

Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program

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Background: Among asthmatic subjects, bronchodilator response (BDR) to inhaled β_2 -adrenergic agonists is variable, and the significance of a consistent response over time is unknown.

Objective: We assessed baseline clinical variables and determined the clinical outcomes associated with a consistently positive BDR over 4 years in children with mild-to-moderate persistent asthma.

Methods: In the 1041 participants in the Childhood Asthma Management Program, subjects with a change in FEV₁ of 12% or greater (and 200 mL) after inhaled β_2 -agonist administration at each of their yearly follow-up visits (consistent BDR) were compared with those who did not have a consistent BDR.

Results: We identified 52 children with consistent BDRs over the 4-year trial. Multivariable logistic regression modeling demonstrated that lower baseline prebronchodilator FEV₁ values (odds ratio, 0.71; $P < .0001$), higher log₁₀ IgE levels (odds ratio, 1.97; $P = .002$), and lack of treatment with inhaled corticosteroids (odds ratio, 0.31; $P = .009$) were associated with a consistent BDR. Individuals who had a consistent BDR had more hospital visits ($P = .007$), required more prednisone bursts ($P = .0007$), had increased nocturnal awakenings caused by asthma ($P < .0001$), and missed more days of school ($P = .03$) than nonresponders during the 4-year follow-up.

Conclusions: We have identified predictors of consistent BDR and determined that this phenotype is associated with poor clinical outcomes. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, consistent bronchodilator response, outcomes

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Asthma, one of the most common chronic respiratory diseases worldwide, is characterized by airway inflammation, increased airway responsiveness to a variety of stimuli, and airflow obstruction that is at least partially reversible with inhaled bronchodilators.¹ Current treatment guidelines recommend the use of inhaled corticosteroids and inhaled β_2 -adrenergic agonists for individuals with mild-to-moderate persistent asthma.² However, response to inhaled β_2 -adrenergic agonists is highly variable among asthmatic individuals.³ Bronchodilator response (BDR), which is an improvement in FEV₁ after inhalation of a β_2 -adrenergic agonist, is an important asthma-related phenotype. In a study of 81 adults with chronic airflow obstruction, a single positive BDR measurement was associated with a slower longitudinal decrease in FEV₁ compared with those without a BDR at baseline.⁴ Moreover, Tantisira et al⁵ showed that a higher baseline level of BDR is an independent positive predictor of higher subsequent levels of lung function in asthmatic children. It is plausible that the longitudinal improvement in lung function associated with a single positive measurement of BDR might be related to the absence of significant airway remodeling, but in the clinical setting it is traditionally believed that a consistently positive BDR implies ongoing bronchoconstriction or inadequately treated disease. To date, there is a paucity of data about the clinical implications of a persistently positive response to bronchodilators in individuals being treated with conventional doses of asthma controller medications.⁶ Understanding the implications of a consistent BDR, a phenotype that is easily measured, would allow clinicians to effectively assess asthma treatment regimens

Abbreviations used

ATS: American Thoracic Society
 BDR: Bronchodilator response
 CAMP: Childhood Asthma Management Program
 FVC: Forced vital capacity

in the outpatient setting. The objective of this study is to identify the clinical predictors of consistent BDR and to determine the clinical implications of this phenotype.

Researchers are attempting to elucidate the clinical characteristics and genetic pathways that influence response to asthma therapies. Consistent response to inhaled β_2 -adrenergic agonists indicates repeatability of therapeutic response, suggesting that it is at least a partially heritable trait.^{7,8} Therefore consistent response to bronchodilators might be an important phenotype for future investigation in pharmacogenetic studies and might allow us to better tailor medication regimens on an individual basis. Nevertheless, for a fully predictive model, we need more information on the clinical and demographic characteristics, as well as the clinical implications, of the consistent response phenotype. Using repeated BDR measurements from the Childhood Asthma Management Program (CAMP), a randomized controlled trial of more than 1000 children with mild-to-moderate persistent asthma, our present study aims to determine which baseline clinical variables predict a consistent response to inhaled β_2 -adrenergic agonists and to define the clinical outcomes associated with this phenotype.

METHODS**Study population**

CAMP was a multicenter, randomized, double-blind, placebo-controlled trial established to investigate the long-term effects of commonly prescribed asthma treatment regimens. In total, 1041 children were randomized to receive inhaled budesonide, inhaled nedocromil, or placebo. Participants were subsequently followed for a mean of 4.3 years with lung function studies and questionnaires at regular intervals. Phenotypic characteristics including lung function parameters, IgE levels, peripheral blood eosinophil counts, response to inhaled bronchodilator, response to methacholine, family history, and environmental exposures were recorded over the 4-year follow-up period. Trial design, methodology, and the primary outcomes analysis of the CAMP have been previously published.^{9,10}

At enrollment, CAMP participants had mild-to-moderate persistent asthma based on the presence of symptoms, the use of inhaled bronchodilators at least twice weekly, or the use of daily asthma medication for at least 6 months in the year before screening.¹⁰ Spirometry was performed at least 4 hours after short-acting bronchodilator use and 24 hours after long-acting bronchodilator use. Spirometry was required to meet American Thoracic Society (ATS) criteria for acceptability and reproducibility. At least 3 spirometric maneuvers were performed, with at least 2 reproducible maneuvers required for each test. BDR to albuterol was assessed at randomization and at all subsequent visits during which a methacholine challenge was not performed. Postbronchodilator spirometric values were obtained at least 15 minutes after the administration of 2 puffs of albuterol (90 μ g per puff).

Approval was obtained from the institutional review boards at each of the CAMP-participating institutions before initiation of the trial. Informed consent was obtained from the parent or guardian of the participant, and the child's assent was obtained before study enrollment.

Consistent BDR phenotype

BDR was expressed as the percentage change in FEV₁ as follows: $BDR = 100 \times [(Post-FEV_1 - pre-FEV_1) / pre-FEV_1]$. In accordance with ATS

guidelines, consistent BDR was defined as a BDR of at least 12% of the control value and a concomitant increase in 200 mL at each yearly follow-up visit.¹¹ Those who did not achieve either of these criteria were designated nonresponders. Using repeated measurements of BDR obtained at each yearly visit allowed us to capitalize on the longitudinal nature of the CAMP data.

Clinical predictors of consistent BDR

The candidate list of phenotypes measured at the time of randomization in the clinical trial included markers of asthma severity, lung function parameters, atopy, and common environmental exposures. Because pulmonary function data are routinely adjusted for age, height, sex, and race, an *a priori* decision was made to force these covariates into the final logistic regression model.

Distributions of the continuous predictors were inspected for normality and missing data. Total IgE levels, eosinophil counts, and PC₂₀ values were log-transformed for this analysis. All continuous phenotypes remained in the model as linear predictors for the model-building process.

Univariate analyses included *t* tests for continuous, normally distributed data and Fisher exact tests for binary and categorical predictors. Because of concerns over collinearity, all predictors found to be significant on univariate analysis were placed into a forward selection logistic regression model by using a selection entry criterion of a *P* value of .05.

Because a similar cohort was not readily available for validation of our model, bootstrap resampling was performed on 1000 samples from the CAMP population. Bootstrap resampling is a statistical method to assess the stability of results and hence the generalizability of our model to other populations. Differences in the effect estimates, odds ratios, and *P* values between our original model and the bootstrap samples were assessed. The stability of effect estimates after bootstrap resampling suggests that a model will be generalizable to other similar populations.

Clinical outcomes associated with consistent BDR

Poisson regression models adjusted for age, sex, treatment group, and baseline prebronchodilator FEV₁ values were used to analyze clinical outcomes associated with the consistent BDR phenotype (Proc GENMOD, SAS version 8.1; SAS Institute, Inc, Cary, NC). Proc GENMOD is a statistical method that accounts for repeated measurements and the correlation between the outcomes measured. Outcomes assessed were the total number of hospital visits (including emergency department visits and hospitalizations), number of prednisone bursts required, days of school missed because of asthma, and number of nights awakened because of asthma symptoms during the 4-year study period.

Predictors of short-term consistent BDR and associated outcomes

Because we realize that changes in asthma medication are often made based on short-term follow-up, a short-term consistent BDR phenotype was also analyzed. Short-term consistent responders were those with a BDR greater than 12% and 200 mL at baseline and the first 2 follow-up visits of the clinical trial (2 and 4 months). A total of 80 children met this definition of short-term consistently positive BDRs. Clinical outcomes associated with short-term consistent response were then analyzed by using Poisson regression models with appropriate covariate adjustments.

Sensitivity analysis

Because no clear consensus exists about the definition of reversibility in subjects with airflow obstruction,¹¹⁻¹³ a sensitivity analysis was performed to assess the appropriateness of our cutoff point for dichotomization. Differences of a 2% change in FEV₁ of greater than or less than the 12% cutoff were analyzed to assess the stability of the effect estimates of each of the variables in our multivariable logistic regression model. Decreasing the BDR definition by 2% per visit to a 10% improvement in FEV₁ after inhaled bronchodilators, which represents the mean response to bronchodilators for the entire cohort, also provided a notable increase in sample size, thereby increasing the power of this analysis.

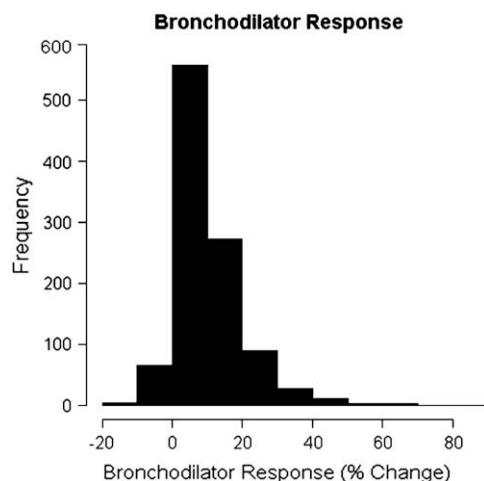


FIG 1. Distribution of baseline BDRs in the CAMP study. The histogram demonstrates the distribution of BDRs at randomization of the 1041 children participating in the CAMP.

Because the ATS guidelines also suggest using an improvement in forced vital capacity (FVC) of greater than 12% and 200 mL as a clinical indicator of a significant BDR, using similar methods to those described above, we performed a secondary analysis using a consistent response phenotype based on FVC criteria.

RESULTS

Observational data from CAMP nicely illustrate the heterogeneous nature of the response to inhaled β_2 -adrenergic agonists in children with mild-to-moderate persistent asthma. The distribution of response to bronchodilators at randomization is shown in Fig 1. The distributions of BDRs at each of the yearly follow-up visits were similar to that shown. As expected, the vast majority of children in the CAMP demonstrated a variable response to inhaled β_2 -adrenergic agonists at each of their yearly follow-up visits. Although a large number of individuals had a BDR of greater than 12% and 200 mL at one of the yearly follow-up visits (Fig 2), of the 1041 children randomized in the CAMP, 52 subjects had a BDR of greater than 12% and 200 mL at each of their yearly follow-up visits and thus were considered to have a consistently positive BDR. Mean BDRs of the 2 groups at each of the yearly follow-up visits are shown in Fig 3. Of note, the SE bars do not overlap at any of the 4 time points, demonstrating that dichotomization of BDRs at the 12th percentile results in good separation of the 2 groups.

Baseline characteristics of consistent BDRs and nonresponders and results of the univariate analyses are outlined in Table I. The mean BDR in those with a consistent BDR was a 26% change in FEV₁ compared with a 9% change in FEV₁ of the nonresponders ($P < .0001$). Univariate analyses suggest that patients with a consistently positive BDR had lower baseline FEV₁ values and FEV₁/FVC ratios than nonresponders (both $P < .0001$). There was also a significant association with higher IgE levels in children with a consistently positive BDR compared with nonresponders ($P = .0007$). Individuals in the placebo and nedocromil groups were more likely than those receiving inhaled corticosteroids to have a consistently positive BDR to β_2 -adrenergic agonists ($P = .02$). Age, sex, race, and height were not significantly associated with a consistently positive BDR on univariate analysis.

Multivariate logistic regression modeling demonstrates that when adjusted for age, sex, race, and height, those with a lower

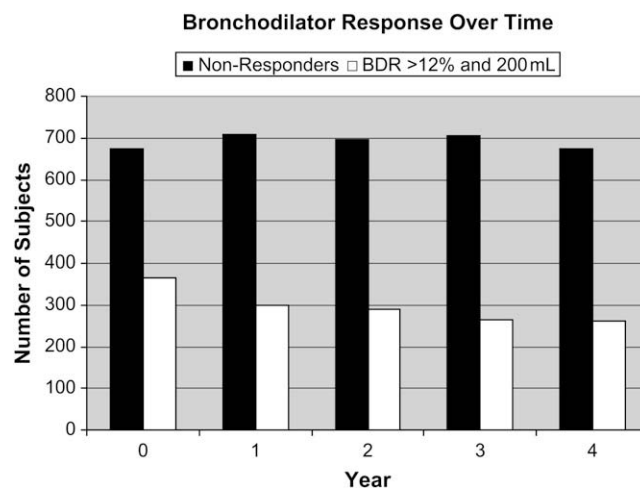


FIG 2. Number of subjects with BDRs at each yearly follow-up visit. The graph demonstrates the number of subjects who had a positive BDR at each yearly follow-up visit. Nonresponders (solid columns) had less than a 12% and 200-mL improvement in FEV₁ values after inhaled bronchodilator administration. Responders (open columns) had a BDR if improvement was greater than 12% and 200 mL.

baseline FEV₁ value, those with higher baseline IgE levels, and those not treated with inhaled corticosteroids were more likely to have a consistent BDR (Table II).

Bootstrap resampling on 1000 samples was performed for validation of the model (Table II). All significant predictors in the multivariate logistic regression model were robust to bootstrap resampling. Interestingly, the bootstrap results indicate that individuals with increased airways responsiveness were also more likely to have a consistent BDR. Thus lower FEV₁ values at baseline, higher IgE levels, increased airways hyperresponsiveness, and lack of treatment with inhaled corticosteroids were associated with a consistent BDR, even when the bootstrapping procedure was used to generate P values after 1000 iterations.

We then determined the relevance of a consistently positive BDR by analyzing the clinical outcomes related to this trait. The consistent BDR phenotype was significantly associated with poor clinical outcomes (Table III). For example, subjects with consistently positive BDRs were found to have significantly lower mean prebronchodilator FEV₁ (percent predicted) values at the end of the 4-year trial than nonresponders (80% in those with consistent BDRs vs 93.6% in nonresponders, $P < .0001$). Furthermore, the consistent BDR group had significantly higher numbers of emergency department visits and hospitalizations during follow-up than nonresponders ($P = .007$). Individuals with a consistently positive BDR also required more frequent prednisone bursts during the 4-year trial than nonresponders ($P = .0007$). Furthermore, subjects with consistent BDRs were 1.40 times more likely to have nocturnal awakenings and missed more days of school because of their asthma than nonresponders ($P < .0001$ and $P = .03$, respectively).

Because medication changes made in the clinical setting are often based on short-term follow-up, a short-term consistent BDR phenotype was analyzed. A total of 80 children fulfilled the definition of short-term consistently positive BDRs (BDR >12% and 200 mL at randomization and the first 2 follow-up visits). Of note, odds ratios with short-term follow-up were similar to those in our initial model, suggesting the stability of the model using

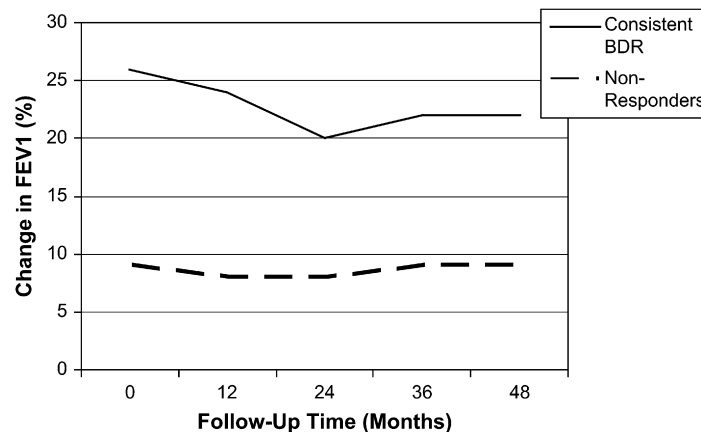


FIG 3. Mean BDRs at yearly visits in responders and nonresponders. The graph shows the mean BDR as the percentage change in FEV₁ in consistent responders (solid line) versus nonresponders (dashed line) at each of the yearly follow-up visits in the trial.

TABLE I. Characteristics of patients randomized in the CAMP

Characteristic	Consistent BDR	Nonresponders	P value
No. at randomization	52	989	
Age at randomization (y)*	8.38 (1.9)	8.97 (2.0)	.05
Age at asthma onset (y)	2.27 (1.8)	3.11 (2.4)	.002
Sex			
Male	37 (71%)	584 (59%)	.11
Female	15 (29%)	405 (41%)	
Race			
White	34 (65%)	677 (68%)	.07
African American	13 (25%)	125 (13%)	
Hispanic	3 (6%)	95 (10%)	
Other	2 (4%)	92 (9%)	
Treatment group			
Budesonide	8 (15%)	303 (31%)	.02
Nedocromil	17 (33%)	295 (29%)	
Placebo	27 (51%)	391 (40%)	
Baseline height (cm)	131.02 (15.9)	133.68 (13.7)	.18
Baseline BMI	17.93 (3.4)	18.18 (3.4)	.63
Smoking history	0	0	
Intrauterine smoke exposure	13 (25%)	137 (14%)	.04
Baseline BDR	26%	9%	<.0001
Baseline prebronchodilator FEV ₁ (L)	1.45 (0.5)	1.67 (0.5)	<.0001
Baseline prebronchodilator FVC (L)	1.96 (0.8)	2.09 (0.6)	.24
Baseline prebronchodilator FEV ₁ /FVC (%)	69.1 (8.1)	80.3 (8.0)	<.0001
Baseline IgE level†‡	2.94 (0.6)	2.6 (0.7)	.0007
Baseline PC ₂₀ ‡	−0.54 (1.0)	0.13 (1.2)	<.0001
Baseline eosinophil level‡	2.60 (0.5)	2.49 (0.5)	.15
Prebronchodilator FEV ₁ at 48-mo follow-up visit (% predicted)	80.1 (13.5)	93.6 (13.9)	<.0001

*Mean (SD).

†Median (interquartile range).

‡Log transformed.

either short-term or longitudinal data (Table IV). Furthermore, the short-term consistent response phenotype was also associated with poor clinical outcomes, including lower FEV₁ (percent predicted) values after 4 years of follow-up ($P < .0001$). Individuals with a short-term consistent response also had increased hospital

TABLE II. Baseline predictors of consistent response to bronchodilators*: Results of the multivariable logistic regression model

Predictor	OR	95% CI	Bootstrap P value
Age (y)	0.71	0.50-1.01	.34
Height (cm)	1.13	1.06-1.2	.005
Sex (female)	0.47	0.24-0.93	.25
Race (white)	0.57	0.29-1.2	.21
Baseline prebronchodilator FEV ₁ (L)	0.71	0.63-0.81	.001
Inhaled corticosteroid treatment group	0.31	0.13-0.75	.001
Log IgE level (IU/L)	1.97	1.18-3.3	.001
Log PC ₂₀ (mg/mL)	0.77	0.57-1.03	.01

Odds ratios (OR) and 95% CIs for each variable obtained from multivariable logistic regression models adjusted for all variables in the table.

*BDR greater than 12% and 200-mL absolute change in FEV₁ at each yearly follow-up visit.

visits because of their asthma and required more prednisone bursts during follow-up (both $P < .0001$). Moreover, short-term consistent responders were 1.36 times more likely to be awakened at night because of asthma symptoms and 1.26 times more likely to miss school over the course of the 4-year trial (Table V). Therefore the clinical predictors of consistently positive BDRs might be used to make clinicians more vigilant in monitoring symptoms, treatment response, and re-evaluation of treatment options among children with asthma, even after only short-term follow-up periods.

A sensitivity analysis was performed to determine the appropriateness of the 12% and 200-mL thresholds for dichotomization. In total, 84 children met the criteria for a BDR of greater than 10% at each yearly follow-up visit. Despite differences in sample size and power, differences of 2% change in FEV₁ above or below the 12% cutoff point created only minor alterations in the multivariate model for prediction of consistent response (see Table E1 in this article's Online Repository at www.jacionline.org). Of note, in addition to the other clinical predictors of consistent BDRs, increased airways responsiveness to methacholine was also found to be a significant predictor of consistent BDRs by using the alternate definition of a greater than 10% change in FEV₁ values at each yearly follow-up visit. This difference is likely to be related to increased power, given the larger sample size.

TABLE III. Association of consistent responder status with exacerbations and symptoms over 4 years*

Variable	Rate ratio	95% CI	P value
Hospital visits (ED visits and hospitalizations)	1.80	1.20-2.80	.007
Oral steroid bursts	1.52	1.20-1.95	.0007
Nights awakened	1.40	1.20-1.65	<.0001
School missed (d)	1.43	1.03-1.99	.03

ED, Emergency department.

*Poisson regression models adjusted for age, sex, treatment group, and baseline prebronchodilator FEV₁.BDR greater than 12% and 200-mL absolute change in FEV₁ at each yearly follow-up visit.**TABLE IV.** Baseline predictors of short-term consistent response* to bronchodilators: Results of the multivariable logistic regression model

Predictor	OR	95% CI
Age (y)	0.87	0.66-1.16
Height (cm)	1.12	1.07-1.18
Sex (female)	0.80	0.47-1.35
Race (white)	0.65	0.38-1.28
Baseline prebronchodilator FEV ₁ (L)	0.68	0.26-0.89
Inhaled corticosteroid treatment group	0.48	0.26-0.89
Log IgE level (IU/L)	1.89	1.23-2.92
Log PC ₂₀ (mg/mL)	0.83	0.66-1.06

Odds ratios (OR) and 95% CIs for each variable obtained from multivariable logistic regression models adjusted for all variables in the table.

*BDR greater than 12% and 200 mL at randomization and the first 2 follow-up visits (2 months and 4 months).

Moreover, clinical outcomes of consistent BDR with the 10% cut-off point were also associated with poor clinical outcomes (see Table E2 in this article's Online Repository at www.jacionline.org). Therefore changing the BDR definition by 2% per visit, yielding a 10% improvement in FEV₁ values after inhaled bronchodilators, resulted in effect estimates similar to those obtained with the 12% change model.

A total of 28 individuals fulfilled the ATS FVC requirement for consistently positive BDRs at each yearly visit. Lower baseline FEV₁ values and higher IgE levels were significant predictors of consistent BDRs by using the FVC criteria (see Table E3 in this article's Online Repository at www.jacionline.org). Moreover, the consistent BDR phenotype using FVC criteria was also associated with poor clinical outcomes, including increased oral prednisone requirements and increased nocturnal awakenings because of asthma (see Table E4 in this article's Online Repository at www.jacionline.org). A sensitivity analysis with FVC criteria was not performed.

DISCUSSION

Before this study, there had been little research into the clinical predictors of consistent response to inhaled β_2 -adrenergic agonists or the clinical outcomes associated with this asthma phenotype. With more than 1000 patients with repeated measures of BDRs and a notable variability in response to bronchodilators, CAMP is a good cohort in which to study the consistent BDR phenotype. Based on the current analysis, it is clear that certain clinical parameters are associated with consistency in response to inhaled β_2 -adrenergic agonists over time. Our data suggest that

TABLE V. Association of short-term consistent response to bronchodilators with exacerbations and symptoms over 4 years*

Variable	Rate ratio	95% CI	P value
Hospital visits (ED visits and hospitalizations)	1.53	1.24-1.89	<.0001
Oral prednisone bursts	1.72	1.55-1.85	<.0001
Nights awakened	1.36	1.30-1.43	<.0001
School missed (d)	1.26	1.17-1.34	<.0001

ED, Emergency department.

*Poisson regression models adjusted for age, sex, treatment group, and baseline prebronchodilator FEV₁.

BDR greater than 12% and 200 mL at randomization and the first 2 follow-up visits (2 months and 4 months).

lower baseline FEV₁ values, higher IgE levels, and failure to treat with inhaled corticosteroids are associated with children having a consistent response to bronchodilators over a 4-year period. Furthermore, the results of the current study demonstrate that a consistent response to bronchodilators is associated with poor clinical outcomes in children with mild-to-moderate persistent asthma. Unlike previous suggestions that individuals with a single positive measurement of the BDR benefit from inhaled steroids alone, individuals with a consistently positive response might require inhaled corticosteroids at higher-than-conventional doses, environmental modification, and possible consideration of alternative classes of asthma treatments. We have shown that this phenotype is associated with lower prebronchodilator FEV₁ (percent predicted) values at 4 years, increased hospital visits, more oral steroid bursts, and more frequent nocturnal awakenings caused by asthma symptoms. Given the clinical implications of the consistent BDR phenotype, a thorough understanding of the clinical variables identified by our model will improve a clinician's understanding of the prognosis and treatment options for this type of asthmatic patient. Because similar clinical outcomes were found in individuals with the short-term consistent response phenotype, clinicians can use this phenotype to modify asthma treatment regimens based on the persistence of a positive BDR, even with short follow-up intervals.

In asthmatic subjects a single measurement of the BDR has been associated with higher FEV₁ values in both children and adults. Tantisira et al⁵ showed that a single higher baseline measurement of the BDR was an independent predictor of higher levels of prebronchodilator FEV₁ at 4 years in the CAMP. Their results corroborate previous demonstrations that a single positive measurement of the BDR is an even stronger predictor of future lung function in individuals treated with inhaled corticosteroids. Thus when we began this analysis, we hypothesized that a consistently positive BDR would be associated with good clinical outcomes, especially in individuals already being treated with inhaled corticosteroids; however, that was not the case. Unlike previous studies demonstrating that a single baseline measurement of the BDR is associated with higher levels of lung function over time, repeated positive measures of the BDR are associated with lower levels of FEV₁ (percent predicted) at 4 years. There are several biologic explanations for the differences noted between consistent responders and nonresponders. Because failure to treat with inhaled corticosteroids was one of the determinants of the consistent response phenotype, it is possible that these individuals had higher levels of airway inflammation than nonresponders, contributing to lower longitudinal lung function and suggesting that responders were undertreated for their asthma.

Moreover, children randomized to receive inhaled corticosteroids had higher prebronchodilator FEV₁ values, making both the absolute change and percentage change in FEV₁ values much smaller in this subgroup. Thus, these individuals were less likely to have a consistently positive response to bronchodilators over time. Nevertheless, given concerns for residual confounding by treatment group, we restricted the outcomes analyses to individuals randomized to the placebo and nedocromil treatment groups and obtained similar results (data not shown).

Subjects with consistently positive BDRs also had lower baseline FEV₁ values than nonresponders. Given previous research showing that a lower baseline FEV₁ value is itself associated with increased exacerbation rates,¹⁴ the low baseline FEV₁ value predictive of consistent response might also explain some of the poor clinical outcomes associated with this group. However, even when adjusted for baseline FEV₁ values, subjects with consistent BDRs had poorer clinical outcomes than nonresponders, suggesting that the poor clinical outcomes associated with the consistent BDR phenotype are independent of the effects of FEV₁ alone.

Our study supports recent findings by Martin et al¹⁵ that the BDR itself was predictive of short-term response to inhaled corticosteroids in adults with asthma. Szeffler et al¹⁶ have also shown that asthmatic patients with higher exhaled nitric oxide values, higher total eosinophil counts, lower PC₂₀ values, lower lung function (including FEV₁), and higher serum IgE values were more likely to respond to inhaled corticosteroids. Of note, many of the determinants of a positive response to inhaled corticosteroids are also predictors of the consistent BDR phenotype. Because inhaled corticosteroids are now a cornerstone of asthma treatment, it is clear that subjects with childhood asthma found to have a consistently positive BDR to β_2 -adrenergic agonists and who are not already taking inhaled corticosteroids would benefit from the addition of inhaled corticosteroids. However, children who demonstrate a consistently positive response to inhaled bronchodilators who are already taking conventional doses of inhaled corticosteroids should have their corticosteroid dose re-evaluated or should be considered for addition of a different class of asthma medication. Of note, the correlation of the consistent BDR phenotype with increased IgE levels also suggests that environmental evaluation and intervention might be beneficial in these individuals.

Interestingly, 8 individuals randomized to the corticosteroid arm of the CAMP were classified as having a consistently positive BDR. These individuals maintained a consistent response to bronchodilators in spite of treatment with conventional doses of inhaled corticosteroids. These children might be a unique subgroup with steroid-insensitive asthma. Of note, these individuals demonstrated higher IgE and eosinophil levels than everyone else, suggesting that they might ultimately benefit from a discussion of medication adherence or inhaler technique, an increase in the dose of steroids, or the addition of other asthma treatment modalities, including immunologic therapy.¹⁷⁻²⁰ These individuals warrant further evaluation.

The sensitivity analysis performed as part of this study raises the possibility that the traditional 12% and 200-mL cutoff point for the BDR might in fact be too conservative in the clinical management of pediatric patients. To date, there is no clear consensus about what constitutes reversibility in patients with asthma.¹¹ Furthermore, there are even fewer data regarding BDRs in pediatric populations. Although improvements in FEV₁ values of less than 8% after bronchodilator use are considered to be

within the natural variability of the measurement, improvements at or greater than this 8% cutoff point might in fact represent a clinically relevant response.¹¹ In this study individuals who had a BDR of 10% had clinical outcomes similar to those with a BDR of 12% and 200 mL, suggesting that an even lower BDR threshold should prompt either dose escalation of asthma therapy or the addition of other treatment interventions.

The phenotypic characteristics found here to be predictive of a consistently positive response to inhaled bronchodilators can explain only a small portion of the variability in response to β_2 -adrenergic agonists. Other predictors, including genetic determinants, might contribute to variability in response. In fact, previous data suggest that up to approximately 60% of the population's variability in response to bronchodilators can be attributed to genetic differences.²¹ Genetic predictors of BDRs are currently under investigation.²²⁻²⁴

CAMP was limited to children with mild-to-moderate persistent asthma. Because patients with severe asthma were excluded from the trial, it is possible that some clinical variables associated with consistent BDRs in patients with more severe asthma were missed. Thus, it is possible that our predictive model is appropriate for children with mild-to-moderate asthma and might not be generalizable to patients with severe asthma. This limitation was addressed by using a parsimonious model based on few predictors, which decreases the risk of overfitting, making it easier for this model to generalize to other childhood asthma populations. Moreover, it is unclear whether our findings apply to adult asthmatic subjects who have longstanding asthma and might have more airway remodeling than children with asthma. This issue will need to be studied in an adult asthmatic population.

In conclusion, as demonstrated in CAMP, children with asthma clearly have a heterogeneous response to β_2 -adrenergic agonists. Moreover, the response to bronchodilator therapy is clearly of prognostic significance in asthma. Although this study sheds light on some of the clinical variables that contribute to the variability in response to inhaled bronchodilators, it is clear that other predictors not captured in our model are involved. A better understanding of genetic predictors, environmental exposures, and gene-environment interactions is required to fully account for the heterogeneity in response to asthma medications. An understanding of these complex interactions in addition to the clinical variables that predict medication response in the current analysis will allow us to more reliably determine individual-based asthma treatments and might lead to better treatment guidelines in the future.

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Clinical implications: Given its association with poor clinical outcomes, a consistently positive response to inhaled bronchodilators should prompt clinicians to re-evaluate their patient's asthma medication regimens in the outpatient setting.

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