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Authors
Coverstone, Andrea M
Bacharier, Leonard B
Wilson, Bradley S
et al.

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Clinical significance of the bronchodilator response in children with severe asthma

Andrea M. Coverstone, MD[1], **Leonard B. Bacharier, MD**[1], **Bradley S. Wilson, MA**[1], **Anne M. Fitzpatrick, PhD**[2], **W. Gerald Teague, MD**[3], **Wanda Phipatanakul, MD, MS**[4], **Sally E. Wenzel, MD**[5], **Benjamin M. Gaston, MD**[6], **Eugene R. Bleecker, MD**[7], **Wendy C. Moore, MD**[8], **Sima Ramratnam, MD**[9], **Nizar N. Jarjour, MD**[9], **Ngoc P. Ly, MD, MPH**[10], **John V. Fahy, MD, MSc**[10], **David T. Mauger, PhD**[11], **Kenneth B. Schechtman, PhD**[1], **Huiqing Yin-DeClue, PhD**[1], **Jonathan S. Boomer, PhD**[1], **Mario Castro, MD, MPH**[1]

[1]Washington University School of Medicine in Saint Louis, St. Louis, MO

[2]Emory University School of Medicine, Atlanta, GA

[3]University of Virginia School of Medicine, Charlottesville, VA

[4]Boston Children's Hospital, Boston, MA

[5]University of Pittsburgh School of Medicine, Pittsburgh, PA

[6]Rainbow Babies and Children's Hospital, Cleveland, OH

[7]University of Arizona, Tucson, AZ

[8]Wake Forest University School of Medicine, Winston-Salem, NC

[9]University of Wisconsin School of Medicine, Madison, WI

[10]University of California, San Francisco School of Medicine, San Francisco, CA

[11]Pennsylvania State University School of Medicine, Hershey, PA

Abstract

Background: Our objective was to determine those characteristics associated with reversibility of airflow obstruction and response to maximal bronchodilation in children with severe asthma through the Severe Asthma Research Program (SARP).

Methods: We performed a cross-sectional analysis evaluating children ages 6–17 years with non-severe (NSA) and severe asthma (SA). Participants underwent spirometry before and after 180 μg of albuterol to determine reversibility (≥12% increase in FEV_1). Participants were then given escalating doses up to 720 μg of albuterol to determine their maximum reversibility.

Results: We evaluated 230 children (n=129 SA, n=101 NSA) from 5 centers across the U.S. in the SARP I and II cohorts. SA (OR 2.08, 95%CI 1.05 to 4.13), second-hand smoke exposure (OR 2.81, 95%CI 1.23 to 6.43), and FeNO (OR 1.97, 95%CI 1.35 to 2.87) were associated with increased odds of airway reversibility after maximal bronchodilation, while higher pre-

Corresponding Author: Andrea M Coverstone, 1 Children's Place, Campus Box 8116, Saint Louis, MO 63110, Telephone: (314)454-2694, Fax: (314)454-2515, acoverstone@wustl.edu.

bronchodilator FEV_1% predicted (OR 0.91, 95%CI 0.88 to 0.94) was associated with decreased odds. In an analysis using the SARP III cohort (n=186), blood neutrophils, IgE and FEV_1% predicted were significantly associated with bronchodilator reversibility. In addition, children with bronchodilator response have greater healthcare utilization. Bronchodilator reversibility was associated with reduced lung function at enrollment and one-year follow-up though less decline in lung function over one year compared to those without reversibility.

Conclusions: Lung function, that is FEV_1 % predicted, is a predictor of bronchodilator response in children with asthma. Additionally, smoke exposure, higher FeNO or IgE level, and low peripheral blood neutrophils are associated with greater likelihood of bronchodilator reversibility. Bronchodilator response can identify a phenotype of pediatric asthma associated with low lung function and poor asthma control.

Keywords

Asthma; pediatrics; bronchodilator response

Introduction

The presence of reversible airflow obstruction in response to bronchodilators is one major criterion used to diagnose asthma in children. A significant bronchodilator response in asthma is typically considered a 12% increase in FEV_1 percent predicted following 2–4 puffs (180–360μg) of albuterol via MDI or 2.5–5mg of nebulized albuterol[1]. The Severe Asthma Research Program (SARP) has conducted multiple investigations that have helped characterize severe asthma in children[2,3]. Using a technique of maximal bronchodilator testing with escalating doses of albuterol, children in SARP with severe asthma (SA) had a significant improvement in their FEV_1 following albuterol; however, their best FEV_1 remained lower than children with mild-to-moderate asthma[3]. Furthermore, airflow limitation, defined as a reduction in FEV_1/FVC, improved after maximal bronchodilation in both participants with SA and mild-to-moderate asthma, but the participants with SA had a larger increase in FEV_1/FVC% predicted than the mild-to-moderate group. Despite these studies, the risk factors associated with a significant bronchodilator response within children with SA and its clinical implications have not been fully evaluated.

In this study, we examined data from pediatric participants enrolled in the SARP I and II cohorts (2003–2011) and SARP III cohort (2012-present) who underwent maximal bronchodilation testing in order to determine factors that predict bronchodilator response in children with SA. We hypothesized that children with SA would be more likely to demonstrate bronchodilator reversibility (≥12% improvement in FEV_1) of airflow limitation than those with mild-to-moderate asthma and would be less likely to reach a plateau for reversibility following maximal bronchodilation. In addition, we evaluated whether those with a bronchodilator response had greater morbidity and healthcare utilization.

Methods

Subjects

We examined data from children enrolled in the National Heart, Lung and Blood Institute supported SARP I (2003–2006) and II (2006–2011) across 5 centers in the United States (Emory University, University of Pittsburgh, University of Virginia, Wake Forest University and Washington University in Saint Louis) and within 7 centers for SARP III (Emory University, University of Pittsburgh, University of Virginia/Rainbow Babies and Children's Hospital, University of Wisconsin-Madison, Boston Children's, University of California San Francisco, and Washington University in Saint Louis). Participants were between 6 and 17 years of age with physician-diagnosed asthma, and had to demonstrate ≥12% FEV_1 increase following bronchodilator administration (180 mcg albuterol) or evidence of bronchial hyperresponsiveness by methacholine challenge at time of enrollment. Participants were characterized as having either SA, as defined by 2000 American Thoracic Society (ATS) workshop criteria (SARP I/II)[4] and 2014 European Respiratory Society/ATS consensus guidelines (SARP III)[5], or non-severe asthma (NSA). For children taking inhaled corticosteroids (ICS), the dose had to be stable for at least 6 months prior to characterization. We defined high-dose ICS as ≥440μg per day of fluticasone or equivalent ICS for children less than 12 years of age and ≥880μg per day of fluticasone or equivalent ICS for children 12 to 17 years of age. Site-specific IRB approval was obtained for all locations and parents/legal guardians provided informed consent prior to enrollment.

Characterization

For the baseline characterization visit, all participants underwent physical examination, provided medical and asthma history, and completed asthma questionnaires[6]. We obtained peripheral blood to measure total white blood cells, eosinophils, neutrophils, and serum IgE levels. We performed percutaneous skin testing for 16 different allergens (SARP I/II) or serum-specific allergen testing (SARP III; ImmunoCAP assay). Fractional exhaled nitric oxide (FeNO) measurements were obtained via offline (n = 64) or online (n = 144) methods in SARP I/II and online measures were used in SARP III (NIOX or Vero, Circassia, Chicago, IL). Pulmonary function tests were performed during this baseline characterization visit.

Pulmonary function tests

Prior to performing spirometry, participants withheld short-acting bronchodilators for a minimum of 4 hours, long-acting beta-agonists (LABA) for a minimum of 12 hours, and leukotriene antagonists for a minimum of 24 hours. We allowed participants to continue use of ICS therapy prior to spirometry as long as they were not in combination with a LABA. An Aerochamber® (Monaghan Medical Corporation, Plattsburg, NY) or similar device was used with all albuterol administration.

For maximum bronchodilator testing, spirometry was repeated after 180, 360, 540, and up to a maximum 720μg of albuterol sulfate. If FEV_1 differed by less than 5% between 360 and 540μg of albuterol, then the final dose of albuterol (720μg) was not given. We calculated percent difference using the following formula: percent difference = ($FEV_1^{6\ puffs}$–

$FEV_1^{4\ puffs}$)/$FEV_1^{4\ puffs}$ x 100. The participants' best FEV_1, FVC, FEV_1/FVC, and $FEF_{25–75}$ values and percent predicted from 3 reproducible maneuvers were recorded fifteen minutes after each bronchodilation. The percent predicted values were calculated using standard reference equations[7].

For purposes of this study, we define bronchodilator (BD) reversibility as a 12% or greater increase in FEV_1 from baseline, using the relative difference (FEV_1^{postBD}-FEV_1^{preBD}/FEV_1^{preBD}). The absolute difference (FEV_1^{postBD}-FEV_1^{preBD}) was also calculated and reported separately in the Supplement for the SARP III cohort.

Statistical Analysis

Independent samples *t*-tests of continuous variables and Chi-square tests of categorical variables were performed to compare characteristics between asthma groups. Fisher Exact tests were used as appropriate. To compare those with and without a bronchodilator response, we used 2-group *t*-tests for means and chi-square for proportions. Kruskal-Wallis was used as appropriate. Analysis of covariance (ANCOVA) was performed to determine if there was a difference in the change in lung function between the two asthma severity groups with baseline lung function adjusted as an independent variable. Logarithmic transformation was applied to baseline FEV_1/FVC and non-parametric rank ANCOVA was used for the analysis of maximum percent change in FEV_1 post-bronchodilator due to non-normal distribution. Spearman's correlations were used to determine the relationship between variables of interest. When comparing characteristics between those with and without a bronchodilator response, those variables with, P values <0.1 in the univariate analysis were included in the multivariate logistic regression for reversibility. Methacholine PC_{20} was excluded from multivariate modeling because a large proportion of participants were missing this data. Due to FeNO being collected in both offline and online methods, these two variables were combined and log transformed for use in multivariate analysis. Multivariate analysis was performed with and without log transformed FeNO because of the variability in measurement and that 12 subjects were missing this value. Stepwise procedure was used to identify the factors independently associated with reversibility. Odds ratio (OR) and its corresponding 95% confidence interval were reported. A value of $P<0.05$ was considered significant. All analyses were performed with the SAS 9 software (SAS Institute, Cary, NC).

Replication Analysis

Given the longitudinal protocol in SARP III, we wanted to replicate the analysis of the SARP I-II cohort to confirm our findings in a large, similar cohort, as well as determine long-term clinical implications of the baseline findings. All analyses performed on the SARP I-II cohort were repeated for the SARP III cohort.

Results

SARP I-II Results

We first analyzed data from 230 participants, 129 SA participants and 101 NSA participants, enrolled in SARP I-II. Baseline demographics and characteristics of children with SA and NSA are compared in Table 1.

Children with SA had greater pre-bronchodilator (pre-BD) airflow limitation and obstruction compared to children with NSA (E-Table 1). These measures remained lower in SA than NSA despite maximal bronchodilation; however, the maximum relative increase in FEV_1 was greater in SA than NSA (FEV_1% increase 22.2±20.1 vs 12.8±11.1, p<0.001). For all children (n=220), the average bronchodilator response after 180μg of albuterol was 11.8%, and increased to 18.2% with maximal bronchodilation. After 180μg of albuterol, children with NSA on average increased their FEV_1 by 8.4%, while children with SA increased by 14.4% (p=0.005; E-Table 1). A plateau of reversibility was not achieved in many, as both groups continued to increase FEV_1 with escalating doses of albuterol; however, the increase was greater in participants with SA than NSA (Figure 1a and 1b). This difference between groups was not statistically significant after the maximal dose, however, only a small number (n=25) of participants required the highest albuterol dose. There was no difference in the dose of albuterol required to reach 12% reversibility among asthma severity groups (p=0.74) (E-Table 2).

There was a tendency for males to have greater airflow obstruction, but we found no statistically significant difference between males and females in pre-BD FEV_1% predicted (89.2±17% vs 93.6±18%, p = 0.07). There was no significant difference in bronchodilator response for maximal FEV_1% predicted (103.5±15% vs 107.6±16%, p=0.051) or maximum percent increase in FEV_1% predicted (18.1±18%vs 18.2±17%, p=0.89) between males and females. Males, however, demonstrated greater airflow limitation with lower FEV_1/FVC ratios before (0.76±0.1 vs 0.78±0.1, p=0.03) and after maximal bronchodilation (0.84±0.08 vs 0.87±0.07, p<0.001).

There was a strong positive correlation between pre-BD lung function and both maximum FEV_1% predicted and maximal increase in FEV_1 (Figure 2). After adjusting for pre-BD FEV_1% predicted, gender and presence of a positive skin test, there was a significant association between the maximum increase in FEV_1% predicted and SA (p=0.001).

Clinical Implications of Bronchodilator Response—Among all children, 112 of 220 (51%) had a significant increase in FEV_1 of at least 12% following maximal bronchodilator testing. Only 6 of the 112 (5%) did not achieve a 200mL difference in FEV_1, however, we chose to keep them in the analysis (all had a change of at least 130mL and absolute volume change is of less significance in children with smaller lung capacity). Eighty of the 112 participants (71.4%) with bronchodilator reversibility had SA while 32 (28.6%) had NSA. Participants with a 12% relative bronchodilator response had longer duration of asthma, greater atopy, more smoke exposure and greater healthcare utilization (Table 2).

Among children with SA, those that demonstrated bronchodilator reversibility were older, had lower lung function, higher FeNO and peripheral blood eosinophils, longer duration of asthma, and more second-hand smoke exposure compared to those without a bronchodilator response (E-Table 3).

In a multivariate logistic regression model, SA was associated with significantly increased odds of airway reversibility after maximal bronchodilation, as was second-hand smoke exposure (Table 3a). Higher pre-BD FEV_1% predicted was associated with decreased odds of reversibility in children with and without SA (Table 3a and 3c). With addition of FeNO to the model, both FeNO and pre-BD FEV_1% were predictive of reversibility (Table 3b and 3c). While FeNO (log transformed) was correlated with asthma severity ($r=0.15$, $p=0.04$), bronchodilator reversibility ($r=0.34$, $p<0.0001$), and pre-BD FEV_1% predicted ($r=-0.24$, $p=0.0007$), there was no correlation of FeNO with second-hand smoke exposure ($r=0.12$, $p=0.08$). There is a weak but statistically significant correlation of smoke exposure with reversibility ($r=0.18$, $p=0.01$); though we found no correlation of the amount of smoke exposure (days/week or hours/day exposed to smoke) with reversibility ($p>0.05$).

A separate analysis using the absolute change in FEV_1 after bronchodilator demonstrated FeNO and pre-BD FEV_1% predicted remained significant predictors of bronchodilator response (E-table 5a and 5b). There is a strong correlation between the relative and absolute change in maximal FEV_1% predicted (E-Figure 1).

Replication analysis using SARP III Pediatric cohort

We then replicated the analysis of bronchodilator response in 186 children enrolled in SARP III - 109 children with SA and 77 children with NSA. In general, children enrolled in SARP III had less severe asthma than SARP I-II as demonstrated by a lower prevalence of intubation (9.2% vs 25%, $p=0.002$), ER visits in the prior 12 months (68.8% vs 80.5%, $p=0.04$), and less exposure to smoke (13.5% vs 22.3%, $p=0.022$). One exception was more participants in SARP III had at least 3 or more steroid bursts in the prior year (76.4% vs 57.8% $p=0.003$) compared to SARP I-II.

Differences in characteristics between those with and without a bronchodilator response in SARP III are shown in E-Table 4. Within this cohort, percent blood neutrophils and pre-BD FEV_1 % predicted were significant predictors of bronchodilator reversibility in all children and those with SA (Table 4a and 4b), with lower lung function and lower neutrophil percentage indicative of greater bronchodilator response. In addition, IgE was noted as a predictor in all children with asthma (see Table 4a). When using an absolute difference in FEV_1 % predicted, significant predictors included SA, aeroallergen sensitivity, FeNO, and hospital admission in the previous year (E-Table 4c and 4d).

Given the prospective nature of the SARP III cohort, we wanted to determine if having a significant bronchodilator response at enrollment (baseline) correlated with clinical outcomes one year later (n=140). For participants with reversibility at baseline, their lung function was lower at baseline (FEV_1 % predicted 84.8 ± 15.2 vs 96.3 ± 17.0, $p<0.0001$) and at one-year follow-up (FEV_1%predicted 83.3 ± 15.8 vs 94.0 ± 13.1, $p<0.001$) compared to those without. Participants with reversibility had less decline in lung function at one-year

follow-up compared to those without reversibility (absolute change in FEV_1%: 0.3±13.3 vs −5.1±10.1%, p=0.01). There was a negative correlation between having a bronchodilator response at baseline and lung function at one-year (FEV_1/FVC r=−0.49, p<0.001 and FEV_1 r=−.39, p<0.001), but a positive correlation between baseline reversibility and change in lung function over one year (r=0.29, p=0.0003).

The Asthma Control Test (ACT) score was lower at the one year follow-up for children with a bronchodilator response at baseline compared to those without reversibility (19.1 vs 20.6, p=0.04). However, there were no other differences in measures of asthma control or severity.

Discussion

In this large study of SA in children, we clarify the relationship between pre-BD lung function and the maximal achievable lung function following bronchodilation. Children with SA demonstrated greater pre-BD airflow obstruction and bronchodilator reversibility than NSA. This study expands upon our earlier findings within the pediatric SARP cohort,[2,3] in that we found that SA, FeNO, and lung function were significantly associated with maximal bronchodilator reversibility. Interestingly in this prospective longitudinal cohort, bronchodilator reversibility was associated with reduced lung function at baseline and at one-year follow-up though less decline in lung function over one year compared with those without reversibility.

Our study confirms the findings described by Yancey, et al. of an association between lung function and reversibility[8]. In a retrospective review of 30,816 participants with asthma, baseline FEV_1% predicted was inversely related to bronchodilator reversibility. In contrast, Ouksel, et al. determined that the response to bronchodilator was greater when the predicted FEV_1 was larger, however, this was only when using absolute values and not percent predicted and only 15 of 30 participants were children[9]. Furthermore, this study did not address the response to escalating doses of bronchodilator. Our findings along with these previous studies stress the importance of taking into account pre-bronchodilator lung function when examining the bronchodilator response in participants with asthma.

We found that a diagnosis of SA, second-hand smoke exposure, FeNO and pre-BD lung function were strongly associated with a bronchodilator response in children with asthma. Sorkness, et al. examined maximal bronchodilator response in adults to determine predictors of persistent airflow obstruction[10]. They found that severe asthma, male gender and increasing age were independent predictors of lower maximal FEV_1% predicted. Surprisingly, we did not find that gender or age was a predictor of reversibility in our pediatric cohort. While males demonstrated more airflow limitation, the response to bronchodilator was not different from females.

Several studies have examined the effects of in-utero, perinatal and second-hand smoke exposure on lung function, development of asthma, and response to therapy[11–16]. Smoke exposure may increase bronchial reactivity[11] and has been shown to alter responses to bronchodilators as well as reduce symptoms and need for bronchodilation after treatment with leukotriene receptor antagonists[12,13]. It is unclear whether smoke exposure alters

bronchodilator responsiveness through alterations in airway inflammation, smooth muscle reactivity or remodeling. The association of smoke exposure and bronchodilator response was not replicated in SARP III; however, smoke exposure was significantly lower in SARP III compared to SARP I-II.

As in our study, FeNO has been shown to correlate with bronchodilator response in adults[17] as well as a small cohort of children[18]. Another study showed a relationship between FeNO and lung function in both asthmatic children and children with allergic rhinitis[19]; however, others have found that this association was only in seen in children with atopic disease[20]. Indeed, most of our patients were atopic which may explain our ability to detect such a relationship. Addition of FeNO to our model removed the significant effect of smoke exposure on bronchodilator response. Smoke exposure may have an effect on FeNO levels thus there may be some interaction between these variables we did not detect in our correlations ($p=0.08$)[21,22]. FeNO is considered a marker of airway inflammation, typically eosinophilic or Type 2 inflammation. Individuals with elevated FeNO as well as IgE levels are more likely to respond with increases in FEV_1 upon treatment with ICS[23,24]. It is possible that FeNO can help identify a phenotype of asthma with less fixed airflow limitation and greater response to asthma treatment. In COPD, neutrophilic inflammation is associated with nonreversible airflow limitation while eosinophilic inflammation, though less common, is associated with improvement in lung function with bronchodilators[25,26]. In the SARP III cohort, lower peripheral blood neutrophil percent was predictive of a maximal bronchodilator response, perhaps, again, identifying a group less at risk of fixed airflow obstruction.

Several studies have examined the relationship between bronchodilator response and lung function. Vonk et al. showed that fixed airflow obstruction, defined as FEV_1 <80% predicted and bronchodilator response <9% following 800μg salbutamol, after 21–33 years of follow-up was more likely when patients had less bronchial hyperreactivity and reversibility at the initial visit, suggesting lack of bronchodilator response may in fact be detrimental for future lung function[27]. It is unclear whether airway remodeling is associated with fixed airflow obstruction[28,29]. In biopsies of adults with SA, airway wall area and thickness percentage were positively correlated with a response to bronchodilator, though bronchodilator response itself was associated with baseline lung function and SA[30]. Tillie-Leblond et al. found that in children with persistent symptoms and obstruction (FEV_1 <80% predicted) there was an increase in airway smooth muscle and vascular density compared to children with persistent symptoms but normal lung function[28]. We are unable to conclude whether a response to bronchodilators, or lack thereof, is related to underlying pathological mechanisms such as airway remodeling in children.

Longitudinal assessment of 1,041 children through the Childhood Asthma Management Program (CAMP) showed that bronchodilator response at baseline was predictive of higher future level of lung function in children with mild-to-moderate asthma, and this association was strongest in those receiving ICS compared to nedocromil or placebo. While this suggests a positive association for bronchodilator response, the conclusions of this study were aimed at the treatment-specific effects and suggests children with bronchodilator response may better respond to ICS than those without[31]. Indeed, bronchodilator response

can be predictive of sustained improvement in FEV_1 after initiation of ICS[23]. Additionally, CAMP demonstrated that those who consistently had a bronchodilator response at each of their yearly follow-up visits over 4 years, had lower baseline FEV_1, higher IgE levels, and less treatment with ICS compared to those who did not[32]. Our data are consistent with these findings, indicating those with a bronchodilator response had lower lung function at baseline and one year; however, they had less decline in lung function over time than those without. While it is possible, this could be related to regression to the mean for lung function, we believe that the bronchodilator response is both an indicator of a more severe asthma phenotype with lower lung function and worse asthma control, as well as an indicator of those more likely to respond to treatment.

We also found that bronchodilator response is associated with increased healthcare utilization, greater oral corticosteroids bursts and hospitalizations at baseline. In CAMP, children with a consistent bronchodilator response over 4 years were more likely to have hospitalizations, prednisone bursts, missed school days and nocturnal awakenings at baseline as well as more exacerbations in the following year compared to those children without[32]. Hefler, et al found that, in 246 subjects 13 years and older with asthma, a bronchodilator response was associated with lower baseline lung function and ACT scores, and a positive correlation with change in ACT scores and FEV_1 after albuterol. We did not find a significant difference in healthcare utilization at one-year follow-up in those with a bronchodilator response, however, asthma control scores were worse in this group.

Finally, the use of a relative 12% change in FEV_1 as a threshold for a significant bronchodilator response has been called into question[33,34]. We found that after 180 μg of albuterol, the average response in SA met the ATS criteria threshold for significance, while that of NSA was lower at 8.4% and only met criteria after maximal bronchodilation. Our study suggests that while a 12% bronchodilator response may be expected in children with SA after 180 μg of albuterol, children with mild-to-moderate asthma may need higher doses to reach that threshold. Alternatively, we could consider a lower threshold in that subgroup, given that those with SA continue to achieve improvements in FEV_1 with higher albuterol doses, but the increase in FEV_1 is smaller in NSA.

We recognize our study has several limitations. First, we recognize that not all findings between SARP I-II and SARP III were replicated and that may have been driven by differences in the cohorts, such as asthma severity and smoke exposure. Additionally, using an absolute bronchodilator response versus a relative response may be controversial, however we found using the absolute change did not significantly alter our overall conclusions. We recognize the limitations of stepwise logistic regression and the potential to impact the variable selection process[35]. As our study is inherently exploratory, were are unable to use the preferred causal methods of prediction. Further research with different data sets would be required to validate the results of the stepwise procedure. We also recognize that children's airways are a dynamic entity and that we cannot make conclusions regarding long-term outcomes. Others have demonstrated the utility of multiple measurements, e.g. FeNO combined with bronchodilator response when finding predictors for loss of asthma control, likely of greater importance in the growing child[36].

In this study, we demonstrated that lung function, in particular FEV_1 % predicted, is a significant predictor of the response to bronchodilator in children with asthma, and that smoke exposure, higher FeNO and IgE level, and lower peripheral blood neutrophils, may also identify those most likely to have reversibility of airflow obstruction following maximal bronchodilation. Maximal bronchodilator response is associated with more asthma exacerbations and hospitalizations at baseline as well as worse lung function and asthma control at one year of follow-up. We have identified a bronchodilator phenotype of pediatric asthma that is associated with worse health outcomes. Further prospective evaluation with ultra-low dose CT chest imaging[37] may help determine the pathophysiologic role of airway remodeling in these children with and without a bronchodilator response. Newer asthma therapies including biologics might alter this process in children with SA but this remains to be proven.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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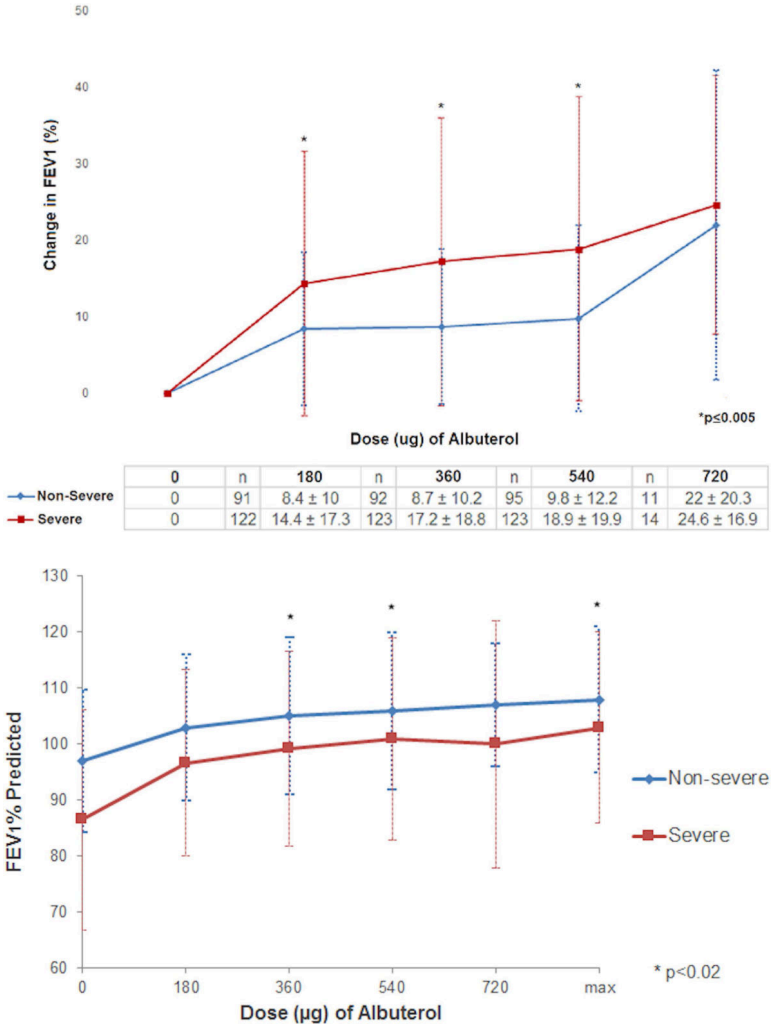
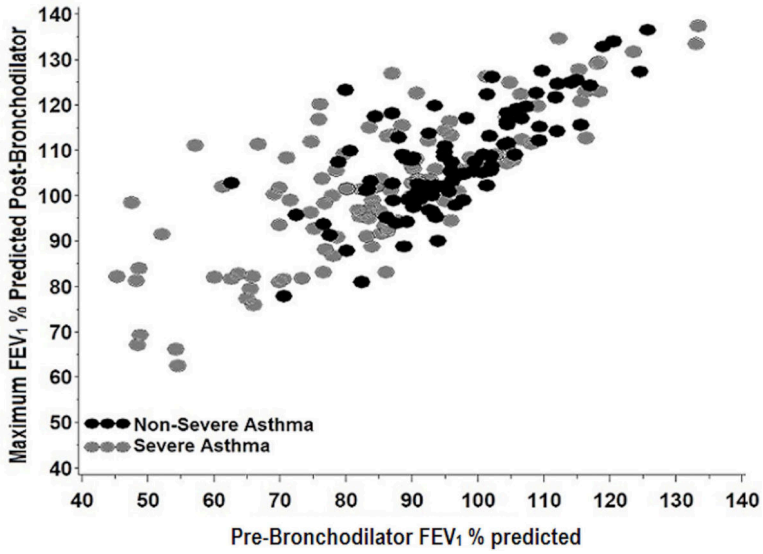


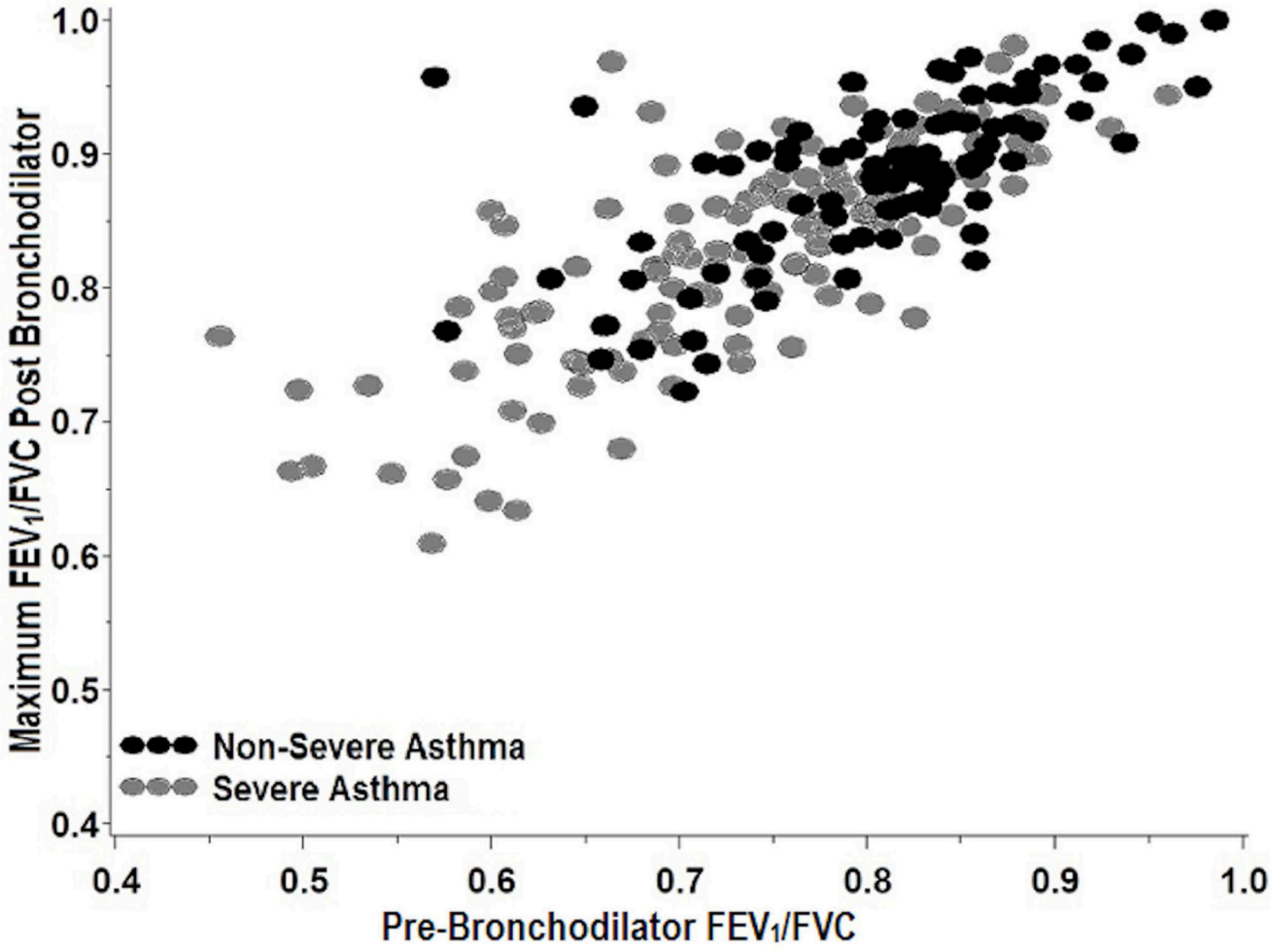
	0	n	180	n	360	n	540	n	720
Non-Severe	0	91	8.4 ± 10	92	8.7 ± 10.2	95	9.8 ± 12.2	11	22 ± 20.3
Severe	0	122	14.4 ± 17.3	123	17.2 ± 18.8	123	18.9 ± 19.9	14	24.6 ± 16.9

Figure1a:

Cumulative percent change in FEV1 for increasing amounts of bronchodilator for patients with asthma enrolled in SARP I-II.

1b: Maximal lung function following bronchodilator in children with asthma enrolled in SARP I-II.





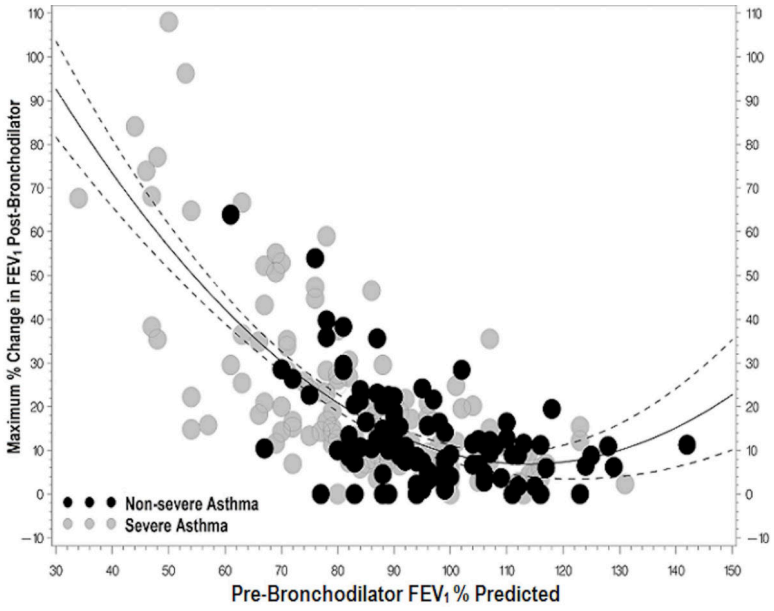


Figure2a.

Maximum FEV1% predicted following bronchodilators shows a strong positive correlation with pre-BD FEV1% predicted ($r=0.81$, $p < 0.001$). Participants with lower pre-BD lung function have lower maximal FEV1% predicted while participants with higher pre-BD lung function maintain higher maximal FEV1% Predicted.

2b. Maximum FEV1/FVC (log transformed) following bronchodilators shows strong correlation with pre-BD FEV1/FVC (log transformed) ($r=0.77$, $p < 0.0001$). Participants with greater airflow limitation after maximal bronchodilation have greater pre-BD airflow limitation.

2c. Maximum percent change in FEV1 following bronchodilators shows moderate negative correlation with pre-BD FEV1% predicted using quadratic fit ($r=-0.55$, $p < 0.001$). Participants with lower pre-BD lung function had a greater bronchodilator response than participants with higher pre-BD lung function.

Table 1.

Demographics and clinical characteristics of children with asthma enrolled in SARP I-II

	Non-severe Asthma (n=101)	Severe Asthma (n=129)	p value
Demographics			
Age enrollment, yr	11.5 ± 3.1	11.8 ± 3.0	0.43
Duration of asthma, yr	7.6 ± 4.4	9.8 ± 3.4	<0.001
Age of asthma onset, yr	3.9 ± 3.4	2.0 ± 2.3	<0.001
Female, n (%)	45 (44.6)	54 (41.9)	0.68
African-American, n (%)	51 (50.5)	86 (66.7)	0.01
Second-hand smoke exposure, n (%)	22 (22.0)	29 (22.5)	0.93
Medical history			
BMI Z-score	0.95 ± 0.99	0.88 ± 1.20	0.65
History of acute/recurrent sinusitis, n (%)	42 (42.0)	60 (46.9)	0.46
History of GERD, n (%)	10 (10.5)	52 (44.8)	<0.001
History of allergies, n (%)	90 (92.8)	119 (93.7)	0.79
History of skin rash, n (%)	50 (49.5)	78 (60.5)	0.097
Family History			
Asthma (1st degree relative), n (%)	70 (70.7)	92 (71.9)	0.85
Eczema (1st degree relative), n (%)	50 (50.0)	60 (47.2)	0.57
Clinical characteristics			
Positive skin reaction to allergens, n (%)	62 (72.9)	89 (83.2)	0.09
# of positive skin reactions	2.65 ± 2.63	3.48 ± 2.73	0.02
% neutrophil in peripheral blood	48.9 ± 12.7	44.7 ± 15.1	0.12
% eosinophil in peripheral blood	4.95 ± 3.50	6.64 ± 4.85	0.004
Total IgE in blood, IU/mL	544 ± 1334	708 ± 1187	0.02
Offline eNO ppb [N=64]	9.62 ± 5.51	14.6 ± 9.07	0.009
Online eNO ppb [N=144]	39.6 ± 44.4	41.4 ± 35.2	0.80
PC20, mg/dl [N=123]	3.78 ± 5.09	2.66 ± 4.66	0.03
FEV_1 <80% Predicted, n (%)	6 (6.3)	42 (33.6)	<0.001
Persistent airway obstruction*, n (%)	12 (12.0)	40 (31.0)	0.001
Healthcare utilization			
On high-dose ICS, n (%)	12 (11.9)	122 (97.6)	<0.001
On systemic corticosteroids, n (%)	0	21 (16.3)	<0.001
More than 3 OCS bursts in last year, n (%)	15 (14.9)	74 (57.8)	<0.001
ER/urgent care for asthma in past year, n (%)	44 (43.6)	114 (88.4)	<0.001
Admission for respiratory disorder in past year, n (%)	10 (10.0)	76 (59.4)	<0.001
ICU for asthma in past year, n (%)	4 (4.0)	36 (28.1)	<0.001
History of intubation for asthma, n (%)	9 (8.9)	32 (25.0)	0.002
Use of anti-IgE therapy, n (%)	0	10 (7.8)	0.003

*Persistent airway obstruction is defined by baseline FEV_1 <80 % predicted or diurnal PEF variability >20% over 2 weeks.

Table 2.

Clinical characteristics associated with bronchodilator reversibility in children with asthma enrolled in SARP I and II

	FEV_1 increase <12% (n=108)	FEV_1 increase ≥12% (n=112)	p-value
Demographics			
Age enrollment, yr	11.5 ± 3.1	12.0 ± 2.9	0.19
Duration of asthma, yr	8.1 ± 4.3	9.7 ± 3.6	0.004
Age of asthma onset, yr	3.3 ± 3.2	2.3 ± 2.5	0.008
Female, n (%)	47 (43.5)	47 (42.0)	0.82
African-American, n (%)	59 (54.6)	73 (65.2)	0.11
Second-hand smoke exposure, n (%)	15 (14.0)	35 (31.3)	0.002
Severe asthma, n (%)	45 (41.7)	80 (71.4)	<0.001
Clinical characteristics			
Positive skin reaction to allergens, n (%)	69 (75.8)	75 (81.5)	0.35
# of positive skin reactions	2.6 ± 2.5	3.6 ± 2.9	0.01
% eosinophil in peripheral blood	4.9 ± 3.5	6.9 ± 4.9	0.002
% neutrophil in peripheral blood	46.9 ± 14.1	45.3 ± 14.7	0.48
Total IgE in blood, IU/mL	607 ± 1476	692 ± 1065	0.02
Offline eNO ppb [N=64]	10.5 ± 6.9	15.4 ± 8.9	0.005
Online eNO ppb [N=144]	31.9 ± 40.8	47.9 ± 38.4	0.001
PC20, mg/dl [N=123]	2.96 ± 3.78	2.78 ± 4.77	0.04
Pre-bronchodilator FEV_1 % predicted	101 ± 13	81 ± 16	<0.001
Healthcare utilization			
Use of high-dose ICS n (%)	50 (46.7)	79 (72.5)	<0.001
More than 3 OCS bursts in last year, n (%)	33 (30.6)	51 (46.0)	0.02
ER/urgent care for asthma in past year, n (%)	69 (64.5)	83 (74.8)	0.098
Admission for respiratory disorder in past year, n (%)	52 (48.2)	77 (68.8)	0.002
ICU for asthma in the past year, n (%)	19 (17.8)	19 (17.0)	0.88
History of intubation for asthma, n (%)	16 (14.8)	23 (20.7)	0.25

Table 3.

Predictors of bronchodilator reversibility in children with asthma enrolled in SARP I-II

a. Predictors of 12% relative bronchodilator reversibility in all children with asthma (n=220)

Variables	Odds ratio	95% CI	p value
Exposure to second-hand smoke	2.81	1.23 to 6.43	0.014
Severe asthma	2.08	1.05 to 4.13	0.036
Pre-bronchodilator FEV_1 % predicted	0.91	0.88 to 0.94	<0.001

b. Predictors of 12% relative bronchodilator reversibility in *all* children with asthma, including exhaled nitric oxide (n=200)

Variables	Odds ratio	95% CI	p value
Log FeNO *	1.97	1.35 to 2.87	0.0005
Pre-bronchodilator FEV_1 % predicted	0.91	0.88 to 0.94	<0.001

c. Predictors of 12% relative bronchodilator reversibility in children with *severe* asthma, including exhaled nitric oxide (n=117)

Variables	Odds ratio	95% CI	p value
Log FeNO *	3.045	1.624 to 5.709	0.0005
Pre-bronchodilator FEV_1 % predicted	0.91	0.87 to 0.95	<0.001

* offline and online eNO combined

Variables included: severe asthma, asthma duration, age of asthma onset, #positive skin tests, pre-BD FEV_1 (L), pre-BD FEV_1% predicted, second-hand smoke exposure, % blood eosinophils, IgE, 3+OCS burst in last year, ER/Urgent care in past year, admission in past year

* offline and online eNO combined

Variables included: severe asthma, asthma duration, age of asthma onset, #positive skin tests, pre-BD FEV_1 (L), pre-BD FEV_1% predicted, second-hand smoke exposure, % blood eosinophils, IgE, 3+OCS burst in last year, ER/Urgent care in past year, admission in past year, FeNO

* offline and online eNO combined

Variables included: asthma duration, age at enrollment, pre-BD FEV_1 (L), pre-BD FEV_1% predicted, second-hand smoke exposure, % blood eosinophils, ICU admission, FeNO

Table 4.

Predictors of bronchodilator reversibility in children with asthma enrolled in SARP III

a. Predictors of 12% relative bronchodilator reversibility in *all* children with asthma

Variables	Odds ratio	95% CI	p value
Blood neutrophil %	0.97	0.94 to 0.997	0.031
Total serum IgE	1.00	1.00 to 1.001	0.036
Pre-bronchodilator FEV_1 % predicted	0.95	0.93 to 0.97	<0.0001

b. Predictors of 12% relative bronchodilator reversibility in children with *severe* asthma

Variables	Odds ratio	95% CI	p value
Blood neutrophil %	0.95	0.92 to 0.98	0.005
Pre-bronchodilator FEV_1 % predicted	0.95	0.93 to 0.99	0.004

Variables included: race, second hand smoke status, asthma severity, % blood eosinophils (log), % blood neutrophils (log), total IgE (log), FeNO, pre-BD FEV_1% predicted, ER/Urgent care in past year, ICU admission

Variables included: race, % blood eosinophils (log), % blood neutrophil (log), FeNO, pre-BD FEV_1% predicted, admission in past year, history of intubation