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J Allergy Clin Immunol. Author manuscript; available in PMC 2010 August 1.

Published in final edited form as:
J Allergy Clin Immunol. 2009 August ; 124(2): 213–221.e1. doi:10.1016/j.jaci.2009.05.036.

Asthma morbidity among inner-city adolescents receiving guidelines-based therapy: Role of predictors in the setting of high adherence

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Capsule Summary
Among 546 inner-city adolescents with asthma receiving guidelines-based therapy, future asthma symptoms and exacerbations were somewhat predicted by baseline symptoms and lung function measurements. Neither exhaled nitric oxide nor other markers of inflammation or atopy predicted future disease activity.

Clinical Implications
Markers of allergic sensitization, airway hyperresponsiveness, and airway inflammation do not predict future asthma exacerbations in inner city adolescents who are receiving guidelines-based therapy and who are adherent to their treatment regimens.

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Abstract

Background—With the expanding effort to provide guidelines-based therapy to adolescents with asthma, attention must be directed to evaluating which factors predict future asthma control when guidelines-based management is applied.

Objective—We evaluated the role of F_{ENO}, markers of allergic sensitization, airway inflammation and measures of asthma severity in determining future risk of asthma symptoms and exacerbations in adolescents and young adults participating in the Asthma Control Evaluation (ACE) study.

Methods—Five hundred forty-six inner-city residents, ages 12 through 20 years, with persistent asthma were extensively evaluated at study entry for predictors of future symptoms and exacerbations over the subsequent 46-weeks during which guidelines-based, optimal asthma management was offered. Baseline measurements included: F_{ENO}, total IgE, allergen-specific IgE, allergen skin test reactivity, asthma symptoms, lung function, peripheral blood eosinophils, and, for a subset, airway hyperresponsiveness and sputum eosinophils.

Results—The baseline characteristics we examined accounted for only a small portion of the variance for future maximum symptom days and exacerbations, 11.4% and 12.6%, respectively. Future exacerbations were somewhat predicted by asthma symptoms, albuterol use, previous exacerbations and lung function while maximum symptom days were predicted , also to a modest extent, by symptoms, albuterol use and previous exacerbations but not lung function.

Conclusion—Our findings demonstrate that the usual predictors of future disease activity have little predictive power when applied to a highly-adherent, persistent asthma population that is receiving guidelines-based care. Thus, new predictors need to be identified that will be able to measure the continued fluctuation of disease that persists in highly adherent, well-treated populations such as the one studied.

Keywords

asthma; exhaled nitric oxide; inner-city; allergic sensitization; airway inflammation; asthma severity

Introduction

Asthma is a complex disease of the airways that is characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness and underlying inflammation.

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The interrelationships between these various features determine the clinical manifestations, influence the severity of the disease processes, and serve as a target for treatment in asthma.

The most recent Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma [1] recommend assessing asthma severity and achieving control as key components to effective asthma care. Assessments of asthma severity and control incorporate two important domains, which are distinct but likely interrelated: 1) current impairment, i.e. the frequency and intensity of symptoms and functional limitations; and 2) future risk, i.e. the likelihood of asthma exacerbations or progressive loss of lung function. [2] An unresolved question is whether baseline asthma assessments, atopic status and airway inflammation can predict future asthma control i.e., the level of impairment and exacerbation frequency in the face of guidelines-based management.

The above question constitutes the focus of this report. More specifically, we first sought to examine what participant characteristics best predict future asthma symptoms and exacerbations among asthma patients receiving guidelines-directed treatment and who are adherent to this treatment. To answer this question, we evaluated, not only baseline measurements of current impairment (asthma symptoms), but also, a number of additional objective measurements that reflect airway inflammation ($F_{E}NO$, sputum and blood eosinophilia), atopic status (total IgE, number of positive skin tests, specific IgE against common aeroallergens) and lung function (FEV_1 percent predicted, FEV_1/FVC, and post-bronchodilator percent change in FEV_1). In addition, we analyzed the relationship among $F_{E}NO$, asthma symptoms, other markers of inflammation, atopy and lung function.

The aims of this study were secondary aims of the Asthma Control Evaluation (ACE) study, which was implemented to determine whether guidelines-directed treatment, supplemented by $F_{E}NO$ as a biomarker, would improve asthma outcomes compared to a guidelines-based approach alone in a high risk inner-city population. [3]

Methods

Study Population and Design

In brief, 546 participants, aged 12 to 20 years, with physician-diagnosed asthma were enrolled at 10 urban locations across the United States. Eligibility was limited to residents of census tracts in which at least 20% of households had incomes below the federal poverty threshold. In addition, individuals had to have evidence of moderate to severe persistent disease. Those receiving long-term control therapy were required to have symptoms of persistent disease or uncontrolled asthma while those who were not on long term control therapy had to have symptoms of persistent asthma and evidence of uncontrolled disease [1, 3]. Participants had to sleep at least 4 nights per week in one home (to ensure consistent exposure to the same household environment) and had to be a non-smoker for 1 year prior to recruitment with a urinary cotinine level < 100 ng/mL at enrollment. All appropriate institutional review boards approved this study. Written informed consent was obtained from each participant or their parent or legal guardian. Adolescents ages 12 to 17 provided assent.

The ACE study was a randomized, double-blind, parallel-group trial with a 3-week run-in to characterize participants, establish asthma treatment, and evaluate adherence. After run-in, participants were randomized to either a Reference Group (guidelines-based care) or $F_{E}NO$ Group (exhaled nitric oxide (eNO) added to guidelines-based care) for a 46-week treatment period. Follow-up visits were conducted every 6 to 8 weeks during the treatment period. Findings presented in the current manuscript relate to data collected at the enrollment visit (Week 0), 3 weeks later at the randomization visit (Week 3), and during the follow-up period (Weeks 9 [visit 3] through 49 [visit 8]). From Week 0 to week 49, study participants received

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guidelines-directed asthma treatment using algorithms prepared by the study investigators. [3] Treatment of all participants included inhaled corticosteroids (fluticasone) at various doses with or without long-acting beta adrenergic agonists (salmeterol). More difficult-to-control participants also received cysteinyl leukotriene receptor antagonists (montelukast).

Measurement of $F_{\varepsilon NO}$

$F_{\varepsilon NO}$ was measured for all study participants at the randomization visit employing a technique modified after Silkoff et al [4] and following American Thoracic Society guidelines. [5] $F_{\varepsilon NO}$ was measured (flow rate 50 ml/s) with a rapid-response chemiluminescent analyzer (NIOX™ System, Aerocrine; Sweden). [6]

Total and Allergen-specific Serum IgE

At the randomization visit, a venous blood sample was obtained from all study participants for measurement of serum total IgE and allergen-specific IgE to cockroach (*Blatella germanica*), house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cats (cat epithelium and dander), and mold (*Alternaria alternata*). Serum IgE was measured with the UniCap System (Phadia; Uppsala, Sweden).

Skin Tests

Skin testing was performed during the randomization visit by the puncture method on the volar surface of the forearm using a Multi-Test II device (Lincoln Diagnostics; Decatur, IL). Allergen extracts were obtained from Greer Laboratories (Lenoir, NC). The online repository lists the 14 extracts, concentrations, and positive and negative controls, and describes the test methods andassessment of results.

Blood eosinophils

At the randomization visit, a venous blood sample was obtained from all study participants for determination of total serum eosinophil count by local clinical laboratories.

Sputum Induction and Processing

A subset of participants from four research sites (Dallas, Denver, New York, and Tucson) underwent sputum induction at the randomization visit. Sputum was induced by inhalation of hypertonic saline solution (3%) as previously described by Fahy et al[7]using a DeVilbiss Ultra-Sonic Pico #3207 nebulizer (Nouvag; Lake Hughes, CA). Participants with pre-albuterol $FEV_1 \geq 70\%$ of predicted (206 of 213, 97%; 1 of 206 refused) underwent sputum induction following pre-treatment with albuterol. Slides were prepared and stained at the local laboratories. Differential cell counts were performed centrally by a blinded technician. Refer to online repository for specific details regarding sputum analysis.

Spirometry

Spirometry was performed by certified technicians, according to American Thoracic Society standards,[8] using a Jaeger Masterscreen (VIASYS Healthcare GmbH; Hoechberg, FRG). Spirometry was performed pre- and post-bronchodilator treatment at baseline, using 4 puffs of albuterol MDI administered via Aerochamber®. All pulmonary function tests were centrally overread for quality control purposes; the overreading failures, which account for slightly over 3% (171/5169) of all procedures performed, have been excluded from analysis.

Methacholine Challenge

At the randomization visit, a subset of participants from four research sites (Dallas, Denver, New York, and Tucson) underwent methacholine challenge testing as previously described by

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Strunk et al. [9] Airway responsiveness was measured by determining the concentration of methacholine required to produce a drop in FEV_1 of 20% compared to a control (post-diluent) level (PC_{20}) after the administration of increasing concentrations of methacholine using the small volume nebulizer-tidal breathing technique. Refer to online repository for specific details regarding the methacholine challenge procedure. Individuals who did not reach PC_{20} (37 of 144, 26%) were assigned an upper limit of detection of 26 mg/ml. All methacholine challenge procedures and interpretations were overread for purposes of quality assurance; the overreading failures (37 of 181, 20%) have been excluded from analysis.

Asthma Impairment and Risk Outcomes

The primary outcomes were maximum symptom days and exacerbations. Maximum symptom days per two-week recall and exacerbations were assessed at each visit during the 46-week treatment period. Maximum symptom days, as used in previous inner-city asthma studies, [10, 11] were defined as the largest value among the following variables reported over the prior 2 weeks: (1) number of days with wheezing, chest tightness or cough; (2) number of nights of sleep disturbance; and (3) number of days when activities were affected. This measure allows asthma symptoms to be correctly gauged whether the study participant expresses their asthma as reduction in play, sleep disturbance, or wheeze. An asthma exacerbation was defined as a hospitalization, unscheduled visit (including emergency department visits), or prednisone course for asthma.

Statistical Analyses

Partial Pearson's correlations were calculated for the entire study population to measure the strength of relationships between two variables, while controlling the effect of site, race, age and study group. The primary objective of these analyses was the identification of predictors of future asthma control while receiving guidelines-based therapy. Symptoms and $F_{E}NO$ at randomization, not baseline, were used since only at randomization, after the 3-week run-in, were the participants receiving well-characterized standardized asthma medical management. Similar analyses were also performed for the Reference Group (guidelines-based care) only (n=270) and no significant differences were apparent (data not shown).

Multivariate analyses were carried out on the average maximum symptom days and exacerbations during follow-up. Longitudinal analyses were not possible because post-randomization exacerbation values were sparse. The order in which the variables were entered into the analyses was set *a priori* based on ease and cost of obtaining the clinical measurements. To maximize the sample size for these analyses (N=477), we excluded variables obtained only on a subset of participants (methacholine PC_{20} and sputum eosinophils).

The purpose of relative importance is to quantify the relative contribution of an individual variable to the model's total explanatory value. [12] To control for the study design and possible confounders, we adjusted these analyses for study group, site, race and age. Assessment of relative importance in multivariate analysis is simple when all variables are uncorrelated. Each variable contribution is just the R^2 from univariate regression, and all univariate R^2 values add up to the full model R^2. When variables are correlated, the order in which the variables are entered into the model affect their relative contribution. The effects of this ordering can be minimized by averaging sequential sums of squares over all possible orderings of variables, decomposing R^2 into non-negative contributions. These are computer-intensive methods that have been achievable recently as a result of the advances in computational capabilities. To examine further the relation between the individual variables and $F_{E}NO$, we combined them into *a priori* specific domains and determined 95% confidence intervals through bootstrap (5000 bootstrap samples) to assess the variability of the relative importance and investigate pairwise differences.

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Log-transformations of skewed data (F_{ENO}, methacholine PC_{20}, total IgE, allergen-specific IgE, sum of the five allergen-specific IgEs, blood and sputum eosinophils) were used for partial correlations and multivariate analyses. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc; Cary, NC) and the R system for statistical computing version 2.7.0. [13] The calculation of relative importance was conducted using the R add-on package relaimpo. [14]

Results

Participant Characteristics at Randomization (Table 1)

Of the 546 participants enrolled, 53% were male and 64% were African American. Table 1 describes additional demographic characteristics of the population as well as asthma-related symptoms, lung function, atopic status and degree of allergic inflammation at randomization. The mean number of maximum symptom days over a 2-week period decreased significantly from 5.6 ± 4.6 at enrollment to 2.3 ± 2.9 after the 3-week run-in period at randomization (mean within participant reduction: 3.4 days/2 weeks, p<0.001). Mean FEV_1 (% of predicted value) at randomization was 95.8% ± 15.7. Despite the decrease in maximum symptom days between enrollment and randomization, half of the participants (274 of 546) had F_{ENO} levels ≥ 20 ppb and 75% (401 of 534) had serum IgE levels ≥ 100 kU/L at randomization. Moreover, twenty-six percent (40 of 157) had sputum eosinophilia defined as an eosinophil % of sputum white blood cells ≥ 2%. [15] Marked airway hyperresponsiveness also existed with 62% (89 of 144) having a PC_{20} < 8 mg/ml. Finally, the majority of participants had one or more positive skin tests (88%) with the median number of positive tests being 5 of 14 total tests placed (interquartile range 2-7). Allergic sensitization was most prevalent to cockroach (61.2%), cat (58.2%), molds (51.6%), and dust mites (46.9%). In addition to skin testing, allergen-specific IgE levels were measured for five allergens (*Alternaria alternata*, cat, *D. pteronyssinus*, *D. farinae*, and German cockroach), (Table 1). For each of the allergens tested, between 40 and 50% of the participants had allergen-specific IgE levels greater than 0.35 kU_A/L.

Adherence to treatment was 88.6% at randomization and averaged 86.6% during follow-up (Visits 3-8). Despite these high level of adherence, 388 of 539 (72%) ACE participants with follow-up data had at least one visit with poor asthma control (more than 3 days of symptoms or 1 night of symptoms in 2 weeks or FEV1 < 80% of personal best) of which 137 (25%) had even more severe morbidity (14 days of symptoms or more than 4 nights of symptoms in the last 2 weeks or FEV1 < 70% of personal best).

Importance of different variables (asthma-related symptoms, lung function, allergic biomarkers, and inflammatory biomarkers) in predicting future symptoms and exacerbations

We sought to determine which clinical variables measured at randomization were best associated with future risk of asthma exacerbations and maximum symptom days (both measures of risk were assessed during the follow-up period, i.e. study weeks 9 through 49). As shown in Table 2, modest but significant correlations were demonstrated between several asthma-related symptom variables and future maximum symptom days and exacerbations. Maximum symptom days (r=0.25, p<0.001), days of albuterol use (r=0.27, p<0.001), and nights of albuterol use (r=0.19, p<0.001), measured at randomization, all predicted future maximum symptom days. The latter two variables (days of albuterol use [r=0.13, p=0.003] and nights of albuterol use [r=0.21, p<0.001]) also correlated with future exacerbations as did post-bronchodilator percent change in FEV_1 at enrollment (r=0.19, p<0.001), and FEV_1/FVC ratio (r=−0.10, p=0.026) and F_{ENO} (r=0.11, p=0.010) measured at the randomization visit. Neither methacholine sensitivity nor any of the allergic or inflammatory biomarkers (except F_{ENO} as noted) were associated with maximum symptom days or exacerbations measured during the 46 weeks of follow-up.

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When using relative importance measures, asthma symptom variables, especially albuterol use, independently explained most of the variability in future maximum symptom days (R^2=6.2%) and exacerbations (R^2=5.8%) (Figure 1). Post-bronchodilator percent change in FEV_1 also was found to play a role in explaining future exacerbations. Table 3 presents three different models that evaluate the additional contribution of F_{ENO} to various combinations of conventionally-measured parameters in predicting future maximum symptom days and asthma exacerbations. For model 1, symptoms, which are a composite of four variables and F_{ENO} were the only predictors considered; for model 2, symptoms, lung function measurements, and F_{ENO} were considered; and for model 3, symptoms, lung function measurements, inflammatory and allergic biomarkers, and F_{ENO} were considered. As shown, asthma-related symptoms alone (days with symptoms, days and nights of albuterol use in the 2 weeks prior to randomization, and exacerbations in the year prior to enrollment) explained future maximum symptom days and exacerbations variance significantly (R^2 =9.9% [p<0.05] for maximum symptom days; R^2= 8.6% [p<0.001] for exacerbations). The addition of lung function measurements to asthma-related symptoms significantly increased the percent of variation explained for future exacerbations (models 2 and 3) (R^2=3.3% [p<0.001]) but not for maximum symptom days. None of the other variables (inflammatory markers, atopic markers, or F_{ENO}) further contributed to the prediction of either future maximum symptom days or exacerbations.

Correlations between F_{ENO} and asthma-related symptoms, lung function, and allergic and winflammatory biomarkers measured at randomization

We found significant correlations between F_{ENO} and all the parameters evaluated, except for most asthma-related symptom measurements (Table 4). The strongest correlation was between F_{ENO} and PC_{20} (r=−0.49, p<0.001). Moderate correlations were seen between F_{ENO} and other lung function parameters (post-bronchodilator percent change in FEV_1 [r=0.31, p<0.001]; FEV_1 % predicted [r=−0.16, p<0.001]; FEV_1/FVC [r=−0.29, p<0.001]) as well as with allergic biomarkers (total IgE [r=0.37, p<0.001]; sum of the five allergen-specific IgEs [r=0.35, p<0.001]) and inflammatory biomarkers (blood eosinophils [r=0.39, p<0.001]; sputum eosinophils [r=0.38, p<0.001]). Amongst the symptom variables, maximum symptom days had a small, but significant correlation (r=0.09, p=0.044) with F_{ENO}, but other variables such as school days missed and days and nights of albuterol use showed no significant correlation.

Relative importance of different parameters for determining F_{ENO} at randomization

Using multivariate analyses, we focused on the relative importance of various parameters in determining F_{ENO}. As shown in Figure 2 Panel A, PC_{20} (R^2=13.8%) and FEV_1/FVC ratio (R^2=8.5%) explained most of the variability of F_{ENO}, followed by the number of positive skin tests and sputum/blood eosinophils. All parameters considered together accounted for 50.3% of the F_{ENO} variance. In Figure 2 Panel B, the various parameters were grouped into specific domains: lung function (methacholine PC_{20}, FEV_1/FVC, FEV_1 % of predicted, and post-bronchodilator percent change in FEV_1, inflammation (blood and sputum eosinophils), atopy (number of positive skin tests, total IgE, and sum of the five allergen-specific IgEs) and symptoms (maximum symptom days, days of albuterol use, nights of albuterol use, and exacerbations). Once again, the lung function (R^2=26.0%) domain explained most of the F_{ENO} variability followed by the inflammation (R^2=12.7%) and atopy (R^2=8.5%) domains. There was minimal relationship between F_{ENO} and the asthma symptom domain.

Discussion

Our study reveals that factors often used to predict future asthma risk in poorly- controlled populations, are of no clinical benefit in predicting future risk in a well-treated, highly adherent population of inner-city adolescents and young adults with persistent asthma. We did find that future maximum symptom days and exacerbations could be predicted, but only to a minor

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extent, using a combination of asthma-related symptoms and lung function measurements that included FEV_1 % predicted, FEV_1/FVC, and post-bronchodilator percent change in FEV_1. However, these predictors explained only approximately 12.6% and 11.4% of the variance (Figure 1) for exacerbations and maximum symptom days, respectively. Moreover, the independent contributions of degree of inflammation (as measured by F_{ENO}, sputum and blood eosinophils), and degree of atopy, all measured at randomization, were minimal.

The literature suggests that an increased risk of symptoms and exacerbations may be predicted by numerous factors including recent asthma exacerbations [16], poor asthma control[17, 18], severe airway obstruction [19, 20], history of intensive care admissions or frequent emergency department visits [21], elevated F_{ENO} levels [20, 22], allergen sensitivity and exposure [23-25], depression [26], and poor attitudes about the use of asthma medicines. [27] Moreover, numerous studies have examined baseline predictors of treatment response and loss of asthma control. Such predictor variables examined in these studies have included baseline levels of serum IgE and eosinophil cationic protein, F_{ENO}, PC_{20}, pulmonary function measurements and asthma symptoms. Sputum eosinophils too have been examined in longitudinal studies and have been found to be useful as a predictor of asthma deterioration after ICS reduction. [28-32]

Indeed while predictors of future asthma symptoms and exacerbations have been extensively studied, no single study has evaluated all of these potential predictive factors together and none has examined these factors in a well-treated, highly adherent population. Thus, a unique attribute of our work is that, unlike previous studies, an attempt was made to identify predictors of future asthma risk in a highly adherent population of inner-city adolescents and young adults who were receiving optimal care (i.e., guidelines-based medical management) for the entire 46 weeks of follow-up. Interestingly, none of four major asthma-related factors (symptoms, lung function measurements, allergic biomarkers, and inflammatory biomarkers) measured at baseline were useful in predicting future risk of disease as measured by future asthma symptoms and exacerbations. It must be pointed out, however, that our inability to identify useful predictors was not due to resolution of disease since we found that disease activity was not completely eliminated.

Another unique aspect of our study was the type of analyses that were performed. Like Pharoah et al. [33] did in analyzing breast cancer outcomes, another polygenic disease, we applied a model that looked at predictor variables in combination, as opposed to applying a model that evaluated simple univariate correlations only. In applying this type of model, Pharoah et al. found that seven established common breast-cancer susceptibility alleles, in combination, explained only 5% of the genetic risk for this disease. In comparison, the factors we examined accounted for a little over 10% of the variance in maximum symptom days and exacerbations (11.4% and 12.6%, respectively). Importantly, we also showed that complex measurements such as methacholine sensitivity and sputum eosinophils, along with IgE measurements and blood eosinophils, did not explain any of the remaining variance of these outcomes.

In our analyses, we found that baseline F_{ENO} levels at randomization were related to future asthma exacerbations (Table 2). However, this relationship did not hold up in our multivariate models (Figure 1, Table 3). Thus, while baseline F_{ENO} levels were found to be correlated with a number of inflammatory or lung function measurements, this biomarker was not a good predictor of future asthma risk, as defined by future maximum symptom days and asthma exacerbations. Others too have demonstrated relationships between F_{ENO} and allergen sensitivity [9, 34], methacholine PC_{20} 9, [34, 35], and blood and/or sputum eosinophils. [9, 34-40] In the few studies that have found relationships between F_{ENO} levels and future exacerbations [20, 22, 41, 42], the study designs and/or participant populations were quite different from those of our study. In particular, our study population had very high adherence to a guidelines-based treatment algorithm.

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Previous inner-city studies have demonstrated that cockroach sensitivity and exposure are associated with increased asthma-associated morbidity.[23, 24] In the current study, there was no relationship between atopy and future asthma risk, and allergen exposure was not considered in the analysis. Because the purpose of the current study was to identify predictive markers that could be readily measured by the practicing physician, allergen exposure was not analyzed.

In conclusion, we found that when well-treated, adherent populations of patients with persistent asthma are evaluated for determinants of future disease risk, asthma-related symptoms and lung function measurements are only somewhat predictive of future maximum symptoms days and exacerbations. Furthermore, more complex baseline measurements, such as $F_{E}NO$ levels, inflammatory markers and markers of atopy are not predictive of future disease risk. These findings highlight the need to identify better clinical predictors, perhaps including indices that are independent of inflammation, for asthma morbidity in treated populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Asthma Control Evaluation was a collaboration of the following institutions and investigators (principal investigators are indicated by asterisks):

Johns Hopkins University, Baltimore, MD – P Eggleston*, E Matsui, R Wood, K Callahan, M Mensa, L Campbell, R Merrill, P Huffman, D Bunce, H Bradly; ***Boston University School of Medicine, Boston, MA*** – G O'Connor*, S Steinbach, N Kozlowski; ***Children's Memorial Hospital, Chicago, IL*** – J Pongracic*, R Kumar, J Kim, R Story, A Donnell, S Desai, A Murthy, S Boudreau-Romano, K Koridek, T Kearney, S Pohlman, J Milam, H Negron, I Flexas; Case Western Reserve University School of Medicine, Cleveland, OH – C Kercsmar*, J Chmiel, M Hart, T Myers, Tracy Dillard, Jackie Juricka, C Kane, V Lockhart-Blue, M Rogers, K Ross, P Vavrek; ***UT Southwestern Medical Center at Dallas, TX*** – R Gruchalla*, V Gan, W Neaville, N Gorham, J Teeple, I Dougherty, T George; ***National Jewish Health, Denver, CO*** – S Szefler*, A Liu*, J Henley, M Anderson (Denver Health Medical Center), C Campos, P Pinedo, L Soto, M Gleason, R Covar, J Spahn, K Breese, K Patterson, M White, D Sundstrom, H Leo, N Jain, B Song, K Carel, L Stewart, B Macomber, C Mjaanes, A Schiltz, R Harbeck; ***Mount Sinai School of Medicine, New York, NY*** – M Kattan*, H Sampson, C Lamm, M Pierce, A Ting, E Sembrano, L Peters, A Valones, M Duarte, Y Fernandez-Pau, P Yaniv, R Castro, M Mishoe, Y Kucuk; Washington University School of Medicine, St Louis, MO – G Bloomberg*, R Strunk, L Bacharier, T Oliver-Welker; The University of Arizona College of Medicine, Tucson, AZ – W Morgan*, M Brown, T Guilbert, F Martinez, E Morales, K Otsuka, M Celaya, D Castellanos, S Ehteshami, M Fierro, G Garcia, J Goodwin, W Hall, Y Meza, J Priefert, J Rennspies, G Terrazas, M Vasquez, R Weese; ***Children's National Medical Center, Washington, DC*** – S Teach*, K Stone, D Quint, A. Newcomer, S. Staples, J. Schmidt, E. Dunbar, R. Chirumamilla; Statistical and Clinical Coordinating Center, Rho, Inc, Chapel Hill, NC – H Mitchell*, G David, A Calatroni, M Curry, M Walter, J Wildfire, A Hodges, R Budrevich, B Shaw, R Bailey, G Allen; Scientific Coordination and Administrative Center, Madison, WI – W Busse*, C Sorkness, R Kelley, P Heinritz, G Crisafi; National Institute of Allergy and Infectious Diseases, Bethesda, MD – P Gergen, A Togias, E Smartt, M Smolskis, M Fenton.

The study also gratefully acknowledges receiving donated product from GlaxoSmithKline (study drugs) and Lincoln Diagnostics, Inc. (skin testing materials).

Funding

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, under Contracts number NO1-AI-25496 and NO1-AI-25482, and from the National Center for Research Resources, National Institutes of Health, under grant RR00052, M01 RR00533, M01RR0071, 5UL1RR024992-02, and 5M01RR020359-04.

Abbreviations

ACE, Asthma Control Evaluation
FE_{NO}, Fraction of exhaled nitric oxide in parts per billion (ppb)FEV_1, Forced expiratory volume in one second

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FEV_1/FVC, Ratio of FEV_1 and forced vital capacity
ICS, Inhaled corticosteroid
IgE, Immunoglobulin E
kU/L, Kilo units/liter
kU_A/L, Kilo units (allergen-specific)/liter
Mg, Milligram
mL, Milliliter
mm, Millimeter
ng, Nanogram
PC_{20}, Provocative concentration of methacholine causing a 20% fall in FEV_1
WBC, White blood cells
wt/vol, Weight/volume

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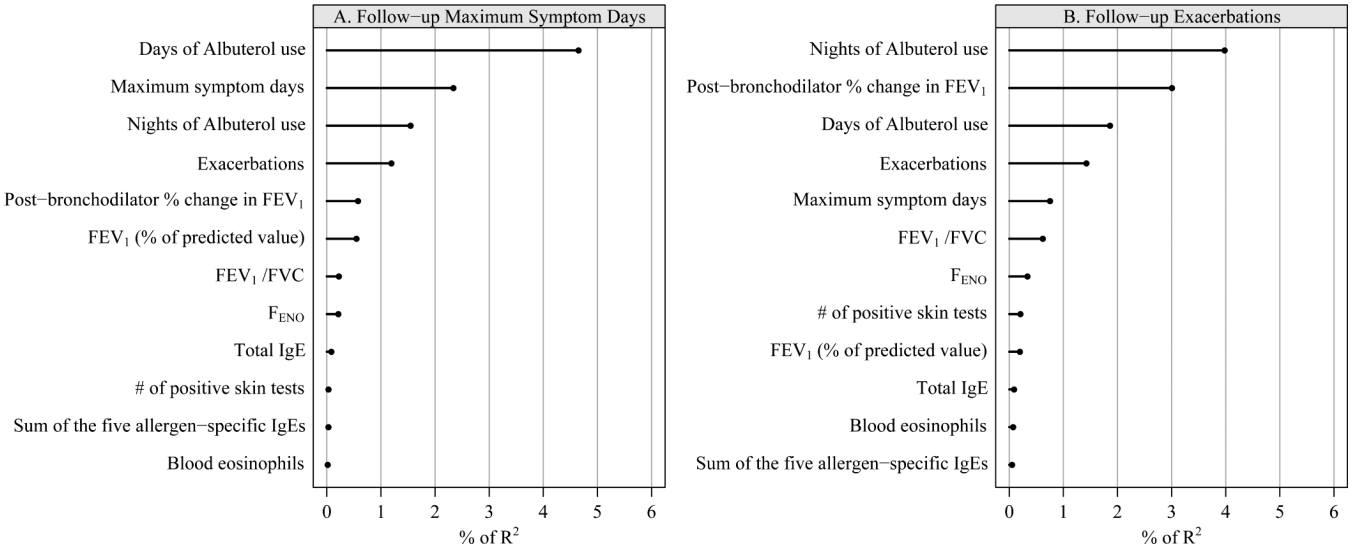

Figure 1.

Relative importance of baseline characteristics for predicting maximum symptom days (Panel A) and exacerbations (Panel B) during follow-up (Visits 3 to 8). Combined these baseline characteristics explain 11.4 and 12.6 percent of the variation for maximum symptom days and exacerbations, respectively.

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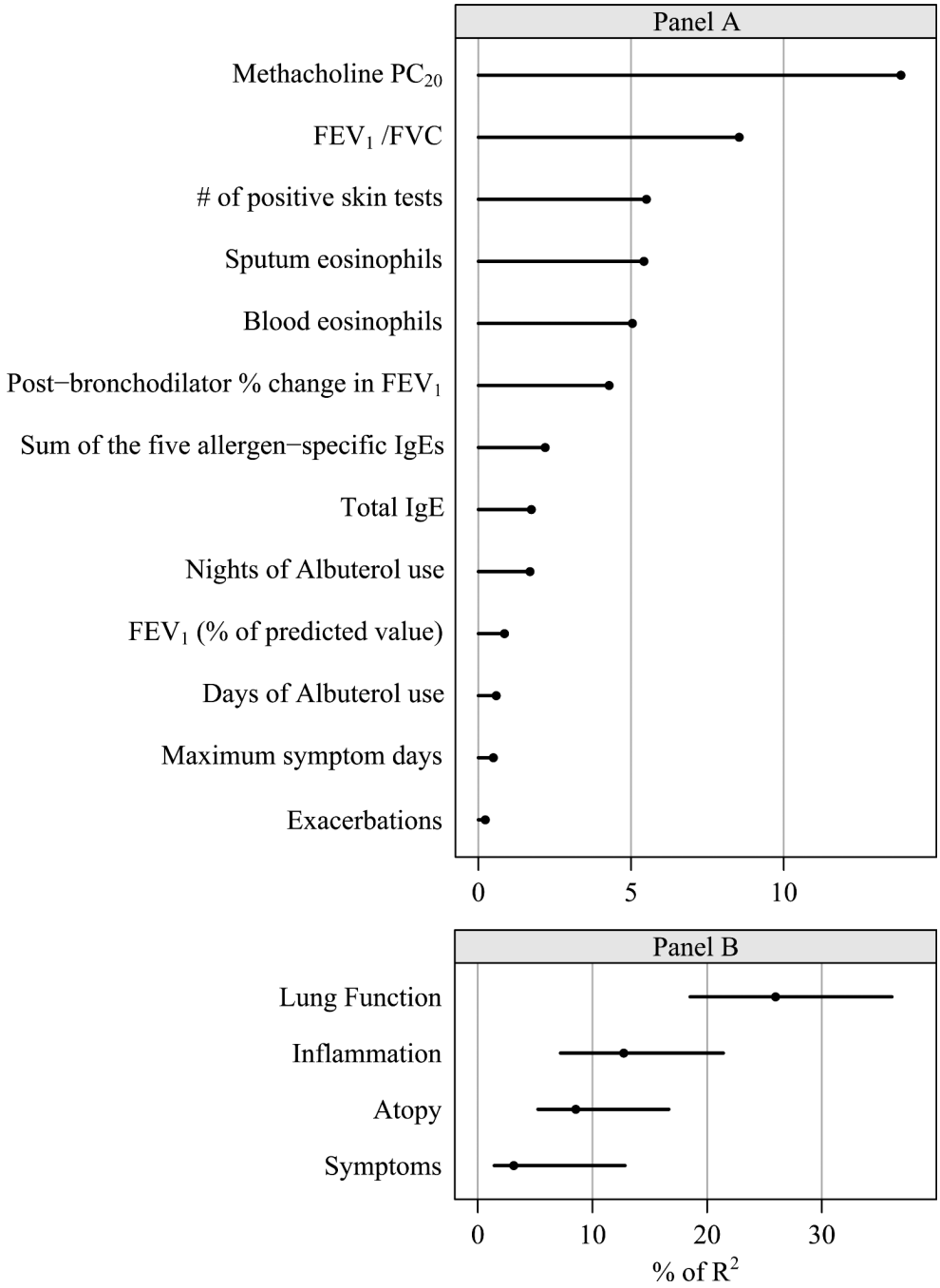

Figure 2.

Relative importance of baseline characteristics for predicting baseline FE_{NO}. Panel A shows individual variables while panel B combines the variables into specific domains with 95% confidence interval. Domains are defined as lung function (methacholine PC_{20}, FEV_1/FVC, FEV_1 % of predicted, and post-bronchodilator percent change in FEV_1), inflammation (blood and sputum eosinophils), atopy (number of positive skin tests, total IgE, and sum of the five allergen-specific IgEs) and symptoms (maximum symptom days, days of albuterol use, nights of albuterol use, and exacerbations). Combined these baseline characteristics explain 50.3 percent of the variation in FE_{NO}.

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Table 1

Participant Characteristics at Randomization[*] (N=546[†])

Demographics	
Age at recruitment (yr)	14.4 ± 2.1
Male (%)	52.7
Race / ethnic group (%)	
African American	63.6
Hispanic	22.9
Other or mixed	13.6
Caretaker completed high school (%)	76.5
Household income <$15,000 (%)	52.2
≥ 1 household member employed (%)	82.4
At least one smoker in household (%)	40.7
History of hay fever, allergic rhinitis or eczema (%)	53.5
Asthma-related symptoms at randomization (no. of days / last 2 wks)	
Maximum symptom days	2.3 ± 2.9
Wheezing, cough, tightness in the chest	2.0 ± 2.8
Slow down or stop play or activities	1.1 ± 1.8
Nights awake because of asthma	0.6 ± 1.5
School days missed	0.2 ± 0.8
Days of Albuterol use	1.4 ± 2.6
Nights of Albuterol use	0.5 ± 1.6
≥ 1 Exacerbation in year prior to recruitment (%)[‡]	78.9
Mean post-randomization asthma-related symptoms (no. of days / last 2 wks)	
Maximum symptom days	2.0 ± 1.7
School days missed	2.0 ± 0.4
Days of Albuterol use	1.1 ± 1.7
Nights of Albuterol use	0.5 ± 0.9
Exacerbation rate (per year)[‡]	0.7 ± 1.1
Lung function	
FEV_1 (% of predicted value)	95.8 ± 15.7
FEV_1/FVC	80.1 ± 8.7
Post-bronchodilator percent change in FEV_1 (Visit 1)	8.1 (3.9 – 15.1)
Methacholine PC_{20} (mg/ml)[§//]	3.5 (0.8 – 26.0)
Allergic biomarkers	
Total IgE (kU/L)	262 (100 – 658)
Allergen-Specific IgE ≥ 0.35 kU_A/L (%)	
Alternaria	41.4
Cat	50.7
Dust mite, *D. pteronyssinus*	47.6
Dust mite, *D. farinae*	47.5
German Cockroach	48.3
Number of positive skin tests of 14 total	5 (2 – 7)
Skin test sensitivity[¶]	

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≥ 1 Positive skin test	87.9 %
Cat	58.2 %
Dog	13.7 %
Dust mite	46.9 %
Mold	51.6 %
Cockroach	61.2 %
Rodent	38.2 %
Inflammatory biomarkers	
Blood eosinophils (per μ1)	211 (118 – 373)
Sputum eosinophils (% of WBC)[§]	0.9 (0.0 – 2.0)
FE_{NO} (ppb)	20.1 (11.2 – 40.6)

[*] Plus-minus values are means ± SD. Interquartile range is provided in parentheses with medians. FEV_1 denotes Pre-bronchodilator forced expiratory volume in one second, FE_{NO} fractional exhaled nitric oxide, IgE immunoglobulin E, WBC white blood cells, PC_{20} provocation concentration of a bronchoconstrictor agonist causing a 20% fall in FEV_1.

[†] Results were available for the following number of children: 468 for caretaker completed high school; 502 for household income; 477 for smoker in household; 398 for school days missed; 532 for Pre-bronchodilator FEV_1 (% of predicted) and Pre-bronchodilator FEV_1/FVC; 521 for Post-bronchodilator percent change in FEV_1; 534 for total IgE; 531 for skin test sensitivity and 533 for blood eosinophils.

[‡] Exacerbations are a combined measure of prednisone usage, asthma-related unscheduled visits and hospitalizations.

[§] Measurements taken at 4 sites only.

[//] Individuals (N=37) who did not reach PC_{20} were assigned an upper limit of detection (26 mg/ml).

[¶] Dust Mite includes participants who are skin test positive to *Der p* or *Der f*. Mold to *Alternaria tenuis*, *Cladosporium herbarum*, *Aspergillis* mix, or *Penicillium notatum*. Roach to American and German cockroach mix or German cockroach. Rodent to mouse or rat epithelia.

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Table 2

Pearson correlations of baseline participant characteristics with follow-up symptoms and exacerbations (Visits 3 – 8).*

	N	Maximum Symptom Days	Exacerbations
Asthma-related symptoms at randomization (no. of days / last 2 wks)			
Maximum symptom days	546	0.25 (<0.001)	0.01 (0.77)
Wheezing, cough, tightness in the chest	546	0.25 (<0.001)	0.00 (0.962)
Slow down or stop play or activities	546	0.19 (<0.001)	0.05 (0.237)
Nights awake because of asthma	546	0.14 (0.001)	0.03 (0.478)
School days missed	381	0.08 (0.116)	0.08 (0.128)
Days of Albuterol use	546	0.27 (<0.001)	0.13 (0.003)
Nights of Albuterol use	546	0.19 (<0.001)	0.21 (<0.001)
Lung function			
FEV_1 (% of predicted value)	532	0.07 (0.132)	−0.02 (0.698)
FEV_1/FVC	532	−0.01 (0.798)	−0.1 (0.026)
Post-bronchodilator percent change in FEV_1 (Visit 1)	521	0.07 (0.098)	0.19 (<0.001)
Methacholine PC_{20}†‡	144	−0.10 (0.237)	−0.08 (0.354)
Allergic biomarkers			
Total IgE‡	534	0.01 (0.765)	0.06 (0.192)
Allergen-specific IgE‡			
Alternaria	533	0.05 (0.268)	0.04 (0.418)
Cat	533	−0.01 (0.848)	0.03 (0.478)
Dust mite, *D. pteronyssinus*	534	0.02 (0.656)	0.06 (0.195)
Dust mite, *D. farinae*	533	0.04 (0.381)	0.07 (0.098)
German cockroach	534	0.04 (0.342)	0.06 (0.200)
Sum of the five allergen-specific IgEs	534	0.01 (0.794)	0.06 (0.192)
Number of positive skin tests	531	0.01 (0.826)	0.03 (0.437)
Skin test wheal size (mm)			
Alternaria	531	−0.01 (0.776)	−0.03 (0.543)
Cat	531	0.00 (0.934)	0.04 (0.366)
Dust mite, *D. pteronyssinus*	531	−0.04 (0.424)	−0.02 (0.657)
Dust mite, *D. farinae*	531	0.01 (0.824)	0.05 (0.291)
German Cockroach	531	0.03 (0.554)	0.03 (0.430)
Mouse	531	0.01 (0.823)	0.06 (0.162)
Rat	531	−0.02 (0.685)	0.01 (0.743)
Dog	531	−0.04 (0.379)	−0.02 (0.710)
Inflammatory biomarkers‡			
Blood eosinophils	533	0.02 (0.699)	0.06 (0.135)
Sputum eosinophils†	157	−0.03 (0.701)	0.05 (0.564)
FE_{NO}	546	0.01 (0.897)	0.11 (0.010)

*Values are Pearson correlations adjusted for site, race, age and study group with p-values in parentheses. FE_{NO} denotes fractional exhaled nitric oxide, IgE immunoglobulin E, WBC white blood cells, PC_{20} provocation concentration of a bronchoconstrictor agonist causing a 20% fall in FEV_1.

†Measurements taken at 4 sites only.

[‡]Log-transformed data were used for determination of Pearson correlations.

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Table 3

Percent of variation in follow-up asthma outcomes explained by symptoms, lung function, biomarkers and FE_{NO} as measured at randomization*

	Follow-up outcomes‡			
Predictors from Randomization§	**Max Symptom Days**		**Exacerbations**	
Model 1 – Symptoms + FE_{NO}				
Site, race, age, gender and study group	10.8		2.2	
. . . + Symptoms	20.7	†	10.8	†
. . . + FE_{NO}	20.9		11.4	
Model 2 – Symptoms and lung function + FE_{NO}				
Site, race, age, gender and study group	10.8		2.2	
. . . + Symptoms	20.7	†	10.8	†
. . . + Lung Function	21.7		14.1	†
. . . + FE_{NO}	22.1		14.2	
Model 3 – Symptoms, lung function, atopy and inflammation + FE_{NO}				
Site, race, age, gender and study group	10.8		2.2	
. . . + Symptoms	20.7	†	10.8	†
. . . + Lung Function	21.7		14.1	†
. . . + Inflammation	21.7		14.3	
. . . + Atopy	21.8		14.7	
. . . + FE_{NO}	22.2		14.8	

*Order variables were entered in to the model was set a priori based on ease and cost of clinical measurements. Values are percent of variation explained (R^2).

†Variable improves R^2 ($p<0.05$).

‡Max Symptom Days is the mean of all post-randomization measurements. Exacerbations are a combined measure of the number of asthma-related hospitalizations, unscheduled clinic visits and prednisone bursts during follow-up.

§Symptoms includes four variables: days with symptoms, days and nights of albuterol usage in the 2 weeks before randomization, and exacerbations in the year prior to recruitment. Lung function includes 3 variables: FEV_1 percent predicted and FEV_1/FVC measured at randomization plus post-bronchodilator percent change in FEV_1 measured at enrollment. Inflammation represents blood eosinophils. Atopy includes 2 variables: number of positive skin tests and total IgE.

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Table 4

Pearson correlations of participant characteristics with $_{FE}NO$ at randomization*

	N	$_{FE}NO$‡
Asthma-related symptoms at randomization (no. of days / last 2 wks)		
Maximum symptom days	546	0.09 (0.044)
Wheezing, cough, tightness in the chest		0.08 (0.055)
Slow down or stop play or activities		0.04 (0.316)
Nights awake because of asthma		0.05 (0.238)
School days missed	381	0.03 (0.581)
Days of Albuterol use	546	0.07 (0.092)
Nights of Albuterol use	546	0.07 (0.094)
Lung function		
FEV_1 (% of predicted value)	532	−0.16 (<0.001)
FEV_1/FVC	532	−0.29 (<0.001)
Post-bronchodilator percent change in FEV_1 (Visit 1)	521	0.31 (<0.001)
Methacholine PC_{20}†‡	144	−0.49 (<0.001)
Allergic biomarkers		
Total IgE‡	534	0.37 (<0.001)
Allergen-specific IgE‡		
Alternaria	533	0.20 (<0.001)
Cat	533	0.23 (<0.001)
Dust mite, *D. Pteronyssinus*	534	0.23 (<0.001)
Dust mite, *D. Farinae*	533	0.21 (<0.001)
German cockroach	534	0.12 (0.006)
Sum of the five allergen-specific IgEs	534	0.35 (<0.001)
Number of positive skin tests	531	0.29 (<0.001)
Skin test wheal size (mm)	531	
Alternaria		0.15 (0.001)
Cat		0.18 (<0.001)
Dust mite, *Der p*		0.10 (0.018)
Dust mite, *Der f*		0.13 (0.002)
German Cockroach		0.14 (0.002)
Mouse		0.11 (0.015)
Rat		0.12 (0.005)
Dog		0.18 (<0.001)
Inflammatory biomarkers‡		
Blood eosinophils	533	0.39 (<0.001)
Sputum eosinophils†	157	0.38 (<0.001)

*Values are Pearson correlations adjusted for site, race, age and study group with p-values in parentheses. $_{FE}NO$ denotes fractional exhaled nitric oxide, IgE immunoglobulin E, PC_{20} provocation concentration of a bronchoconstrictor agonist causing a 20% fall in FEV_1.

†Measurements taken at 4 sites only.

‡Log-transformed data were used for determination of Pearson correlations.