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Clinical Predictors and Outcomes of Consistent Bronchodilator Response in the Childhood Asthma Management Program

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Abstract

Background—Among asthmatics, bronchodilator response (BDR) to inhaled ß$_2$- 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-moderate persistent asthma.

Methods—In the 1,041 participants in the Childhood Asthma Management Program (CAMP), subjects with a change in FEV$_1$ of 12% or greater (and 200mLs) after inhaled ß$_2$ agonist 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 BDR over the 4-year trial. Multivariable logistic regression modeling demonstrated that baseline pre-bronchodilator FEV$_1$ (OR=0.71, p<0.0001), log 10 IgE level (OR=1.97, p=0.002), and lack of treatment with inhaled corticosteroids (OR=0.31, p=0.009) were associated with a consistent BDR. Individuals who had a consistent BDR had more hospital visits (p=0.007), required more prednisone bursts (p=0.0007), had increased nocturnal awakenings due to asthma (p<0.0001), and missed more days of school (p=0.03) than non-responders during the 4-year follow-up.

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Conclusions—We have identified predictors of consistent BDR and determined that this phenotype is associated with poor clinical outcomes.

Keywords

asthma; consistent bronchodilator response; outcomes

Introduction

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 by inhaled bronchodilators [1]. Current treatment guidelines recommend the use of inhaled corticosteroids and inhaled ß$_2$- adrenergic agonists for individuals with mild-moderate persistent asthma [2]. However, response to inhaled ß$_2$-adrenergic agonists is highly variable among asthmatic individuals [3]. Bronchodilator response (BDR), which is an improvement in forced expiratory volume in one second (FEV_1) after inhalation of a ß$_2$- 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 decline in FEV_1 compared to those without a bronchodilator response at baseline [4]. Moreover, Tantisira et al. showed that a higher baseline level of bronchodilator response is an independent positive predictor of higher subsequent levels of lung function in asthmatic children [5]. It is plausible that the longitudinal improvement in lung function associated with a single positive measurement of bronchodilator response may be related to the absence of significant airway remodeling, but in the clinical setting it is traditionally believed that a consistently positive bronchodilator response implies ongoing bronchoconstriction or inadequately treated disease. To date, there are little 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 bronchodilator response, a phenotype that is easily measured, would allow clinicians to effectively assess asthma treatment regimens in the outpatient setting. The objective of this study is to identify the clinical predictors of consistent bronchodilator response 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 ß$_2$- adrenergic agonists indicates repeatability of therapeutic response, suggesting that it is at least a partially heritable trait [7, 8]. Therefore, consistent response to bronchodilators may be an important phenotype for future investigation in pharmacogenetic studies and may 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 over 1,000 children with mild-moderate persistent asthma, our present study aims to determine which baseline clinical variables predict a consistent response to inhaled ß$_2$-adrenergic agonists and to define the clinical outcomes associated with this phenotype.

Methods

Study Population

The Childhood Asthma Management Program (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 1,041 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, immunoglobulin E (IgE) levels, peripheral blood eosinophil counts, response to inhaled bronchodilator, response to methacholine, family history, and environmental exposures were recorded over the four-year follow-up period. Trial design, methodology, and the primary outcomes analysis of CAMP have been previously published[9, 10].

At enrollment, CAMP participants had mild-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 prior to screening [10]. Spirometry was performed at least 4 hours after short-acting bronchodilator use and 24 hours after long-acting bronchodilator use. Spirometry performance was required to meet American Thoracic Society criteria for acceptability and reproducibility. At least three spirometric maneuvers were performed, with at least two reproducible maneuvers required for each test. Bronchodilator response to albuterol was assessed at randomization and at all subsequent visits during which a methacholine challenge was not performed. Post-bronchodilator spirometric values were obtained at least 15 minutes after the administration of 2 puffs of albuterol (90 mcg/puff).

Approval was obtained from the Institutional Review Board at each of the CAMP participating institutions prior to the initiation of the trial. Informed consent was obtained from the parent or guardian of the participant, and the child's assent was obtained prior to study enrollment.

Consistent Bronchodilator Response Phenotype

Bronchodilator response (BDR) was expressed as the percent change in FEV_1 (100 × [post FEV_1 - pre FEV_1/pre FEV_1]). In accordance with American Thoracic Society (ATS) guidelines, consistent BDR was defined as a BDR of at least 12% of control and a concomitant increase in 200mLs at each yearly follow-up visit [11]. Those who did not achieve either of these criteria were designated non-responders. Using repeated measurements of BDR obtained at each yearly visit allowed us to capitalize upon the longitudinal nature of the CAMP data.

Clinical Predictors of Consistent Bronchodilator Response

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. Since pulmonary function data are routinely adjusted for age, height, gender, 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 PC_{20} values (provocative concentration of methacholine causing a 20% fall in FEV_1) 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's exact tests for binary and categorical predictors. Due to concerns over collinearity, all predictors found to be significant on univariate analysis were placed into a forward selection logistic regression model using a selection entry criterion of p=0.05.

Since a similar cohort was not readily available for validation of our model, bootstrap resampling was performed on 1,000 samples from the CAMP population. Bootstrap resampling is a statistical method to assess 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 Bronchodilator Response

Poisson regression models adjusted for age, gender, treatment group, and baseline pre-bronchodilator FEV_1 were used to analyze clinical outcomes associated with the consistent BDR phenotype (Proc GENMOD, SAS version 8.1; SAS Institute; 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 due to asthma, and the number of nights awakened due to asthma symptoms during the four-year study period.

Predictors of Short-Term Consistent BDR and Associated Outcomes

Since 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 mLs at baseline and the first two follow-up visits of the clinical trial (2 and 4 months). A total of 80 children met this definition of short-term consistently positive BDR. Clinical outcomes associated with short-term consistent response were then analyzed using Poisson regression models with appropriate covariate adjustments.

Sensitivity Analysis

Since no clear consensus exists about the definition of reversibility in subjects with airflow obstruction [11,12, 13], a sensitivity analysis was performed to assess the appropriateness of our cut-point for dichotomization. Differences of 2% change in FEV_1 above or below the 12% cut-off 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 FEV_1 following 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.

Since the ATS guidelines also suggest using an improvement in Forced Vital Capacity (FVC) of greater than 12% and 200mLs as a clinical indicator of a significant bronchodilator response, 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 $ß_2$- adrenergic agonists in children with mild-moderate persistent asthma. The distribution of response to bronchodilators at randomization is shown in Figure 1. The distributions of BDR at each of the yearly follow-up visits were similar to that shown. As expected, the vast majority of children in CAMP demonstrated a variable response to inhaled $ß_2$- adrenergic agonists at each of their yearly follow-up visits. Although a large number of individuals had a BDR greater than 12% and 200mLs at one of the yearly follow-up visits (Figure2), of the 1,041 children randomized in CAMP, 52 subjects had a BDR greater than 12% and 200mLs at each of their yearly follow-up visits and thus were considered to have a consistently positive BDR. Mean BDR of the two groups at each of the yearly follow-up visits is shown in Figure 3. Of note, the standard error bars do not overlap at any of the four time points, demonstrating that dichotomization of BDR at the 12^{th} percentile results in good separation of the two groups.

Baseline characteristics of consistent BDR and non-responders and results of the univariate analyses are outlined in Table 1. The mean bronchodilator response in those with a consistent

BDR was 26% change in FEV_1, compared to a 9% change in FEV_1 of the non-responders ($p<0.0001$). Univariate analyses suggest that patients with a consistently positive BDR had lower baseline FEV_1 and FEV_1/FVC ratios than non-responders (both $p<0.0001$). There was also a significant association with higher IgE levels in children with a consistently positive BDR compared with non-responders ($p=0.0007$). Individuals in the placebo and nedocromil groups were more likely than those on inhaled corticosteroids to have a consistently positive BDR to ß$_2$- adrenergic agonists ($p=0.02$). Age, gender, 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, gender, race, and height, those with a lower baseline FEV_1, those with higher baseline IgE levels, and those not treated with inhaled corticosteroids were more likely to have a consistent BDR (Table 2).

Bootstrap resampling on 1,000 samples was performed for validation of the model (Table 2). 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 bronchodilator response. Thus, lower FEV_1 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 1,000 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 3). For example, subjects with consistently positive BDR were found to have significantly lower mean pre-bronchodilator FEV_1 (percent predicted) at the end of the 4-year trial than non-responders (80% in consistent BDR vs. 93.6% in non-responders, $p<0.0001$). Furthermore, the consistent BDR group had significantly higher numbers of emergency department visits and hospitalizations during follow-up than non-responders ($p=0.007$). Individuals with a consistently positive BDR also required more frequent prednisone bursts during the four-year trial than non-responders ($p=0.0007$). Furthermore, subjects with consistent BDR were 1.40 times more likely to have nocturnal awakenings and missed more days of school due to their asthma than non-responders ($p<0.0001$ and $p=0.03$, respectively).

Since 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 BDR (BDR>12% and 200mLs at randomization and the first two follow-up visits). Of note, odds ratios using short-term follow-up were similar to those in our initial model, suggesting stability of the model using either short-term or longitudinal data (See Table 4). Furthermore, the short-term consistent response phenotype was also associated with poor clinical outcomes, including lower FEV_1 levels (percent predicted) after four years of follow-up ($p<0.0001$). Individuals with a short-term consistent response also had increased hospital visits due to their asthma and required more prednisone bursts during follow-up (both $p<0.0001$). Moreover, short-term consistent responders were 1.36 times more likely to be awakened at night due to asthma symptoms and 1.26 times more likely to miss school over the course of the 4-yr trial (see Table 5). Therefore, the clinical predictors of consistently positive BDR may 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 200mLs threshold for dichotomization. In total, 84 children met criteria for a BDR of greater than 10%

at each yearly follow-up visit. Despite differences in sample size and power, differences in 2% change in FEV_1 above or below the 12% cut-off created only minor alterations in the multivariate model for prediction of consistent response (Online Supplement Table E1). Of note, in addition to the other clinical predictors of consistent bronchodilator response, increased airways responsiveness to methacholine was also found to be a significant predictor of consistent BDR using the alternate definition of >10% change in FEV_1 at each yearly follow-up visit. This difference is likely to be related to increased power, given the larger sample size. Moreover, clinical outcomes of consistent BDR using the 10% cut-off were also associated with poor clinical outcomes (Online Supplement Table E2). Therefore, changing the BDR definition by 2% per visit, yielding a 10% improvement in FEV_1 following 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 BDR at each yearly visit. Lower baseline FEV_1 and higher IgE levels were significant predictors of consistent BDR using the FVC criteria (Online Supplement Table E3). Moreover, the consistent BDR phenotype using FVC criteria was also associated with poor clinical outcomes including increased oral prednisone requirements and increased nocturnal awakenings due to asthma (Online Supplement Table E4). A sensitivity analysis using FVC criteria was not performed.

Discussion

Prior to this study, there had been little research into the clinical predictors of consistent response to inhaled $ß_2$-adrenergic agonists or the clinical outcomes associated with this asthma phenotype. With over 1,000 patients with repeated measures of bronchodilator response 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 $ß_2$- adrenergic agonists over time. Our data suggest that lower baseline FEV_1 levels, higher IgE levels, and failure to treat with inhaled corticosteroids are associated with children having a consistent response to bronchodilators over a four-year period. Furthermore, the results of the current study demonstrate that consistent response to bronchodilators is associated with poor clinical outcomes in children with mild-moderate persistent asthma. Unlike previous suggestions that individuals with a single positive measurement of bronchodilator response benefit from inhaled steroids alone, individuals with a consistently positive response may require inhaled corticosteroid 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 pre-bronchodilator FEV_1 (percent predicted) values at four years, increased hospital visits, more oral steroid bursts, and more frequent nocturnal awakenings due to 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. Since 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 asthmatics, a single measurement of bronchodilator response has been associated with higher FEV_1 values in both children and adults. Tantisira et al. showed that a single higher baseline measurement of bronchodilator response was an independent predictor of higher levels of pre-bronchodilator FEV_1 at four years in CAMP [5]. Their results corroborate previous demonstrations that a single positive measurement of bronchodilator response is an even stronger predictor of future lung function in individuals treated with inhaled corticostoroids[5].

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 BDR is associated with higher levels of lung function over time, repeated positive measures of BDR are associated with lower levels of FEV_1 (percent predicted) at four years. There are several biologic explanations for the differences noted between consistent responders and non-responders. Since 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 non-responders, contributing to lower longitudinal lung function and suggesting that responders were undertreated for their asthma. Moreover, children randomized to receive inhaled corticosteroids had higher pre-bronchodilator FEV_1 values, making both the absolute change and percent-change in FEV_1 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 BDR also had lower baseline FEV_1 than non-responders. Given previous research showing that lower baseline FEV_1 is itself associated with increased exacerbation rates[14], the low baseline FEV_1 predictive of consistent response may also explain some of the poor clinical outcomes associated with this group. However, even when adjusted for baseline FEV_1, subjects with consistent BDR had poorer clinical outcomes than non-responders suggesting that the poor clinical outcomes associated with the consistent BDR phenotype are independent of the effects of FEV_1 alone.

Our study supports recent findings by Martin et al. that bronchodilator response itself was predictive of short-term response to inhaled corticosteroids in adults with asthma[15]. Szefler et al. have also shown that asthmatic patients with higher exhaled nitric oxide values, higher total eosinophil counts, lower PC20 values, lower lung function including FEV_1, and higher serum IgE values were more likely to respond to inhaled corticosteroids[16]. Of note, many of the determinants of a positive response to inhaled corticosteroids are also predictors of the consistent BDR phenotype. Since inhaled corticosteroids are now a cornerstone of asthma treatment, it is clear that childhood asthmatics found to have a consistently positive BDR to $ß_2$- adrenergic agonists and who are not already on inhaled corticosteroids would benefit from the addition of inhaled corticosteroids. However, children who demonstrate a consistently positive response to inhaled bronchodilators who are already on 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 also suggests that environmental evaluation and intervention may be beneficial in these individuals.

Interestingly, eight individuals randomized to the corticosteroid arm of 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 may be a unique subgroup with steroid-insensitive asthma. Of note, these individuals demonstrated higher IgE and higher eosinophil levels than everyone else, suggesting that they may 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 18 19 20]. These individuals warrant further evaluation.

The sensitivity analysis performed as part of this study raises the possibility that the traditional 12% and 200mL cut-off for BDR may 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 bronchodilator response in pediatric populations. Although improvements in FEV_1 of less than 8% after bronchodilator are considered to be within the natural variability of the measurement, improvements at or above this 8% cut-off may 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 200mLs, 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 $ß_2$- adrenergic agonists. Other predictors including genetic determinants may 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 BDR are currently under investigation[22, 23, 24].

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

In conclusion, as demonstrated in CAMP, children with asthma clearly have a heterogeneous response to $ß_2$- adrenergic agonists. Moreover, the response to bronchodilator therapy is clearly of prognostic significance in asthma. While 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 may lead to better treatment guidelines in the future.

Clinical Implication

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CAMP	Childhood Asthma Management Program
BDR	Bronchodilator Response
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
FF	Ratio of Forced Expiratory Volume in One Second over Forced Vital Capacity
IgE	Immunoglobulin E

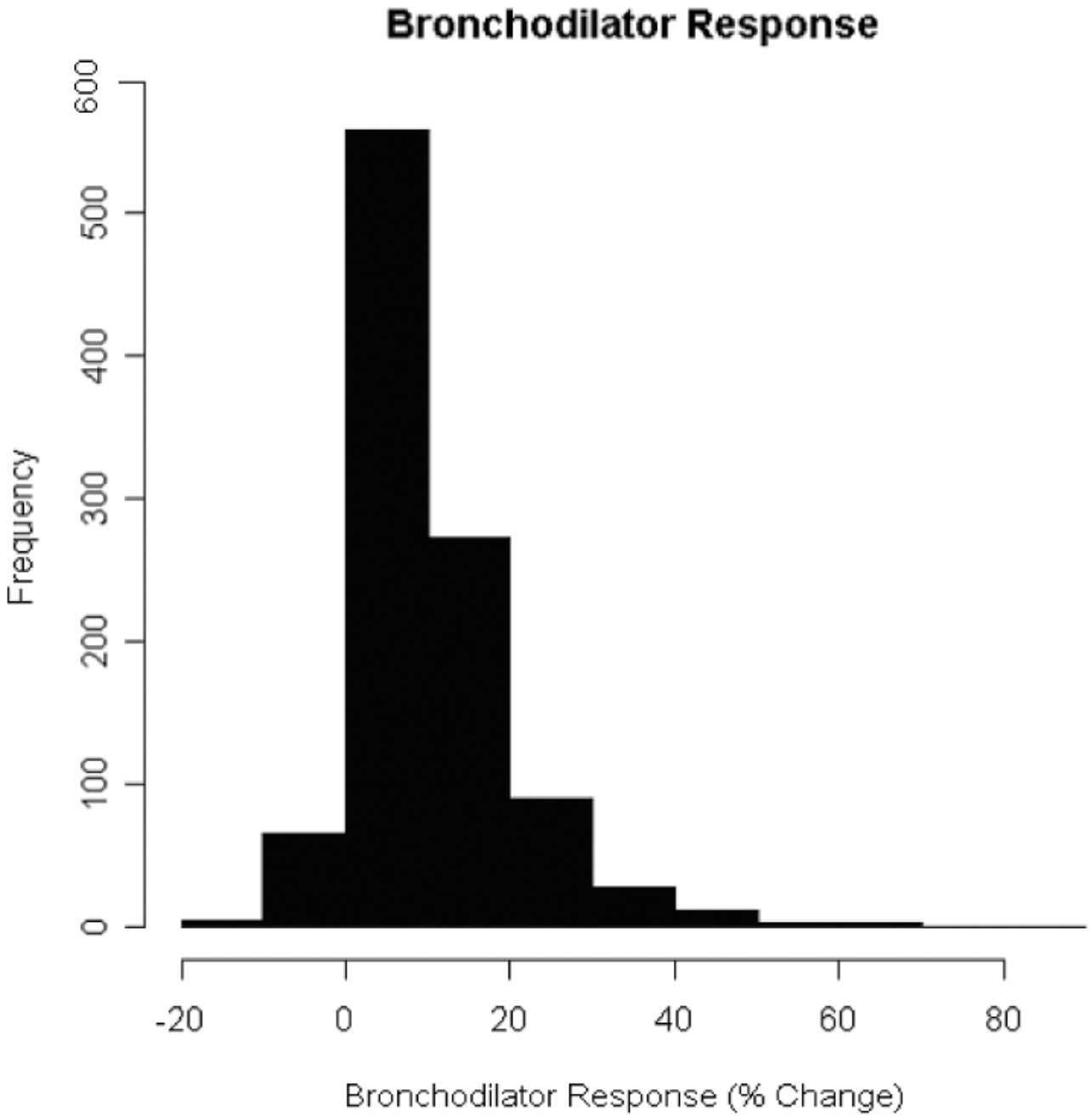

Figure 1. Distribution of Baseline Bronchodilator Response in CAMP

A histogram demonstrating the distribution of bronchodilator response at randomization of the 1,041 children participating in the Childhood Asthma Management Program.

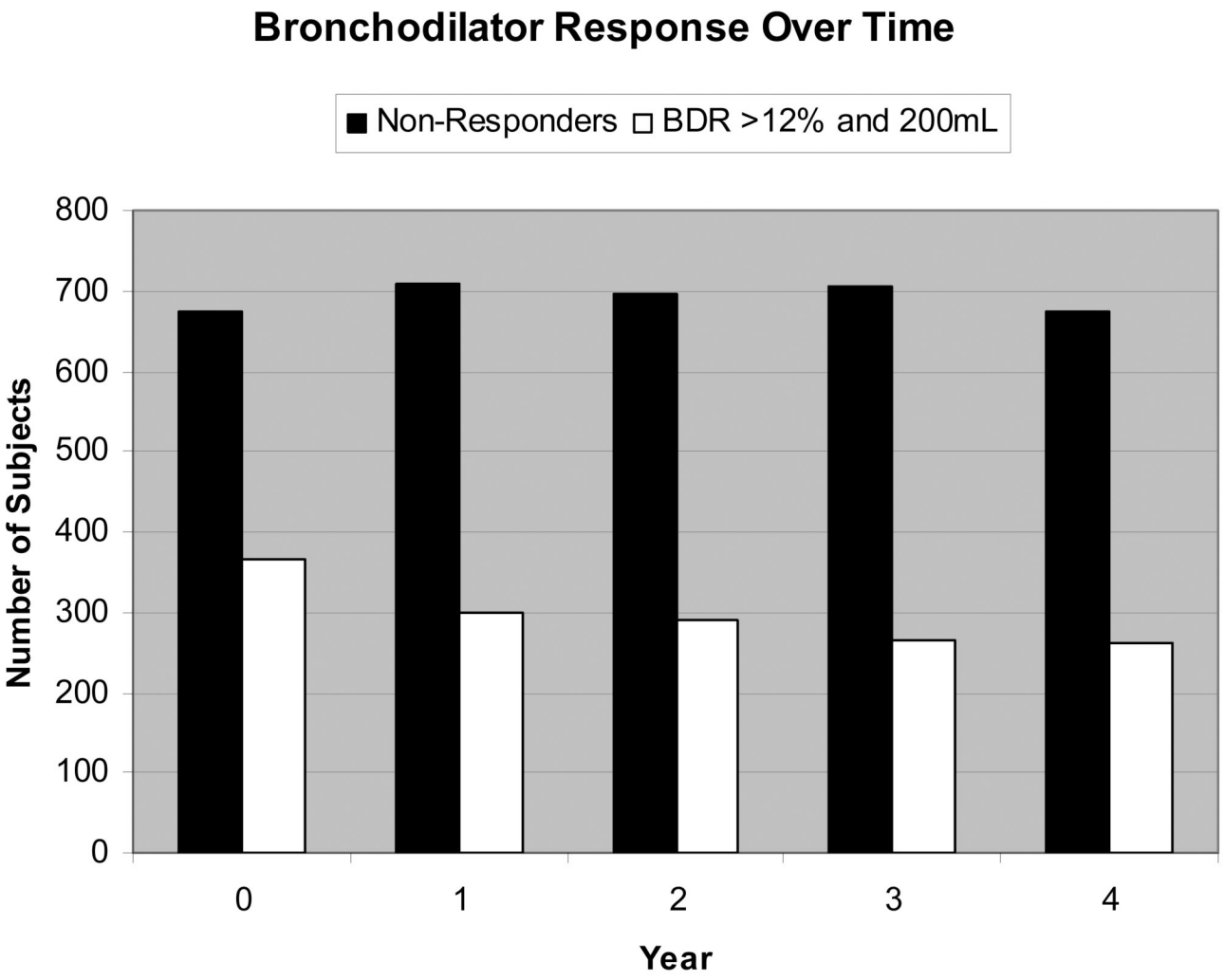

Figure 2. Number of Subjects with Bronchodilator Response at Each Yearly Follow-Up Visit

A graph demonstrating the number of subjects that had a positive bronchodilator response at each yearly follow-up visit. Non-responders (black) had less than a 12% and 200mLs improvement in FEV_1 following inhaled bronchodilator. Responders (white) had a BDR>12% and 200mLs.

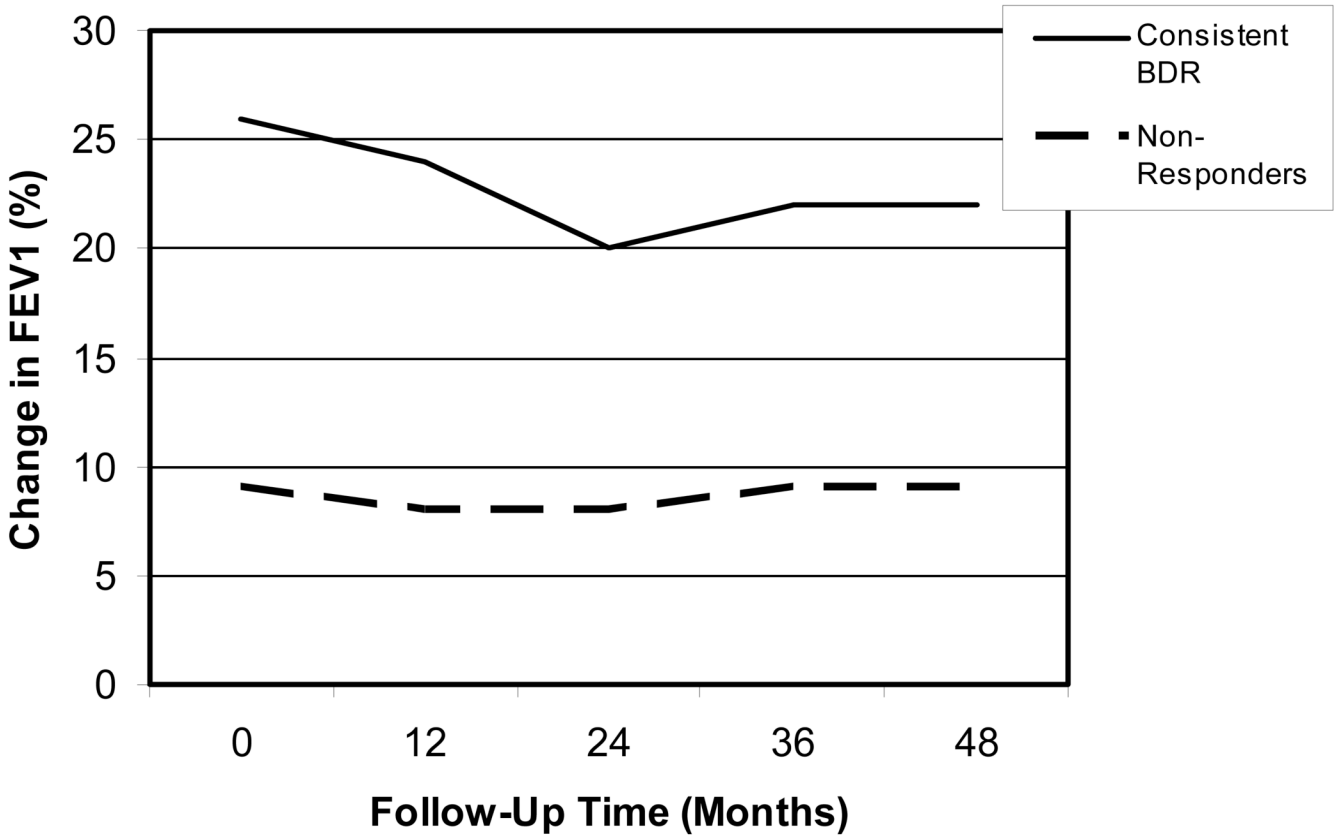

Figure 3. Mean Bronchodilator Response at Yearly Visits in Responders and Non-responders

Graph showing the mean bronchodilator response as the percent change in FEV_1 in consistent responders (solid line) versus non-responders (dashed line) at each of the yearly follow-up visits in the trial

Table 1

Characteristics of Patients Randomized in CAMP

Characteristic	Consistent BDR	Non-Responders	p value
N at Randomization	52	989	
Age at Randomization*	8.38 (1.9)	8.97 (2.0)	0.05
Age at Asthma Onset	2.27 (1.8)	3.11 (2.4)	0.002
Gender			0.11
Male	37(71%)	584(59%)	
Female	15(29%)	405 (41%)	
Race			0.07
White	34 (65%)	677(68%)	
African American	13 (25%)	125 (13%)	
Hispanic	3 (6%)	95(10%)	
Other Race	2 (4%)	92 (9%)	
Treatment Group			0.02
Budesonide	8(15%)	303 (31%)	
Nedocromil	17 (33%)	295 (29%)	
Placebo	27 (51%)	391 (40%)	
Baseline Height (cm)	131.02 (15.9)	133.68 (13.7)	0.18
Baseline BMI	17.93 (3.4)	18.18 (3.4)	0.63
Smoking History	0	0	
Intrauterine Smoke Exposure	13 (25%)	137 (14%)	0.04
Baseline Bronchodilator Response (%)	26%	9%	<0.0001
Baseline Pre-Bronchodilator FEV_1 (L)	1.45 (0.5)	1.67 (0.5)	<0.0001
Baseline Pre-Bronchodilator FVC (L)	1.96 (0.8)	2.09 (0.6)	0.24
Baseline Pre-Bronchodilator FEV1/FVC (%)	69.1 (8.1)	80.3 (8.0)	<0.0001
Baseline IgE Level** †	2.94 (0.6)	2.6 (0.7)	0.0007
Baseline PC_{20} **	-0.54 (1.0)	0.13 (1.2)	<0.0001
Baseline Eosinophil Level**	2.60 (0.5)	2.49(0.5)	0.15

Characteristic	Consistent BDR	Non-Responders	p value
Pre-Bronchodilator FEV_1 at 48 Month Follow-up Visit (% predicted)	80.1 (13.5)	93.6 (13.9)	<0.0001

* Mean (standard deviation)

† Median (interquartile range)

** Log transformed

Table 2

Baseline Predictors of Consistent Response to Bronchodilators: Results of the Multivariable Logistic Regression Model

Predictor	Odds Ratio	95% Confidence Interval	Bootstrap p value
Age (years)	0.71	0.50-1.01	0.34
Height (cm)	1.13	1.06-1.2	0.005
Gender (female)	0.47	0.24-0.93	0.25
Race (white)	0.57	0.29-1.2	0.21
Baseline Pre-bronchodilator FEV1 (L)	0.71	0.63-0.81	0.001
Inhaled Corticosteroid Treatment Group	0.31	0.13-0.75	0.001
Log IgE Level (IU/L)	1.97	1.18-3.3	0.001
Log PC_{20} (mg/ml)	0.77	0.57-1.03	0.01

Odds ratios and 95% Confidence Intervals for each variable obtained from multivariable logistic regression models adjusted for all variables in the table

** BDR>12% and 200mLs absolute change in FEV_1 at each yearly follow-up visit

Table 3

Association of Consistent Responder Status with Exacerbations and Symptoms over 4 Years*

Variable	Rate Ratio	95% Confidence Interval	p value
Hospital Visits (ED visits and hospitalizations)	1.80	1.20-2.80	0.007
Oral steroid bursts	1.52	1.20-1.95	0.0007
Nights awakened	1.40	1.20-1.65	<0.0001
School missed (days)	1.43	1.03-1.99	0.03

* Poisson regression models adjusted for age, gender, treatment group, and baseline pre-bronchodilator FEV_1

** BDR>12% and 200mLs absolute change in FEV_1 at each yearly follow-up visit

Table 4

Baseline Predictors of Short-term Consistent Response** to Bronchodilators: Results of the Multivariable Logistic Regression Model.

Predictor	Odds Ratio	95% Confidence Interval
Age (years)	0.87	0.66-1.16 (0.33)
Height (cm)	1.12	1.07-1.18 (<0.0001)
Gender (female)	0.80	0.47-1.35 (0.39)
Race (white)	0.65	0.38-1.28 (0.12)
Baseline Pre-bronchodilator FEV1 (L)	0.68	0.26-0.89 (<0.0001)
Inhaled Corticosteroid Treatment Group	0.48	0.26-0.89 (0.02)
Log IgE Level (IU/L)	1.89	1.23-2.92 (0.004)
Log PC_{20} (mg/ml)	0.83	0.66-1.06 (0.13)

Odds ratios and 95% Confidence Intervals for each variable obtained from multivariable logistic regression models adjusted for all variables in the table

** BDR>12% and 200mLs at randomization and the first two follow-up visits: (2 months and 4 months)

Table 5

Association of Short-term Consistent Response to Bronchodilators with Exacerbations and Symptoms over 4 Years *

Variable	Rate Ratio	95% Confidence Interval	p value
Hospital Visits (ED visits and hospitalizations)	1.53	1.24-1.89	<0.0001
Oral prednisone bursts	1.72	1.55-1.85	<0.0001
Nights awakened	1.36	1.30-1.43	<0.0001
School missed (days)	1.26	1.17-1.34	<0.0001

* Poisson regression models adjusted for age, gender, treatment group, and baseline pre-bronchodilator FEV_1

** BDR>12% and 200mLs at randomization and the first two follow-up visits: (2 months and 4 months)