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Adding Exhaled Nitric Oxide to Guideline-based Asthma Treatment in Inner-City Adolescents and Young Adults: a randomized controlled trial

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Abstract

Background—Preliminary evidence is equivocal regarding the role of exhaled nitric oxide in clinical asthma management. This study evaluates the usefulness of eNO as an adjunct to asthma guidelines-based clinical care among inner-city adolescents and young adults.

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Methods—A randomized, double-blind, parallel-group trial was conducted with 546 inner-city participants, aged 12–20 years, with persistent asthma (Clinicaltrials.gov Identifier: NCT00114413). A run-in characterization period of 3 weeks on an initial controller regimen preceded a 46-week double-blind treatment strategy. Participants were randomized to either, treatment based on NAEPP guidelines alone (Reference Group) or the guidelines plus FE_{NO} measurements (FE_{NO} Group). Primary outcome was asthma symptom days and secondary outcome was acute asthma exacerbations.

Findings—During the 46-week treatment period, the number of asthma symptom days, pulmonary function, unscheduled care visits, and hospitalizations did not differ between the treatment groups (mean asthma symptom days were 1.93 [95% CI 1.74-2.11] in the FE_{NO} group vs. 1.89 [1.71-1.74] in the control group; difference 0.04 [-0.29-0.22], p=0.7796). The FE_{NO} Group received a significantly higher inhaled corticosteroid dose (118.9 mcg/day difference, 95% CI: 48.5-189.3, P=0.0010) as compared to the Reference Group. Asthma symptoms remained low in both groups following randomization with 57% (306/534) of the participants well controlled for at least 80% of visits..

Interpretation—A coordinated asthma management program facilitated achieving good control in the majority of participants. The addition of FE_{NO} as a control indicator resulted in a higher dose of inhaled corticosteroids without a clinically important improvement in symptomatic asthma control.

Keywords

asthma; biomarker; exhaled nitric oxide; inhaled corticosteroid; inner-city asthma; long-acting ß$_2$-agonist; medication adherence; asthma exacerbations; asthma outcomes; asthma guidelines; impairment; risk

Background

Asthma is a complex respiratory disorder characterized by variable and recurring symptoms, airflow obstruction, and underlying airway inflammation. In 2007, the NHLBI-Expert Panel 3 updated Guidelines for the Diagnosis and Management of Asthma proposed that, in order to achieve asthma control, treatment should aim at regulating the current manifestations of impairment, i.e., symptoms, need for rescue treatment, limitations of activity, and pulmonary function, as well as reducing future risk[1, 2].

Asthma symptoms and exacerbations are theoretically linked to underlying airway inflammation but are not direct indicators of the inflammatory state. The application of biomarkers that are more closely associated with airway inflammation could improve asthma control by better directing treatment. FE_{NO} is a marker of airway inflammation[3] and is increased during periods of uncontrolled asthma[4-12] and reduced during treatment with anti-inflammatory agents[13-21]. Although previous trials have evaluated the use of FE_{NO} as an alternative to conventional symptom-driven therapy modification[22-25], studies to date have not evaluated a clinically more relevant question, whether adding FE_{NO} to guideline-based management can improve asthma control.

The NIAID Inner-City Asthma Consortium elected to study the application of FE_{NO} measurement as an adjuvant to guideline-directed management of asthma in a population of inner-city adolescents and young adults characterized by high levels of atopy, allergen exposure, and poor asthma control[26-30].

Methods

A total of 546 participants, aged 12 to 20 years, with asthma were enrolled at ten centers (see Appendix). Eligibility was limited to residents of urban census tracts in which at least 20

percent of households had incomes below the federal poverty threshold. Participants had a physician diagnosis of asthma. Individuals receiving long-term control therapy were required to have symptoms of persistent asthma or evidence of uncontrolled disease. Individuals not receiving long-term control therapy were required to have both symptoms of persistent asthma and evidence of uncontrolled disease defined by NAEPP guidelines[1, 2]. The protocol was approved by all institutional review boards. Written informed consent was obtained from each participant or their parent or legal guardian. Adolescents ages 12 to 17 provided assent.

Study Design

The study was a randomized, double-blind, parallel-group trial with a 3-week run-in to characterize participants, establish treatment, and evaluate adherence (Figure 1e-repository). At the initial visit, current medication regimens and adherence, asthma symptoms, pulmonary function, skin test sensitivities and control levels (Table 1e-repository) were assessed. Physicians selected one of six treatment steps (Table 2e-repository). Trained asthma counselors reinforced medication use, adherence, and environmental control. Participants were excluded after the run-in if controller adherence was <25%. Participants with a urinary cotinine >100 mg/ml were ineligible to exclude active smokers. All prescribed medications were provided without charge, and study participants were given a 24-hour telephone number for medical advice.

After run-in, subjects were assigned by centralized block randomization with a block size of ten to receive either a Reference Group (guideline-based care) or FE_{NO} Group (exhaled nitric oxide (eNO) added to guideline-based care). The randomization sequence was generated from a random number table and was stratified by site. Investigators and patients were blinded to treatment assignment.

At each visit conducted every 6 to 8 weeks, FE_{NO}, lung function, asthma symptoms, rescue medication use, adherence, healthcare utilization, and missed school days were evaluated (Figure 1e-repository). Adherence was based on Diskus® built-in dose counter and structured questionnaire.

Treatment Determination

Symptoms, rescue medication use, pulmonary function, and adherence were used to determine control level (4 levels; Level 1 = well controlled). FE_{NO} was measured (flow rate 50 ml/s) with a rapid-response chemiluminescent analyzer (NIOX™ System, Aerocrine, Sweden) following American Thoracic Society guidelines[31]. FE_{NO} was measured for each participant at every visit, but only influenced treatment of the FE_{NO} Group. Control level and FE_{NO} data were entered into a computer program which generated two treatment options for the blinded physician, one for the Reference Group and another for the FE_{NO} Group. The treatment options were derived from protocol-defined treatment steps (Table 2e-repository). Medication was adjusted based on control and adherence (Table 3e-repository). Medication was only reduced after two consecutive visits with good control (Control level 1). When adherence was ≥50%, and FE_{NO} was elevated, the FE_{NO} Group was eligible to receive an additional one step increase in treatment compared to what would be given to the Reference Group. For safety reasons, FE_{NO} was not allowed to increase treatment on the third consecutive visit without elevated symptoms. Also low FE_{NO} alone was not allowed to reduce therapy without a corresponding reduction in symptoms. An unblinded coordinator dispensed the appropriate treatment plan based on the participant's group assignment.

Primary Outcome Measures

The primary outcome was the mean of maximum symptom days per two-week recall at each visit during the 46-week treatment period. Maximum symptom days, as used in previous inner-

city asthma studies[32, 33] 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; (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 is reported. The mean of maximum symptom days for all visits was then calculated. The study was powered with a 90% confidence level of detecting at least a 0.70 difference in maximum symptom days per two weeks.

Statistical Methods

The average maximum symptom days per person per 2 weeks in the control group was assumed to be 4.2 days (SD: 2.4) for power calculations[33]. To detect a clinically meaningful group difference of 0.70 days per person per two weeks with 90% power (α=0.05 two sided), 165 subjects per group were required. Anticipating that 30-35% of subjects would not complete the study, we augmented the sample by 34% and targeted a total enrollment of 500 participants (250 per group); the final enrollment was 546. The difference in post-randomization asthma-related outcomes between groups was analyzed with a linear mixed model with fixed effects for treatment group and visit, with adjustment for levels at randomization and study site.

Utilization outcomes include hospitalizations, unscheduled ED or clinic visits, prednisone courses for asthma and asthma exacerbations. Asthma exacerbations are a composite outcome that includes hospitalizations, unscheduled visits, and prednisone use. These were rare events, so instead of analyzing the data longitudinally, we summed the events over the course of the study and analyzed using a logistic regression of any versus none.

Analyses were performed according to intention to treat with alpha level 0.05. Post-hoc sub-analyses were conducted to identify characteristics associated with favorable response to FE_{NO} -based management. Sub-analyses were conducted for heterogeneity of treatment effects across a fixed set of 9 characteristics using a statistical test for interaction.[34] All statistical analyses, including the block randomization procedure outlined earlier, were performed using SAS software (version 9.1.3, SAS Institute).

Role of the Funding Source

This trial was funded through a contract with the Division of Allergy, Immunology, and Transplantation, NIAID/NIH. DAIT staff participated in protocol development, study oversight, regulatory reporting, and monitoring study conduct. NIH staff, principal investigator, and all co-investigators did not have access to outcome data until the trial was closed. Thereafter, the principal investigator, all co-investigators, and NIH staff had access to all study data. S. Szefler had final responsibility for the decision to submit for publication.

Findings

Study Population

Between September 2004 and December 2005, 780 subjects were screened and 546 were randomized, mean age 14.4 years (Interquartile range (IQR): 13–16 years) (Figure 1). Symptoms at randomization were high (Table 1): over three-quarters of participants exceeded Control Level 1 and 57% (313/546) of participants were Control Levels 3 and 4, consistent with moderate to severe asthma. Forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 over forced vital capacity (FEV_1/FVC) were modestly reduced with 22.5% (119/529) of participants having an FEV_1 % <80% predicted [35]. Most participants had at least one positive skin test (87.9%, 467/531) with the median number of positive tests being 5 (IQR:2-7)

of 14 total tests placed. FE_{NO} levels at randomization were generally elevated with 63.6% (347/546) of participants having $FE_{NO} \geq 20$ ppb.

Except for employment, there were no significant differences between groups in demographic characteristics (Table 2; Table 4e-repository). Over 90% (90.5%, 494/546) of randomized participants completed the one-year study with comparably low drop-out and treatment failure rates between groups (Figure 1).

Treatment during the run-in resulted in an increased amount of controller medication compared to pre-study levels: 219 mcg change (95% CI: 199 – 238; P<0.0001) in inhaled corticosteroid (ICS) (fluticasone) dose and 6.04 mcg change (95% CI: 0.78 – 11.30; P=0.0243) in long-acting ß$_2$-agonist (LABA) dose. This change led to a substantive improvement in asthma control with a reduction in maximum symptom days to 2.3 days per two weeks (mean within participant reduction: 3.4 days/2 weeks 95% CI: 3.0 – 3.8; P<0.0001; Figure 2a). Mean Asthma Control Test™ (ACT™) score also improved by 3.0 points (95% CI: 2.7 – 3.4; P<0.0001). At randomization, most participants (70.5%, 385/546) were at Control Level 1, however 12.4% (68/546) were poorly controlled at Levels 3 and 4. FEV_1 % predicted improved (mean change: 3.3%, 95% CI: 2.4 – 4.2; P<0.0001; Figure 2b) as did FEV_1/FVC ratios (2.2, 1.6 – 2.8; P<0.0001). FE_{NO} levels decreased to a median 20.1 ppb (IQR: 11.2 – 40.6; mean reduction: 12.9 ppb, 95% CI: 10.1-15.6; P<0.0001).

Response to Intervention

Intent-to-treat analysis demonstrated no differences between groups for maximum symptom days, other asthma symptoms, or ACT™ scores over the study period (Table 3). Following randomization, asthma symptoms remained low in both groups (Figure 2A). Control levels were not different between groups over the study with 57.3% (306/534) well controlled for at least 80% of visits. Only 22.8% (122/534) demonstrated poor control (Level 3 or 4) for at least 20% of visits (FE_{NO} Group: 22.1%, 59/267; Reference Group: 23.6%, 63/267; χ^2=0.17, P=0.6801). Spirometry (Figure 2B), FE_{NO} (Figure 2C), and adherence (Figure 2D) were not significantly different between groups during the study; however, despite the level of control achieved, only 35.6% (190/534) of all participants had FE_{NO} levels <20 ppb on at least 80% of post-randomization visits. Medication adherence averaged 86.6% (SD: 27.7) during the study. FE_{NO} was significantly lower when adherence was ≥50% (Geometric mean of 23.9 vs. 30.8 ppb for adherence <50%; Ratio of means: 1.28, 95% CI: 1.24 – 1.34; P<0.0001).

More participants in the Reference Group had at least one prednisone course (FE_{NO} 32.1%, 95% CI: 25.3 – 36.7 vs. Reference 42.0%, 95%CI: 35.1 – 47.4; Mean Difference: 10.3, 95% CI: 2.1 – 18.54; P=0.137; Table 3); however, there was no difference in the mean number of courses per year between groups (FE_{NO} 0.66, SE: 0.085 vs. Reference 0.84, SE: 0.085, Mean Difference:0.17, 95% CI: -0.08 - 0.41; P=0.14). Overall healthcare utilization rates were low (mean 0.04 hospitalizations per participant year, SD: 0.25). There were no significant differences between groups for hospitalizations, unscheduled visits, or exacerbations (Table 3). These exacerbation measures were remarkably lower in both groups when compared with the year prior to the study (Table 3 versus Table 2, respectively). Missed school days and caretaker disruption were not different between groups.

To explore whether the intervention could prove effective for some subgroups, a series of post-hoc, exploratory analyses were performed. Testing for heterogeneity of treatment effects across levels of 9 pre-randomization characteristics showed that the effect of the intervention varied with levels of BMI (BMI ≥ 30, Interaction P= 0.0117; BMI percentile > 97; Interaction P=0.0291), number of positive skin tests (≥ 10 positive tests, Interaction P=0.0170) and serum IgE levels (>460 kU/L, Interaction P=0.0072). The intervention was effective in these groups. For example, among participants with BMI ≥ 30, the treatment group had 0.60 fewer maximum

symptom days per 2 weeks than the control group (95% CI: 0.08-1.13, P=0.0245). A similar treatment effect was found for those with a high number of positive skin tests (0.84, 0.11-1.58, P=0.0243) and among those with high serum IgE (0.51, 0.05-0.96, P=0.0296). Characteristics, such as age, gender and pre-randomization asthma severity, lung function and FE_{NO} were not associated with differences between study groups.

Medication Burden

The FE_{NO} Group received supplemental treatment due to elevated FE_{NO} at 405 (26%) of the 1,558 visits. The rate of reduction in ICS use was greater in the Reference Group than the FE_{NO} Group (P=0.0054 for difference in slope), resulting in a difference of 118.9 mcg of inhaled fluticasone per day by the final visit (95% CI: 48.5-189.3; P=0.0010; Figure 2E). By study conclusion, 52.1% (139/267)of the Reference Group had at least a one step reduction as compared to 39.3% (105/267) in the FE_{NO} Group (χ^2=8.723, P=0.0031). Although the rate of reduction in LABA dose was not different between groups, 56.3% (SE: 3.1) of the Reference Group were on LABA at the end of the study as compared to 64.8% (SE: 3.0) in the FE_{NO} Group (Mean Difference: 8.5, 95% CI: 0.04 – 16.93; P=0.0490; Figure 2F).

Adverse Events

The four most common adverse events in ACE were upper respiratory tract infections (331 total events; 37.5% [205/546] of population with at least one event), headaches (242; 27.2% [149/546]), white blood cell abnormalities (235; 27.1% [148/546]) and upper respiratory signs and symptoms (191; 21.6% [118/546]). These events were distributed evenly between treatment groups.

Interpretation

Our study applied a guidelines-based asthma treatment approach[1, 2] and sought to determine whether measurement of FE_{NO} added value to commonly used control measures. Whereas prior studies had typically replaced symptom and pulmonary function with a measure of FE_{NO} as the basis for determining asthma treatment, our study was designed to evaluate the utility of FE_{NO} in combination with standard symptom-based approaches to treatment. We believe this study design more realistically reflects the management approach in which the clinician would employ a measure of airway inflammation, as reflected by exhaled nitric oxide, as an adjunct to symptoms and pulmonary function rather than as a replacement.

This study provides several important observations. First, the application of current asthma treatment guidelines leads to good asthma control in the majority of inner-city adolescents and young adults. Second, the addition of FE_{NO} in guiding asthma therapy maintained a higher dose of ICS and LABA therapy. This FE_{NO} effect had a small impact on the need for prednisone bursts, but did not produce an overall improvement in asthma symptoms, lung function and health care utilization.

The theoretic basis of our algorithm was that an elevated FE_{NO} level would identify those patients with continuing airway inflammation who need increased controller medications. Therefore it was not unexpected that the FE_{NO} group received higher amounts of medication over the course of the study. This increase in treatment, however, did not result in any clinical important outcomes. Four other small clinical trials, two in adults[24, 25] and two in children[22, 23] have used FE_{NO} in asthma managaement. Two general approaches were used in these studies either using FE_{NO} as a guide for steroid reduction, or using FE_{NO} in conjunction with symptoms to guide therapy. Pulmonary function were used to influence therapy in some but not all of the studies.

Petsky et al[36] published a meta-analysis involving these four studies that concluded there was no difference between the FE_{NO} and non- FE_{NO} guided groups in asthma exacerbations, symptoms, or spirometry. The decreased steroid use reported among adults whose treatment was guided by FE_{NO} was discounted as the finding was based on a post-hoc study analysis and not replicated in other studies. A major limitation of the studies included in the meta-analysis was their small size, single location, and varying outcomes. The ACE study addressed many of these concerns with its multi-site, large sample size, and standardized measures. The ACE study findings clearly demonstrate that the lack of effect of FE_{NO} in asthma management was not due to the aforementioned design problems with the previous studies.

It may appear unusual to employ symptoms both as a measure for determining treatment and as the primary outcome. However, for management purposes, the control levels which determined treatment included a range of symptom days, as well as pulmonary function measures. For example, control level 1 included the range 0 to 3 days of symptoms over the prior 2 weeks. Therefore, for asthma management purposes, a person with 0 symptom days would be treated the same as a person with 3 symptom days. For our outcome, symptom days were used as a continuous variable and the study was powered to detect a change of 0.70 days between groups. Although symptoms were employed to determine treatment, the analytic approach examined symptoms two months subsequent to the treatment adjustment to assess the effect of FE_{NO}. Therefore the use of symptoms as both the main outcome of the study and one of several criteria used to adjust therapy does not bias the study against finding a difference.

It is possible that the applied FE_{NO} cut-points were too high and that lower cut-points, especially those identifying good control (less than 20 ppb), should have been used. However, lower cut-points would have lead to even higher dose of ICS with no guarantee of clinical benefit. Further, while the 4 studies included in the review by Petsky et al[36] used a single FE_{NO} cut-point ranging from 15 to 35 ppb, the ACE algorithm used 4 cut-points ranging from 20 to 40 ppb. The use of multiple cut-points over this extended range would increase the potential for FE_{NO} to influence therapy regardless of baseline level of severity. FE_{NO} resulted in therapeutic changes in approximately 26% of the study visits indicating FE_{NO} cut points were operational.

The FE_{NO} Group experienced a significant reduction in the risk of requiring at least one prednisone course for asthma exacerbations. Since the risk of asthma exacerbation is not tightly correlated with ongoing asthma symptoms and pulmonary function, titration of treatment according to FE_{NO} may have greater potential to reduce exacerbations than to improve day to day control. However, measures of asthma exacerbations, such as unscheduled visits and hospitalizations, did not differ between groups (Table 3).

The post-hoc analyses of intervention effects within various sample strata suggest that FE_{NO}-guided treatment may offer benefits in subsets of inner-city asthmatics. Among those subgroups of participants with greater obesity, higher blood eosinophil count, and greater atopy, the FE_{NO} Group showed a larger decrease in asthma symptom days. FE_{NO} measurements may be particularly helpful in obese patients because symptoms related to dyspnea may be difficult to interpret for assessing asthma control[37]. In addition, obesity, elevated blood eosinophils, and a high degree of atopy may be associated with airway inflammation that makes the measurement of FE_{NO} more germane to the assessment of asthma control. These post-hoc subgroup findings are intriguing but should be interpreted with caution.

In summary, in treating inner-city adolescents and young adults with asthma to achieve greater control, FE_{NO} measurements along with symptoms and spirometry did not reduce asthma impairment as compared to titrating therapy according to symptoms and spirometry alone. FE_{NO} monitoring slowed the rate the clinician could lower the inhaled steroid dose. The

observed decrease in the percent of participants requiring ≥1 prednisone bursts is of questionable clinical significance as other indicators of exacerbation did not change. Therefore, in the context of our study, measurements of FE_{NO} add limited benefit to a carefully applied guidelines approach to asthma management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix 1

List of ACE investigators and institutions and acknowledgements

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; Boston University School of Medicine, Boston, MA—G. O'Connor*, S. Steinbach, N. Kozlowski, K. Burkart; Children's Memorial Hospital, Chicago, IL—J. Pongracic*, R. Kumar, J. S. Kim, R. Story; Case Western Reserve University School of Medicine, Cleveland, OH—C. Kercsmar*, J. Chmiel, M. Hart, K. Ross; UT Southwestern Medical Center at Dallas, TX—R. Gruchalla*, V. Gan, W. Neaville; National Jewish Medical and Research Center, Denver, CO—S. Szefler*, A. Liu*, M. Gleason, R. Covar, J Spahn; Mount Sinai School of Medicine, New York, NY—M. Kattan*, H. Sampson, C. Lamm, A. Ting, E. Sembrano, L. Peters; Washington University School of Medicine, St Louis, MO—G. Bloomberg*, R. Strunk, L. Bacharier; The University of Arizona College of Medicine, Tucson, AZ—W. Morgan*, M. Brown, T. Guilbert; Children's National Medical Center, Washington, DC—S. Teach*, K. Stone; Statistical and Clinical Coordinating Center—Rho, Inc, Chapel Hill, NC—H. Mitchell*, B. Shaw, A. Calatroni; Scientific Coordination and Administrative Center—University of Wisconsin, Madison, WI—W. Busse*, C. Sorkness, P. Heinritz; National Institute of Allergy and Infectious Diseases, Bethesda, MD—P. Gergen, E. Smartt.

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Appendix 2

Author contributions and conflict of interest

All authors contributed to the design and conduct of the study. The writing group for this manuscript included S.J. Szefler, P. Gergen, M. Kattan, H. Mitchell, W.J. Morgan, G.T. O'Connor, J.A. Pongracic, C.A. Sorkness, and S.J. Teach. All other authors reviewed the manuscript and provided substantial feedback. J.J. Wildfire and H. Mitchell were responsible for conducting all analyses.

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Abbreviations

eNO

exhaled nitric oxide

NHLBI
National Heart Lung and Blood Institute

NAEPP
National Asthma Education and Prevention Program

NIAID
National Institute of Allergy and Infectious Diseases

FE_{NO}
fraction of exhaled nitric oxide in parts per billion (ppb)

ICS
inhaled corticosteroid

ACE
Asthma Control Evaluation

IQR
Interquartile range

FEV_1
forced expiratory volume in 1 second

FEV_1/FVC
ratio of FEV_1 and forced vital capacity

SD
Standard Deviation

IgE
immunoglobulin E

LABA
long-acting ß$_2$-agonist

ACT™
Asthma Control Test™

BMI
Body Mass Index

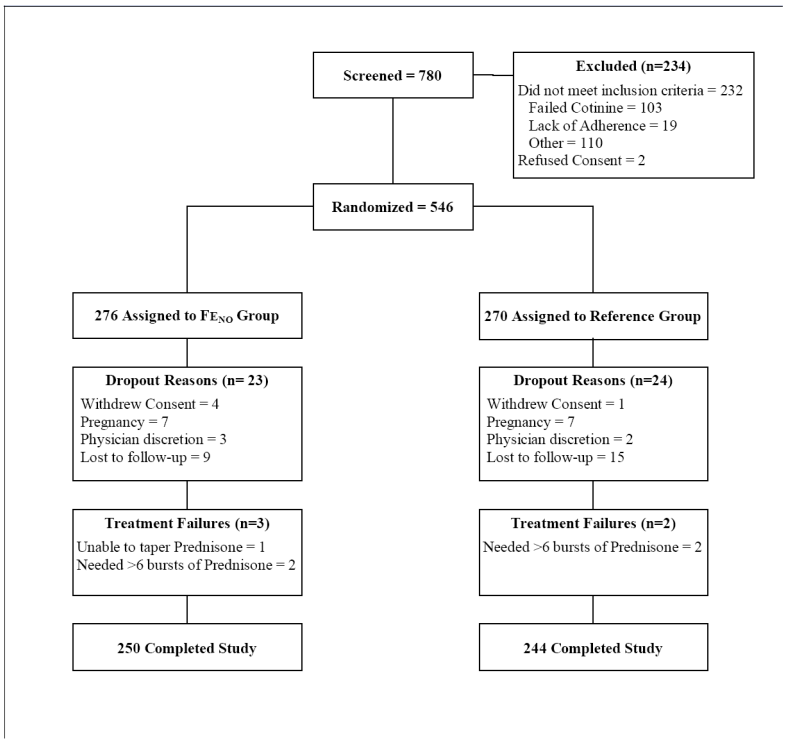

Figure 1. Consort Diagram

Consort Diagram showing the flow of participants from enrollment to completion of study.

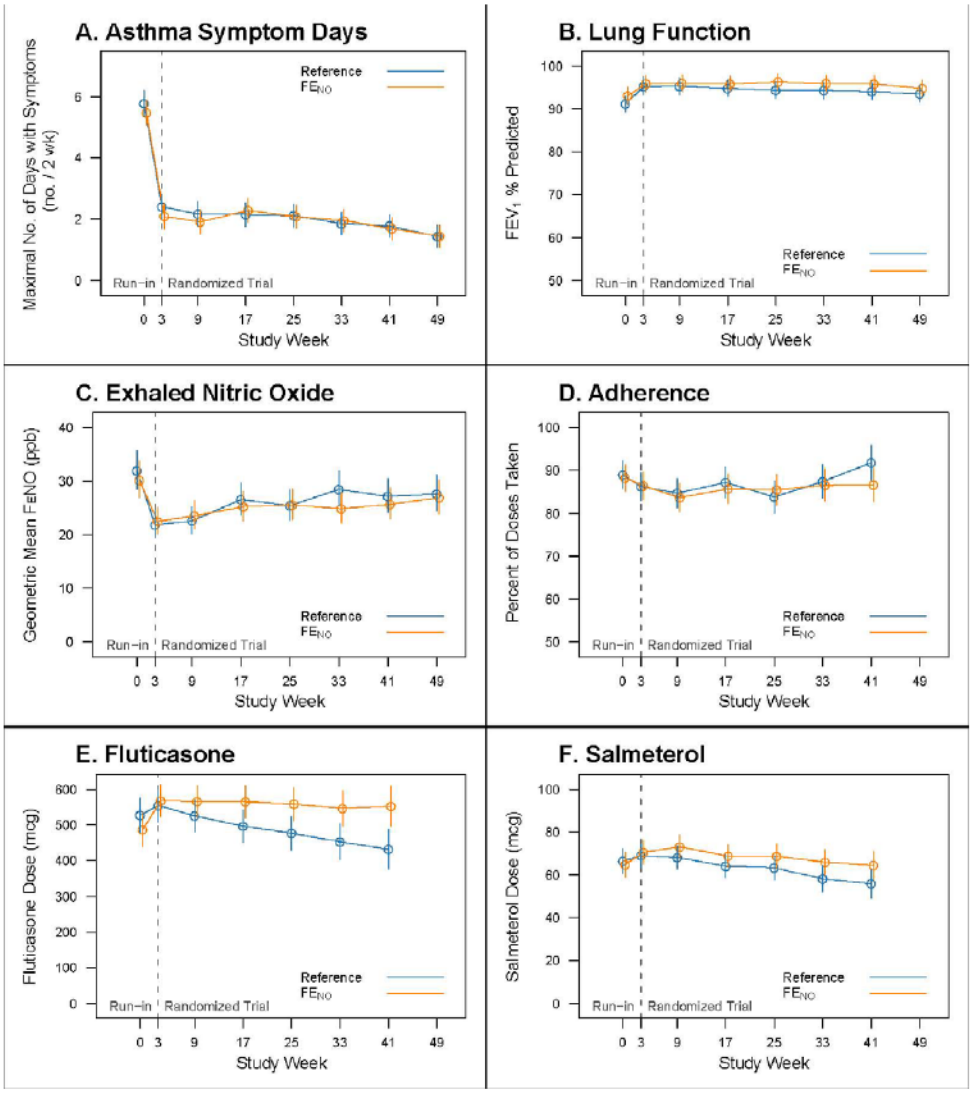

Figure 2. Asthma Outcomes and Medications by Study Visit*

Mean values and 95% confidence intervals for asthma outcomes, pulmonary function and medications burden through the course of the study with maximum symptom days (Panel A), FEV_1 % predicted (Panel B), exhaled nitric oxide levels (Panel C), adherence by percent of doses taken (Panel D), inhaled corticosteroid dose in mcg/day (Panel E), and long-acting $ß_2$-agonist therapy in mcg/day (Panel F). The first three weeks constitute the run-in period.

* Data for treatment related variables (Panels D,E and F) is presented through the final treatment assessment at week 41, whereas follow-up data panels (Panels A,B and C) continue through week 49, the end of the study period

Table 1

Asthma Status of 546 Randomized ACE Participants at Enrollment

Asthma-related symptoms at enrollment (no. of days / last 2 wks)	
Maximum symptom days	5.6 ± 4.6
Days of wheeze, chest tightness or cough	4.5 ± 4.1
Days of interference with activities	3.3 ± 4.1
Nights of sleep disruption	2.7 ± 3.7
School days missed	0.7 ± 1.4
Asthma Control Test™	
ACT™ score in the last month	18.2 ± 4.2
Lung function and exhaled nitric oxide level at enrollment	
FEV_1 (% of predicted value)	92.1 ± 16.6
FEV_1/FVC	77.8 ± 9.4
FE_{NO} (ppb)	31.7 (14.1 – 65.4)
Asthma-related health care use in the year prior to enrollment (%)	
≥ 1 Hospitalizations	14.7 (80/546)
≥ 1 Unscheduled visits	68.7 (375/546)
≥ 1 Prednisone courses	52.0 (284/546)
≥ 1 Exacerbations	78.9 (431/546)

Plus-minus values are means ± SD. Interquartile range is provided in parentheses with medians. Counts are provided in parentheses with percentages. Of the 546 study participants, more than 491 (90%) responded for all characteristics except for school days missed (398 responses).

Table 2

Characteristics of the 546 ACE Participants at Randomization

	FE_{NO} Group (n=276)	Reference Group (n=270)
Demographics		
Age at recruitment (yr)	14.4 ± 2.1	14.4 ± 2.1
Male (%)	52.9 (146/276)	52.6 (142/270)
Race / ethnic group (%)		
Black	66.3 (183/276)	60.7 (164/270)
Hispanic	22.5 (62/276)	23.3 (63/270)
Other or mixed	11.2 (31/276)	15.9 (43/270)
Caretaker completed high school (%)	78.4 (182/232)	74.6 (176/236)
≥ 1 household member employed (%)	85.9 (237/276)	78.9 (213/270)
Household income <$15,000 (%)	48.2 (121/251)	56.2 (141/251)
Asthma characteristics		
Duration of asthma (yr)	10.7 ± 4.3	10.5 ± 4.3
Asthma Control Test™		
ACT™ score in the last month	21.1 ± 3.6	21.3 ± 3.2
Asthma-related symptoms (no. of days / last 2 wks) at randomization		
Maximum symptom days	2.1 ± 2.7	2.4 ± 3.0
Days of wheeze, chest tightness or cough	1.8 ± 2.7	2.2 ± 3.0
Days of interference with activities	1.2 ± 1.9	1.0 ± 1.7
Nights of sleep disruption	0.6 ± 1.5	0.6 ± 1.4
School days missed	0.2 ± 0.6	0.3 ± 1.0
Lung function and exhaled nitric oxide level at randomization		
FEV_1 (% of predicted value)	95.9 ± 15.5	95.7 ± 15.9
FEV_1/FVC	79.8 ± 9.0	80.4 ± 8.3
FE_{NO} (ppb)	20.5 (11.5 - 45.3)	19.7 (10.9 - 38.0)
Asthma-related health care use in the year prior to enrollment (%)		
≥ 1 Hospitalizations	14.5 (40/276)	14.8 (40/270)
≥ 1 Unscheduled visits	67.8 (187/276)	69.6 (188/270)
≥ 1 Prednisone courses	52.2 (144/276)	51.9 (140/270)
≥ 1 Exacerbations	79.3 (219/276)	78.5 (212/270)

Plus-minus values are means ± SD. Interquartile range is provided in parentheses with medians. Counts are provided in parentheses with percentages. Of the 546 study participants more than 491 (90%) responded for all characteristics except for the following: 468 for caretaker completed high school; 471 for duration of asthma; 381 for school days missed.

Table 3

Effect of Intervention on Asthma Symptoms and Health Care Use During 46 Weeks of Follow-up

	FE_{NO} n=276	Reference n=270	Diff	P Value
Asthma-related symptoms (no. of days / last 2 wks)				
Maximum symptom days	1.93 ± 0.09	1.89 ± 0.09	0.04 (-0.22 – 0.29)	0.7796
Days of wheeze	1.71 ± 0.09	1.69 ± 0.09	0.03 (-0.21 – 0.26)	0.8291
Days of activity interference	0.87 ± 0.07	0.95 ± 0.07	-0.08 (-0.26 – 0.10)	0.3817
Nights of sleep disruption	0.52 ± 0.05	0.50 ± 0.05	0.03 (-0.11 – 0.16)	0.7054
School days missed	0.19 ± 0.03	0.23 ± 0.03	-0.04 (-0.12 – 0.05)	0.3846
Asthma Control Test™				
ACT™ score in the last month	21.89 ± 0.12 21.83 ± 0.12	0.06 (-0.28 – 0.40)	0.7212	
Lung function				
FEV_1 (% of predicted value)	96.3 ± 0.5	95.5 ± 0.5	0.8 (-0.51 – 2.07)	0.2338
FEV_1/FVC	80.3 ± 0.3	79.7 ± 0.3	0.6 (-0.13 – 1.34)	0.1055
Asthma-related health care use (%)				
≥ 1 Hospitalizations *	3.3 ± 1.1	4.1 ± 1.2	-0.8 (-4.0 – 2.3)	0.6136
≥ 1 Unscheduled visits	21.3 ± 2.7	22.7 ± 2.7	-1.4 (-9.3 – 6.7)	0.7427
≥ 1 Prednisone courses	32.1 ± 2.9	42.0 ± 3.1	-10.3 (-18.5 – -2.2)	0.0137
≥ 1 Exacerbations	37.0 ± 2.7	43.6 ± 2.1	-6.5 (-14.4 – 1.4)	0.1068

Plus-minus values are means ± SE or difference (95% CI). Values are adjusted for study site and levels at randomization unless noted.

* Unadjusted due to sparse data.