eosinophil count (OR, 1.07 [95% CI, 1.00–1.13]). In contrast, different characteristics emerged when the timing of the exacerbation was evaluated in relationship to the season of its occurrence. Fig 1 and Table II show the results of the univariate models to predict exacerbations for each season.

Fall season (September–November). During the fall, when the highest proportion of participants experienced an exacerbation (28.8%), the strongest risk factors for an exacerbation included an exacerbation during the prior season, which was nearly twice as strong as such events over the previous year (prior season: OR, 5.37 [95% CI, 2.53–11.39] vs previous year: OR, 2.89 [95% CI, 1.60–5.23]); increasing number of positive allergen skin test results (OR, 1.10 [95% CI, 1.01–1.19]); positive allergen skin test results for rodents (OR, 2.05 [95% CI, 1.14–3.68]) or cockroach (OR, 1.93 [95% CI, 1.03–3.61]); increased total IgE levels (OR, 1.90 [95% CI, 1.08–3.36]) and allergen-specific IgE levels to house dust mite (*Dermatophagoides farinae*) and cockroach (OR, 1.46 [95% CI, 1.02–2.09] and OR, 1.48 [95% CI, 1.06–2.06], respectively); increased FENO value (OR, 3.63 [95% CI, 1.64–8.04]); and decreased pulmonary function (FEV₁: OR, 0.98 [95% CI, 0.96–1.00] and FEV₁/FVC ratio [x100] 0.97 [95% CI, 0.94–1.00]).

Winter season (December–February). Although 15.9% of the participants experienced an asthma exacerbation during the winter, there were few univariate associations to predict these events. Again, an exacerbation during the previous season (fall) was related to winter exacerbations (OR, 2.66; 95% CI, 1.21–5.83) but not exacerbations in the previous year. The only other relationships observed with winter exacerbations were with decreased pulmonary function measures (FEV₁ percent predicted: OR, 0.97 [95% CI, 0.95–0.99] and FEV₁/FVC ratio [x100]: OR, 0.94 [95% CI, 0.91–0.99]).

Spring season (March–May). Unlike the fall and winter, spring exacerbations were most closely associated with an exacerbation during the previous year (OR, 4.34 [95% CI, 2.26–8.30]) but not an exacerbation in the prior season. Other associations with spring exacerbations were a decrease in exacerbation risk with increasing age (OR, 0.90 [95% CI, 0.82–0.98]) and an increase in risk with a lower FEV₁/FVC ratio (OR, 0.96 [95% CI, 0.93–0.99]), higher requirement for ICS (OR, 1.18 [95% CI, 1.01–1.38]), and increased Composite Asthma Severity Index score (OR, 1.11 [95% CI, 1.00–1.24]).

Summer season (June–August). Although fewer participants had an exacerbation during the summer (14.5%), a number of factors related to exacerbations at this time of year: impaired pulmonary function, as measured by FEV₁/FVC (x100) ratio (OR, 0.94 [95% CI, 0.89–0.99]); allergic sensitivity to *Alternaria* species (OR, 1.64 [95% CI, 1.02, 2.63]); increased blood eosinophil counts (OR, 1.13 [95% CI, 1.01–1.27]); requirement for higher levels of ICS to maintain control (OR, 1.34 [95% CI, 1.06–1.70]); and an exacerbation in the previous season (OR, 2.53 [95% CI, 1.05–6.08]).

Multivariate prediction models

Seven risk factors that had been significant in 1 or more univariate seasonal models were selected to serve as independent

TABLE I. Characteristics of study participants

	ACE study (n = 253)	ICATA study (n = 147)	Combined (n = 400)
Age of participants at screening (y)*	14.0 (13.0-15.0)	11.0 (8.00-14.0)	13.0 (12.0-15.0)
Male sex	134 (53.0%)	84 (57.1%)	218 (54.5%)
Race/ethnicity			
Black	153 (60.5%)	83 (56.5%)	236 (59.0%)
Hispanic	58 (22.9%)	62 (42.2%)	120 (30.0%)
Other/missing	42 (16.6%)	2 (1.4%)	44 (11.0%)
Caretaker completed at least high school	167 (74.2%)	103 (72.0%)	270 (73.4%)
Household income <\$15,000/y	133 (56.1%)	80 (54.4%)	213 (55.5%)
One or more household members employed	200 (79.1%)	115 (78.2%)	315 (78.8%)
One or more smokers in household	93 (36.8%)	65 (44.2%)	158 (39.5%)
BMI percentile at screening*	89.6 (63.3-97.5)	86.6 (60.1-97.5)	88.8 (62.9-97.5)
Asthma-related symptoms (no. of days in preceding 2 wk) at randomization*†	2.0 (0.0-3.0)	2.0 (0.0-4.0)	2.0 (0.0-4.0)
ACT (score in preceding month) at randomization‡			
Controlled	193 (76.6%)	95 (64.6%)	288 (72.2%)
Uncontrolled	59 (23.4%)	52 (35.4%)	111 (27.8%)
FEV ₁ (% predicted value) at randomization*	96.4 (85.2-106.0)	90.9 (80.9-103.0)	94.2 (83.8-105.0)
FEV ₁ /FVC ratio (x100) at randomization*	81.4 (75.5-86.2)	79.4 (72.7-84.1)	80.7 (74.5-85.8)
FENO (ppb) at randomization*	18.8 (10.6-37.3)	21.4 (10.3-39.1)	19.6 (10.5-37.9)
ICS treatment regimen at randomization§			
Low dose	77 (30.4%)	42 (28.6%)	119 (29.8%)
Medium dose	73 (28.9%)	83 (56.5%)	156 (39.0%)
High dose	103 (40.7%)	22 (15.0%)	125 (31.2%)
One or more hospitalizations in 6 mo before recruitment	37 (14.6%)	30 (20.4%)	67 (16.8%)

ACT, Asthma Control Test.

*Values are medians (interquartile ranges) or frequencies (percentages).

†The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.

‡Scores on the Childhood Asthma Control Test and the Asthma Control Test were combined.

§Six treatment steps were established, which is consistent with National Asthma Education and Prevention Program guidelines,¹³ to standardize prescribing patterns according to levels of asthma severity. Steps 1 and 2 applied to mild asthma, step 3 to moderate asthma, and steps 4 through 6 to severe asthma. At step 0, the recommendation was for no asthma control medication or albuterol as needed. At step 1, the recommendation was for budesonide, 180 µg once a day. At step 2, the recommendation was for budesonide, 180 µg twice a day. At step 3, the recommendation was for budesonide, 360 µg twice a day. At step 4, the recommendation was for fluticasone-salmeterol (Advair, GlaxoSmithKline), 250 µg fluticasone and 50 µg salmeterol twice a day. At step 5, the recommendation was for Advair, 250 µg and 50 µg twice a day plus montelukast once a day. At step 6, the recommendation was for Advair, 500 µg and 50 µg twice a day plus montelukast once a day. The doses for montelukast were 5 mg per day for children ≤14 years of age and 10 mg per day for those ≥15 years of age.

predictors in the multivariate analysis (age, exacerbation history in the previous season, ICS treatment step, FEV₁/FVC ratio, FENO values, blood eosinophil counts, and allergy, as measured by combining the explained variance of positive skin test results with total IgE levels). First, the relative strength of these predictors was assessed, and different patterns by season emerged (Fig 2). The multivariate models explained a significant portion of the variance in all 4 seasons, with the best predictive power occurring in the fall (30.5% variance explained). A history of an exacerbation in the last season was the most important predictor in the fall and winter, whereas a higher ICS requirement was the most important factor in the spring and summer. Allergic sensitization and FEV₁/FVC ratio played a major role in all seasons.

Prediction of exacerbations

Participant risk was assessed with the same 7 risk factors used in the multivariate models. Each participant was given a risk score by rating the participant as high, medium, or low risk for each of the risk factors and then adding up risk scores (2 points for high, 1 point for medium, and 0 points for low) in all 7 components (see Table E2). These risk scores show a difference in exacerbation rates for high- and low-risk participants (Fig 3 and see Table E3 in this article's Online Repository at www.jacionline.org). In the fall, for example, participants in the highest-risk tertile had

a 46% exacerbation rate, whereas the participants in the lowest-risk tertile had a 19% rate (OR, 3.41; 95% CI, 1.73-6.72). Similar patterns were seen in the other seasons with 3.21-, 2.32-, and 2.31-fold increases in the exacerbation rate for high-risk participants in the summer, winter, and spring, respectively (highest tertile vs lowest tertile; see Table E3).

DISCUSSION

Our analysis of exacerbations on a seasonal basis derived from the control treatment arms of the ACE⁴ and ICATA¹⁸ studies from the Inner-City Asthma Consortium reveals a number of important factors relevant to the identification of inner-city children at high risk for asthma exacerbations. First, our ability to predict exacerbations based on commonly used characteristics of patients varies greatly by season. In the fall these factors predict 30.5% of the variance, a highly clinically significant percentage, whereas in the spring and winter they have less predictive ability. Surprisingly, in summer, a time of lower asthma disease activity, our predictive ability approximated that in spring or winter (Fig 3).

Second, predictors vary across seasons. A recent exacerbation and impaired pulmonary function are important predictors in nearly every season, but allergic sensitization, peripheral blood eosinophil counts, FENO values, and required ICS treatment step (a surrogate for asthma severity) vary more widely across the seasons.

TABLE II. Univariate associations between seasonal use of prednisone during the double-blind phase and explanatory variables*

	Overall		Fall		Winter		Spring		Summer		Interaction ‡
No. (%) of patients with an exacerbation	151/400 (37.8%)		65/226 (28.8%)		34/214 (15.9%)		56/281 (19.9%)		27/188 (14.5%)		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	
Baseline predictors†											
Age (y)	0.96 (0.89-1.02)	.17	1.02 (0.91-1.15)	.73	0.91 (0.78-1.06)	.22	0.90 (0.82-0.98)	.02	1.10 (0.94-1.29)	.22	
Sex (male vs female)	0.80 (0.54-1.17)	.25	0.77 (0.43-1.38)	.38	0.90 (0.43-1.89)	.79	0.97 (0.54-1.75)	.93	0.44 (0.18-1.03)	.06	
Race (black vs other)	0.85 (0.57-1.25)	.41	0.81 (0.45-1.46)	.49	1.04 (0.49-2.22)	.91	0.99 (0.55-1.78)	.97	0.47 (0.19-1.17)	.105	
BMI percentile (≥85% vs not)	1.16 (0.79-1.73)	.44	1.18 (0.66-2.13)	.57	1.28 (0.61-2.69)	.52	1.10 (0.61-1.98)	.74	0.98 (0.43-2.23)	.97	
Allergen skin tests (no. of positive tests of 14)	1.02 (0.96-1.08)	.51	1.10 (1.01-1.19)	.03	0.95 (0.84-1.07)	.42	1.00 (0.90-1.10)	.93	0.97 (0.85-1.09)	.58	§
Mite skin tests (yes vs no)	0.75 (0.50-1.10)	.14	1.37 (0.77-2.45)	.28	0.56 (0.26-1.19)	.13	0.59 (0.32-1.07)	.09	0.67 (0.29-1.56)	.35	
Rodent skin tests (yes vs no)	1.34 (0.90-2.01)	.14	2.05 (1.14-3.68)	.02	1.11 (0.52-2.37)	.78	1.03 (0.56-1.87)	.93	0.85 (0.36-2.01)	.71	
Cockroach skin tests (yes vs no)	1.15 (0.77-1.75)	.50	1.93 (1.03-3.61)	.04	0.99 (0.47-2.10)	.98	0.95 (0.51-1.75)	.87	0.74 (0.31-1.77)	.50	§
Mold skin tests (yes vs no)	1.05 (0.71-1.55)	.82	1.50 (0.84-2.68)	.17	0.65 (0.30-1.41)	.27	0.95 (0.53-1.71)	.86	1.07 (0.46-2.49)	.88	
Total IgE (log-transformed [kU/L])	1.66 (1.14-2.48)	.01	1.90 (1.08-3.36)	.03	1.91 (0.94-3.86)	.07	1.19 (0.66-2.16)	.56	1.32 (0.58-2.99)	.51	
sIgE <i>Dermatophagoides farinae</i> (log-transformed [kU/L])	1.22 (0.98-1.54)	.08	1.46 (1.02-2.09)	.04	1.28 (0.83-1.96)	.26	0.99 (0.71-1.39)	.97	1.29 (0.83-2.02)	.26	
sIgE <i>Dermatophagoides pteronyssinus</i> (log-transformed [kU/L])	1.21 (0.96-1.52)	.10	1.43 (0.99-2.05)	.05	1.29 (0.84-2.00)	.25	0.98 (0.69-1.39)	.92	1.27 (0.80-1.99)	.31	
sIgE cockroach (log-transformed [kU/L])	1.17 (0.94-1.47)	.15	1.48 (1.06-2.06)	.02	1.08 (0.71-1.63)	.72	1.03 (0.74-1.44)	.85	0.98 (0.62-1.55)	.92	
sIgE <i>Alternaria</i> species (log-transformed [kU/L])	1.13 (0.90-1.41)	.30	1.09 (0.77-1.53)	.63	0.89 (0.57-1.40)	.62	1.06 (0.76-1.48)	.74	1.64 (1.02-2.63)	.04	
Blood eosinophils (% of white blood cells)	1.07 (1.00-1.13)	.03	1.08 (0.99-1.17)	.09	1.01 (0.91-1.13)	.80	1.04 (0.95-1.14)	.4	1.13 (1.01-1.27)	.04	
Previous season predictors†											
Asthma-related symptoms (days in preceding 2 wk)	0.98 (0.92-1.04)	.51	1.00 (0.89-1.12)	.95	1.03 (0.93-1.15)	.59	0.99 (0.90-1.09)	.84	1.00 (0.87-1.14)	.98	
ACT in preceding month (uncontrolled vs controlled)	0.85 (0.53-1.33)	.48	0.84 (0.36-1.99)	.70	1.33 (0.60-2.94)	.48	0.80 (0.36-1.76)	.58	1.03 (0.41-2.62)	.95	
FEV ₁ (% predicted)	0.98 (0.97-0.99)	<.001	0.98 (0.96-1.00)	.01	0.97 (0.95-0.99)	.01	0.99 (0.97-1.00)	.11	0.98 (0.96-1.01)	.15	
FEV ₁ /FVC ratio (x100)	0.96 (0.93-0.97)	<.001	0.97 (0.94-1.00)	.03	0.94 (0.91-0.99)	.01	0.96 (0.93-0.99)	.02	0.94 (0.89-0.99)	.02	
FENO (log-transformed [ppb])	1.61 (0.98-2.68)	.06	3.63 (1.64-8.04)	.001	0.56 (0.21-1.49)	.25	1.06 (0.49-2.31)	.89	2.54 (0.86-7.53)	.09	§
Exacerbations in previous year (yes vs no)	2.61 (1.85-3.68)	<.001	2.89 (1.60-5.23)	<.001	1.85 (0.89-3.87)	.10	4.34 (2.26-8.30)	<.001	1.71 (0.75-3.92)	.20	§
Exacerbations in previous season (yes vs no)	2.50 (1.65-3.61)	<.001	5.37 (2.53-11.39)	<.001	2.66 (1.21-5.83)	.02	1.53 (0.73-3.20)	.26	2.53 (1.05-6.08)	.04	§
ICS treatment (treatment steps)	1.15 (1.04-1.27)	.004	1.06 (0.90-1.23)	.49	1.10 (0.91-1.34)	.33	1.18 (1.01-1.38)	.03	1.34 (1.06-1.70)	.01	
Composite Asthma Severity Index in preceding 2 mo	1.08 (1.00-1.16)	.05	1.08 (0.94-1.25)	.27	1.07 (0.93-1.23)	.37	1.11 (1.00-1.24)	.05	1.16 (0.99-1.36)	.07	

Values in boldface indicate statistical significance.

ACT, Asthma Control Test; sIgE, specific IgE.

*Values are ORs for exacerbations during each overall/season (columns) for the listed predictors (rows). Predictors are continuous variables, unless otherwise noted.

†For the overall column, all predictors are measured at either study enrollment or randomization. For the seasonal columns (fall, winter, spring, and summer) baseline predictors are measured at study enrollment; the baseline measure is used, regardless of season. Previous season predictors are measured during the season before the exacerbation outcome season; for example, maximum symptom days from the summer are used to predict fall exacerbations and so on.

‡Test of interaction among seasonal predictors of exacerbations.

§Significant interactions ($P < .10$) are noted, with the interpretation being that the effect of the predictor is different by season.||Six treatment steps were established, which is consistent with the guidelines of the National Asthma Education and Prevention Program.¹³

Finally, the level of a patient's risk factors in the immediately preceding season is important for predicting an asthma exacerbation in the subsequent season. For example, a history of a summer exacerbation, higher FENO values, and impaired pulmonary function are all relatively strong predictors of fall exacerbations. This information provides further evidence that, among high-risk subjects, consideration should be given to escalating treatment before the fall season to prevent a subsequent exacerbation rather than reducing asthma long-term control therapy in the summer. Our findings also suggest that follow-up

visits for youth with asthma should be strategically timed to address specific risk factors relevant to the individual patient for the upcoming season.

This close examination of patients' risk factors throughout the year suggests a necessity for more careful seasonal analysis of features associated with asthma exacerbations. In children and adolescents, viral respiratory tract infections are perhaps the most important factor associated with exacerbations. Johnston et al²¹ reported that in children aged 9 to 11 years, 80% to 85% of asthma exacerbations are associated with upper respiratory tract viral

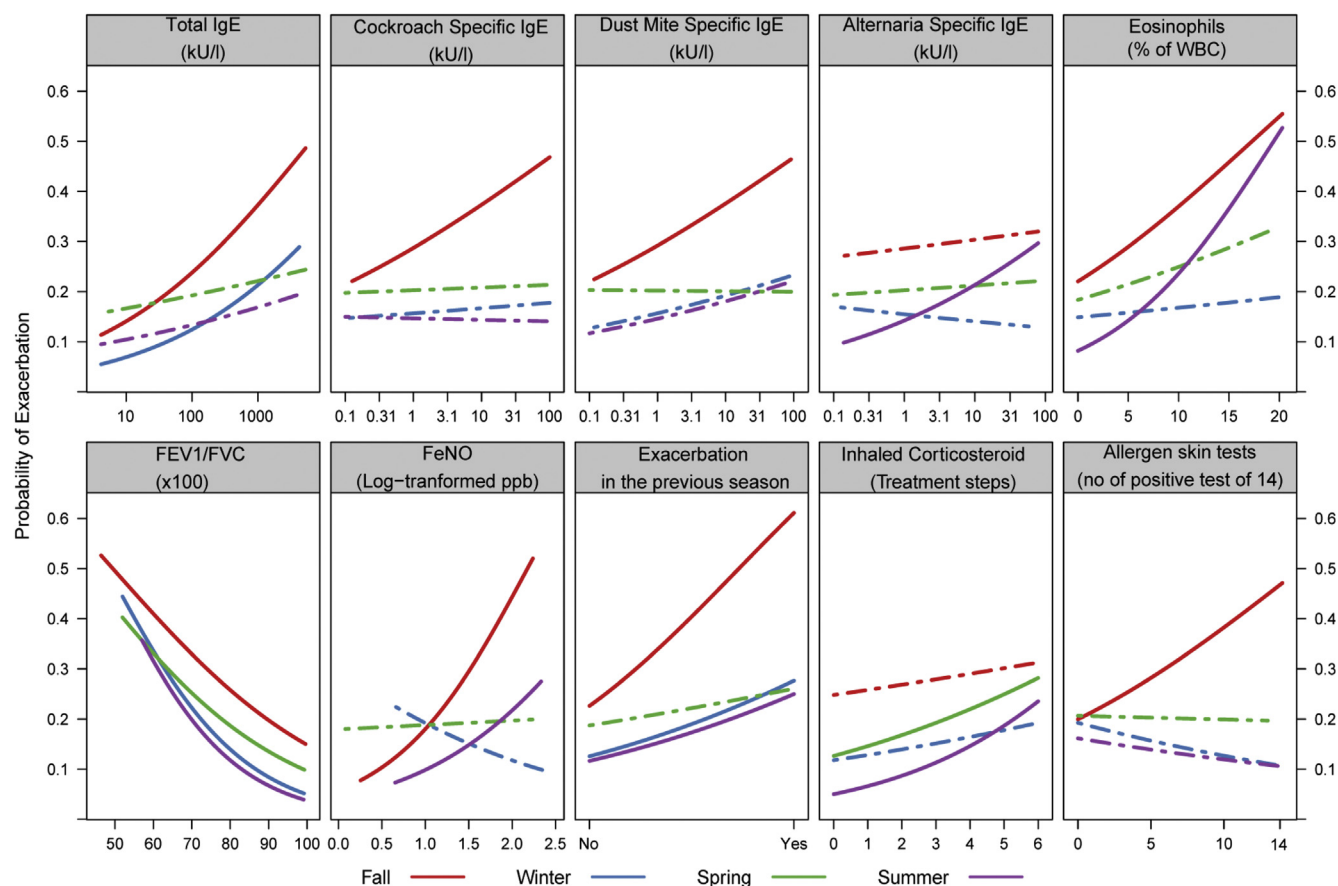


FIG 1. Univariate associations of baseline predictors (total IgE levels, specific IgE levels, number of positive skin test results, and eosinophil counts) and previous season predictors (FEV₁/FVC ratio, FeNO value, exacerbation in the previous season, and ICS step requirement) with the probability of exacerbation by season. Solid lines are for marginally significant associations ($P < .10$), and dashed lines are for nonsignificant associations.

infections. Of the infections identified, rhinovirus has been the most commonly detected infectious agent in exacerbations,^{22,23} but other viruses, including human metapneumovirus, influenza, and parainfluenza, might play a smaller role.^{10,24} Our findings point to the likelihood that other highly relevant factors also work in combination with the anticipated viral infections to trigger exacerbations. Our analyses demonstrate that some of these factors are important all year around, such as pulmonary functions and previous exacerbations, whereas others vary by season, such as allergy and FeNO values.

During the fall, risk factors included evidence for a role for multiple allergic sensitizations (dust, rodent, and cockroach). These seasonal associations might be due to higher exposures in the fall as youth return to school and spend more time indoors, and they might explain the high prevalence of fall exacerbations because both rhinovirus infections and seasonal allergic symptoms are present at this time of year. The importance of IgE sensitization to fall exacerbations is also supported by our report that omalizumab nearly eliminated the fall seasonal flare of these events in inner-city children and adolescents.¹⁸ Allergic sensitization was otherwise not significantly associated with seasonal exacerbations, with the exception of *Alternaria* species in the summer, when humidity encourages its growth indoors.

We did not find a relationship between BMI or environmental tobacco smoke and risk for exacerbation either overall or for any individual season. In contrast, in a far larger cohort of 10,700 patients aged 5 to 17 years, Schatz et al²⁵ found a linear increase in the proportion of patients experiencing exacerbations during the fall and winter by BMI category (normal, overweight, and obese). These different findings might reflect the different racial/ethnic composition of the populations and the greater proportion of overweight/obese subjects in our cohort.

Previous reports of correlates of exacerbation have tended to evaluate the association of exacerbations over longer periods, typically over 1 year, and not by season. In addition, correlates were typically measured either at the start of the study period or at the time of the exacerbation. These studies,^{14,26} similar to ours, found factors seemingly important throughout the year. For example, Covar et al¹⁴ sought to determine the factors associated with exacerbations in children with persistent asthma by analyzing data collected during the 48-week Childhood Asthma Research and Education network's Pediatric Asthma Controller Trial study.²⁷ Among the 48% of children aged 6 to 14 years who experienced exacerbations, multivariate analysis found only a history of an asthma exacerbation requiring systemic corticosteroids in the past year to be associated with a subsequent exacerbation. In contrast, our analysis focused on exacerbations

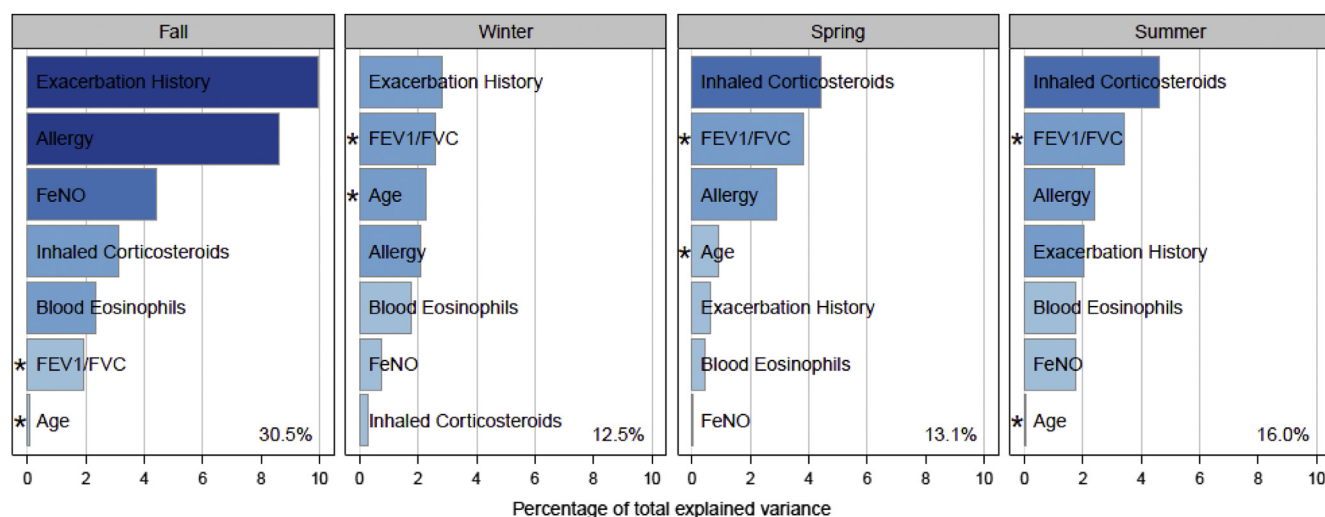


FIG 2. Multivariate models for associations of baseline and previous season predictors of exacerbations. Baseline predictors were allergy (skin test results and total IgE levels) and age. Previous season predictors were FEV₁/FVC ratio, FENO value, exacerbation history, and ICS step requirement. The length and color of the bars indicate the strength of association between the predictor and seasonal exacerbation, as measured by variance explained. The total predictive power of a multivariate model containing all 7 predictors is annotated in the *bottom right corner*. Negative associations are indicated with an *asterisk*.

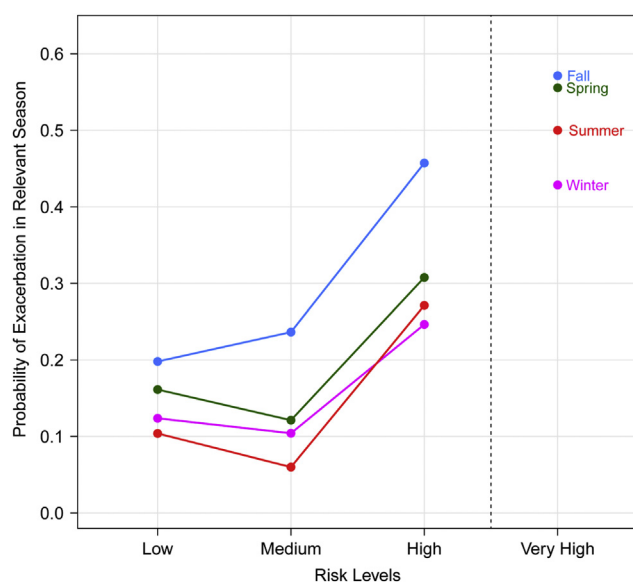


FIG 3. Seasonal exacerbation prevalence by risk level. Each participant had an exacerbation risk level calculated for each season using a simple index of 7 risk factors (allergy, age, FEV₁/FVC ratio, FENO value, exacerbation in the previous season, and ICS step requirement). Seasonal risk levels were then divided into tertiles (labeled *Low*, *Medium*, and *High*), which are plotted against observed exacerbation rates in the ACE and ICATA studies. An additional risk group (*Very High*) was added for participants with a risk index in the top 10%.

by season and found specific characteristics to be associated with increased seasonal risk. For example, higher FENO values, as measured in the summer months and baseline allergic sensitization to cockroach, dust mite, and rodent, were specifically associated with a high risk for fall exacerbations. The observation that FENO values might have a seasonal role in predicting exacerbations is novel. In a recent study of a similar inner-city and largely minority pediatric cohort, McCormack

et al²⁸ found no relationship between increased FENO values and exacerbations. However, they did not stratify by season. Other studies have found the role of FENO values in predicting exacerbations among adults to be more variable.^{29,30}

Another unique feature of our approach was an effort to identify the effect of combinations of risk factors, which, we propose, enhance the ability to predict asthma exacerbations. We derived a predictive index, which indicates that the odds of an exacerbation increases 2 to 3 times when comparing subjects between the highest and lowest tertiles of index scores. The additive and even synergistic nature of exacerbation risk factors has been suggested by other studies examining a more limited number of risk factors. For example, the risk of hospitalization for an asthma exacerbation increased approximately 3 to 4 times in subjects sensitized and exposed to cockroach allergen compared with subjects not sensitized, not exposed, or both.³¹ Similarly, a viral infection can further increase exacerbation risk in the presence of both allergen sensitization and exposure.³² Exposure to high levels of sulfur dioxide or nitrogen oxides at the time of an upper respiratory tract infection has also been reported to increase the risk of an asthma exacerbation.³³ A recent secondary analysis of 7446 largely adult patients with asthma found an exponential increase in the risk of an exacerbation that reaches 45% within the following 6 months based on an index composed of 5 predictors: BMI, Asthma Control Questionnaire,³⁴ postbronchodilator FEV₁, reliever use, and Global Initiative for Asthma treatment step.²⁶

A major strength of this study is that the population of 400 inner-city children and adolescents with moderate-to-severe persistent asthma were extensively characterized and closely managed with guideline-based care by asthma specialists throughout the observation period. Despite this careful supervision with standardized management approaches, more than one third (37.5%) experienced at least 1 exacerbation during the study period. As anticipated, the highest rate of exacerbations (28.8% of participants) occurred during the fall months, and the

lowest rate occurred in the summer. However, exacerbations were not infrequent in the summer. In a previous study of a similar population, a decrease in reported wheezing in summer was found, but even in the summer, levels remained significant.⁸ The occurrence of an exacerbation during the prior summer was the best predictor of fall exacerbations. Although predictability of an asthma exacerbation in the other seasons was not as strong as during the fall, our study was able to identify risk factors of importance for each of these seasons. Those factors were different than the features associated with high risk for fall exacerbations.

Our study is a retrospective, *post hoc* analysis with limitations, and some caution must be used when generalizing these findings to other populations of children and adolescents with asthma, as well as to adults. First, our study population included urban and largely minority children and adolescents with moderate-to-severe asthma. The associated characteristics for high risk of a seasonal exacerbation might differ in other populations.

Second, the median age of our combined cohort was 13 years, which is older than the peak age for exacerbations in pediatric asthma. Of note, however, younger children are well represented in the final combined cohort: 87 (21.8%) of 400 were 6 to 11 years old.

Third, our population was aggressively treated under a standardized protocol based on a guideline-based approach with a high degree of adherence. As a consequence of this high adherence, we did not find that inadequate treatment or poor adherence to prescribed treatment was a major risk factor for exacerbations in contrast to other studies.¹⁵ In fact, the treatment factor in our analyses reflects the underlying severity of the disease that requires control of the impairment domain. Therefore this prompts the question of whether other features of the disease predispose these patients to a higher risk for an asthma exacerbation and that these domains of asthma control are distinct.

Fourth, our population did not include patients with intermittent or mild persistent asthma. Although it is known that these groups have lower rates of exacerbations than the population included in these analyses, our findings do not examine their risk factors for exacerbation.

Fifth, treatment adjustments or systemic corticosteroid courses administered in the previous season might influence the variables measured in a subsequent season. Nevertheless, the point of our study was to assess seasonal risk factors for exacerbation within the context of ongoing guideline-driven care. As such, from a clinical perspective, we could not prevent the interplay of the preseasonal factors. They evolved as they did while the patients were managed by our guideline-based treatment algorithms.

Sixth, patients in the ACE and ICATA studies were followed for a maximum of 1 year under guideline-driven therapy, making it impossible to assess the effect of exacerbations in the corresponding season of the prior year. Patients would not have been under our guideline-driven treatment algorithm during that period, however.

Seventh, we examined host risk factors exclusively and did not examine environmental factors.

A final limitation is that we do not have specific IgE measurements to tree pollen or other seasonal allergens available as allergic risk factors.

This study identifies host factors placing individual patients at high risk for an asthma exacerbation at specific seasons within the year. Our observations might inform development of preventative strategies that can then more effectively reduce the risk for these seasonal exacerbations. Our findings also highlight the need to continue the search for new predictors of exacerbations, especially in the winter and spring. Validation and extension of these findings to other patient populations should result in developing a more individualized approach to asthma management that takes into consideration identifiable factors that could, in turn, affect improved management of the risk domain of asthma control versus impairment. Finally, the identification of risk factors by season might provide a platform to gain greater insight and knowledge of exacerbations, which appear to differ by cause depending on the season of occurrence.

Clinical implications: Inner-city children remain at risk for asthma exacerbations despite appropriate therapy. Because their risk factors vary by season, strategies to prevent them might need to differ as well.

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TABLE E1. Study details

	ACE study	ICATA study
Study duration	The study consisted of a 3-week run-in period after the screening visit (visit 1) and a 46-week treatment period after the randomization visit (visit 2) in which participants are placed either in the reference strategy group (treatment) or the biomarker strategy group (control).	Each participant was randomized to receive subcutaneous treatment or placebo injections once every 2 or 4 weeks for a total of 60 weeks (15 or 30 injections). The first 4 weeks (screening [visit 1] to randomization [visit 2]) were an asthma stabilization phase, and the following 60 weeks of the double-blind period, as well as the 24-week open-label period, consisted of step-up and step-down therapy according to a treatment algorithm based on NAEPP guidelines.
Sites	Baltimore; Boston; Chicago; Cleveland; Dallas; Denver; New York; St Louis; Tucson; and Washington, DC	Boston; Chicago; Cleveland; Dallas; Denver; New York; Tucson; and Washington, DC
Inclusion criteria	Participants to be included in the ACE study were as follows: 1. Male and female subjects aged 12-20 years, inclusive, at the screening visit. 2. Those with a clinical diagnosis of asthma by a physician made >1 year ago, as reported at recruitment, <i>or</i> for participants who received an asthma diagnosis <1 year ago, whose symptoms have been present >1 year, as reported at recruitment. 3. Those, as reported at recruitment, who were currently receiving long-term asthma control therapy and either had symptoms consistent with persistent asthma (criterion 3a) or had evidence of uncontrolled disease (criterion 3b) or who were not currently receiving long-term asthma control therapy and have symptoms consistent with persistent asthma (criterion 3a) and evidence of uncontrolled disease (criterion 3b). 3a. Those with evidence of persistent asthma, as defined by the NAEPP "Expert panel report 2: guidelines for the diagnosis and management of asthma" (1997), which includes asthma symptoms ≥ 3 days per week during the last 2 weeks, sleep disturbed because of asthma ≥ 3 times in the past month, or albuterol use (metered-dose inhaler or nebulizer) for quick relief at least 8 times in the past 2 weeks, not including use as a preventive for exercise. 3b. Those with evidence of uncontrolled disease as defined by ≥ 1 of the following additional criteria: i. 1 asthma-related unscheduled visit to an ED, UC, or clinic in the previous 12 months; ii. 1 asthma-related overnight hospitalization in the previous 12 months; or iii. ≥ 1 burst of oral corticosteroids or equivalent in the previous 12 months. 4. Those whose primary place of residence was in one of the preselected recruitment census tracts that contains $\geq 20\%$ of households below the US government poverty level. 5. Those who met pretreatment eligibility requirements for trial enrollment (acceptable medical history and physical examination results). 6. Those who were nonsmokers and had not used smokeless tobacco products for 1 year before recruitment.	Participants who meet <i>all</i> of the following criteria are eligible for enrollment. Participants can be reassessed if not initially eligible: 1. Male and female subjects aged 6 to 20 years, inclusive, at recruitment. 2. Those with combined body weight and total serum IgE levels suitable for omalizumab dosing. 3. Those with a diagnosis of asthma by a physician made >1 year ago, as reported at recruitment <i>or</i>, for participants who received an asthma diagnosis <1 year ago, whose symptoms had been present >1 year, as reported at recruitment. 4. Those who, as reported at recruitment, were currently receiving long-term asthma control therapy and either had symptoms consistent with persistent asthma (criterion 4a) or had evidence of uncontrolled disease (criterion 4b) or who were not currently receiving long-term asthma control therapy and have symptoms consistent with persistent asthma (criterion 4a) <i>and</i> had evidence of uncontrolled disease (criterion 4b). 4a. Evidence of persistent asthma, as defined by the NAEPP "Expert Panel Report 2: guidelines for the diagnosis and management of asthma" (1997), which includes at least 1 of the following criteria: i. asthma symptoms ≥ 3 days per week during the last 2 weeks; ii. sleep disturbed because of asthma ≥ 3 times in the past month; or iii. albuterol use (metered-dose inhaler or nebulizer) for quick relief ≥ 8 times in the past 2 weeks, not including use as a preventive for exercise. 4b. Evidence of uncontrolled disease, as defined by at least 1 of the following criteria: i. ≥ 2 asthma-related unscheduled visits to an ED, UC, or clinic in the previous 6 months for participants <12 years old or in the previous 12 months for participants ≥ 12 years old or ii. ≥ 1 asthma-related overnight hospitalizations in the previous 6 months for participants <12 years old or in the previous 12 months for participants ≥ 12 years old. 5. Those with a positive skin prick test response to ≥ 1 perennial allergen (ie, dust mite, cockroach, mold, cat, dog, rat, or mouse) documented at the prescreening visit. 6. Those whose primary place of residence was in one of the preselected recruitment census tracts that contains $\geq 20\%$ of households below the US government poverty level documented at the screening visit. 7. Those who were able to perform spirometry (according to ICATA Manual of Operations criteria) at the screening visit. 8. Those who were willing to sign the written informed consent form or whose parent or legal guardian was willing to sign the written informed consent form (age appropriate) before initiation of any study procedure. 9. Those who were willing to sign the assent form, if age appropriate. 10. Those who had a history of clinical varicella or administration of varicella vaccine. These subjects have some form of insurance that covers the costs of medications at the prescreening visit. Coverage must be in effect from prescreening through randomization to be enrolled.

(Continued)

TABLE E1. (Continued)

	ACE study	ICATA study
	- Those who were able to perform exhaled nitric oxide measurement procedures and spirometry according to American Thoracic Society guidelines, as assessed at the screening visit (can be rescheduled once). - Those who were willing to sign the written informed consent form or whose parent or legal guardian was willing to sign the written informed consent form (age appropriate) before initiation of any study procedure. - Those who were willing to sign the assent form, if age appropriate. - Those who had a history of clinical varicella or administration of varicella vaccine.	
Exclusion criteria	Participants to be excluded were as follows: - Those whose adherence to the controller medication between visits 1 and 2 was <25% (see Section 4.5 for determining treatment adherence). - Those who were defined as having mild intermittent asthma at visit 1 (see Section 4.1; can be rescheduled once). - Those who had a life-threatening asthma exacerbation in the last 5 years requiring intubation or mechanical ventilation or resulting in a hypoxic seizure. - Those who were pregnant or lactating. Female subjects of child-bearing potential must remain abstinent or use a medically acceptable birth control method throughout the study. This is not for safety but because it might be difficult to assess asthma control because lung function might change, making it difficult to interpret outcome measures. - Those who had significant medical illnesses other than asthma, such as any hematologic, endocrine, respiratory (other than asthma), or cardiac condition requiring daily medications; significant neurological disorder requiring daily medications; any clotting disorder; any obvious severe mental retardation that prohibits the participant from answering questions or following instructions; any autoimmune disease; any immune deficiency; or any other serious medical condition (eg, juvenile diabetes mellitus, hypothyroidism or hyperthyroidism, hemophilia, Von Willebrand disease, sickle cell disease, cerebral palsy, rheumatoid arthritis, lupus, psoriasis, hyper-IgE syndrome, or allergic bronchopulmonary aspergillosis). - Those who were unable to use a metered-dose inhaler for administration of a β-agonist rescue medication or use a dry powder inhaler for administration of asthma controller regimens. - Those with known hypersensitivity to any medications commonly used for the treatment of asthma. - Those who were receiving hyposensitization therapy.	Participants who met any of the following criteria were <i>not</i> eligible for enrollment but could be reassessed: - Those who had received systemic prednisone (or equivalent) during the 2 weeks before the randomization visit (can be rescheduled according to the ICATA Manual of Operations). - Those who have received systemic prednisone (or equivalent) for >30 days of the past 60 days before recruitment (can be reassessed according to the ICATA Manual of Operations). - Those who, at randomization (visit 2), were assigned treatment level step 1 <i>and</i> who did not have evidence of uncontrolled disease from 6 months before recruitment through randomization for participants <12 years old or from 12 months before recruitment through Randomization for participants ≥ 12 years old. Evidence of uncontrolled disease is defined as ≥ 2 asthma-related unscheduled visits to an ED, UC, or clinic <i>or</i> ≥ 1 asthma-related overnight hospitalizations. - Those who are pregnant or lactating. Female subjects of child-bearing potential (postmenarche) must be abstinent or use a medically acceptable birth control method throughout the study (eg oral, subcutaneous, mechanical, or surgical contraception). - Those with acute sinusitis or chest infection that required treatment with antibiotics within 1 month of the screening visit (can be rescheduled according to the ICATA Manual of Operations). - Those with clinically significant laboratory abnormalities (not associated with the study indication) at the prescreening visit. - Those with platelet levels $<100 \times 10^9/L$ at the prescreening visit. - Those who were participating in another asthma-related pharmaceutical study or intervention study or who have participated in another asthma-related pharmaceutical study or intervention study in the month before recruitment. - Those who did not sleep ≥ 4 nights per week in one home. - Those who lived with a foster parent; not applicable if participant was able to provide consent. - Those who did not have access to a telephone (needed for scheduling appointments). - Those who planned to move from the area during the study period. - Those who had been treated with anti-IgE therapy within 1 year of recruitment. - Those who were receiving or had received hyposensitization therapy to any allergen in the past year before recruitment. - Those who had received hyposensitization therapy to dust mite, <i>Alternaria</i> species, or cockroach for ≥ 6 months in the past 3 years before recruitment. Participants who meet any of the following criteria are <i>not</i> eligible for enrollment and <i>cannot</i> be reassessed, except where noted:

(Continued)

TABLE E1. (Continued)

ACE study	ICATA study
9. Those who were planning to move from the area within the next 12 months. 10. Those who would not allow the study physician, an asthma specialist, to manage their disease for the duration of the study or who were not willing to change their asthma medications to follow the protocol. 11. Those who did not have a home evaluation completed within 4 weeks of the screening visit (can be rescreened). 12. Those who did not primarily speak English (or Spanish at centers with Spanish-speaking staff). 13. Those whose caretaker did not primarily speak English (or Spanish at centers with Spanish-speaking staff); not applicable if participant was able to provide consent. 14. Those who were participating in another asthma-related pharmaceutical study or intervention study or who had participated in another asthma-related pharmaceutical study or intervention study in the month before recruitment. 15. Those who did not sleep ≥ 4 nights per week in one home. 16. Those who lived with a foster parent; not applicable if participant is able to provide consent. 17. Those who did not have access to a telephone (needed for scheduling appointments). 18. Those who were receiving therapy with an exclusionary drug during the time specified (see appendix 1). 19. Those who had a urine cotinine level >100 ng/mL at screening (visit 1).	16. Those with significant medical illnesses other than asthma, such as any infectious, hematologic, renal, hepatic, endocrine, respiratory (other than asthma), gastrointestinal, neurological, or cardiac condition requiring daily medications; any clotting disorder; any obvious severe mental retardation that prohibits the participant from answering questions or following instructions; any autoimmune disease; any immune deficiency; or any other serious medical condition (eg, cystic fibrosis, bronchiectasis, type I diabetes, hemophilia, Von Willebrand disease, sickle cell disease, cerebral palsy, rheumatoid arthritis, lupus, psoriasis, hyper-IgE syndrome, parasite infections, Wiskott-Aldrich syndrome, or allergic bronchopulmonary aspergillosis). 17. Those who had taken any of the following medications <i>within 4 weeks</i> of the screening visit (visit 1): monoamine oxidase inhibitors (phenelzine, tranylcypromine); tricyclic and tetracyclic antidepressants; oral β-blockers; anticonvulsants (carbamazepine, phenobarbital, phenytoin, mephobarbital, primidone, ethosuximide, methsuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, valproic acid, divalproex sodium, and zonisamide); macrolide antibiotics* (erythromycin, azithromycin, clarithromycin, dirithromycin, and troleandomycin); rifampin*; ketoconazole*; sibutramine* (*can be rescreened if this therapy is short-lived). 18. Those with known hypersensitivity to any ingredients, including excipients (sucrose, histidine, polysorbate 20) of the study medication or drugs related to omalizumab (eg, mAbs, polyclonal gamma globulin). 19. Those who had currently diagnosed cancer, were currently being investigated for possible cancer, or who had a history of cancer. 20. Those who would not allow the study physician, an asthma specialist, to manage their disease for the duration of the study or who were not willing to change their asthma medications to follow the protocol. 21. Those who did not primarily speak English (or Spanish at centers with Spanish-speaking staff). 22. Those whose caretaker did not primarily speak English (or Spanish at centers with Spanish-speaking staff); not applicable if participant was able to provide consent. 23. Those with a history of severe anaphylactoid or anaphylactic reaction(s).

ED, Emergency department; NAEPP, National Asthma Education and Prevention Program; UC, urgent care.

TABLE E2. Scoring schema for derivation of the seasonal prediction index

Variable	Baseline/seasonal	Low (0 points)	Medium (1 point)	High (2 points)
Age at recruitment (y)	Baseline characteristic	13-20		6-12
Total IgE (kU/L)	Baseline characteristic	0-100	100-300	>300
Allergen skin tests (positive results of 14)	Baseline characteristic	0-4	5-7	8-14
Blood eosinophils (%)	Baseline characteristic	0-2	2-6	6-22
Exacerbation in previous season	Previous season	No		Yes
ICS (treatment steps)	Previous season	Step 0-3	Step 4-5	Step 6
FEV ₁ /FVC ratio (x100)	Previous season	>85	75-85	<75
FENO (ppb)	Previous season	0-15	15-40	>40

TABLE E3. Combined predictors results

	Fall		Winter		Spring		Summer	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Index (continuous variable)	1.27 (1.13-1.41)	<.001	1.18 (1.03-1.34)	.02	1.17 (1.04-1.32)	.01	1.26 (1.08-1.48)	.004
Index (tertiles)								
Low (<33%)	Reference		Reference		Reference		Reference	
Medium (33% to 66%)	1.25 (0.57-2.77)	.58	0.82 (0.27-2.49)	.73	0.72 (0.3-1.73)	.46	0.55 (0.14-2.18)	.40
High (>66%)	3.41 (1.73-6.72)	<.001	2.32 (1.02-5.23)	.04	2.31 (1.20-4.44)	.01	3.21 (1.27-8.14)	.01