

Bronchodilation and bronchoconstriction: Predictors of future lung function in childhood asthma

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Background: Persistently low levels of lung function are associated with subsequent symptoms in patients with asthma as children.

Objectives: We hypothesized that objective measures of baseline pulmonary function would be independently associated with future lung function in the Childhood Asthma Management Program and that these associations might vary with treatment. **Methods:** We evaluated the association of FEV₁, airway responsiveness, and bronchodilator response at randomization as predictors of longitudinal growth in FEV₁ at the 48-month follow-up visit in the 1041 Childhood Asthma Management Program participants.

Results: Baseline levels of airway responsiveness and bronchodilator response were significantly associated with baseline level of lung function. In multivariate models, higher bronchodilator response ($\beta = 0.22$; $P < .0001$), log PC₂₀ ($\beta = 1.82$; $P < .0001$), and FEV₁ ($\beta = 0.58$; $P < .0001$) at randomization were each associated with higher levels of prebronchodilator FEV₁, as a percent of predicted, after 4 years. Similar associations were noted for prebronchodilator forced vital capacity and FEV₁/forced vital capacity ratio. Baseline bronchodilator response was a particularly powerful predictor of lung function improvements while on inhaled

corticosteroids, whereas airway responsiveness was a better predictor in subjects not randomized to any controller medications.

Conclusion: We conclude that baseline bronchodilator response, airway responsiveness, and level of FEV₁ are independent predictors of subsequent level of FEV₁ in childhood asthma and may have treatment-specific prognostic significance for persistence of symptoms into early adulthood. **Clinical implications:** In asthma, bronchodilator and bronchoconstrictor responses are independent predictors of future lung function and should not be used interchangeably; bronchodilator response may indicate good response to inhaled corticosteroids. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: FEV₁, PC₂₀, methacholine, bronchodilator, corticosteroid, asthma, natural history

Asthma is a leading cause of pediatric hospitalizations and school absences.¹ However, the natural history of childhood asthma and the factors that modify this history have yet to be defined fully. Although an estimated 30% to

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Abbreviations used

BD: Bronchodilator response at randomization
 CAMP: Childhood Asthma Management Program
 FVC: Forced vital capacity
 lnPC₂₀: Natural log–transformed PC₂₀

70% of children improve or outgrow their asthma,²⁻⁴ a significant proportion of patients with asthma as children remain symptomatic into adulthood. Low spirometric flow, as measured by FEV₁ persisting from childhood into early adulthood has consistently been associated with continued asthma symptoms as adults.⁴⁻⁶ Low FEV₁ also predicts subsequent asthma attacks in children and adults and relapse of asthma symptoms on withdrawal of therapy.⁷⁻⁹ FEV₁ is endorsed by the National Asthma Education and Prevention Program as an important means for grading asthma severity.¹⁰ Therefore, determination of factors influencing longitudinal measures of lung function, including FEV₁, in childhood asthma has clinical and prognostic significance.

In identifying factors influencing FEV₁ over time, several objective measures of pulmonary function, including baseline level of lung function, airway responsiveness, and bronchodilation, have been independently evaluated.¹¹ In general, levels of FEV₁ tend to track over time with lower basal levels of FEV₁ predicting lower FEV₁ at subsequent time points.^{4,12-15} Greater airway hyperresponsiveness, measured by PC₂₀ or similar measure, has also been consistently associated with subsequent decrements in FEV₁.^{4,16-18} Studies of the relationship of basal bronchodilator response to subsequent measurements of FEV₁ have produced conflicting results, however, with some studies associating high bronchodilator response with relative improvement^{19,20} and others with subsequent decrements in FEV₁.²¹ Of concern, because bronchodilator response and airway responsiveness are tightly linked to baseline FEV₁, associations noted with these measures of airway tone may actually be a proxy for associations with FEV₁. To date, no longitudinal study of childhood asthma has focused on the simultaneous evaluation of all 3 of these correlated objective measures as predictors of future lung function.

We hypothesized that baseline bronchodilator response, airway responsiveness, and level of lung function would each independently predict improved lung function over time in patients with asthma as children. We tested this hypothesis in the subjects participating in the Childhood Asthma Management Program (CAMP). Incorporating all 3 predictors into the same analytic model allows assessment of the association of each predictor over and above the other 2, addressing the concern about the correlation of measures of airway tone with basal level of lung function. Because there is a paucity of information regarding its association with subsequent lung function in children, we focused on bronchodilator response as a predictor of primary interest. In addition, because biological interactions between β -agonist

(which mediate bronchodilator responsiveness) and glucocorticoid pathways exist,^{22,23} we hypothesized that the association of bronchodilator response with subsequent lung growth would be enhanced in children taking inhaled corticosteroids.

METHODS

Study population

The CAMP was a multicenter, randomized, double-blind clinical trial testing the safety and efficacy of inhaled budesonide or nedocromil each versus placebo over a period of a mean 4.3 years. Trial design, methodology, and primary clinical outcome results have been published.^{24,25} Each patient's parent or guardian signed a consent statement, with each child providing assent. Institutional Review Board approval was obtained for all participating CAMP centers and the data coordinating center. Entry criteria included asthma symptoms and/or medication use for ≥ 6 months in the previous year and airway responsiveness with a PC₂₀ ≤ 12.5 mg/mL to methacholine. A 6-week screening period that included therapy with only as-needed albuterol preceded randomization. The children had mild-to-moderate asthma, as defined by the presence of symptoms or use of an inhaled bronchodilator as least twice weekly or by the use of daily medication for asthma.²⁵ Visits with spirometry occurred at randomization, 2 and 4 months after randomization, and every 4 months thereafter. Methacholine studies were performed during the screening period, at 8 months, then yearly. Bronchodilator response to albuterol was assessed at randomization and all subsequent visits in which methacholine was not administered. Adherence to therapy was measured biweekly via use of diary cards.^{24,25}

Pulmonary function testing

Spirometry and methacholine testing were performed at least 4 hours after use of short-acting bronchodilators and 24 hours after use of long-acting bronchodilators.²⁴ At least 3 maneuvers meeting American Thoracic Society standards were required, with at least 2 reproducible (FEV₁ and forced vital capacity [FVC] within 5% of best) maneuvers required for each test. Equations used to predict average values of lung function measures for age, sex, and height were race-corrected.^{26,27} Postbronchodilator values were obtained at least 15 minutes after administration of 2 puffs of albuterol (90 μ g/puff). Airway responsiveness was performed by standardized procedures.²⁴

Measures

The primary outcome was prebronchodilator FEV₁ as a percent predicted (FEV₁%). Other outcomes included prebronchodilator FVC as a percent of predicted and FEV₁/FVC ratio. In contrast with the primary clinical trial,²⁵ we focused on prebronchodilator measurements, because these measurements have been the standard for other natural history^{4,12-15} and clinical trial^{28,29} studies of asthma in children. Each was measured as an absolute value at the 4-year follow-up visit (primary analytic outcome) and as a percent change from baseline.

Our predictors included bronchodilator response (BD) and prebronchodilator FEV₁% at randomization, as well as PC₂₀ values obtained during screening. BD was calculated by using raw values of FEV₁ via the following equation:

$$BD = 100 * (\text{postbronchodilator FEV}_1 - \text{prebronchodilator FEV}_1) / \text{prebronchodilator FEV}_1$$

PC₂₀ values were natural log–transformed (lnPC₂₀). The specific baseline lung function measure used (ie, FEV₁, FVC, or FEV₁/FVC) in a given analysis corresponded to the comparable 4-year outcomes.

TABLE I. Baseline population characteristics

	Overall	Inhaled corticosteroid	Nedocromil	Placebo
N at randomization	1041	311	312	418
Age (y)*	8.9 ± 2.1	9.0 ± 2.1	8.8 ± 2.1	9.0 ± 2.2
Sex (%)				
Male	621 (59.7)	181 (58.2)	206 (66.0)	234 (56.0)
Female	420 (40.3)	130 (41.8)	106 (34.0)	184 (44.0)
Race (%)				
White	711 (68.3)	201 (64.6)	218 (69.9)	292 (69.9)
African American	138 (13.3)	44 (14.2)	38 (12.2)	56 (13.4)
Hispanic	98 (9.4)	32 (10.3)	29 (9.3)	37 (8.9)
Other	94 (9.0)	34 (10.9)	27 (8.7)	33 (7.9)
Baseline pre-BD FEV ₁ %*	93.7 ± 14.3	93.6 ± 14.4	93.4 ± 14.5	94.2 ± 14.0
Baseline post-BD FEV ₁ %*	103.0 ± 12.7	103.2 ± 13.2	102.3 ± 12.7	103.3 ± 12.2
Baseline BD*	10.7 ± 10.3	11.2 ± 10.7	10.4 ± 9.7	10.6 ± 10.3
Baseline PC ₂₀ †	1.11 ± 3.22	1.08 ± 3.20	1.17 ± 3.31	1.07 ± 3.18
N with 48-month FEV ₁	934	281	272	381

*Mean ± SD.

†Geometric mean.

Statistical analysis

The interdependency of each primary predictor with each of the other predictors was investigated via correlation coefficients and smoothed 3 variable plots. Subsequently, the univariate and multivariate associations of the predictors with our outcomes were estimated by using 2 time point linear regression models. Finally, we evaluated treatment-specific associations by stratified analyses and incorporation of formal interaction terms within our multivariable regression models. Collinearity diagnostics³⁰ were also performed for the multivariate models. All analyses were conducted in SAS version 8.0 (Cary, NC). Results are reported as β -coefficients, defined as the unit change in an outcome, given a 1-unit change in the predictor. Figures were generated by using SigmaPlot version 8.02 (Point Richmond, Calif).

RESULTS

Population characteristics

The characteristics of the CAMP children analyzed are shown in Table I. There were 1041 children randomized to 3 treatment groups; more than 90% of these completed the 4-year spirometric examination. These children were predominantly white, with baseline FEV₁ prebronchodilator and postbronchodilator in the normal range. The mean bronchodilator response at randomization was 10.7%, and the PC₂₀ values were consistent with a high degree of airways responsiveness (with lower PC₂₀ values indicating greater airways responsiveness). During the trial, there was no significant difference in adherence when comparing budesonide versus nedocromil ($P = .08$) or placebo ($P = .34$; data not shown).

Correlations among baseline values of BD, PC₂₀, and FEV₁%

Correlation coefficients at baseline among BD, lnPC₂₀, and FEV₁% were calculated to assess interdependency of these measures with one another. The high correlations noted suggest that portions of the variability in

longitudinal lung function outcomes for an individual predictor might be attributable to one of the other predictors if that predictor was not accounted for in multivariate modeling (Fig 1). The correlation coefficient, r , for BD with lnPC₂₀ was -0.36 , for BD with prebronchodilator FEV₁% was -0.60 , and for lnPC₂₀ with prebronchodilator FEV₁% was 0.29 (all P values $<.0001$). Higher bronchodilator response correlated with lower values of FEV₁% and PC₂₀. PC₂₀ values positively correlated with FEV₁%, as previously noted.³¹

Univariate analyses

For the entire cohort, higher BD was associated with positive percent changes over a period of 4 years in level of prebronchodilator FEV₁ ($\beta = 0.72 \pm 0.05$; $P < .0001$; Fig 2) and FVC ($\beta = 0.38 \pm 0.04$; $P < .0001$) as a percent of predicted, as well as FEV₁/FVC ratio ($\beta = 0.31 \pm 0.03$; $P < .0001$).

Increased baseline lnPC₂₀ was associated with higher levels of prebronchodilator FEV₁% at 4 years ($\beta = 3.18 \pm 0.38$; $p < .0001$) and higher FEV₁/FVC ratio ($\beta = 2.40 \pm 0.24$; $p < .0001$). However, airways responsiveness did not correlate with subsequent FVC as a percent of predicted. Not surprisingly, all measures of baseline level of lung function (FEV₁%, FVC%, and FEV₁/FVC), strongly predicted comparable future level of lung function, with higher levels at baseline associated with better lung function 4 years later (data not shown).

Multivariate analyses

Given the correlations between our predictors, we evaluated the relationship of each with lung function outcomes after adjusting for the effects of the other 2 primary predictors and other covariates in the models (Table II). The magnitude of each of the associations changed significantly after incorporation of the other primary predictors, suggesting that each was a confounder

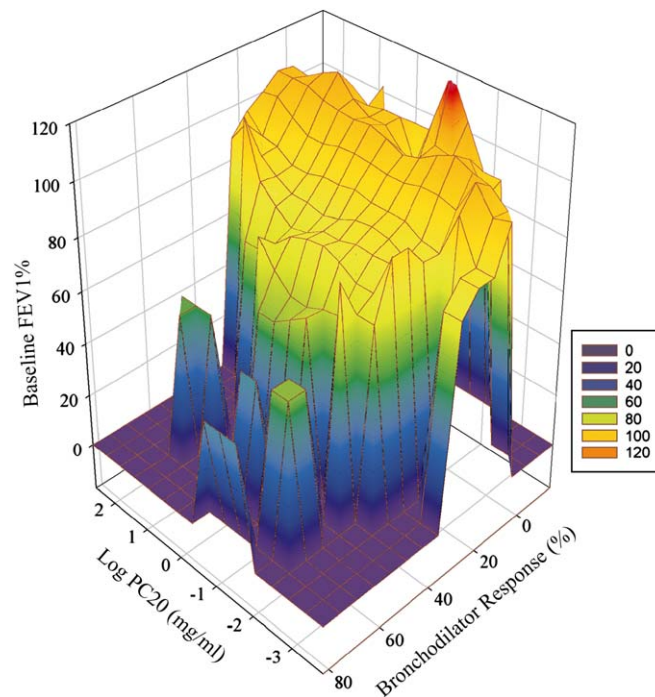


FIG 1. Interdependency of bronchodilator response, PC₂₀, and FEV₁ at baseline. Baseline bronchodilator response, PC₂₀, and FEV₁ are all significantly correlated with one another. Higher bronchodilator responses are strongly correlated with lower values of both FEV₁% and PC₂₀. Graphically, these effects are jointly demonstrated by the graded slope that begins on the back corner and continues out toward the reader. Increased airway responsiveness (lower PC₂₀ values) also correlate with lower FEV₁%.

of the others. Nevertheless, each predictor remained significantly associated after adjustment for the other 2, suggesting that each has an independent relationship with the outcomes over time. Collinearity diagnostics failed to demonstrate the presence of significant collinearity among the predictors of interest.

In the multivariate models, after adjustment for baseline level of lung function and PC₂₀, larger BDs were associated with increases in level of prebronchodilator lung function at 4 years, as manifested by FEV₁% predicted (Table II). On average, each unit increase in baseline bronchodilator response was associated with a 0.22-unit increase in FEV₁% over time. For example, a CAMP subject with a baseline FEV₁ of 90% of predicted and baseline bronchodilator responses 1 SD above normal (20.5%), would, on average, have a prebronchodilator FEV₁ of 94.5% of predicted after 4 years, whereas a child with the same baseline FEV₁% (and baseline PC₂₀) with a bronchodilator response 1 SD below normal (0.5%) would demonstrate, on average, no change in FEV₁ over time. Similar changes were noted for FVC% and FEV₁/FVC.

As with the univariate models, higher baseline lnPC₂₀ were associated with increase in absolute level of FEV₁% and FEV₁/FVC. In all models, increases in baseline level of lung function (FEV₁%, FVC%, and FEV₁/FVC) continue strongly to predict increases in comparable future level of lung function.

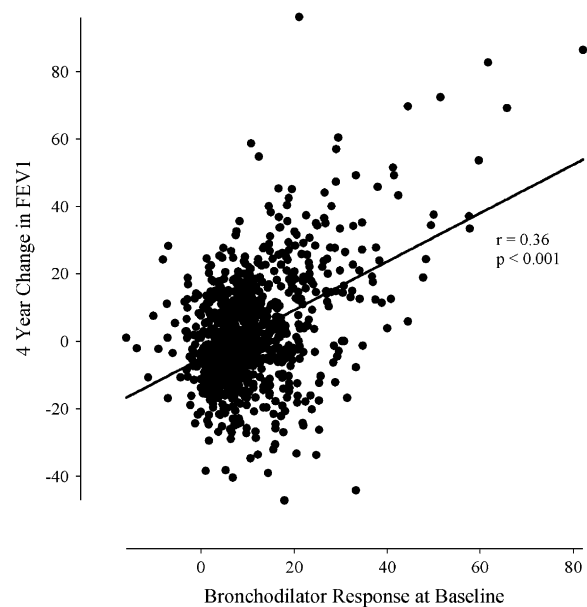


FIG 2. Bronchodilator response at baseline correlates with 4-year improvements in prebronchodilator lung function. Higher baseline bronchodilator response is significantly correlated with functional gains in level of FEV₁ as a percent of predicted. Similar findings were noted for FVC% and FEV₁/FVC ratio (data not shown).

TABLE II. Overall associations of baseline measures with prebronchodilator lung function outcomes at 4 years*†

Baseline measure	FEV ₁ % at 4 years		FVC% at 4 years		FEV ₁ /FVC at 4 years	
	β	P	β	P	β	P
Bronchodilator response (%)	0.22 ± 0.05	<.0001	0.23 ± 0.04	<.0001	0.14 ± 0.03	<.0001
lnPC ₂₀ (mg/mL)	1.82 ± 0.36	<.0001	0.76 ± 0.32	.02	0.92 ± 0.21	<.0001
FEV ₁ % at randomization‡	0.58 ± 0.03	<.0001	0.57 ± 0.03	<.0001	0.76 ± 0.04	<.0001

*All analyses include the 3 primary predictors as covariates.

†Adjusted for age, sex, race, treatment group assignment, clinic, duration of asthma, and any skin test reactivity at baseline.

‡FVC% and FEV₁/FVC at randomization used in place of FEV₁% for the FVC and FEV₁/FVC analyses at 4 years, respectively.

TABLE III. Treatment-stratified associations of baseline measures with prebronchodilator lung function outcomes at 4 years*†

	Inhaled corticosteroid		Nedocromil		Placebo	
	β	P	β	P	β	P
FEV ₁ %						
Bronchodilator response (%)	0.34 ± 0.08	<.0001	0.15 ± 0.10	.12	0.15 ± 0.08	.04
lnPC ₂₀ (mg/mL)	0.51 ± 0.67	.45	2.16 ± 0.68	.002	2.71 ± 0.57	<.0001
FEV ₁ % at randomization	0.69 ± 0.06	<.0001	0.48 ± 0.07	<.0001	0.58 ± 0.06	<.0001
FVC%						
Bronchodilator response (%)	0.24 ± 0.07	.0003	0.14 ± 0.07	.04	0.24 ± 0.06	<.0001
lnPC ₂₀ (mg/mL)	−0.21 ± 0.61	.73	0.98 ± 0.55	.08	1.25 ± 0.51	.02
FVC% at randomization	0.63 ± 0.05	<.0001	0.50 ± 0.05	<.0001	0.60 ± 0.04	<.0001
FEV ₁ /FVC						
Bronchodilator response (%)	0.18 ± 0.05	.0002	0.25 ± 0.06	<.0001	0.04 ± 0.04	.37
lnPC ₂₀ (mg/mL)	0.84 ± 0.39	.03	0.74 ± 0.38	.05	1.30 ± 0.33	.0001
FEV ₁ /FVC at randomization	0.81 ± 0.06	<.0001	0.88 ± 0.07	<.0001	0.65 ± 0.06	<.0001

*All analyses include the 3 primary predictors as covariates.

†Adjusted for age, sex, race, clinic, duration of asthma, and any skin test reactivity at baseline.

Treatment-stratified multivariate analyses

To assess whether the associations were altered by asthma therapy, we stratified the multivariate analyses by CAMP treatment group (Tables III, IV). The association of BD with prebronchodilator FEV₁% was more than twice as strong in the inhaled steroid group compared with placebo (interaction $P = .02$). That is, the presence of a large bronchodilator response at baseline strongly predicted improved FEV₁ over time in those children randomized to inhaled corticosteroids. A similar association of BD with prebronchodilator FEV₁/FVC was noted in children randomized to inhaled corticosteroids compared with placebo (interaction $P = .05$). The BD response as a predictor of FEV₁% in children randomized to nedocromil was similar in magnitude to that of the children randomized to the placebo group.

In contrast with BD, no association was apparent for lnPC₂₀ with FEV₁% for children on inhaled corticosteroids, whereas a strong association of decreased airways responsiveness (higher lnPC₂₀) with improved lung function was noted for children in the placebo group for these outcomes (interaction $P = .003$). Again, the magnitude of the association of lnPC₂₀ with FEV₁% in the nedocromil group paralleled that of the placebo group. Although higher lnPC₂₀ was associated with improved prebronchodilator FEV₁/FVC in the corticosteroid group, the

TABLE IV. Graphical summary of multivariable associations of baseline measures with prebronchodilator FEV₁% after 4 years

	Overall	Inhaled corticosteroid	Placebo
↑ Bronchodilator response	↑↑	↑↑	↑
↑ PC ₂₀	↑↑	↔	↑↑
↑ FEV ₁ %	↑↑	↑↑	↑↑

↑↑, Strongly associated; ↑, weakly associated; ↔, not associated.

magnitude of this association remained greater in the placebo group. There were no treatment-specific interactions when evaluating baseline levels of lung function to their comparable 4-year levels.

DISCUSSION

In this large cohort of patients with asthma as children, we have demonstrated that increased bronchodilator response, higher PC₂₀ to methacholine (decreased airway responsiveness), and increased level of spirometric function at baseline each independently predict higher future level of lung function (Table IV). These findings are novel

in that no previous study has simultaneously evaluated all 3 of these predictors in the same cohort. Our analytic design permits the conclusion that the effects of bronchodilator response and airway responsiveness extend over and above those related to the correlation of these predictors with baseline level of lung function alone. Although we initially analyzed the whole cohort together as representative of clinical practice (treatment of mild-to-moderate childhood asthmatics varies widely), we also specifically sought to evaluate the natural history of disease by focusing on the placebo group and the effect of inhaled corticosteroids by focusing on the budesonide group. Our predictors did vary with treatment, with bronchodilator response a stronger predictor of future lung function while on inhaled corticosteroids, whereas PC_{20} was almost exclusively associated with response in the placebo group.

Our results indicate that baseline bronchodilator response is an independent positive predictor of subsequent levels of lung function in childhood asthmatics. Only 1 previous longitudinal study of 56 patients with asthma as children²¹ evaluated this phenotype, associating high bronchodilator reversibility with increased likelihood of moderate or severe asthma (along with low FEV_1 values) as an adult. However, this study did not adjust for baseline FEV_1 in its statistical models. Therefore, confounding by severity is likely; those children with the highest bronchodilator response would tend to have the lowest baseline FEV_1 . The interrelationships between our predictors supports this (Fig 1). The importance of adjusting for baseline severity in assessing the relationship of FEV_1 to airways responsiveness has been emphasized³² and is readily applicable to bronchodilator response as well.

Several previous studies in children with asthma have evaluated a broad range of airway responsiveness and FEV_1 , but not bronchodilator response, in relation to subsequent lung function. In studies of 101 childhood asthmatics followed into adulthood⁴ and 557 children followed for 10 years,¹⁷ both degree of airways responsiveness and level of FEV_1 were strong determinants of future symptoms and level of lung function. Roorda et al,¹⁵ however, noted that $FEV_1\%$, but not PC_{10} , predicted level of FEV_1 as adults in a cohort of 406 children. However, children on inhaled corticosteroids were included in this latter study; these numbers were not detailed. Our data support airway responsiveness as an independent predictor of the natural history of untreated asthma and baseline level of lung function as a consistently strong predictor of subsequent level of lung function irrespective of treatment.

It has been argued that the determinants of bronchoconstriction (PC_{20}) are biologically and mechanistically distinct from those of bronchodilation,^{19,33-35} and they should be evaluated as independent phenotypes. In 81 adults with chronic airflow obstruction, both lower airway hyperreactivity and greater bronchodilator response were independently associated with slower decline in FEV_1 over a period of 2 to 21 years of follow-up.¹⁹ Extrapolating, a slower decline in FEV_1 in adults may equate to enhanced growth in FEV_1 in children, indicating that

our data for pediatric subjects with asthma parallel these results. Moreover, our data strongly support bronchodilator response and bronchoconstrictor response as distinct phenotypes that should not be used interchangeably. This is particularly true in the prediction of the effects of treatment.

In addition to the overall associations of our 3 predictors with longitudinal lung function, we report a significant effect modification for bronchodilator reversibility in association with use of inhaled corticosteroids (Table III). Interestingly, higher baseline bronchodilator response has been associated with improved FEV_1 after therapy with inhaled corticosteroids in 2 other studies.^{36,37} A recent randomized, crossover study evaluated predictors of response to montelukast and to fluticasone in children.³⁸ Bronchodilator response was only marginally associated with FEV_1 response to inhaled steroids after 16 weeks of treatment (8 weeks on each medication). However, enhanced bronchodilator response did predict greater differential response to inhaled corticosteroids compared with leukotriene antagonists, supporting our conclusion that BD may be a useful predictor of response to inhaled corticosteroid medications in asthma.

Biologically, there are several reasons that may explain the enhanced association of BD with subsequent lung function with the use of inhaled corticosteroids. First, decreased BD may be a proxy for airway remodeling. There is evidence suggesting that airway remodeling may occur from an early age in childhood asthma^{39,40}; smooth muscle hypertrophy is an integral part of the changes accompanying the remodeling process. Higher basal bronchodilator response, therefore, may represent those individuals who have yet to undergo significant remodeling and are most likely to improve their lung function over time generally and respond to inhaled corticosteroids specifically. Interactions between the glucocorticoid and β -agonist pathways^{22,23} may also contribute to the improved long-term outcomes in patients with higher BDs, if one considers bronchodilator response as a proxy for β -agonist receptor number and/or function. Finally, BD may be a marker for inflammation. A study of serial bronchial biopsy specimens in 9 patients with asthma demonstrated a tight correlation between change in bronchodilator responsiveness and change in eosinophils ($r = 0.77$; $P = .016$) after 8 weeks of inhaled corticosteroid therapy.⁴¹ Because eosinophilic inflammation is typically steroid-responsive, this correlation may explain the improved outcomes with steroid usage compared with placebo.

There are some potential limitations to this study. The CAMP participants had mild to moderate persistent asthma, with an average duration of diagnosis at enrollment of 5 years.²⁵ Therefore, it is difficult to extrapolate our results to children with either *de novo* or more severe asthma. These findings may also not be generalizable beyond the clinical trial setting to patients with asthma at other stages of life. However, each of our predictors has been separately demonstrated to have predictive value in older children and adults. Because PC_{20} values were

obtained 2 weeks before actual randomization, there is potential for these values to have changed by the time that the other predictors were measured. However, all children were on the same therapy throughout the 6-week screening period (as-needed albuterol), and FEV₁% did not vary between the 2 visits (data not shown), making this unlikely. Finally, a previous CAMP publication noted that a higher FEV₁% at baseline was a predictor of subjects with significant decrements in their pulmonary function as measured in percent predicted over time,⁴² seemingly in conflict with our reported association of higher baseline FEV₁ with increased pulmonary function over time. However, the other publication focused on postbronchodilator measures and noted that a portion of their reported association might have been a result of regression to the mean; both of these aspects differ from the current study's focus on prebronchodilator measures and adjustment for differences in baseline FEV₁ in all multivariable models.

In conclusion, increased baseline measures of lung function, PC₂₀ to methacholine, and bronchodilator response are each independently associated with improved levels of lung function over time in children with asthma. These results provide novel insights into the natural history of childhood asthma. They may also be of significance in the prediction of those at risk for persistent asthma later in life. That the bronchodilator response is an independent predictor of future pulmonary function in children lends further support to the mechanistic differences inherent in constriction, as opposed to relaxation, of airway tone. Furthermore, there is evolving evidence that the bronchodilator response may be used as a good baseline predictor of therapeutic success with inhaled corticosteroids in the amelioration of airways obstruction, justifying its widespread use in clinical practice.

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