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The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity

Devika R. Rao, MD[1], **Jonathan M. Gaffin, MD, MMSc**[1], **Sachin N. Baxi, MD**[2], **William J. Sheehan, MD**[2], **Elaine B. Hoffman, PhD**[3], and **Wanda Phipatanakul, MD, MS**[2]

[1]Department of Respiratory Diseases, Children's Hospital, Boston

[2]Department of Allergy and Immunology, Children's Hospital, Boston

[3]Harvard School of Public Health, Harvard Medical School, Boston, MA

Abstract

Objective—The forced expiratory volume in one second (FEV1), felt to be an objective measure of airway obstruction, is often normal in asthmatic children. The forced expiratory flow between 25% and 75% of vital capacity (FEF25-75) reflects small airway patency and has been found to be reduced in children with asthma. The aim of this study was to determine if FEF25-75 is associated with increased childhood asthma severity and morbidity in the setting of a normal FEV1, and to determine if bronchodilator responsiveness (BDR) as defined by FEF25-75 identifies more childhood asthmatics than does BDR defined by FEV1.

Methods—The Children's Hospital Boston Pulmonary Function Test database was queried and the most recent spirometry result was retrieved for 744 children diagnosed with asthma between 10–18 years of age between October 2000 and October 2010. Electronic medical records in the 1 year prior and the 1 year following the date of spirometry were examined for asthma severity (mild, moderate or severe) and morbidity outcomes for three age, race and gender-matched subgroups: group A (n= 35) had a normal FEV1, FEV1/FVC and FEF25-75; Group B (n= 36) had solely a diminished FEV1/FVC; and Group C (n=37) had a normal FEV1, low FEV1/FVC and low FEF25-75. Morbidity outcomes analyzed included the presence of hospitalization, emergency department visit, intensive care unit admission, asthma exacerbation, and systemic steroid use.

Results—Subjects with a low FEF25-75 (Group C) had nearly 3 times the odds (OR 2.8, $p<0.01$) of systemic corticosteroid use and 6 times the odds of asthma exacerbations (OR 6.3, $p>0.01$) compared with those who had normal spirometry (Group A). Using FEF25-75 to define bronchodilator responsiveness identified 53% more subjects with asthma than did using a definition based on FEV1.

Conclusions—A low FEF25-75 in the setting of a normal FEV1 is associated with increased asthma severity, systemic steroid use and asthma exacerbations in children. In addition, using the percent change in FEF25-75 from baseline may be helpful in identifying bronchodilator responsiveness in asthmatic children with a normal FEV1.

Corresponding Author: Wanda Phipatanakul, MD, MS, Children's Hospital Boston, Division of Allergy and Immunology, Fegan 6, 300 Longwood Ave., Boston, MA 02115, Phone: 617-355-6117; Fax: 617-730-0310, wanda.phipatanakul@childrens.harvard.edu. Devika Rao, MD, Children's Hospital Boston, Division of Respiratory Diseases, 300 Longwood Ave, Mailstop 208, Boston, MA 02215, Phone: 617-355-8803; Fax:, devika.rao@childrens.harvard.edu

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Keywords

spirometry; childhood asthma; FEF_{25-75}; bronchodilator responsiveness

Introduction

Asthma, the most common chronic pediatric condition, afflicts an estimated 7.1 million children in the United States (1) and is the reason for 13 million missed school days per year (2). Childhood asthma can often present a diagnostic challenge to the medical professional. Evidence of airway obstruction may not be present on exam, and the clinical history provided by the child and/or parent can be inaccurate (3, 4). The National Asthma Education and Prevention Program (NAEPP) Expert Review Panel-3 provides guidelines for the diagnosis and management of asthma and notes that spirometry is an essential objective method used in diagnosing asthmatic children (4). Furthermore, it is recommended to follow spirometry in order to monitor asthma control after therapy initiation.

A disadvantage to using spirometry in asthma management is that the forced expiratory volume in 1 second (FEV_1), which is felt to be reproducible and an appropriate measure of airway obstruction, is often normal even in children with symptoms of uncontrolled asthma (5–7). Therefore, it is difficult to utilize this variable both in the clinical setting and in epidemiological and clinical trials, in which reliable objective measures of clinical outcomes are needed to provide recommendations for practice. Although there are no recommendations regarding the utility of the percent predicted forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) by the American Thoracic Society (ATS) or the NAEPP, this measurement may have clinical significance in managing childhood asthma. The FEF_{25-75} is reflective of small airway patency and is reduced in asthmatics with a history of wheezing (8). However, the role of a low FEF_{25-75} in the context of normal FEV_1 in predicting asthma morbidity has not been well described.

The objectives of this study were to describe the distribution of spirometry values in a large cohort of asthmatic children and to determine if a low FEF_{25-75} in the setting of a normal FEV_1 is associated with significant asthma morbidity. Our hypothesis was that a low FEF_{25-75} would be associated with poor asthma outcomes in asthmatic children with a normal FEV_1. We also aimed to determine if a larger number of childhood asthmatics have bronchodilator responsiveness as defined by the percent change in FEF_{25-75} than defined by the percent change in FEV_1.

Materials and methods

Pulmonary Function Test database query

The Children's Hospital Boston Pulmonary Function Test (PFT) database (Morgan Scientific, Haverhill, MA) contains over 64,000 individual pulmonary function tests from 1986 to the present. The database was queried with the following inclusion criteria: age at testing from 10–18 years, date of test between October 2000 and October 2010, pre and post-bronchodilator testing, and diagnosis of asthma. The diagnosis was a physician-made diagnosis required at the time of spirometry testing and transferred into the database as an ICD-9 code listed for each subject. The most recent spirometry test was retrieved. Specifically, pre- and post-bronchodilator FEV_1 (expressed as percent predicted), FEV_1/FVC (actual ratio), FEF_{25-75} (expressed as percent predicted) and the percent change of each of these three variables after bronchodilation were retrieved from the database for analysis. Post-bronchodilator spirometry was obtained at least 15 minutes after patients received 5 mg of nebulized albuterol. Additionally, age at testing, race, gender, and date of test was

obtained. Age was restricted to 10–18 years old in order to increase the likelihood of reliable spirometry data as older children tend to have better technique. Subjects were excluded if they had a diagnosis of cystic fibrosis, bronchopulmonary dysplasia (BPD), scoliosis, or restrictive lung disease. This study was approved by the Children's Hospital, Boston Committee on Clinical Investigation (IRB).

Spirometry was performed with rolling-seal volume sensing spirometers (Morgan Scientific, Haverhill, MA, USA). Standard spirometry instruction was given prior to efforts and each effort was coached by an experienced PFT technician in a dedicated pediatric PFT laboratory housed in the pulmonary clinic. Spirometry was performed in the seated position with a nose clip. Multiple maneuvers were obtained from each patient, and the spirometry values associated with the best maneuver were input into the PFT database as the values for a specific date of testing. Thirty of the spirometric maneuvers were randomly reviewed by a single investigator to ensure that the test was in accordance with the American Thoracic Society guidelines for standardization of spirometry (9). Age, sex and ethnicity-appropriate prediction equations were used to calculate percent predicted values for FEV_1, FEV_1/FVC and FEF_{25-75} (10). Bronchodilator responsiveness (BDR) was calculated as the percent change from baseline for FEV_1, FEV_1/FVC and FEF_{25-75} given by the following equation using FEV_1 as an example: BDR = (post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / (pre-bronchodilator FEV_1) * 100

Comparison of subjects with normal spirometry to those with normal FEV_1 and abnormal FEF_{25-75}

A total of 756 subjects 10–18 years old had pre and post-bronchodilator spirometry measured. Twelve subjects were excluded from analysis as 10 had restrictive lung disease, 1 had cystic fibrosis and 1 had bronchopulmonary dysplasia (BPD).

Based on the 2007 NAEPP guidelines, the following values were used to identify normal spirometry values: $FEV_1 \geq 80\%$ predicted and $FEV_1/FVC \geq 85$ (11). A normal FEF_{25-75} was defined as ≥ 60% predicted. There are no published guidelines regarding normal values for FEF_{25-75}, therefore we used a value corresponding to one standard deviation from the mean FEF_{25-75} for all 744 spirometry results obtained from the initial query. The following values were used to define an abnormal BDR for each spirometric variable: $FEV_1 \geq 12\%$, FEF_{25-75} change ≥ 30%, which was obtained by using one standard deviation from the mean.

Electronic medical records in the 1 year prior and the 1 year following the date of spirometry were examined for asthma severity (mild, moderate or severe) and for morbidity outcomes for three age, race and gender-matched subgroups: group A (n= 35) had a normal FEV_1, FEV_1/FVC and FEF_{25-75}; Group B (n= 36) had a solely diminished FEV_1/FVC; and Group C (n=37) had a normal FEV_1, abnormal FEV_1/FVC and abnormal FEF_{25-75} (Figure 1). Age was considered matched if the two cases were born within 18 months of one another. For the purposes of this paper, Group A will be referred to as having "normal" spirometry, Group B as "the low FEV1/FVC" group, and Group C as "the low FEF_{25-75} group." Asthma severity was determined by the primary care, pulmonary or allergy physician documentation in the month during which the spirometry was obtained. In the absence of an explicitly documented classification, asthma severity was determined according to the NAEPP 2007 guidelines based on documented symptoms (12). The use of a controller medication including inhaled corticosteroid, oral leukotriene antagonist, long acting beta agonist or combination medication was also recorded. Morbidity outcomes included the presence of hospitalization, emergency department visit, intensive care unit admission, asthma exacerbation, and systemic steroid use. These outcomes were measured as binary variables.

Statistical Analysis

For this matched case-control study, odds ratios and 95% confidence intervals were computed as a ratio of discordant pairs. For this matched case-control study, odds ratios and 95% confidence intervals were computed as a ratio of discordant pairs. The cases were those subjects in either Groups B (low FEV_1/FVC) or C (low FEV_1/FVC and low FEF_{25-75}). Control subjects were matched for age (date of birth within 18 months of one another), gender and sex, and were classified into Group A, in which subjects had a normal FEV_1, normal FEV_1/FVC and normal FEF_{25-75}. A discordant pair was defined as 1) a pair in which the subject in either Group B or C had the specific adverse asthma outcome and the matched subject in the control (Group A) did not have that specific outcome or 2) a pair in which the control subject in Group A had the adverse asthma outcome and the corresponding matched subject in either Group B and C did not have that specific outcome. The odds ratio was computed as the ratio of number of discordant pairs. To test for symmetry (test of whether the marginal proportions are significantly different) in the matched-data tables, an exact binomial test was used in lieu of McNemar's for dichotomous outcomes because of the many small cell counts. Bowker's Test of Symmetry was calculated for asthma severity since it has three categories. The number of positive discordant pairs divided by the total number of discordant pairs was used as a proportion and tested against an exact binomial test at 0.5. Analyses were performed in SAS 9.1.3 (Cary, NC) or SPSS v19 (Chicago, IL).

Results

The categorization of subjects according to various spirometric abnormalities is shown in Figure 1. There were 654 subjects (88%) who had a normal FEV_1, and of these subjects, slightly more than half had an additionally normal FEV_1/FVC and FEF_{25-75}. There were 304 subjects with a normal FEV_1 (46%) who also had a low FEV_1/FVC. Of these 304 subjects with a normal FEV1 and low FEV_1/FVC, 48 subjects (16%) had a low FEF_{25-75}.

The average values for pre-bronchodilator FEV_1, FEV_1/FVC and FEF_{25-75} and bronchodilator response are depicted in Table 1 for subjects classified according to different spirometric abnormalities. The 48 subjects with an abnormal FEF_{25-75} and FEV_1/FVC had significantly lower mean spirometric values compared to those subjects with all normal spirometry ($n=350$, $p<0.01$) and to those with only a low FEV_1/FVC ($n=256$, $p<0.001$). The mean FEV_1 was 88% for this group, the mean FEV_1/FVC was 70 and the mean FEF_{25-75} was 52%. This group also had a significantly higher level of bronchodilator response ($p>0.001$) with mean values of 13%, 11% and 44% for FEV_1, FEV_1/FVC and FEF_{25-75}, respectively.

The bronchodilator responsiveness by either FEV_1 or FEF_{25-75} criteria for all 744 subjects is depicted in Table 2. The number of total cases with BDR present or absent according to the two different definitions is shown. A total of 120 (16%) subjects had BDR defined by FEV_1; however, using FEF_{25-75} as a marker of BDR identified an additional 64 subjects who otherwise would have not been identified when using a definition of BDR based on FEV_1. This represents a 53% increase in the number of subjects defined as having BDR. By contrast, 23 subjects who were identified as having BDR when using FEV_1 would have not otherwise been identified using FEF_{25-75}.

Selected demographics for all 744 subjects and for the three age, race and gender-matched subgroups used for analysis of asthma outcomes are shown in Table 3. The majority of the 744 subjects were white (86%). There was a higher percentage of black and Latino patients included in the subgroups compared to the profile of all subjects. The subjects were approximately 50% male across groups.

The percentages of subjects in the three matched groups with adverse clinical outcomes in the year before and after the date of spirometry are shown in Table 4. Seventy-two percent of subjects with normal spirometry values had mild asthma, while the low FEV_1/FVC and low FEF_{25-75} groups had a higher percentage of moderate and severe asthmatics. The low FEF_{25-75} group had the highest percentage of moderate (54%) and severe (27%) asthmatics overall. The low FEF_{25-75} group also had the highest percentage of subjects with hospitalizations, ICU admissions, ED visits, and exacerbations in the year before and after the date of the spirometry compared to the other groups.

The comparative severity and morbidity data of the three subgroups are depicted in Table 5. The FEF_{25-75} group had significantly higher asthma severity and controller medication use than the control group with normal spirometry. Additionally, the FEF_{25-75} group had nearly 3 times the odds of using systemic corticosteroids and 6 times the odds of asthma exacerbations than those subjects with normal spirometry. The low FEV_1/FVC group was also significantly associated with controller medication use, asthma severity and asthma exacerbations compared to those with normal spirometry. The subjects in the low FEF_{25-75} group did not have a higher risk of severity or morbidity compared with the subjects in the low FEV_1/FVC group.

Discussion

We used a large PFT database to investigate the association between a low FEF_{25-75} and adverse asthma outcomes. We found that having both a low FEF_{25-75} and a low FEV_1/FVC was significantly associated with steroid use, asthma exacerbations and asthma severity, as compared to children with normal spirometry. We also found that defining a positive BDR as a percent change in $FEF_{25-75} \geq 30\%$ increases the number of asthmatics identified compared with only using percent change in FEV_1, as recommended by the NAEPP. These findings provide evidence that FEF_{25-75} in the setting of a normal FEV_1, may be clinically useful in identifying asthmatic children who are at risk for poor asthma outcomes, and that FEF_{25-75} may be a valid outcome measure in clinical trials involving asthmatic children. Further, given that the majority of asthmatic children have a normal FEV_1, the finding that another spirometry measurement is associated with poor asthma outcomes has important implications for clinicians performing spirometry on asthmatic children and for investigators looking for useful asthma outcome measures.

Our study demonstrates that FEF_{25-75} may be a marker of more severe asthma as reflected by overall lower spirometry values and by increased asthma morbidity. We found that those subjects with a lower FEF_{25-75} had significantly lower mean values for FEV_1, FEV_1/FVC and FEF_{25-75}, and they also had a significantly higher bronchodilator response. Further, lower spirometry values in patients with a low FEF_{25-75} translated to worse clinical outcomes. Those asthmatic children with a low FEF_{25-75} had a higher percentage of hospitalizations, systemic steroid use, emergency department visits and asthma exacerbations than children with normal spirometry and those with an isolated low FEV_1/FVC. Thus, there is a small but important subset of asthmatic children with a normal FEV_1 and abnormal FEF_{25-75} who have poor asthma outcomes and likely require close follow-up and more aggressive management.

There are several important findings from our study that could influence the way in which spirometry is used to manage childhood asthma. The presence of lower spirometry values in asthmatic children with a diminished FEF_{25-75} is a novel finding applicable to clinicians who may not suspect the presence of airflow obstruction in the setting of a normal FEV_1. The association we found between low FEF_{25-75} and poor clinical outcomes has been previously described in asthmatic children in a retrospective manner(13); however, Klein et.

al. analyzed outcomes over a two week period while our study included outcomes over a two year period thus increasing the generalizability of the results. Low FEF_{25-75} has also been described as a potentially sensitive marker for airway obstruction (14) even in asymptomatic asthmatics (15) and has been shown to be a marker of methacholine responsiveness in asthmatic children (16). More recently, FEF_{25-75} was shown to predict bronchodilator responsiveness to albuterol (17). Our study further enhances the current understanding of a diminished FEF_{25-75} by identifying specific associated outcomes, namely increased asthma exacerbations, steroid use and asthma severity.

We also demonstrated that asthmatic children with an abnormal FEF_{25-75} had greater bronchodilator responsiveness than subjects with a normal FEF_{25-75}, an important finding given that BDR is associated with poor asthma control (18, 19). The mean BDR in the low FEF_{25-75} group was significantly higher than the average BDR values found in those subjects with normal spirometry and those with an isolated low FEF_1/FVC. Our findings are consistent with the results recently reported by Simon et. al., that an FEF_{25-75} below 65% predicted had a 90% sensitivity for detecting a 20% increase in FEV_1 after bronchodilation (17).

Although BDR has traditionally been defined as the percent change from baseline in FEV_1 after bronchodilator, we attempted to define BDR with the percent change in FEF_{25-75} to delineate a subgroup of asthmatics with a significant increase in small airway caliber after albuterol. We found that using the percent change in FEF_{25-75} to define BDR allowed identification of 53% more subjects who otherwise would be classified as bronchodilator non-responsive. Previous studies have attempted to define bronchodilator responsiveness based on different cutoffs for FEV_1, which range from ≥ 8% change from baseline to using a cutoff of ≥ 12% (18, 19). To our knowledge, our study is the first to describe known asthmatic children categorized as bronchodilator responsive based on FEF_{25-75}.

Our primary interest was to investigate whether a diminished FEF_{25-75} despite a normal FEV_1 reflects airflow obstruction resulting in poor asthma outcomes and worsened severity. The association between FEF_{25-75} and greater morbidity is best explained by how increased small airway obstruction is best reflected by FEF_{25-75}. Severe asthmatic children often have a normal FEV_1 with minimal to no large airway obstruction (5–7), but they may have small airway obstruction undetected by FEV_1 that results in worsened symptoms (20). Small airway obstruction has also been associated with ventilatory defects. De Lange et. al. reported that defects in ventilation detected by hyperpolarized helium-3 MRI were more concordant with an abnormal FEF_{25-75} than both FEV_1 and FEV_1/FVC in a group of asthmatics (21). In addition, FEF_{25-75} may be more sensitive to the increased dysanapsis found in asthma, where disproportionate growth of the airways and the lung parenchyma results in increased airway resistance and depressed mid-flow rates during exhalation (22).

The strengths of our study included the large numbers of subjects available for spirometry analysis in our database. We also utilized a partially prospective design by including the one year following the date of spirometry to determine associations with poor asthma outcomes. Therefore, our findings reflect, to some degree, the ability of FEF_{25-75} to predict future morbidity and severity.

We were limited by lack of well-established norms for a normal FEF_{25-75}. Our study used one standard deviation from the mean as our cutoff value. Other studies have utilized ranges from 60–80% (13–15, 23–25), while another reported that FEF_{25-75} of 65% was 92% specific for predicting bronchial hyperresponsiveness as measured by methacholine challenge (23). Also, the database used in this study was created within a tertiary care center, where more severe asthmatics are likely to seek treatment. Thus, it may be difficult

to generalize the results to a population with a lesser amount of acuity. The retrospective and cross-sectional nature of the study may have limited our ability to assess a full array of potentially confounding factors to the relationship between spirometry and outcomes. Another limitation was that we were unable to track medication compliance rates given the retrospective nature of our study. Also, our pulmonary function testing laboratory routinely uses the Knudson reference equations to generate percent predicted values, and the Knudson equations do not correct for non-white ethnicities and therefore error may have been introduced in our analysis. However, in our comparative analysis, we matched our groups according to age, race and gender, which should minimize the bias introduced by the Knudson reference equations. Finally, we used spirometry results from one point in time and did not assess for the increased variability for which FEF_{25-75} has often been criticized. However, our study suggests that FEF_{25-75} should not be dismissed based on its variability; it still appears to be a useful measurement of airflow limitation based on the clear associations we found with poor clinical outcomes. Further studies with multiple measurements may be helpful in determining whether different cutoff values for FEF_{25-75} is more sensitive and whether persistence of BDR defined by FEF_{25-75} yields poorer outcomes compared with BDR persistence defined by FEV_1.

In conclusion, in childhood asthmatics with a normal FEV_1, FEF_{25-75} should be considered as a potentially important spirometric variable that can be used as a marker of bronchodilator responsiveness, asthma severity and asthma exacerbations both in the clinical and research settings. Future longitudinal studies examining the utility of FEF_{25-75} are necessary in order to better understand the role of FEF_{25-75} in childhood asthma management and its utility as an outcome measure in clinical trials.

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Abbreviations

FEV_1	Forced expiratory volume in 1 second
FVC	forced vital capacity
FEF_{25-75}	forced expiratory flow between 25% and 75% of vital capacity
BDR	bronchodilator responsiveness
PFT	pulmonary function test

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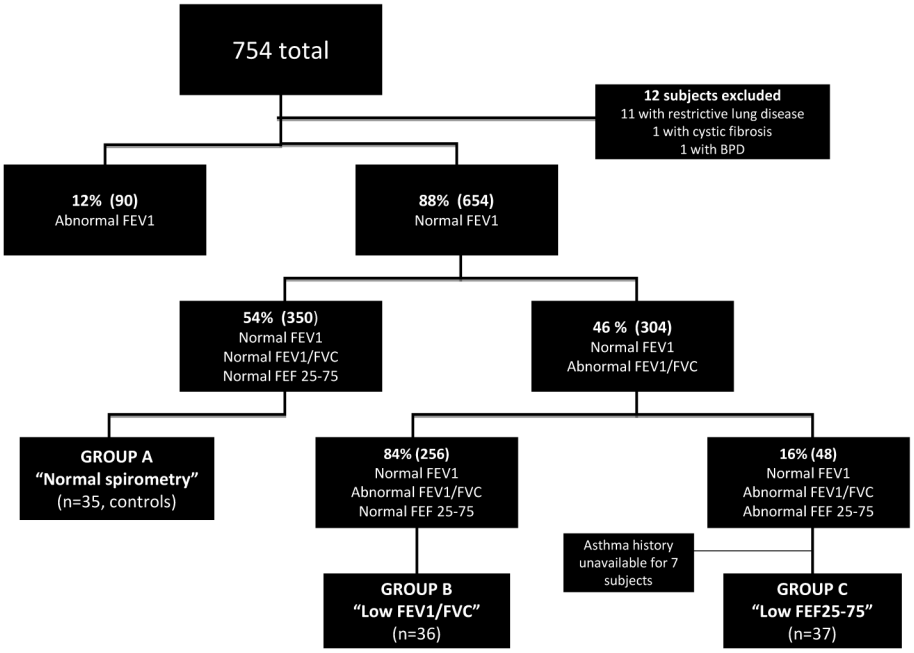

Figure 1.
Distribution of subjects according to spirometric abnormalities

Table 1

Mean values of spirometric variables for all subjects, expressed in % predicted (± SD)

	All subjects (n=744)	Normal FEV_1 Normal FEV_1/FVC Normal FEF_{25-75} (n= 350)	Normal FEV_1 Low FEV_1/FVC Normal FEF_{25-75} (n=256)	Normal FEV_1 Low FEV_1/FVC Low FEF_{25-75} (n=47)
FEV1				
Pre-Bronchodilator	98% (±18)	107% (±13)	100% (±11)	88% (±5) **
BDR	5% (±9)	1.4% (±5)	6% (±6)	13% (±9) **
FEV1/FVC (Ratio)				
Pre-Bronchodilator	83% (±10)	90% (±4)	79% (±4)	70% (±4) **
BDR	4% (±6)	1% (±4)	5% (±5)	11% (±6) **
FEF 25-75				
Pre-Bronchodilator	89% (±30)	112% (±20)	80% (±13)	52% (±5) **
BDR	17% (±26)	7% (±15)	18% (±20)	42% (±30) **

BDR: bronchodilator response, expressed as the percent change from baseline (± SD)

** significant difference compared to values in the two other subgroups (n=350 and n=256); p-value <0.001

Table 2

Cross-tabulation of all 744 subjects with normal and abnormal bronchodilator response (BDR) defined by FEF_{25-75} and FEV_1

	FEF25-75		
	BDR−	**BDR+**	**totals**
FEV1			
BDR−	560	64	624
BDR+	23	97	120
totals	583	161	744

BDR+: bronchodilator response was present; BDR− : bronchodilator response was absent

Table 3

Characteristics of all subjects, and of subjects analyzed in the three age, race, and gender-matched groups

	All subjects (n=744)	Normal Spirometry[a] (n=35)	Low FEV_1/FVC[b] (n=36)	Low $_{FEF25-75}$[c] (n= 37)
Age at testing				
10–12 yrs	39% (288)	34% (12)	36% (13)	38% (14)
13–15 yrs	38% (285)	20% (7)	25% (9)	14% (5)
16–18 yrs	23% (173)	46% (16)	39% (14)	48% (18)
Gender				
Male	54% (399)	49% (17)	50% (18)	49% (18)
Race				
White	86% (637)	66% (23)	64% (23)	62% (23)
Black	10% (74)	23% (8)	22% (8)	22% (8)
Latino	3% (25)	11% (4)	14% (5)	16% (6)
Asian	1% (6)	0% (0)	0% (0)	0% (0)

[a] normal FEV1, FVC and FEF25-75

[b] normal FEV1, low FEV_1/FVC, normal FEF25-75

[c] normal FEV1, low FEV_1/FVC, low FEF25-75

Table 4

Severity and morbidity of subjects with normal FEV1, low FEV1/FVC and low FEF 25-75 age, race, gender-matched controls

	Normal Spirometry[a] (n=35)	Low FEV_1/FVC[b] (n= 36)	Low FEF_{25-75}[c] (n = 37)
Severity of asthma			
Mild	72% (26)	39% (14)	19% (7)
Moderate persistent	19% (7)	47% (17)	54% (20)
Severe persistent	8% (21)	14% (5)	27% (10)
Clinical History			
Hospitalizations	20% (7)	19% (7)	30% (11)
ICU admissions	3% (1)	8% (21)	8% (21)
Steroids	28% (10)	50% (18)	60% (22)
ED visits	25% (9)	33% (12)	46% (17)
exacerbations	25% (9)	60% (22)	70% (26)
Use of controller	69% (25)	100% (36)	95% (35)

Groups are age, race, gender-matched;

[a] normal FEV_1, FEV_1/FVC and FEF_{25-75}

[b] normal FEV_1, low FEV_1/FVC, normal FEF_{25-75}

[c] normal FEV_1, low FEV_1/FVC, low FEF_{25-75}

Table 5

Comparison of morbidity between groups expressed as odds ratios and comparison of asthma severity expressed as test of symmetry

	Odds ratios (95% CI) C to A	Odds ratios (95% CI) B to A
ED visits	2.33 (0.84, 7.41)	1.5 (0.47, 5.12)
hospitalizations	1.67 (0.6, 5.6)	1 (0.07, 14)
ICU admission	3 (0.24, 16)	3 (0.24, 157)
Controller use	***6 (1.3, 55)*** *	***11 (1.6, 473)*** *
Steroid use (non ICS)	***2.8 (1.07, 8.78)***	2.6 (0.87, 9.3)
Asthma exacerbations	***6.3 (1.86, 33.42)*** **	***5.33 (1.53, 28.56)*** *
	Test of symmetry	*Test of Symmetry*
Asthma severity¥	***16.7*** **	***13.36*** *

Italics represents significant test with $p<0.05$.

* $p<0.01$;

** $p<0.001$

ED: emergency department; A: normal FEV_1, FEV_1/FVC and FEF_{25-75};

B: normal FEV_1, low FEV_1/FVC, normal FEF_{25-75}; C: normal FEV_1, low FEV_1/FVC, low FEF_{25-75}

¥ Bowker's test of symmetry for agreement