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Bronchodilator dose responsiveness in children and adolescents: Clinical features and association with future asthma exacerbations

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Abstract

Background.—Bronchodilator reversibility measures are often associated with poor asthma outcomes in children. Whether bronchodilator dose responsiveness is similarly useful in children is unclear.

Objective.—We hypothesized that children and adolescents requiring higher doses of bronchodilator to achieve maximal bronchodilation would have unique risk factors and increased risk of future exacerbation.

Methods.—Children (6–11 years, N=299) and adolescents (12–21 years, N=331) with confirmed asthma underwent clinical phenotyping procedures and a test of maximal bronchodilation with escalating doses of albuterol sulfate up to 720 mcg. Outcome measures were assessed at 12 months and included exacerbations treated with systemic corticosteroids, emergency department (ED) visits and hospitalizations for asthma.

Results.—6.7% of children and 9.3% of adolescents had poor bronchodilator dose responsiveness, defined as attainment of maximal FEV₁ with 720 mcg albuterol. Risk factors included Type-2 inflammation, prior exacerbations, and greater asthma severity; historical pneumonia and tobacco exposure were also risk factors in children. Children and adolescents with poor bronchodilator dose responsiveness did not have increased current symptoms or impaired quality of life, but had ~2-fold increased odds of exacerbation or ED visit and ~3-fold increased odds of hospitalization by 12 months, independent of airflow obstruction.

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Conclusions.—Bronchodilator dose responsiveness may be useful for phenotyping and may be of utility in practice and future studies focused on asthma outcomes or quantification of treatment responses. In children and adolescents, this phenotype of poor bronchodilator responsiveness may be associated with periods of relatively stable disease yet marked airway constriction in response to triggers, including tobacco smoke, respiratory infections/pneumonia, and aeroallergens.

Keywords

Asthma in children; Exacerbation; Airway physiology; Phenotype; Lung function; Bronchodilator reversibility; Type-2 inflammation; Sensitization

Introduction

Airway lability is a characteristic feature of children with asthma. As such, bronchodilator reversibility testing is routinely performed in the clinical setting to confirm the diagnosis of asthma and quantify asthma control.¹ However, the measure is not always repeatable² and specific cut-points for the purpose of asthma diagnosis and evaluation in children are debatable.³ Furthermore, given the variable nature of asthma control, not all children with asthma display a bronchodilator response.⁴

Nonetheless, bronchodilator reversibility has been identified in phenotypic subgroups of children with asthma^{5–11} and may contribute to differing clinical outcomes and disease trajectories.^{12–14} For example, in the Childhood Asthma Management Program, a small subset of children with consistent improvement in forced expiratory volume in one second (**FEV₁**) of 12% or greater after bronchodilator administration at each study visit had more nocturnal symptoms, prednisone bursts, missed days of school and hospitalizations.¹³ Other studies have likewise identified greater bronchodilator reversibility in children with difficult-to-control or severe asthma, who also have greater symptom burden despite inhaled corticosteroid (**ICS**) treatment.^{5–8, 15} Therefore, the Global Strategy for Asthma Management and Prevention recently updated their asthma treatment guidelines to include markedly increased bronchodilator reversibility as a potentially modifiable risk factor for future exacerbations, even in patients with few symptoms.¹

Although the clinical importance of bronchodilator reversibility has been demonstrated, whether bronchodilator dose responsiveness is also useful for asthma phenotype and end outcome assessment is not clear. We therefore characterized bronchodilator dose responsiveness and its associations with asthma exacerbations over 12 months in a sample of children and adolescents 6–21 years of age enrolled in observational asthma research studies at Children’s Healthcare of Atlanta and Emory University in Atlanta, Georgia. Using a test of maximal bronchodilation with up to 720 mcg of albuterol sulfate, we hypothesized that participants achieving maximal FEV₁ with 720 mcg albuterol, compared to participants achieving maximal FEV₁ with 360 mcg or 540 mcg of albuterol, would be distinguished by unique phenotypic risk factors and would have increased odds of an exacerbation, emergency department (**ED**) visit and hospitalization for asthma by 12 months, independent of airflow obstruction.

Methods

Children and adolescents 6 to 21 years of age within the Children's Healthcare of Atlanta medical system were eligible for the study if they had: 1) a physician diagnosis of asthma, 2) no self-reported acute illness or an asthma exacerbation treated with systemic corticosteroids within the preceding four weeks, and 3) historical evidence of either 12% reversibility in FEV₁ or airway hyperresponsiveness evidenced by a provocative concentration of methacholine causing a 20% drop in FEV₁ (PC₂₀) 16 mg/mL. Exclusion criteria included premature birth before 35 weeks of gestation, current smoking <5 pack years, or other chronic airway disorders such as cystic fibrosis, pulmonary aspiration or vocal cord dysfunction. Permission to proceed with this study was granted by the Emory University Institutional Review Board. Informed written consent was obtained from legal guardians or participants (if 18 years of age). Verbal assent was obtained from children 6–10 years and written assent was obtained from children and adolescents 11 to 17 years.

Study design and procedures.

Participants completed an outpatient study visit where questionnaires pertaining to demographics, medical history and symptoms were administered. Composite Asthma Severity Index (CASI) scores were calculated according to the methods of Wildfire et al.¹⁶ with a 4-week modification for symptom recall and a 12-month modification for asthma exacerbations. Asthma-related quality of life over the preceding two weeks was assessed with the Asthma Quality of Life Questionnaire (AQLQ);¹⁷ participants 6–17 years of age completed the pediatric version of the AQLQ instrument that excludes assessment of the environmental domain.¹⁸ Neighborhood (i.e., ZIP code) characteristics were obtained from the 2010–2014 American Community Survey 5-years estimates, Tables S101, S1501, and DP03, available at www.factfinder.census.gov.¹⁹ Exhaled nitric oxide concentrations were measured with a commercial device (NIOX MINO®, Circassia Pharmaceuticals, Chicago, IL). Aeroallergen sensitization was assessed by specific IgE testing (Children's Healthcare of Atlanta, Atlanta, GA) or skin prick testing with 12 extracts: tree mix, grass mix, weed mix, *Ambrosia artemisiifolia*, *Alternaria alternata*, *Aspergillus fumigatis*, *Cladosporium herbarum*, dog dander, cat dander, *Blattella germanica*, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus* (Greer® Laboratories, Lenoir, NC). Venipuncture was also performed for quantification of blood eosinophils (Children's Healthcare of Atlanta).

Spirometry (KoKo® PDS, Ferraris, Louisville, CO) was performed following a bronchodilator withhold as recommended by guidelines from the European Respiratory Society (ERS)/American Thoracic Society (ATS) for bronchodilator reversibility testing.²⁰ Participants withheld short-acting bronchodilators for a minimum of 4 hours, long-acting beta-agonists for a minimum of 12 hours, and leukotriene antagonists for a minimum of 24 hours. Spirometry was repeated after 360 mcg (4 inhalations) of albuterol sulfate administered through a valved holding chamber with a mouthpiece (Aerochamber®, Monaghan Medical Corporation, Plattsburg, NY). Fifteen minutes after the 360 mcg dose, 2 additional albuterol inhalations were administered (total albuterol dose, 540 mcg). If FEV₁ differed by 5% or more between the 360 and 540 mcg albuterol dosages, then the final 2 inhalations of albuterol were given (720 mcg total dose). Percent difference in FEV₁

between albuterol dosages was calculated as a relative change as follows: $(FEV_1^{post} - FEV_1^{previous})/FEV_1^{previous} \times 100$. Best FEV₁, forced vital capacity (**FVC**), and forced expiratory flow at 25–75% of vital capacity (**FEF_{25–75}**) values from 3 reproducible maneuvers were recorded fifteen minutes after each bronchodilation and were interpreted according to Global Lung Function Initiative prediction equations.²¹ A subset of participants, on separate days, also underwent lung volume measurement with a body plethysmograph (MedGraphics Elite Series; Medical Graphics Corporation, St Paul, Minn) for quantification of residual volume (**RV**) and total lung capacity (**TLC**) and bronchoprovocation testing with methacholine concentrations of 0 to 16 mg/mL (Provocholine; Methapharm Inc, Coral Springs, Fla) delivered by a Rosenthal dosimeter (Pulmonary Data Service Instrumentation, Louisville, Colo). Bronchoprovocation was limited to participants with baseline FEV₁ > 70% predicted.

Outcomes.

Participants were telephoned at 6 and 12 months after the study visit and questioned about asthma exacerbations treated with systemic corticosteroids²² and exacerbations resulting in ED visits and hospitalizations. Hospitalizations were verified by a review of medical records.

Statistical analyses.

Data were analyzed with SPSS® Statistics (Version 24, IBM, Armonk, NY) with stratification by age group (6–11 vs. 12–21 years). Clinical features and of children and adolescents achieving maximal bronchodilation with 360 mcg (4 inhalations), 540 mcg (6 inhalations), or 720 mcg (8 inhalations) of albuterol sulfate were compared with chi-square tests and analysis of variance. Post-hoc testing was performed using Tukey's Least Significant Difference tests. The predictive capacity of poor bronchodilator response, defined as needing 720 mcg albuterol to achieve maximal bronchodilation, was assessed with logistic regression. Models were adjusted for age group, sex, ethnicity, race, and baseline airflow obstruction, defined as FEV₁/FVC below the lower limit of normal.²¹ A p value <0.05 was used as the threshold for statistical significance without adjustment for multiple comparisons.

Results

Six hundred thirty children (N = 299) and adolescents (N = 331) were enrolled. Demographic features of the participants, stratified by age group, are shown in Table 1. Age groups differed with regard to race, sex, other self-reported medical conditions including eczema, chronic sinusitis and gastroesophageal reflux, asthma controller medication use, indoor exposures and asthma-related healthcare utilization in the previous year. Household educational attainment and features of the neighborhoods (i.e., ZIP codes) in which the participants resided did not differ between age groups (Table 1).

Lung function and bronchodilation patterns.

In children, maximal bronchodilation was achieved with 360 mcg albuterol in 136 participants (45.5%), 540 mcg in 143 participants (47.8%), and 720 mcg in 20 participants

(6.7%). In adolescents, maximal bronchodilation was achieved with 360 mcg albuterol in 121 participants (36.6%), 540 mcg in 179 participants (54.1%), and 720 mcg in 31 participants (9.4%).

Patterns of bronchodilation with progressive albuterol dosages, stratified by age group, are shown in Figure 1. In children, there were no differences in baseline FEV₁, FVC, FEV₁/FVC or FEF₂₅₋₇₅ percent predicted values between the albuterol dose response groups. However, by definition, children who achieved maximal bronchodilation with 720 mcg albuterol had progressive improvement in FEV₁; this was mirrored by progressive improvements in FVC and FEV₁/FVC but not FEF₂₅₋₇₅ (Figure 1A–D). In adolescents, baseline FEV₁, FVC, FEV₁/FVC and FEF₂₅₋₇₅ percent predicted values differed between albuterol dose response groups and were significantly lower in participants who achieved maximal bronchodilation with 720 mg albuterol. After maximal bronchodilation, FEF₂₅₋₇₅, but not FEV₁ or FVC, remained lower in this group (Figure 1E–H). Associations between the maximal change in FEV₁ and FVC for each albuterol dose response group are shown in Figure 2. Baseline RV/TLC values, methacholine PC₂₀ values, and lung function reversibility measures are also shown in Table 2.

Clinical features associated with bronchodilation patterns.

Other clinical features of children and adolescents, stratified by the dose of albuterol at which maximum bronchodilation was obtained, are shown in Table 3. Children who achieved maximal bronchodilation with 720 mcg albuterol were more likely to report a history of recurrent pneumonia treated with antibiotics, indoor tobacco smoke exposure, a greater intensity of asthma treatment with higher dosages of ICS, more prior hospitalizations, intensive care unit admissions and intubations for asthma exacerbations, and greater asthma severity reflected by higher baseline CASI scores. Adolescents who achieved maximal bronchodilation with 720 mcg albuterol had a slightly longer duration of asthma, more hospitalizations for asthma in the previous year, increased lifetime hospitalizations and intensive care unit admissions for asthma exacerbations, and a higher baseline CASI score (Table 3).

Other asthma-related and inflammatory features of children and adolescents are shown in Figures 3–4. There were no differences in current asthma symptoms (Figure 3A,B) or asthma-related quality of life domain scores (Figure 3C–H) in children or adolescents who achieved maximal bronchodilation with 720 mcg of albuterol compared to the other groups. However, markers of Type-2 inflammation differed; children and adolescents who achieved maximal bronchodilation with 720 mcg of albuterol were both distinguished by a higher percentage of positive aeroallergens (Figure 4) Adolescents (but not children) who achieved maximal bronchodilation with 720 mcg of albuterol also had higher exhaled nitric oxide concentrations and higher blood eosinophil counts (Figure 4).

Predictive capacity of poor bronchodilator dose responsiveness.

The clinical relevance of poor bronchodilator dose responsiveness was assessed with multivariate logistic regression, with the albuterol dose at which maximal bronchodilation was obtained as the predictor and exacerbations treated with systemic corticosteroids, ED

visits, and hospitalizations within 12 months of the study visit as outcomes. 12-month outcomes were available from 293 children (98.0%) and 243 adolescents (73.4%). Features of this subset did not differ from those of the larger sample (data not shown). Exacerbations treated with systemic corticosteroids occurred in 104 children (36%) and 75 adolescents (30.7%). ED visits occurred in 79 children (29%) and 52 adolescents (21%) and hospitalizations occurred in 24 children (8%) and 20 adolescents (8%). To improve power, age groups were merged for outcome analyses and adjusted for covariates including age group.

In analyses adjusted only for age group, maximal bronchodilation with 720 mcg albuterol (versus 360 mcg albuterol) was associated with more than 2-fold increased odds of exacerbation by 12 months (Table 3). This association persisted after adjustment for demographic variables, ICS use, and baseline airflow obstruction. Similarly, children and adolescents who achieved maximal bronchodilation with 720 mcg albuterol also had ~2-fold increased odds of an ED visit and ~3.5-fold increased odds of hospitalization by 12 months in adjusted analyses (Table 3).

Discussion

Our findings highlight the features and clinical importance of a low-prevalent (<10%) phenotype of children and adolescents with poor bronchodilator dose responsiveness, defined as achievement of maximal bronchodilation with 720 mcg of albuterol sulfate, who are at greater risk for life-threatening future exacerbations independent of baseline airflow obstruction. Although poor bronchodilator dose responsiveness not associated with increased self-reported symptoms or decreased quality of life (perhaps due to poor symptom perception), children and adolescents in this group tended to have more Type-2 inflammatory features, greater airway hyperresponsiveness to methacholine, and greater asthma burden/severity reflected by higher CASI scores. These same participants also had ~2-fold increased odds of a subsequent exacerbation or ED visit and ~3-fold increased odds of a subsequent hospitalization for status asthmaticus. Although additional studies are needed, this phenotype may be associated with periods of relatively stable disease yet marked airway constriction in response to triggers, including tobacco smoke, lower respiratory infections/pneumonia, and aeroallergens.

Although the clinical importance of bronchodilator reversibility measurements in children with asthma have been well established,⁵⁻¹⁵ the majority of asthma phenotyping work in children has focused on baseline measures of lung function (namely FEV₁) without consideration of bronchodilation as a variable.²³ In other studies where FEV₁ bronchodilator reversibility was assessed, it did not consistently distinguish phenotypic groups of children.^{6, 10, 24-26} These disparate findings may be due to poor specificity of FEV₁ in children. Indeed, others have shown that FEV₁ values are often normal in children with asthma^{27, 28} and may not discriminate subtle differences in clinical presentation.²⁹ Bronchodilator dose responsiveness studies in children are quite limited but may ultimately better phenotypic heterogeneity. For example, previous reports from the National Heart, Lung and Blood Institute's Severe Asthma Research Program (**SARP**) examined maximal post-bronchodilator pulmonary function indices in children and adolescents 6-17 years with

asthma and noted greater baseline air trapping and airflow limitation that persisted in a subset of participants after maximal bronchodilation.^{5-7, 30} These studies suggested that: 1) at least some children and adolescents have patterns of airway physiology similar to those of adults with severe persistent asthma,³¹ and 2) these patients with air trapping and airflow limitation may be at increased risk for exacerbation.⁵ However, those studies did not examine the dose of albuterol at which maximal bronchodilation was obtained and focused on comparisons between severe and non-severe asthma defined by ERS/ATS criteria.³²

Our observations of increased exacerbation occurrence and severity in children and adolescents with poor bronchodilator dose responsiveness, defined as achievement of maximal bronchodilation with 720 mcg of albuterol sulfate, do have biologic plausibility. These patients with poor bronchodilator responsiveness also had more historical exacerbations and hospitalizations. Other studies have likewise shown that prior exacerbations are a significant predictor of future exacerbations regardless of disease severity or use of controller medications.³³⁻³⁷ Moreover, previous intensive care unit admissions are also strongly predictive of future intensive care unit admissions in children with asthma.³⁸ One study also noted increased bronchodilator reversibility in children with self-reported asthma exacerbations in the previous year irrespective of asthma severity, although that report found no differences in the absolute FEV₁ percent change between children stratified by exacerbation rate (i.e., 1-2 versus >2 exacerbations).³⁹ However, a recent study of 560 inner-city children from Sorkness et al.⁴⁰ identified three obstruction phenotypes in children (none, airflow limitation and air-trapping) and found that children with air trapping had the highest RV/TLC, greatest airway hyperresponsiveness to methacholine, greatest variability in FEV₁ across multiple visits, and greatest exacerbation frequency. Similarly, a cluster of children in the Childhood Asthma Management Research Program with the greatest bronchodilator reversibility also had severe airway hyperresponsiveness, the most reports of prior hospitalizations and the highest rate of emergency department visits, and the highest risk of future exacerbation.²⁶ Similar to our study, the prevalence of this phenotypic cluster was 9.3%.²⁶ A separate analysis of this same population of children also noted associations between exacerbation frequency and the percent increase in post-bronchodilator FEV₁ after methacholine challenge.⁴¹

Sorkness⁴⁰ and others^{26, 42-44} have also noted more features of type-2 inflammation in children and adolescents with air trapping and bronchodilator reversibility, including greater aeroallergen sensitization, higher serum IgE concentrations, higher exhaled nitric oxide concentrations, and higher blood eosinophils. Furthermore, in the cluster of children in the Childhood Asthma Management Research Program with the greatest bronchodilator reversibility, the prevalence of skin test reactivity approached 100%.²⁶ However, those studies did not stratify by age groups. In the present study, although greater aeroallergen sensitization was present in both children and adolescents, exhaled nitric oxide concentrations and blood eosinophils were only elevated in adolescents, perhaps due to greater ICS use and higher ICS dosages in children which may suppress Type-2 inflammatory pathways.⁴⁵ It is also possible that markers of Type-2 inflammation vary by age, as optimal cut-points have not yet been defined for pre-adolescent children. Our observation of greater tobacco smoke exposure in children with marked bronchodilator

reversibility is also aligned with other reports of increased bronchodilator responsiveness in tobacco-exposed infants⁴⁶ and children.⁴⁷

Nonetheless, this study does have a number of limitations. Particularly in children, the albuterol dose response curves did not plateau at the highest albuterol dose. Therefore, we cannot rule out fatigue or issues with albuterol delivery given that delivery can be impacted by multiple variables such as airway closures, airflow heterogeneity, tachyphylaxis, and proximal mucous plugging. It is therefore possible that these physiological factors limited the effects of the initial albuterol dose, and therefore resulted in greater distribution of albuterol with subsequent dosages. Second, inclusion was limited to children with historical evidence of at least 12% FEV₁ bronchodilator reversibility or airway hyperresponsiveness to methacholine. This inclusion was consistent with ERS/ATS guidelines²⁰ which define a change in FEV₁ >12% of baseline (and >200 mL) as “significant bronchodilation” irrespective of age. Therefore, we did not detect phenotypes of fixed airflow obstruction with bronchodilator unresponsiveness that have been previously described in children.⁴⁸ Third, bronchodilator reversibility may not adequately reflect the complex nature of airway smooth muscle tone. Indeed, the degree of bronchodilator reversibility also depends on excitation-contraction signaling pathways and activation of mechanisms that drive smooth muscle shortening, which are also thought to be abnormal in patients with asthma.⁴⁹ There is also no consensus on the dose of bronchodilator to be used for bronchodilator reversibility testing. While most pulmonary function laboratories deliver four separate doses of short-acting beta-agonist (i.e., 400 total mcg salbutamol or 360 mcg albuterol) in accordance with guideline recommendations,²⁰ dose-response studies of salbutamol⁵⁰ and albuterol⁵¹ in adults with asthma demonstrate a log-linear cumulative dose response for FEV₁ evident up to the final dose of 16 cumulative inhalations. Identical dose response studies in children are lacking, but limited evidence suggests a possible plateau of the dose response curve in children,^{52–56} similar our observation of maximal FEV₁ attainment with 360–540 mcg albuterol in the majority of participants in the present study.

It is also difficult to ascertain the role of bronchodilator reversibility independent of airflow obstruction in the assessment of exacerbation risk. Other studies of similar populations of children have clearly shown that the level of airflow obstruction and reversal with bronchodilation contribute to poor symptom control and exacerbation.^{15, 44} For this reason, we adjusted for baseline airflow obstruction in our outcome analyses and found that poor bronchodilator dose responsiveness, defined as attainment of maximal bronchodilation with 720 mcg albuterol, remained a significant independent predictor of exacerbations, ED visits and hospitalizations. We also expressed bronchodilator reversibility measures as both a relative and absolute change in the percentage of predicted values, consistent with recommendations from others who have argued that relative measures are overly dependent on participant morphology⁵⁷ and tend to advantage low initial values,⁵⁸ rendering those values more susceptible to regression toward the mean.²

Finally, because the participants in our study were grouped according to abuterol dose responsiveness on a single day, we also acknowledge that the temporal stability and reproducibility of the dose response groups may be poor and may reflect adherence or access to controller medication and environmental controls and current asthma burden/

severity. Indeed, in a large retrospective analysis of over 30,000 patients with confirmed asthma and historical FEV₁ reversibility of at least 12%, the proportion of bronchodilator reversible patients decreased by 30% and 50% in the placebo and inhaled fluticasone treatment arms at study completion.⁵⁹ However, among the patients who remained reversible, the degree of bronchodilator reversibility was essentially unchanged (26% change for placebo and 15% change for inhaled fluticasone).⁵⁹ A separate report of adults stratified by asthma severity similarly demonstrated low concordance of bronchodilator reversibility measures over 12 months of follow-up, although concordance was somewhat improved in severe patients with greater obstruction and higher baseline bronchodilator reversibility.⁶⁰ Our study population included a convenience sample of children and adolescents presenting to an academic medical center for evaluation and care, irrespective of asthma severity. We did not have enough information to define participants as having “severe” or “non-severe” asthma in the present study since consensus treatment guidelines emphasize the need for 12 months of asthma specialty follow-up with assessment of ICS adherence and management of co-morbid conditions.³² However, the overall prevalence of airflow obstruction (defined as an FEV₁/FVC less than the lower limit of normal) was 43.1% in children and 48.6% in adolescents in our study; this is similar to that observed in non-severe asthma participants enrolled in SARP⁷ and a recent study of inner-city children with persistent asthma irrespective of asthma severity.⁴⁰

In conclusion, poor bronchodilator dose responsiveness necessitating 720 mcg albuterol sulfate for attainment of maximal FEV₁ is present in a small proportion of children and adolescents with asthma but is associated with unique risk factors and increased risk for life-threatening future exacerbations independent of airflow obstruction. Although future studies are needed in diverse populations to confirm the reproducibility of the phenotype and outcome associations, we contend that bronchodilator dose responsiveness may be a useful measure for the purpose of asthma phenotyping and may be of utility in clinical practice and future studies focused on asthma outcomes or quantification of asthma treatment responses, such as biologic studies.

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Abbreviations

ATS	American Thoracic Society
AQLQ	Asthma Quality of Life Questionnaire
CASI	Composite Asthma Severity Index
ED	Emergency department
ERS	European Respiratory Society
FEF_{25–75}	Forced expiratory flow at 25–75% of vital capacity

FEV₁	Forced expiratory volume in one second
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
PC₂₀	Provocative concentration of methacholine causing a 20% drop in FEV1
RV	Residual volume
SARP	Severe Asthma Research Program
TLC	Total lung capacity

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Highlights Box

What is already known about this topic?

Bronchodilator reversibility has been identified in phenotypic subgroups of children with asthma and may contribute to differing clinical outcomes and disease trajectories. Whether bronchodilator dose responsiveness is also useful for phenotype definition and outcome assessment is not clear.

What does this add to our knowledge?

Poor bronchodilator dose responsiveness was identified in <10% of participants but was associated with unique features (i.e., Type-2 inflammation, indoor exposures, prior severe exacerbations) and increased odds of future exacerbation and hospitalization, independent of airflow obstruction.

How does this study impact current management guidelines?

In children and adolescents, poor bronchodilator dose responsiveness may be an independent predictor of future risk and may identify a group of patients at highest risk for life-threatening exacerbations.

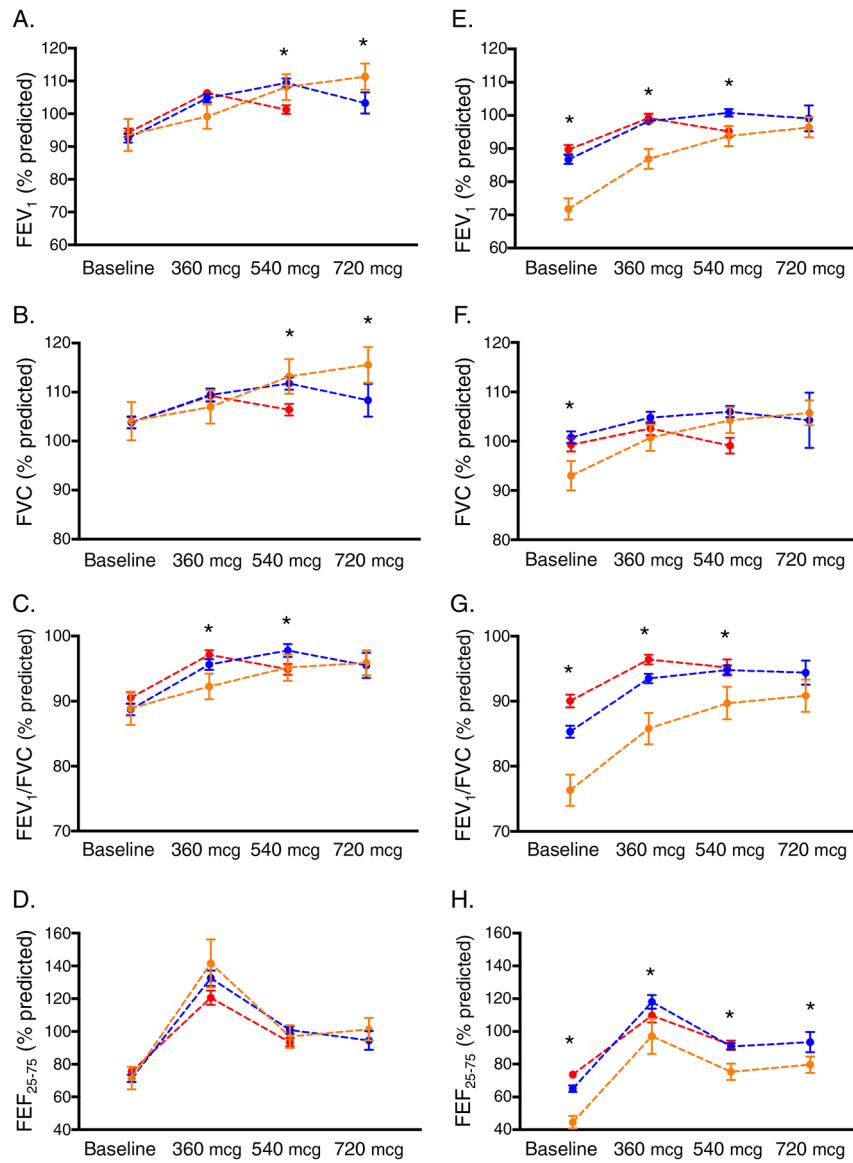


Figure 1. FEV₁, FVC, FEV₁/FVC, and FEF₂₅₋₇₅ percent predicted values in children (panels A–D, respectively) and adolescents (panels E–H, respectively) at baseline and after 360 mcg, 540 mcg, and 720 mcg of albuterol sulfate. Data are stratified by the dosage of albuterol at which maximal bronchodilation was obtained (red = 360 mcg, blue = 540 mcg, orange = 720 mcg). *p < 0.05

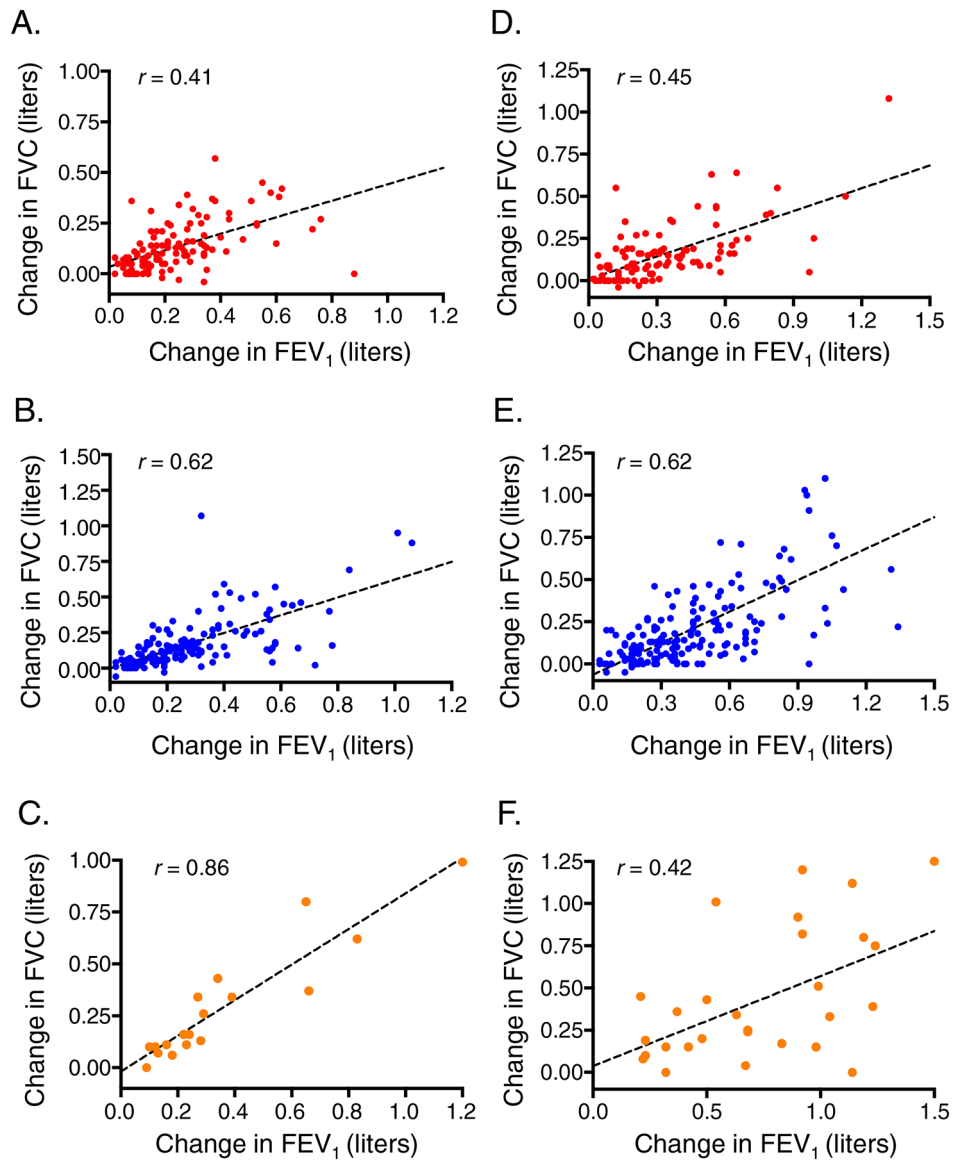


Figure 2. Associations between the maximal change in FEV₁ and FVC for each albuterol dose response group (red = 360 mcg, blue = 540 mcg, orange = 720 mcg).

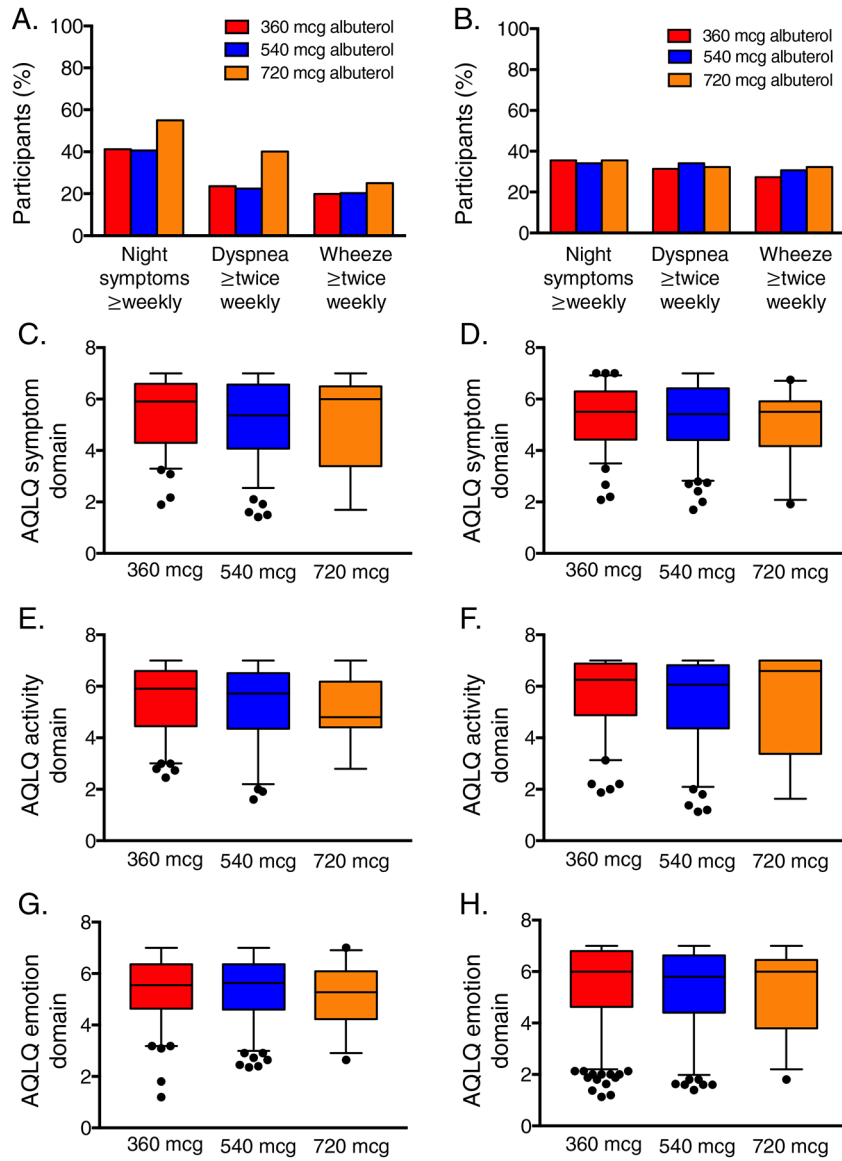


Figure 3. Self-reported symptoms over the previous two weeks (panels A, B) and Asthma Quality of Life Questionnaire (AQLQ) symptom (panels C, D), activity (panels E, F) and emotion (panels G, H) domain scores in children (left) and adolescents (right). Higher AQLQ scores reflect greater quality of life. Whiskers and dots represent 5th-95th percentiles and outliers, respectively. Groups are not statistically different.

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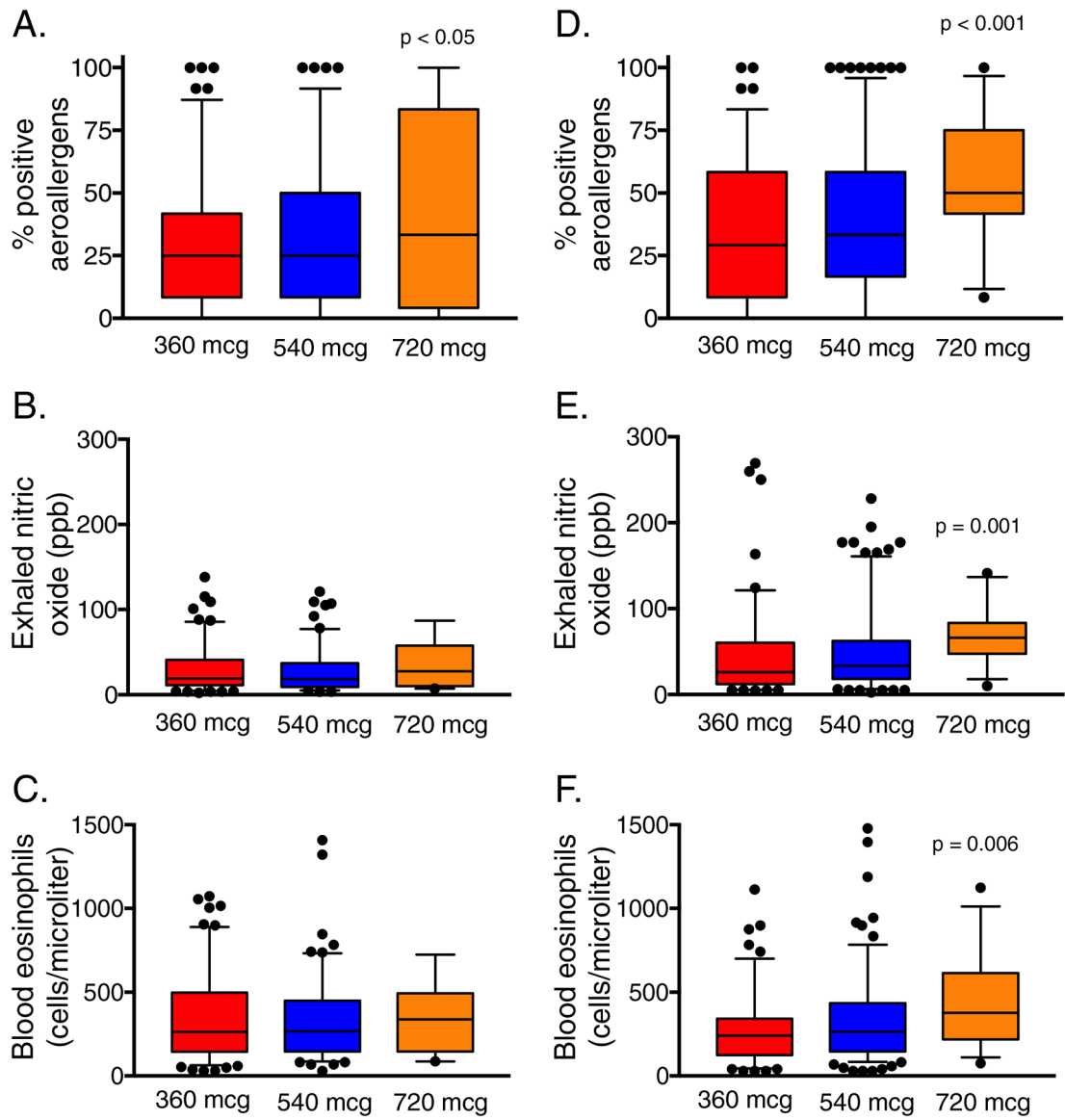


Figure 4.

Percentage of positive aeroallergens, exhaled nitric oxide concentrations, and blood eosinophil counts in children (panels A–C, respectively) and adolescents (panels D–F, respectively) who achieved maximal bronchodilation with 360 mcg (red), 540 mcg (blue), and 720 mcg (orange) of albuterol sulfate. Whiskers and dots represent 5th–95th percentiles and outliers, respectively.

Table 1.Features of the participants. Data represent the mean \pm standard deviation or the number of participants (%).

	All participants N = 630	Children 5–11 years N = 299	Adolescents 12–21 years N = 331
Age (years)	12.8 \pm 4.5	9.1 \pm 1.7	16.2 \pm 3.3
Asthma duration (years)	9.4 \pm 4.7	6.4 \pm 2.8	12.1 \pm 4.5
Males	351 (55.7)	180 (60.2)	171 (51.7)
Race			
White	200 (31.7)	79 (26.4)	121 (36.6)
Black	368 (58.4)	193 (64.5)	175 (52.9)
More than one race	52 (8.3)	25 (8.4)	27 (8.2)
Other	10 (1.6)	2 (0.7)	8 (2.4)
Hispanic ethnicity	44 (7.0)	24 (8.0)	20 (6.0)
Household education level			
Refused	130 (20.6)	49 (16.4)	81 (24.5)
Did not complete high school	26 (4.1)	9 (3.0)	17 (5.1)
High school diploma	82 (13.0)	41 (13.7)	41 (12.4)
Some college/technical training	174 (27.6)	86 (28.8)	88 (26.6)
College degree	218 (34.6)	114 (38.1)	104 (31.4)
ZIP code features	34.6 \pm 16.9	35.0 \pm 17.3	34.2 \pm 16.2
Population (in thousands)			
Unemployment (%)	12.7 \pm 5.8	12.6 \pm 5.6	12.8 \pm 6.1
Bachelor's degree (%)	31.2 \pm 16.2	30.5 \pm 15.4	32.1 \pm 17.1
Families below poverty threshold (%)	19.4 \pm 11.0	18.9 \pm 10.3	19.9 \pm 11.9
Family history			
Father with asthma	149 (23.7)	74 (24.7)	75 (22.7)
Mother with asthma	234 (37.1)	115 (38.5)	119 (36.0)
Other medical conditions			
Allergic rhinitis	558 (88.6)	262 (87.6)	296 (89.4)
Eczema	343 (54.4)	188 (62.9)	155 (46.8)
Obesity	172 (27.3)	82 (27.4)	90 (27.2)
Recurrent pneumonia	289 (45.9)	128 (42.8)	161 (48.6)
Chronic sinusitis	178 (28.3)	64 (21.4)	114 (34.4)
Gastroesophageal reflux	149 (23.7)	49 (16.4)	100 (30.2)
Asthma controller medications			
Inhaled corticosteroid	492 (78.1)	261 (87.3)	231 (69.8)
Long-acting beta agonist	360 (57.1)	160 (53.5)	200 (60.4)
Montelukast	356 (56.5)	185 (61.9)	171 (51.7)
Omalizumab	20 (3.2)	6 (2.0)	14 (4.2)
Indoor exposures			
Cat	98 (15.6)	35 (11.7)	63 (19.0)
Dog	234 (37.1)	103 (34.4)	131 (39.6)

	All participants N = 630	Children 5–11 years N = 299	Adolescents 12–21 years N = 331
Tobacco smoke	113 (18.0)	33 (11.0)	80 (24.2)
Asthma-related healthcare utilization			
Unscheduled physician visit (past year)	424 (67.3)	222 (74.2)	202 (61.0)
Emergency department (past year)	300 (47.7)	169 (56.5)	131 (39.7)
Hospitalization (past year)	148 (23.5)	84 (28.1)	64 (19.3)
Hospitalization (ever)	348 (55.2)	154 (51.5)	194 (58.6)
Intensive care admission (ever)	175 (27.8)	75 (25.1)	100 (30.2)
Intubation for asthma (ever)	80 (12.7)	35 (11.7)	45 (13.6)

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Baseline RV/TLC and methacholine PC₂₀ values and absolute and relative change in FEV₁, FVC, FEV₁/FVC, stratified by the dose of albuterol at which maximum bronchodilation was obtained. Data represent the mean ± standard deviation.

Table 2.

Lung function measure	Children 5–11 years (N = 299)			Adolescents 12–21 years (N = 331)		
	360 mcg N = 136	540 mcg N = 143	720 mcg N = 20	360 mcg N = 121	540 mcg N = 179	720 mcg N = 31
Baseline RV/TLC (ratio) ¹	0.28 ± 0.07	0.28 ± 0.09	0.37 ± 0.11 ^{*,***}	0.26 ± 0.08	0.26 ± 0.10	0.36 ± 0.13 ^{*,***}
Baseline Methacholine PC ₂₀ (mg/mL) ²	3.60 ± 3.87	3.16 ± 4.30	1.22 ± 1.53 ^{*,***}	6.35 ± 8.73	4.43 ± 7.40	0.43 ± 0.29 ^{*,***}
Absolute change ¹						
FEV ₁ (% predicted)	11.2 ± 9.7	16.8 ± 12.7 [*]	17.8 ± 13.4 [*]	8.9 ± 7.6	14.1 ± 9.3 [*]	24.6 ± 13.9 ^{*,***}
FVC (% predicted)	6.1 ± 6.6	9.2 ± 10.1 [*]	12.3 ± 11.0 [*]	3.9 ± 5.7	6.1 ± 7.6 [*]	13.0 ± 13.6 ^{*,***}
FEV ₁ /FVC (% predicted)	6.0 ± 7.3	8.0 ± 8.9 [*]	6.3 ± 6.6	5.8 ± 6.0	8.8 ± 6.2 [*]	14.3 ± 12.4 ^{*,***}
FEF _{25–75} (% predicted)	45.0 ± 51.1	61.0 ± 57.7 [*]	70.0 ± 63.9 [*]	36.0 ± 41.7	52.9 ± 52.8 [*]	56.2 ± 46.7 [*]
Relative change ⁵						
FEV ₁ (% predicted)	14.0 ± 13.4	20.1 ± 19.7 [*]	22.7 ± 23.4 [*]	12.0 ± 13.3	18.9 ± 17.4 [*]	39.6 ± 28.7 ^{*,***}
FVC (% predicted)	6.3 ± 8.1	9.4 ± 11.3 [*]	13.2 ± 14.7 [*]	4.4 ± 6.6	6.6 ± 9.6	16.8 ± 23.0 ^{*,***}
FEV ₁ /FVC (% predicted)	7.2 ± 9.3	9.7 ± 10.9 [*]	7.9 ± 9.3	7.1 ± 7.9	11.3 ± 9.4 [*]	20.3 ± 18.5 ^{*,***}
FEF _{25–75} (% predicted)	80.2 ± 117.4	113.6 ± 136.1 [*]	118.1 ± 107.5	59.2 ± 80.1	108.3 ± 146.1 [*]	140.8 ± 132.4 [*]

* p<0.05 vs. 360 mcg.

*** p<0.05 vs. 540 mcg

¹ Children, 360 mcg, n = 40; 540 mcg, n = 36; 720 mcg, n = 8. Adolescents, 360 mcg, n = 40; 540 mcg, n = 53; 720 mcg, n = 8.

² Children, 360 mcg, n = 55; 540 mcg, n = 47; 720 mcg, n = 9. Adolescents, 360 mcg, n = 65; 540 mcg, n = 104; 720 mcg, n = 10.

Data were logarithmically transformed prior to analyses.

³ Relative change = ((post-bronchodilator value in liters – pre-bronchodilator value in liters)/pre-bronchodilator value in liters)*100

⁴ Absolute change = post-bronchodilator percent predicted value – pre-bronchodilator percent predicted value

Table 3.

Clinical features that distinguish participants who achieved maximal bronchodilation with 720 mcg albuterol. Data represent the mean ± standard deviation or the number of participants (%).

	Children 5–11 years (N = 299)			Adolescents 12–21 years (N = 331)		
	360 mcg N = 136	540 mcg N = 143	720 mcg N = 20	360 mcg N = 121	540 mcg N = 179	720 mcg N = 31
Asthma duration (years)	6.2 ± 3.0	6.7 ± 2.5	6.1 ± 3.3	11.1 ± 4.6	12.6 ± 4.3	12.7 ± 4.4*
Recurrent pneumonia	50 (36.8)	65 (45.5)	13 (65.0)*	51 (42.1)	93 (52.0)	17 (54.8)
Inhaled corticosteroid						
Any dose	112 (82.4)	130 (90.9)*	19 (95.0)*	79 (65.3)	127 (70.9)	25 (80.6)
High dose [†]	67 (49.3)	91 (63.6)*	13 (65.0)*	51 (42.1)	75 (41.9)	16 (51.6)
Long-acting beta agonist	61 (44.9)	86 (60.1)*	13 (65.0)*	70 (57.9)	109 (60.9)	21 (67.7)
Montelukast	77 (56.6)	92 (64.3)	16 (80.0)*	69 (57.0)	87 (48.6)	15 (48.4)
Tobacco smoke exposure	10 (7.4)	18 (12.6)	5 (25.0)*	26 (21.7)	43 (24.0)	11 (35.5)
Hospitalization (ever)	61 (44.9)	79 (55.2)	14 (70.0)*	67 (55.4)	100 (55.9)	27 (87.1)*,**
Hospitalization (past year)	34 (25.0)	43 (30.1)	7 (35.0)	21 (17.4)	32 (17.9)	11 (35.5)*,**
Intensive care admission (ever)	25 (18.4)	40 (28.0)	10 (50.0)*,**	36 (29.8)	47 (26.3)	17 (54.8)*,**
Intubation for asthma (ever)	17 (12.5)	14 (9.8)	6 (30.0)*,**	16 (13.2)	23 (12.8)	6 (19.4)
Composite Asthma Severity Index (CASI) score	7.9 ± 4.0	8.6 ± 3.6	10.2 ± 4.1*	7.6 ± 4.2	7.8 ± 4.2	10.1 ± 3.6***

* p < 0.05 vs. 360 mcg,

** p < 0.05 vs. 540 mcg

[†] As defined by Global Initiative for Asthma 2018 guidelines.¹

Table 4.

Association between albuterol dose response and outcome occurrence by 12 months.

	Adjusted odds ratio (95% confidence interval)		
	Exacerbation	ED visit	Hospitalization
Model 1 ¹			
540 mcg vs. 360 mcg	1.28 (0.87, 1.88)	1.13 (0.74, 1.73)	2.28 (1.07, 4.85)*
720 mcg vs. 360 mcg	2.65 (1.36, 5.17)*	2.70 (1.35, 5.38)*	4.93 (1.82, 13.41)*
Model 2 ²			
540 mcg vs. 360 mcg	1.29 (0.87, 1.90)	1.13 (0.73, 1.74)	2.57 (1.20, 5.52)*
720 mcg vs. 360 mcg	2.59 (1.32, 5.08)*	2.59 (1.29, 5.20)*	4.78 (1.73, 13.21)*
Model 3 ³			
540 mcg vs. 360 mcg	1.15 (0.77, 1.71)	0.97 (0.62, 1.52)	2.26 (1.04, 4.90)*
720 mcg vs. 360 mcg	2.19 (1.10, 4.34)*	2.12 (1.03, 4.32)*	3.87 (1.39, 10.80)*
Model 4 ⁴			
540 mcg vs. 360 mcg	1.07 (0.71, 1.60)	0.93 (0.59, 1.45)	1.98 (0.91, 4.34)
720 mcg vs. 360 mcg	2.10 (1.05, 4.20)*	2.05 (1.01, 4.20)*	3.55 (1.25, 10.10)*

* p < 0.05

¹ Adjusted for age group² Adjusted for age group and demographic features (sex, race, ethnicity)³ Adjusted for age group, demographic features and ICS use⁴ Adjusted for age group, demographic features, ICS use, and baseline airflow obstruction