

Forced expiratory flow between 25% and 75% of vital capacity and FEV₁/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV₁ values

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Background: The assumption that the assessment of forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅) does not provide additional information in asthmatic

children with normal FEV₁ percent predicted has not been adequately tested.

Objective: We sought to determine whether the measurement of FEF₂₅₋₇₅ percent predicted offers advantages over FEV₁ percent predicted and FEV₁/forced vital capacity (FVC) percent predicted for the evaluation of childhood asthma.

Methods: This is a secondary analysis of data from the Pediatric Asthma Controller Trial and the Characterizing the Response to a Leukotriene Receptor Antagonist and Inhaled Corticosteroid trials. Pearson correlation coefficients, Pearson partial correlation coefficients, canonical correlations, and receiver operating characteristic (ROC) curves were constructed.

Results: Among 437 children with normal FEV₁ percent predicted, FEF₂₅₋₇₅ percent predicted, and FEV₁/FVC percent predicted were (1) positively correlated with log₂ methacholine PC₂₀, (2) positively correlated with morning and evening peak expiratory flow percent predicted, and (3) negatively correlated with log₁₀ fraction of exhaled nitric oxide and bronchodilator responsiveness. Pearson partial correlations and canonical correlations indicated that FEF₂₅₋₇₅ percent predicted was better correlated with bronchodilator responsiveness and log₂ methacholine PC₂₀ than were FEV₁ percent predicted or FEV₁/FVC percent predicted. In the ROC curve analysis, FEF₂₅₋₇₅ at 65% of predicted value had a 90% sensitivity and a 67% specificity for detecting a 20% increase in FEV₁ after albuterol inhalation. **Conclusion:** FEF₂₅₋₇₅ percent predicted was well correlated with bronchodilator responsiveness in asthmatic children with normal FEV₁. FEF₂₅₋₇₅ percent predicted should be evaluated in clinical studies of asthma in children and might be of use in predicting the presence of clinically relevant reversible airflow obstruction. (*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: FEF₂₅₋₇₅, bronchodilator responsiveness, asthma, FEV₁/FVC ratio, canonical correlations, ROC curves

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The guidelines of the American Thoracic Society do not suggest that the assessment of forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅) plays a significant role in the measurement of airflow obstruction^{1,2} and, by inference, in the clinical assessment of patients with airflow limitation. Recent studies have demonstrated that asthmatic patients might have ventilatory defects in the presence of a normal FEV₁.^{3,4} There are also

Abbreviations used

CLIC:	Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid
FEF ₂₅₋₇₅ :	Forced expiratory flow between 25% and 75% of vital capacity
FeNO:	Fraction of exhaled nitric oxide
FVC:	Forced vital capacity
NNT:	Number needed to treat
PACT:	Pediatric Asthma Controller Trial
PEF:	Peak expiratory flow
ROC:	Receiver operating characteristic

studies that suggest that FEF₂₅₋₇₅ is more sensitive as an indicator of symptomatic asthma than FEV₁ in children,⁵⁻⁷ as well as adults.^{8,9} Because it does not include flows high in the lung volume, FEF₂₅₋₇₅ is theoretically less effort dependent than FEV₁ and is believed to be a measurement of small airway patency.¹⁰⁻¹² Similarly, FEV₁/forced vital capacity (FVC) ratio has been found to correlate with symptoms and medication use in children, whereas FEV₁ does not.¹³

The current study is a secondary analysis of pulmonary function data derived from 2 multicenter pediatric asthma clinical trials conducted by the Childhood Asthma Research and Education Network and funded by the National Heart, Lung, and Blood Institute: the Pediatric Asthma Controller Trial (PACT)¹⁴ and the Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC) trial.¹⁵

The objective of this study was to determine whether measurement of FEF₂₅₋₇₅ in children contributes additional information about clinical variables and airway inflammation to the information obtained from the gold standard measurement of FEV₁.

METHODS

We evaluated baseline lung function in relation to clinical and physiological outcome data from 2 National Heart, Lung, and Blood Institute Childhood Asthma Research and Education network studies: the PACT and the CLIC trial. PACT¹⁴ enrolled 413 children between the ages of 6 and 14 years with mild-to-moderate persistent asthma. There was a 2- to 4-week run-in period. The CLIC trial¹⁵ enrolled 191 children between the ages of 6 and 17 years with mild-to-moderate persistent asthma. There was a 7- to 10-day run-in period. The CLIC trial excluded children with FEV₁ of less than 70% of predicted value. Children who completed the run-in periods were potentially eligible for entry into this analysis of baseline and run-in data.

An electronic peak flowmeter (AM1; Jaeger-Toennies GmbH, Hoechberg, Germany) was used. Twice-daily entries of asthma symptoms, nighttime awakenings, and rescue albuterol use were recorded in a weekly diary. At the end of the run-in period, the diary and electronic peak flowmeter data were recorded. Subjects with less than 80% compliance in the diary documentation of peak expiratory flow (PEF) measurements, symptom scores, and albuterol use were excluded. Spirometry was performed by Childhood Asthma Research and Education Network–certified pulmonary function technicians, with rereading of results from all sites performed by 2 persons according to a standardized manual of operation to ensure consistency. The tests were performed by using a pneumotachograph-type spirometer interfaced with a personal computer system (Jaeger-Toennies GmbH). Equipment and testing procedures for the maximal expiratory flow-volume maneuvers met American Thoracic Society 1994 spirometric standards,^{16,17} with techniques modified for children less than 8 years of age, as described by Eigen et al¹⁸ and Arets et al.¹⁹ Age-, sex-, and ethnicity-appropriate prediction equations²⁰ were used to calculate percent predicted values for FEV₁ and FVC. Spirometry was performed at least 4 hours after the last use of a short-acting bronchodilator. Bronchodilator responsiveness was tested by repeating spirometry after

administering 4 to 8 puffs of albuterol with a valved holding chamber in a graded maximal bronchodilation test. Exhaled nitric oxide was measured with the NIOX device (Aerocrine, Inc, New Providence, NJ), according to recommended procedures.²¹

White and African American children aged 6 to 7 years were excluded from our analyses because we did not have reliable FEF₂₅₋₇₅ predicted equations for them. Only baseline and run-in data before randomization were analyzed. There were 272 PACT children and 165 CLIC trial children with sufficient baseline data to be included in these secondary analyses. All of the correlational analyses described below were applied to the combined data set with $272 + 165 = 437$ PACT and CLIC children, with an adjustment for the binary indicator of the child's enrolled study.

The baseline measurements were partitioned into 2 distinct sets. Set 1 consisted of the 3 spirometric variables (FEV₁ percent predicted, FEF₂₅₋₇₅ percent predicted, and FEV₁/FVC percent predicted, all before bronchodilation). Set 2 consisted of 9 variables describing clinical (diary symptoms, diary rescue albuterol use, Asthma Control Questionnaire²² scores, and prior asthma hospitalization) and physiological outcomes (morning and evening diary PEF percent predicted, maximum bronchodilator response as a percentage change in FEV₁, methacholine PC₂₀, and fraction of exhaled nitric oxide [FeNO]). Methacholine PC₂₀ values were transformed to log₂ and FeNO values were transformed to log₁₀ to normalize their distributions. The percent predicted spirometric values that we used in the analyses are adjusted for sex, race, height, and age. All of the correlational analyses described below also are adjusted for asthma duration, age at asthma onset, atopic status, and body mass index.

Pearson correlation coefficients and Pearson partial correlation coefficients were constructed between the spirometric variables and the outcome variables. The partial correlation coefficient between a spirometric variable and each of the outcome variables was adjusted for the presence of the remaining 2 spirometric variables. Thus the partial correlation coefficient indicates whether a spirometric variable is correlated with an outcome variable after accounting for the other 2 spirometric variables.

Canonical correlations, a generalization of Pearson correlations, were also performed to determine how 2 sets of variables relate to one another.²³ The Pearson correlation coefficient investigates the linear relationship between 1 spirometric variable and 1 outcome variable. The Pearson partial correlation coefficient demonstrates the linear relationship between 1 spirometric variable and 1 outcome variable while accounting for the other spirometric variables. There are 9 outcome variables and 3 spirometric variables. Therefore the Pearson correlations and the Pearson partial correlations do not provide an adequately thorough analysis and interpretation of the complex relationships that might exist between the set of spirometric variables and the set of outcome variables. Canonical correlation analysis is a multivariate statistical method. It finds the linear combinations of 2 sets of variables that have the largest Pearson correlation. It is a generalization of a Pearson correlation coefficient and investigates the relationships between the 2 sets of variables.

The basic steps of a canonical correlation analysis are as follows:

1. The pair of linear combinations of the 2 sets of variables (sets 1 and 2) that has the largest Pearson correlation is determined. This is called variate pair 1, and the correlation between the 2 linear combinations is the first canonical correlation.
2. Variate pair 2 is the pair of linear combinations that have the largest correlation among all those linear combination pairs that are uncorrelated with variate pair 1, yielding the second canonical correlation.
3. This process is continued until the number of variate pairs equals the number of variables in the smaller of the 2 variable sets. With respect to the PACT and CLIC trial datasets, there were 3 spirometric variables in set 1 and 9 outcome variables in set 2. Thus a maximum of 3 variate pairs and their corresponding canonical correlations can be constructed, although not all 3 of the canonical correlations actually can be statistically significant. The magnitudes of the coefficients of the variables in the variate pairs with significant canonical correlations indicate which variables within set 1 are strongly correlated with variables within set 2.

All correlations were performed with the combined data from PACT and the CLIC trial. These analyses were also performed with the data from each trial separately.

TABLE I. Baseline characteristics of the CLIC trial and PACT cohorts

Baseline characteristics	CLIC trial	PACT	<i>P</i> value* comparing CLIC trial and PACT	CLIC trial and PACT combined
Baseline participants, no.	151	328	—	479
Age (y)	12.8 ± 2.8	10.9 ± 1.7	<.0001	11.5 ± 2.3
Male sex, no. (%)	91 (60.3)	201 (61)	.8323	292 (61)
White, no. (%)	111 (74)	243 (74)	.8940	354 (74)
Hispanic or Latino, no. (%)	40 (27)	82 (25)	.7280	122 (25)
BMI (kg/m ²)	21.8 ± 5.6	21.1 ± 5.1	.2008	21.3 ± 5.3
Duration of asthma (y)	7.6 ± 4.0	6.5 ± 3.3	.0017	6.8 ± 3.6
Spirometric outcomes				
FEV ₁ % predicted	93.9 ± 14.3	98.2 ± 12.6	.0030	96.7 ± 13.3
FEF ₂₅₋₇₅ % predicted	67.3 ± 22.7	73.8 ± 21.4	.0040	71.4 ± 22.1
FEV ₁ /FVC % predicted	90.8 ± 9.6	93.0 ± 8.6	.0511	92.3 ± 9.0
Clinical outcomes				
Diary symptoms (cough and wheeze), 1 wk	0.54 ± 0.43	0.49 ± 0.36	.2474	0.51 ± 0.38
Diary rescue albuterol use	0.82 ± 1.07	0.82 ± 1.00	.9928	0.82 ± 1.02
ACQ score	1.05 ± 0.76	1.14 ± 0.57	.2485	1.11 ± 0.64
Prior hospitalizations, past year	0.26 ± 0.44	0.24 ± 0.43	.5724	0.25 ± 0.43
Diary morning PEF % predicted	76.7 ± 13.4	76.9 ± 15.0	.8703	76.9 ± 14.4
Diary evening PEF % predicted	79.3 ± 13.4	78.7 ± 15.4	.6855	78.9 ± 14.7
Physiological outcomes				
Maximal BD response (% change in FEV ₁)	14.9 ± 10.3	9.4 ± 7.2	<.0001	11.1 ± 8.7
Log ₂ (PC ₂₀ methacholine)	3.3 ± 4.5	2.2 ± 2.8	.0321	2.5 ± 3.4
Log ₁₀ (FeNO)	1.5 ± 0.4	1.4 ± 0.4	.0041	1.4 ± 0.4

ACQ, Asthma Control Questionnaire; BD, bronchodilator; BMI, body mass index.

**P* values were calculated by using the χ^2 test (for categorical variables) or Student *t* test (for continuous variables).

Finally, receiver operating characteristic (ROC) curves were calculated for FEF₂₅₋₇₅ percent predicted and FEV₁/FVC percent predicted to evaluate their sensitivity and specificity in predicting bronchodilator responsiveness.²⁴ We chose to use a prebronchodilator to postbronchodilator increase in FEV₁ of 20% as the target value for the ROC curve because a 12% response was a potential entry criterion for the CLIC trial and because a 20% increase in FEV₁ represents a clinically relevant response.

The PACT and CLIC trial data were also analyzed independently so that those analyses could be compared with each other and with the analyses of the combined data.

RESULTS

Table I shows the baseline characteristics of the CLIC trial and PACT cohorts. The PACT children were slightly younger and had a shorter duration of asthma, higher FEV₁ percent predicted, higher FEF₂₅₋₇₅ percent predicted, lower maximum bronchodilator response, lower methacholine response, and lower exhaled nitric oxide than the CLIC trial children.

Pearson correlation coefficients

The estimated Pearson correlations among the 3 prebronchodilator spirometric variables appear in Table II. The estimated correlations for the combined PACT and CLIC trial data were relatively strong, although they did not exceed 0.80. Therefore multicollinearity was not an issue of concern in the ensuing analyses and results. Similar results were found when the PACT and CLIC trial data were analyzed separately (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org).

The Pearson correlations between the spirometric variables and the outcome variables appear in Table III. None of the spirometric variables was significantly correlated with asthma symptoms, and only FEF₂₅₋₇₅ and FEV₁/FVC demonstrated small negative correlations with rescue albuterol use. However, all variables did demonstrate significant negative correlations with the Asthma Control

TABLE II. CIs and *P* values for testing null correlations among spirometric variables using combined PACT and CLIC trial baseline data

	FEV ₁ % predicted	FEF ₂₅₋₇₅ % predicted	FEV ₁ /FVC % predicted
FEV ₁ % predicted		0.69 (0.62-0.75), <i>P</i> < .0001	0.58 (0.50-0.66), <i>P</i> < .0001
FEF ₂₅₋₇₅ % predicted	0.69 (0.62-0.75), <i>P</i> < .0001		0.79 (0.74-0.83), <i>P</i> < .0001
FEV ₁ /FVC % predicted	0.58 (0.50-0.66), <i>P</i> < .0001	0.79 (0.74-0.83), <i>P</i> < .0001	

Questionnaire score, and FEF₂₅₋₇₅ demonstrated a small negative correlation with prior asthma hospitalization. There was a higher level of correlation between the spirometric variables and the physiological outcomes, including morning and evening PEF percent predicted, bronchodilator response as a percentage change in FEV₁, methacholine PC₂₀, and FeNO. In general, FEF₂₅₋₇₅ and FEV₁/FVC percent predicted were better correlated with the physiological outcome variables than was FEV₁ percent predicted. Indeed, the strongest estimated correlation in Table III was between FEF₂₅₋₇₅ percent predicted and maximum bronchodilator response, in which the *r* value was −0.56 with a 95% CI of −0.62 to −0.49. Similar results were found when the PACT and CLIC trial data were analyzed separately (see Tables E3 and E4 in this article's Online Repository at www.jacionline.org).

Pearson partial correlation coefficients

The Pearson partial correlations also appear in Table III (in columns that are adjacent to the Pearson correlations). The Pearson partial correlation between a spirometric variable and an outcome

TABLE III. Pearson correlation and partial correlation coefficients (with 95% CIs and *P* values for testing null correlations) of spirometric variables with clinical variables using combined PACT and CLIC trial baseline data

	FEV ₁ % predicted correlations	FEV ₁ % predicted partial correlations	FEV ₁ % predicted partial correlations (partialling out clinical variables)	FEF ₂₅₋₇₅ % predicted correlations
Clinical outcomes				
Diary symptoms (cough and wheeze)	0.07 (−0.03 to 0.17), <i>P</i> = .16	0.02 (−0.09 to 0.14), <i>P</i> = .70	0.01 (−0.12 to 0.13), <i>P</i> = .92	0.01 (−0.08 to 0.11), <i>P</i> = .78
Diary rescue albuterol use	−0.09 (−0.19 to 0.01), <i>P</i> = .08	−0.05 (−0.17 to 0.06), <i>P</i> = .44	−0.06 (−0.18 to 0.07), <i>P</i> = .38	−0.13 (−0.23 to −0.03), <i>P</i> = .008
ACQ score	−0.23 (−0.32 to −0.13), <i>P</i> < .0001	−0.19 (−0.21 to 0.02), <i>P</i> = .12	−0.10 (−0.22 to 0.02), <i>P</i> = .10	−0.17 (−0.27 to −0.07), <i>P</i> = .001
Prior hospitalizations	−0.11 (−0.21 to 0.01), <i>P</i> = .03	0.03 (−0.09 to 0.14), <i>P</i> = .65	0.03 (−0.09 to 0.16), <i>P</i> = .59	−0.14 (−0.23 to −0.04), <i>P</i> = .005
Physiological outcomes				
Diary morning PEF % predicted	0.38 (0.29 to 0.46), <i>P</i> < .0001	0.30 (0.19 to 0.40), <i>P</i> < .0001	0.30 (0.19 to 0.40), <i>P</i> < .0001	0.28 (0.18 to 0.37), <i>P</i> < .0001
Diary evening PEF % predicted	0.35 (0.26 to 0.44), <i>P</i> < .0001	0.28 (0.17 to 0.38), <i>P</i> < .0001	0.30 (0.18 to 0.40), <i>P</i> < .0001	0.24 (0.15 to 0.33), <i>P</i> < .0001
Maximal BD response (% change in FEV ₁)	−0.24 (−0.33 to −0.14), <i>P</i> < .0001	0.23 (0.12 to 0.33), <i>P</i> < .0001	0.25 (0.13 to 0.36), <i>P</i> < .0001	−0.56 (−0.62 to −0.49), <i>P</i> < .0001
Log ₂ (PC ₂₀ methacholine)	0.27 (0.17 to 0.37), <i>P</i> < .0001	0.10 (−0.03 to 0.22), <i>P</i> = .12	0.10 (−0.03 to 0.22), <i>P</i> = .12	0.36 (0.26 to 0.45), <i>P</i> < .0001
Log ₁₀ (FeNO)	−0.13 (−0.23 to −0.03), <i>P</i> = .01	0.04 (−0.07 to 0.16), <i>P</i> = .47	0.07 (−0.05 to 0.19), <i>P</i> = .27	−0.22 (−0.31 to −0.13), <i>P</i> < .0001

ACQ, Asthma Control Questionnaire; BD, bronchodilator.

variable is adjusted for the presence of the other 2 spirometric variables. Table III indicates that FEF₂₅₋₇₅ percent predicted and FEV₁/FVC percent predicted are not correlated with diary morning and evening PEF percent predicted when one accounts for FEV₁ percent predicted. In particular, (1) the Pearson correlation between FEF₂₅₋₇₅ percent predicted and diary morning PEF percent predicted is 0.28, but the Pearson partial correlation is 0.02, and (2) the Pearson correlation between FEV₁/FVC percent predicted and diary morning PEF percent predicted is 0.28, but the Pearson partial correlation is 0.06.

The Pearson partial correlation between FEF₂₅₋₇₅ percent predicted and maximum bronchodilator response as a percentage change in FEV₁ is not very different from the Pearson correlation (−0.49 and −0.56, respectively), whereas the Pearson partial correlation between FEV₁/FVC percent predicted and bronchodilator response is drastically lower in magnitude than its Pearson correlation (0.12 and −0.38, respectively). This means that there is a strong correlation between FEF₂₅₋₇₅ percent predicted and bronchodilator response after adjustment for the presence of the other 2 spirometric variables of FEV₁ percent predicted and FEV₁/FVC percent predicted. The Pearson partial correlation between FEV₁ percent predicted and maximum bronchodilator response does not change in magnitude, but it does change in sign (0.23 and −0.24, respectively). Nevertheless, the Pearson partial correlation between FEV₁ percent predicted and maximum bronchodilator response is much weaker than the Pearson partial correlation between FEF₂₅₋₇₅ percent predicted and maximum bronchodilator response (0.23 and −0.49, respectively). Thus FEF₂₅₋₇₅ percent predicted appears to be the most important of the 3 spirometric variables in terms of a relationship with maximum bronchodilator response as a percentage change in FEV₁.

Canonical Correlation coefficients

The results of the canonical correlation analysis appear in Table IV. Only the first 2 canonical correlations are statistically significant (0.65, *P* < .0001; 0.46, *P* < .0001). For the first canonical correlation, the pair of linear combinations of the spirometric variables (set 1) and the clinical variables (set 2) that have the largest Pearson correlation was determined. The standardized coefficients of the canonical correlation indicate that the clinical set of variables depends most on maximum bronchodilator response as a percentage change in FEV₁ (−0.61) and, to a lesser extent, on the diary morning PEF percent predicted (0.32) and the log₂ (PC₂₀ methacholine) value (0.41), whereas the spirometric variables depend most on FEF₂₅₋₇₅ percent predicted (0.88). For the second canonical correlation, the pair of linear combinations of the clinical variables and spirometric variables (variate pair 2) that has the largest Pearson correlation while being uncorrelated with variate pair 1 was determined. The standardized coefficients of the second canonical correlation indicate that the clinical set of variables depends most on diary morning PEF percent predicted (0.82) and the maximum bronchodilator response (0.77), whereas the spirometric variables depend most on FEF₂₅₋₇₅ percent predicted (−1.40) and FEV₁ percent predicted (1.25). The third canonical correlation is not significant (*P* = .23), which indicates that there are no other linear relationships between the clinical and spirometric variables (variate pair 3). The canonical correlation analysis confirms the importance of the relationship between FEF₂₅₋₇₅ percent predicted and the maximum bronchodilator response as a percentage change in FEV₁. Similar results were found when the PACT and CLIC trial data were analyzed separately (see Tables E5 and E6 in this article's Online Repository at www.jacionline.org).

FEF ₂₅₋₇₅ % predicted partial correlations	FEF ₂₅₋₇₅ % predicted partial correlations (partialling out clinical variables)	FEV ₁ /FVC % predicted correlations	FEV ₁ /FVC % predicted partial correlations	FEV ₁ /FVC % predicted partial correlations (partialling out clinical variables)
-0.01 (-0.13 to 0.10), <i>P</i> = .78	-0.03 (-0.15 to 0.09), <i>P</i> = .64	-0.02 (-0.13 to 0.10), <i>P</i> = .78	0.02 (-0.13 to 0.10), <i>P</i> = .77	0.04 (-0.09 to 0.16), <i>P</i> = .54
-0.07 (-0.18 to 0.05), <i>P</i> = .23	-0.05 (-0.18 to 0.07), <i>P</i> = .40	-0.21 (-0.32 to -0.10), <i>P</i> = .0002	-0.05 (-0.16 to 0.07), <i>P</i> = .44	-0.05 (-0.17 to 0.08), <i>P</i> = .44
0.04 (-0.07 to 0.16), <i>P</i> = .49	0.00 (-0.12 to 0.13), <i>P</i> = .98	-0.23 (-0.33 to -0.11), <i>P</i> < .0001	-0.14 (-0.25 to -0.02), <i>P</i> = .02	-0.09 (-0.21 to 0.03), <i>P</i> = .15
-0.11 (-0.22 to 0.01), <i>P</i> = .07	-0.08 (-0.20 to 0.04), <i>P</i> = .19	-0.02 (-0.13 to 0.10), <i>P</i> = .74	0.07 (-0.04 to 0.19), <i>P</i> = .21	0.06 (-0.07 to 0.18), <i>P</i> = .35
0.02 (-0.13 to 0.10), <i>P</i> = .77	-0.01 (-0.12 to 0.11), <i>P</i> = .89	0.28 (0.17 to 0.39), <i>P</i> < .0001	0.06 (-0.06 to 0.17), <i>P</i> = .34	0.04 (-0.07 to 0.16), <i>P</i> = .47
0.01 (-0.12 to -0.11), <i>P</i> = .89	0.00 (-0.13 to 0.12), <i>P</i> = .97	0.23 (0.12 to 0.33), <i>P</i> < .0001	0.02 (-0.10 to 0.13), <i>P</i> = .79	0.00 (-0.12 to 0.12), <i>P</i> = .99
-0.49 (-0.58 to -0.40), <i>P</i> < .0001	-0.49 (-0.58 to -0.39), <i>P</i> < .0001	-0.38 (-0.47 to -0.27), <i>P</i> < .0001	0.12 (0.00 to 0.23), <i>P</i> = .05	0.11 (-0.02 to 0.23), <i>P</i> = .09
0.16 (0.03 to 0.28), <i>P</i> = .01	0.15 (0.03 to 0.27), <i>P</i> = .02	0.40 (0.30 to 0.51), <i>P</i> < .0001	0.10 (-0.03 to 0.22), <i>P</i> = .16	0.08 (-0.05 to 0.20), <i>P</i> = .23
-0.10 (-0.21 to -0.02), <i>P</i> = .02	-0.09 (-0.21 to 0.03), <i>P</i> = .15	-0.25 (-0.35 to -0.13), <i>P</i> < .0001	-0.09 (-0.20 to 0.03), <i>P</i> = .13	-0.07 (-0.19 to 0.06), <i>P</i> = .30

Receiver operating characteristic curves

Because there is controversy regarding which FEF₂₅₋₇₅ percent predicted value differentiates normal versus abnormal findings, a receiver operating characteristic (ROC) curve of FEF₂₅₋₇₅ percent predicted and bronchodilator response as a percentage change in FEV₁ was constructed. The inflection point indicated that the greatest sensitivity and specificity was found with an FEF₂₅₋₇₅ percent predicted of 68%. In particular, the FEF₂₅₋₇₅ at 68% of predicted value had a 94% sensitivity and a 63% specificity for detecting a 20% increase in FEV₁ after albuterol inhalation (Fig 1). The area under the curve was 0.88. For a bronchodilator response of a 12% increase in FEV₁, the area under the curve was 0.77, with no clear inflection point. Similar results were found when the PACT and CLIC trial data were analyzed separately (see Fig E1 in this article's Online Repository at www.jacionline.org). An ROC curve of FEV₁/FVC percent predicted and bronchodilator response also was constructed. The inflection point that had the greatest sensitivity and specificity for FEV₁/FVC percent predicted was found at 95%. The FEV₁/FVC ratio at 95% of predicted value had an 87% sensitivity and a 70% specificity for detecting a 20% increase in FEV₁ after albuterol inhalation. The area under the curve was 0.83. A meaningful ROC curve could not be constructed for an FEV₁ percent predicted that had an area under the curve of 0.62 and no inflection point that could be used to indicate the greatest sensitivity and specificity. Similar results were found when the PACT and CLIC trial data were analyzed separately (see Fig E2 in this article's Online Repository at www.jacionline.org).

To calculate the number needed to test (NNT), we selected the cutoff points that yield equivalent values for sensitivity and

TABLE IV. Canonical correlation analysis between spirometric variables and clinical variables using combined PACT and CLIC trial baseline data

Combined PACT and CLIC trial canonical variate pairs: Standardized coefficients			
	Variate pair 1	Variate pair 2	Variate pair 3
Diary morning PEF % predicted	0.32	0.82	-1.43
Diary evening PEF % predicted	0.05	-0.22	1.94
Maximal BD response (% change in FEV ₁)	-0.61	0.77	-0.17
Log ₂ (PC ₂₀)	0.41	0.20	-0.13
Diary symptoms (cough and wheeze)	0.11	0.32	-0.35
Diary rescue albuterol use	-0.01	-0.14	0.07
Log ₁₀ (FeNO)	-0.01	0.07	0.46
ACQ score	-0.17	-0.37	0.21
Prior hospitalizations	0.07	0.08	-0.31
FEV ₁ % predicted	0.10	1.25	0.58
FEF ₂₅₋₇₅ % predicted	0.88	-1.40	0.83
FEV ₁ /FVC % predicted	0.06	0.58	-1.54
Canonical correlation	0.65, <i>P</i> < .0001	0.46, <i>P</i> < .0001	0.20, <i>P</i> = .23

specificity. The cutoff point that yields equivalent estimates of sensitivity and specificity for FEF₂₅₋₇₅ percent predicted from its ROC curve is 58.2% (sensitivity = specificity = 0.82). The cutoff point that yields equivalent estimates of sensitivity and specificity for FEV₁/FVC percent predicted is 91.6%

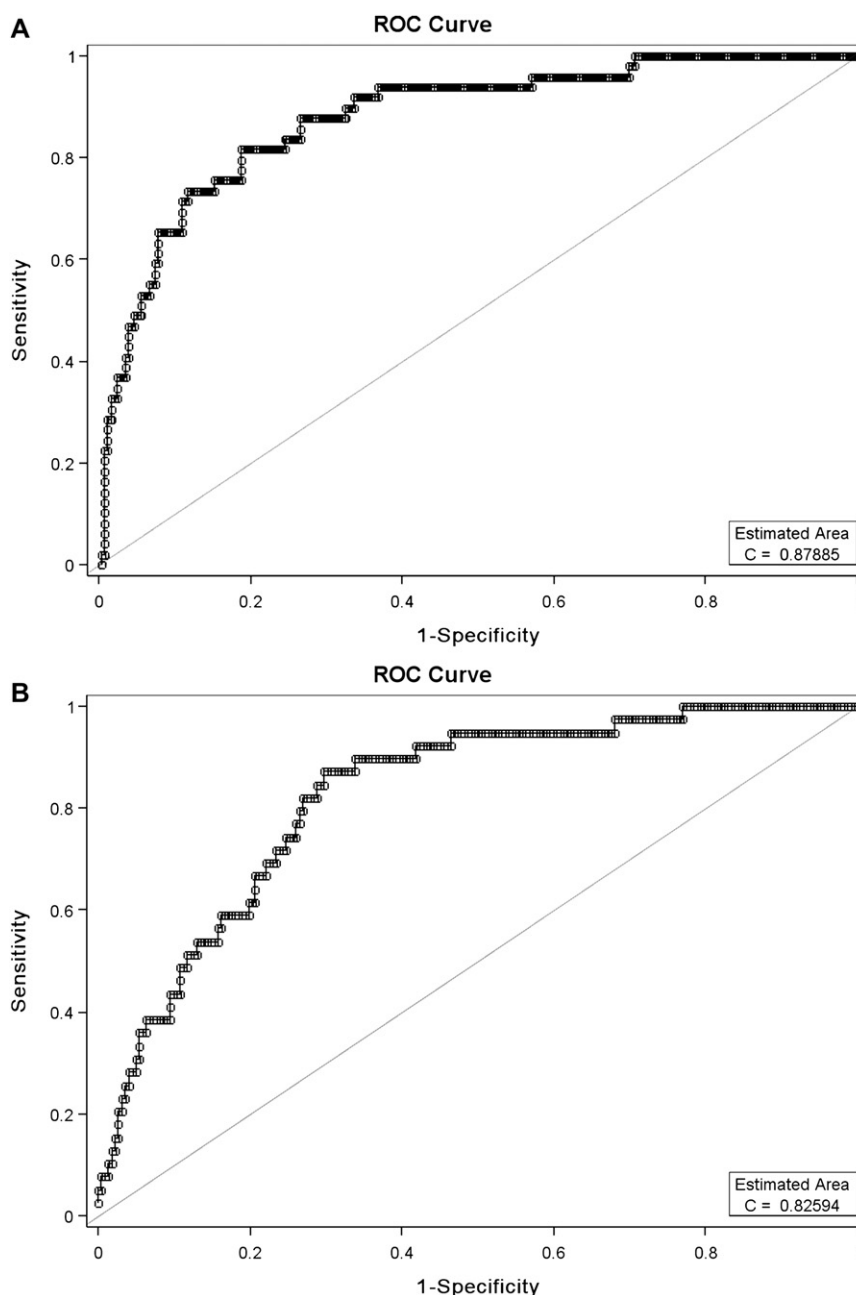


FIG 1. ROC curves of FEV₂₅₋₇₅ percent predicted for bronchodilator responsiveness as a 20% change in FEV₁ (A) and ROC curves of FEV₁/FVC percent predicted for bronchodilator responsiveness as a 20% change in FEV₁ (B). The inflection value for FEV₂₅₋₇₅ is at 68% of predicted value, and that for the FEV₁/FVC ratio is at 95% of predicted value (CLIC trial and PACT combined).

(sensitivity = specificity = 0.74). Thus the NNT = $1/(0.82 - 0.74) = 12.5$. In other words, for every 12.5 children in whom measurements of FEV₂₅₋₇₅ percent predicted and FEV₁/FVC percent predicted are available, 1 child will be identified who would benefit from bronchodilator based on his or her FEV₂₅₋₇₅ percent predicted measurement that was not identified based on his or her FEV₁/FVC percent predicted measurement. An NNT analysis was not performed with FEV₁ percent predicted because its correlation with bronchodilator responsiveness was much weaker than that of both FEV₂₅₋₇₅ percent predicted and FEV₁/FVC percent predicted, and ROC curves with FEV₁ percent predicted

performed too poorly to allow a cutoff point to be developed for an NNT analysis.

DISCUSSION

Asthma is characterized by inflammation of the large and small airways.^{25,26} Small airway obstruction has been demonstrated in asthmatic subjects.²⁷⁻²⁹ FeNO is a measure of airway inflammation in asthma that has been associated with small airway obstruction.³⁰ These 2 features of asthma are believed to be causally related. Air trapping in asthmatic subjects in the presence of

normal FEV₁ has been documented.^{3,4} The midflow rates measured during spirometric testing are believed to represent small airway airflow.^{10,28} The measurement of the midflow rate, FEF₂₅₋₇₅, might be a more sensitive indicator of symptomatic childhood asthma than FEV₁.⁵⁻⁷ FEF₂₅₋₇₅ might better reflect small airways disease than FEV₁ because of peripheral positioning of the airflow choke point in mid-to-low lung volumes and because “slow” lung units contribute gas later in the volume (by definition). FEF₂₅₋₇₅ percent predicted has been demonstrated to be better correlated with air trapping in asthmatic subjects than FEV₁ percent predicted and FEV₁/FVC percent predicted.⁴

We hypothesized that FEF₂₅₋₇₅ percent predicted would correlate with asthma symptoms, asthma medication use, bronchial hyperreactivity, albuterol-induced bronchodilation, and FeNO in 2 groups of children with mild asthma and normal FEV₁ percent predicted. Although FEF₂₅₋₇₅ and FEV₁/FVC percent predicted generally performed better than FEV₁ percent predicted, the striking finding was in their ability to predict response to bronchodilator administration. The Pearson partial correlations and the canonical correlation analysis of the combined CLIC trial and PACT data indicate that FEF₂₅₋₇₅ percent predicted has a stronger relationship with maximum bronchodilator response than does FEV₁/FVC and FEV₁ percent predicted (partial correlations of -0.49, 0.12, and 0.23, respectively). Furthermore, the estimated correlation of -0.49 is a relatively strong correlation in an analysis of biological variables in a population study.

These findings suggest that high FEF₂₅₋₇₅ percent predicted tends to be associated with normal airway patency, with a limited possibility of further bronchodilation. This is in contrast to a high FEV₁ percent predicted in our analyses and supports others' findings of airflow obstruction in asthmatic subjects with normal FEV₁.^{3,4}

FEF₂₅₋₇₅ has previously been found to be significantly low in children with an asthma diagnosis and a history of wheezing.³¹ These investigators also reported that FEF₂₅₋₇₅ was highly correlated with the slope of the methacholine dose-response curve and with the degree of methacholine responsiveness, respectively. Our findings are also consistent with those earlier observations. In addition, a previous study by one of our authors found that FEF₂₅₋₇₅ was significantly lower in transient early and persistent wheezers when they were reassessed at ages 11 and 16 years.³²

A recent study in a small number of patients with mild asthma demonstrated that FeNO was correlated with closing volume, which was used as a measure of small airway obstruction, whereas FeNO was not correlated with percent predicted FEV₁.³⁰ Our results support those findings of a correlation, albeit weak, of small airway patency (FEF₂₅₋₇₅ in our study) and FeNO in a much larger number of patients with mild asthma. However, unlike that report, but like another earlier study,³³ we also found that FeNO also had a weak negative correlation with percent predicted FEV₁. This latter finding in our subjects is at odds with the previously reported lack of a correlation of FEV₁ percent predicted with FeNO.³⁴⁻³⁶ However, the last of these studies in children with persistent asthma, one performed by some of the current investigators, did find a weak negative correlation of FeNO with FEV₁/FVC ratio. Measures of small airway patency were not reported in those previous studies.

The ROC curve analysis demonstrated that 62% predicted FEF₂₅₋₇₅ had a sensitivity of 90% and a specificity of 73% in detecting a 20% or greater increase in FEV₁ after inhalation of albuterol. Percent predicted FEF₂₅₋₇₅ has an NNT of 7 relative to FEV₁/FVC

percent predicted to identify 1 child who would benefit from bronchodilator testing. This suggests that FEF₂₅₋₇₅ is moderately efficacious in identifying otherwise undiagnosed bronchodilator responsiveness. Our finding that FEF₂₅₋₇₅ is sensitive and specific for bronchodilator responsiveness is of interest in the context of previous reports that bronchodilator responsiveness predicts an increase in FEV₁ after inhaled corticosteroid treatment³⁷ and is associated with several indicators of poor asthma control.^{38,39} This finding might be especially useful to clinicians because this clinically significant increase in FEV₁ suggests suboptimal asthma control, provided that the FVC measurements obtained during multiple spirometric studies are comparable and reproducible. It would be of interest to determine whether FEF₂₅₋₇₅ can serve as a surrogate for bronchodilator responsiveness.

What might render FEF₂₅₋₇₅ problematic in a given patient is that the variance is much higher than that of FEV₁. Thus even though FEF₂₅₋₇₅ is more physiologically sensitive, it lacks specificity because of its variability; that is, the lower limit of normal is substantively lower than for FEV₁ or FEV₁/FVC ratio. Therefore it is of limited diagnostic value in detecting an abnormality *per se*. However, if a patient is already known to have asthma, then the sensitivity of FEF₂₅₋₇₅ appears to be valuable in suggesting the likelihood that reversible bronchoconstriction is present. FEV₁/FVC ratio also performed well in predicting bronchodilator response. Ratios of flows divided by volumes, such as FEV₁/FVC, represent a rate constant and have units of 1/s. The FEV₁/FVC ratio describes the average rate constant over the first second of vital capacity. It is likely that one of the reasons that the FEV₁/FVC ratio is so robust is that it averages the rate constants over the first 70% to 95% of the FVC in most children with asthma. It has been suggested that the association of FEV₁/FVC ratio with asthma symptoms and medication use in a previous study was due to the reflection of the increased dysanapsis by the FEV₁/FVC ratio, which is present in asthmatic subjects.¹³ In large studies that have the statistical power to detect low levels of correlation that are statistically significant or that can compensate for the variability about a mean (SEM) to detect group differences, FEF₂₅₋₇₅ is of more use because the variance is compensated for by the large numbers. Under these conditions, the benefit of the increased physiological sensitivity of FEF₂₅₋₇₅ remains.

The strengths of this current study include the large numbers of subjects studied and that all subjects had normal FEV₁ percent predicted. A weakness of this study is that we were not able to determine whether FEF₂₅₋₇₅ predicted the future clinical course because all subjects were treated. Another weakness is that the entry criteria and therefore the study populations of the CLIC trial and PACT were not identical. The CLIC trial excluded children with FEV₁ of less than 70% of predicted value, and PACT excluded children with FEV₁ of less than 80% of predicted value. A final potential weakness is that unpublished work by Dr Ron Sorkness (personal communication) suggests a nonlinear relationship between FEF₂₅₋₇₅ and bronchodilator responsiveness. However, this is not a significant factor when FEV₁ is in the normal range, as in our patient groups.

These results suggest that FEF₂₅₋₇₅ percent predicted should be included among the spirometric data assessed in clinical trials if a 20% bronchodilator response as a percentage change in FEV₁ after albuterol inhalation is not determined. In addition, FEF₂₅₋₇₅ percent predicted is useful to clinicians who have performed spirometry in that it is correlated with bronchodilator responsiveness in children. Its sensitivity is estimated at 90% from the PACT and

CLIC trial studies. These findings need to be verified by additional similar analyses in children. The reproducibility of these results also needs to be tested in data obtained in studies of adult patients.

In conclusion, FEF₂₅₋₇₅ percent predicted was correlated with bronchodilator responsiveness and methacholine PC₂₀ and was sensitive and specific for bronchodilator responsiveness. We believe that the usefulness of FEF₂₅₋₇₅ in asthmatic children with normal FEV₁ percent predicted should be re-evaluated. It appears likely that FEF₂₅₋₇₅ percent predicted can supplement FEV₁ in the clinical evaluation of mild asthma in such children. In addition, this report demonstrates that FEF₂₅₋₇₅ percent predicted is negatively correlated with FeNO in children with mild asthma and a normal FEV₁ percent predicted. These results suggest that FEF₂₅₋₇₅ percent predicted should be evaluated in clinical studies of asthma in children and might be of use in predicting the presence of clinically relevant reversible airflow obstruction.

Clinical implications: FEF₂₅₋₇₅ percent predicted correlates with and is sensitive and specific for bronchodilator responsiveness in asthmatic children with normal FEV₁ percent predicted. This is consistent with airway dysfunction, despite the presence of a normal FEV₁.

REFERENCES

- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Samee S, Altes T, Powers P, de Lange EE, Knight-Scott J, Rakes G, et al. Imaging the lungs in asthmatic patients by using hyperpolarized helium-3 magnetic resonance: assessment of response to methacholine and exercise challenge. *J Allergy Clin Immunol* 2003;111:1205-11.
- de Lange EE, Altes TA, Patrie JT, Gaare JD, Knake JJ, Mugler JP 3rd, et al. Evaluation of asthma with hyperpolarized helium-3 MRI: correlation with clinical severity and spirometry. *Chest* 2006;130:1055-62.
- Weiss ST, Tosteson TD, Segal MR, Tager IB, Redline S, Speizer FE. Effects of asthma on pulmonary function in children. A longitudinal population-based study. *Am Rev Respir Dis* 1992;145:58-64.
- Lebecque P, Kiakulanda P, Coates AL. Spirometry in the asthmatic child: is FEF₂₅₋₇₅ a more sensitive test than FEV₁/FVC? *Pediatr Pulmonol* 1993;16:19-22.
- Valetta EA, Piacentini GL, Del Col G, Boner AL. FEF₂₅₋₇₅ as a marker of airway obstruction in asthmatic children during reduced mite exposure at high altitude. *J Asthma* 1997;34:127-31.
- Lebowitz MD, Holberg CJ, Knudson RJ, Burrows B. Longitudinal study of pulmonary function development in childhood, adolescence, and early adulthood. Development of pulmonary function. *Am Rev Respir Dis* 1987;136:69-75.
- Chiang C-H, Hsu K. Residual abnormalities of pulmonary function in asymptomatic young adult asthmatics with childhood-onset asthma. *J Asthma* 1997;34:15-21.
- McFadden ER, Linden DA. A reduction in maximum mid-expiratory flow rate. A spiropographic manifestation of small airway disease. *Am J Med* 1972;52:725-37.
- Gelb AF, Zamel N. Simplified diagnosis of small-airway obstruction. *N Engl J Med* 1973;288:395-8.
- Frank R, Liu MC, Spannhake EW, Mlynarek S, Macri K, Weinmann GG. Repetitive ozone exposure of young adults. Evidence of persistent airway dysfunction. *Am J Respir Crit Care Med* 2001;164:1253-60.
- Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;170:426-32.
- Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of three controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial (PACT). *J Allergy Clin Immunol* 2007;119:64-72.
- Szefer SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF Jr, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233-42.
- American Thoracic Society Committee of Proficiency Standards for Clinical Pulmonary Function Laboratories. Standardization of spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995;152:1107-36.
- Childhood Asthma Management Program. Childhood Asthma Management Program spirometry manual, version 3.0. Springfield (VA): National Technical Information Service; 1994.
- Eigen H, Bieler H, Grant D, Christoph K, Terrill D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med* 2001;163:619-23.
- Arets HGM, Brackel HJL, van der Ent CK. Forced expiratory manoeuvres in children: do they meet ATS and ERS criteria for spirometry? *Eur Respir J* 2001;18:655-60.
- Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993;15:75-88.
- American Thoracic Society/European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005;171:912-30.
- Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
- Johnson RA, Wichern DW. Applied multivariate statistical analysis. 6th ed. Englewood Cliffs (NJ): Prentice Hall; 2007.
- Zweig M, Campbell G. Receiver-operating characteristics (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993;39:561-77.
- Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997;100:44-51.
- Haley KJ, Sunday ME, Wiggs BR, Kozakewich HP, Reilly JJ, Mentzer SJ, et al. Inflammatory cell distribution within and along asthmatic airways. *Am J Respir Crit Care Med* 1998;158:565-72.
- Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. *J Clin Invest* 1969;48:1097-06.
- Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis* 1990;141:584-8.
- Ueda T, Niimi A, Matsumoto H, Takemura M, Hirai T, Yamaguchi M, et al. Role of small airways in asthma: investigation using high-resolution computed tomography. *J Allergy Clin Immunol* 2006;118:1019-25.
- Battaglia S, den Hertog H, Timmers MC, Lazeroms SP, Vignola AM, Rabe KF, et al. Small airways function and molecular markers in exhaled air in mild asthma. *Thorax* 2005;60:639-44.
- Owby DR, Peterson EL, Johnson CC. Factors related to methacholine airway responsiveness in children. *Am J Respir Crit Care Med* 2000;161:1578-83.
- Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253-8.
- Sippel JM, Holden WE, Tilles SA, O'Hollaren M, Cook J, Thukkani N, et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. *J Allergy Clin Immunol* 2000;106:645-50.
- Baraldi E, Carra S, Dario C, Azzolin N, Ongaro R, Marcer G, et al. Effect of natural grass pollen exposure on exhaled nitric oxide in asthmatic children. *Am J Respir Crit Care Med* 1999;159:262-6.
- Langley SJ, Goldthorpe S, Custovic A, Woodcock A. Relationship among pulmonary function, bronchial reactivity, and exhaled nitric oxide in a large group of asthmatic patients. *Ann Allergy Asthma Immunol* 2003;91:398-404.
- Strunk RC, Szefer SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol* 2003;112:883-92.
- Tantisira KG, Fuhlbrigge AL, Tonascia J, Van Natta M, Zeiger RS, Strunk RC, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. *J Allergy Clin Immunol* 2006;117:1264-71.
- Jones RS. Assessment of respiratory function in the asthmatic child. *BMJ* 1966;2:972-5.
- Sharma S, Litonjua AA, Tantisira KG, Fuhlbrigge AL, Szefer SJ, Strunk RC, et al. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. *J Allergy Clin Immunol* 2008;122:921-8.

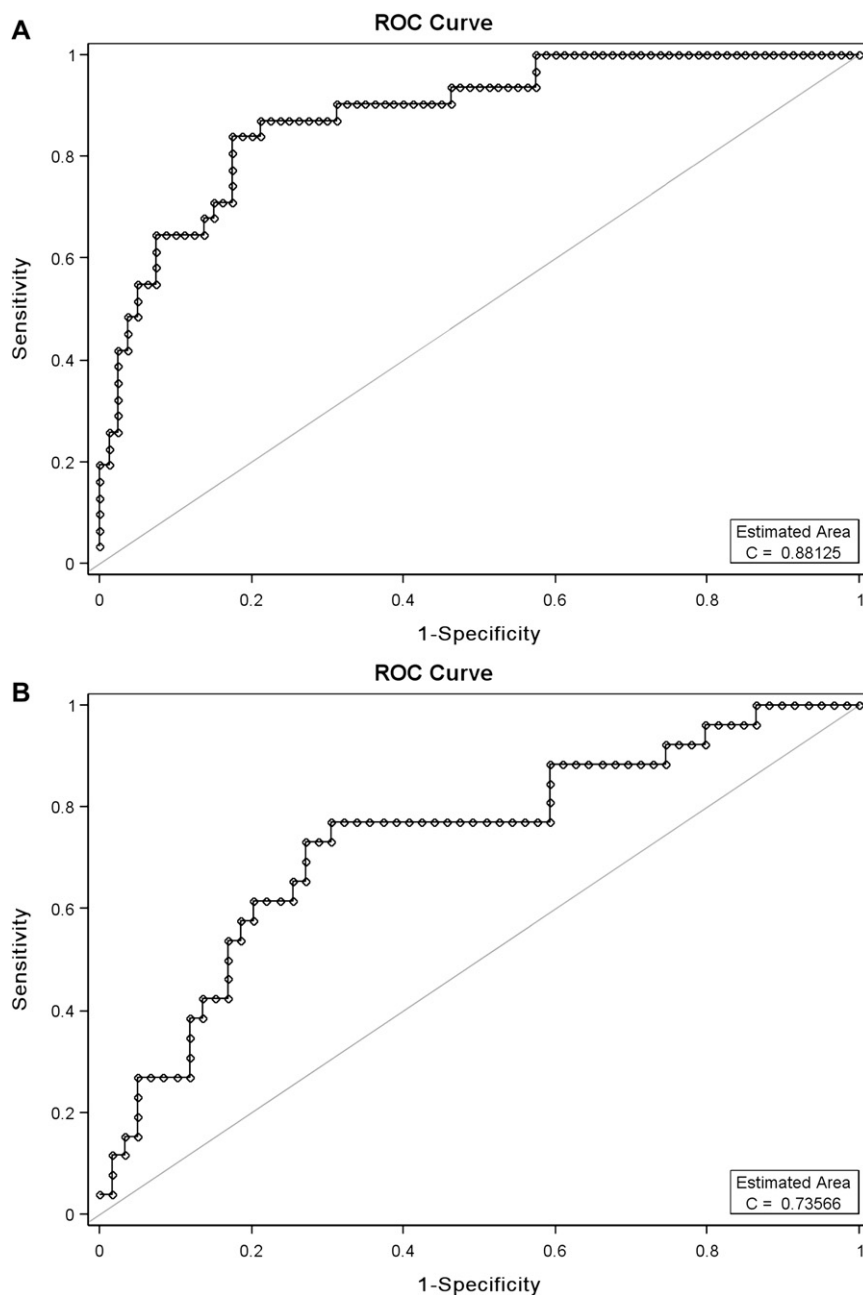


FIG E1. ROC curves of FEV_{25-75} percent predicted for bronchodilator responsiveness as a 20% change in FEV_1 (A) and ROC curves of FEV_1/FVC percent predicted for bronchodilator responsiveness as a 20% change in FEV_1 (B). The inflection value for FEV_{25-75} is at 36% of predicted value, and that for the FEV_1/FVC ratio is at 79% of predicted value (CLIC alone).

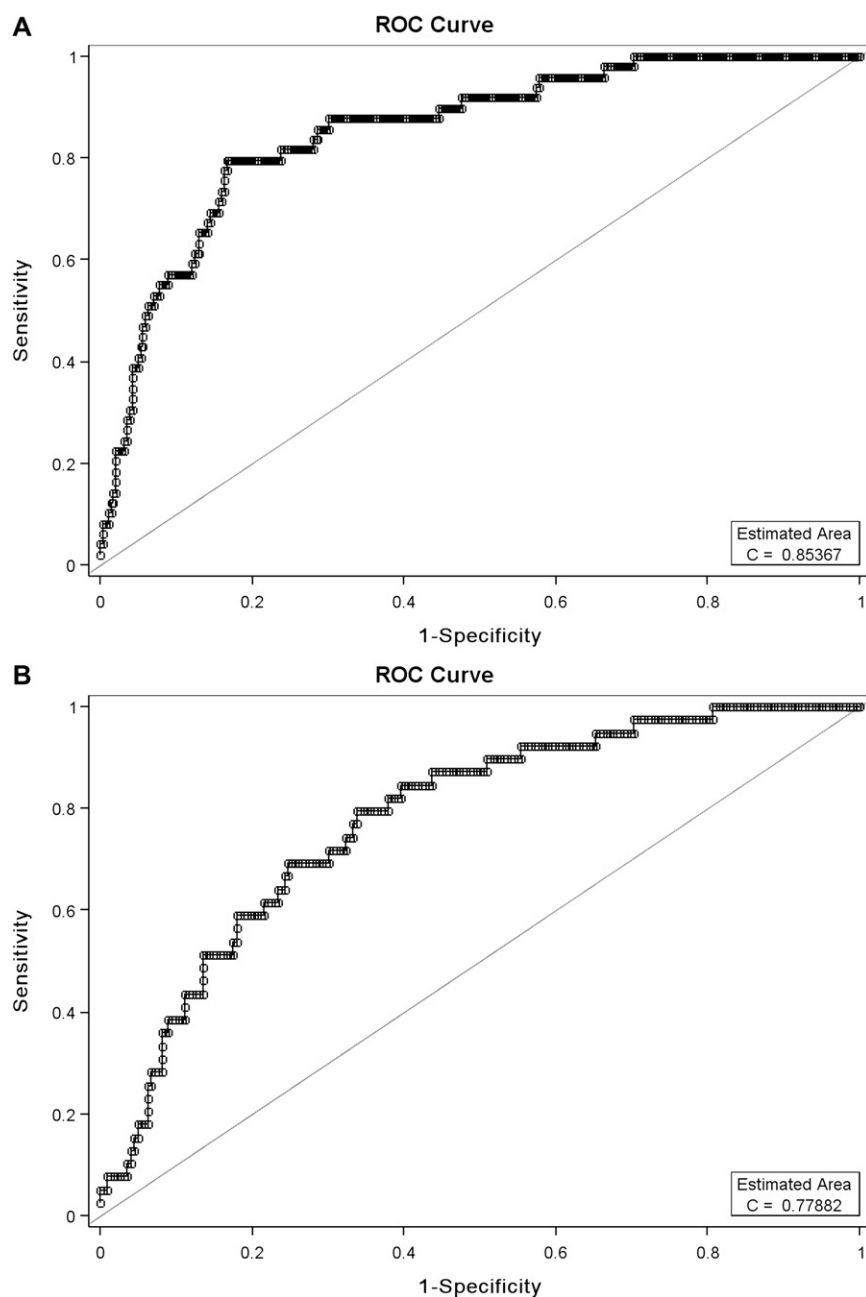


FIG E2. ROC curves of FEV₂₅₋₇₅ percent predicted for bronchodilator responsiveness as a 20% change in FEV₁ (A) and ROC curves of FEV₁/FVC percent predicted for bronchodilator responsiveness as a 20% change in FEV₁ (B). The inflection value for FEV₂₅₋₇₅ is at 50% of predicted value, and that for the FEV₁/FVC ratio cannot be determined (PACT alone).

TABLE E1. CIs and *P* values for testing null correlations) among spirometric variables using CLIC trial baseline data

	FEV₁% predicted	FEF₂₅₋₇₅% predicted	FEV₁/FVC % predicted
FEV ₁ % predicted		0.52 (0.33-0.66), <i>P</i> < .0001	0.64 (0.49-0.75), <i>P</i> < .0001
FEF ₂₅₋₇₅ % predicted	0.64 (0.49-0.75), <i>P</i> < .0001		0.62 (0.46-0.74), <i>P</i> < .0001
FEV ₁ /FVC % predicted	0.52 (0.33-0.66), <i>P</i> < .0001	0.62 (0.46-0.74), <i>P</i> < .0001	

TABLE E2. CIs and *P* values for testing null correlations) among spirometric variables using PACT baseline data

	FEV₁% predicted	FEF₂₅₋₇₅% predicted	FEV₁/FVC % predicted
FEV ₁ % predicted		0.77 (0.70-0.83), <i>P</i> < .0001	0.54 (0.42-0.64), <i>P</i> < .0001
FEF ₂₅₋₇₅ % predicted	0.77 (0.70-0.83), <i>P</i> < .0001		0.88 (0.85-0.91), <i>P</i> < .0001
FEV ₁ /FVC % predicted	0.54 (0.42-0.64), <i>P</i> < .0001	0.88 (0.85-0.91), <i>P</i> < .0001	

TABLE E3. Pearson correlation and partial correlation coefficients (with 95% CIs and *P* values for testing null correlations) of spirometric variables with clinical variables using CLIC baseline data

	FEV ₁ % predicted correlations	FEV ₁ % predicted partial correlations	FEV ₁ % predicted partial correlations (partialling out clinical variables)	FEF ₂₅₋₇₅ % predicted correlations	FEF ₂₅₋₇₅ % predicted partial correlations	FEF ₂₅₋₇₅ % predicted partial correlations (partialling out clinical variables)	FEV ₁ /FVC % predicted correlations	FEV ₁ /FVC % predicted partial correlations	FEV ₁ /FVC % predicted partial correlations (partialling out clinical variables)
Clinical outcomes									
Diary symptoms (cough and wheeze)	0.20 (0.03 to 0.36), <i>P</i> = .02	0.13 (−0.08 to 0.32), <i>P</i> = .22	0.09 (−0.14 to 0.30), <i>P</i> = .45	0.09 (−0.07 to 0.25), <i>P</i> = .26	0.07 (−0.14 to 0.27), <i>P</i> = .50	0.03 (−0.19 to 0.25), <i>P</i> = .78	0.05 (−0.16 to 0.25), <i>P</i> = .65	−0.08 (−0.28 to 0.12), <i>P</i> = .42	−0.02 (−0.24 to 0.20), <i>P</i> = .85
Diary rescue albuterol use	−0.01 (−0.19 to 0.16), <i>P</i> = .87	−0.02 (−0.23 to 0.18), <i>P</i> = .83	−0.02 (−0.23 to 0.18), <i>P</i> = .83	−0.09 (−0.25 to 0.07), <i>P</i> = .27	−0.10 (−0.30 to 0.11), <i>P</i> = .34	−0.10 (−0.30 to 0.11), <i>P</i> = .34	−0.19 (−0.38 to 0.01), <i>P</i> = .06	−0.06 (−0.26 to 0.14), <i>P</i> = .55	−0.06 (−0.27 to 0.15), <i>P</i> = .55
ACQ score	−0.27 (−0.43 to −0.11), <i>P</i> = .002	0.01 (−0.19 to 0.21), <i>P</i> = .92	−0.05 (−0.27 to 0.87), <i>P</i> = .68	−0.21 (−0.37 to −0.04), <i>P</i> = .02	0.03 (−0.17 to 0.23), <i>P</i> = .75	0.02 (−0.23 to 0.19), <i>P</i> = .84	−0.19 (−0.38 to 0.01), <i>P</i> = .06	−0.16 (−0.36 to 0.04), <i>P</i> = .12	−0.01 (−0.31 to 0.13), <i>P</i> = .40
Prior hospitalizations	−0.23 (−0.39 to −0.06), <i>P</i> = .01	−0.05 (−0.25 to 0.16), <i>P</i> = .64	−0.01 (−0.23 to 0.21), <i>P</i> = .93	−0.30 (−0.44 to −0.15), <i>P</i> = .0001	−0.19 (−0.38 to 0.01), <i>P</i> = .06	−0.12 (−0.33 to 0.11), <i>P</i> = .30	−0.09 (−0.29 to 0.11), <i>P</i> = .37	0.09 (−0.12 to 0.29), <i>P</i> = .41	0.12 (−0.11 to 0.33), <i>P</i> = .30
Physiological outcomes									
Diary morning PEF % predicted	0.48 (0.34 to 0.60), <i>P</i> < .0001	0.49 (0.32 to 0.63), <i>P</i> < .0001	0.46 (0.26 to 0.61), <i>P</i> < .0001	0.31 (0.15 to 0.45), <i>P</i> = .0002	0.05 (−0.15 to 0.25), <i>P</i> = .62	0.06 (−0.16 to 0.28), <i>P</i> = .60	0.22 (0.02 to 0.40), <i>P</i> = .03	−0.17 (−0.36 to 0.03), <i>P</i> = .10	−0.10 (−0.32 to 0.13), <i>P</i> = .39
Diary evening PEF % predicted	0.47 (0.32 to 0.59), <i>P</i> < .0001	0.51 (0.34 to 0.65), <i>P</i> < .0001	0.49 (0.30 to 0.64), <i>P</i> < .0001	0.28 (0.12 to 0.43), <i>P</i> = .001	0.11 (−0.10 to 0.31), <i>P</i> = .29	0.10 (−0.13 to 0.32), <i>P</i> = .38	0.14 (−0.07 to 0.33), <i>P</i> = .18	−0.28 (−0.46 to −0.09), <i>P</i> = .01	−0.23 (−0.43 to −0.01), <i>P</i> = .04
Maximal BD response (% change in FEV ₁)	−0.17 (−0.33 to 0.01), <i>P</i> = .06	0.19 (−0.02 to 0.38), <i>P</i> = .06	0.17 (−0.06 to 0.38), <i>P</i> = .14	−0.67 (−0.75 to −0.58), <i>P</i> < .0001	−0.70 (−0.79 to −0.58), <i>P</i> < .0001	−0.74 (−0.83 to −0.62), <i>P</i> < .0001	−0.32 (−0.49 to −0.13), <i>P</i> = .001	0.16 (−0.04 to 0.35), <i>P</i> = .12	0.22 (−0.01 to 0.42), <i>P</i> = .06
Log ₂ (PC ₂₀ methacholine)	0.25 (0.06 to 0.42), <i>P</i> = .01	−0.02 (−0.24 to 0.21), <i>P</i> = .88	−0.01 (−0.24 to 0.23), <i>P</i> = .98	0.38 (0.20 to 0.53), <i>P</i> < .0001	0.25 (0.03 to 0.45), <i>P</i> = .02	0.24 (−0.01 to 0.45), <i>P</i> = .04	0.44 (0.24 to 0.60), <i>P</i> < .0001	0.21 (−0.01 to 0.41), <i>P</i> = .06	0.20 (−0.05 to 0.41), <i>P</i> = .10
Log ₁₀ (FeNO)	0.07 (−0.25 to 0.10), <i>P</i> = .41	0.10 (−0.11 to 0.31), <i>P</i> = .33	0.06 (−0.17 to 0.29), <i>P</i> = .61	−0.20 (−0.36 to −0.04), <i>P</i> = .01	−0.10 (−0.30 to 0.11), <i>P</i> = .34	−0.14 (−0.36 to 0.10), <i>P</i> = .25	−0.19 (−0.38 to 0.01), <i>P</i> = .07	−0.13 (−0.33 to 0.08), <i>P</i> = .21	−0.04 (−0.27 to 0.19), <i>P</i> = .72

ACQ, Asthma Control Questionnaire; BD, bronchodilator.

TABLE E4. Pearson correlation and partial correlation coefficients (with 95% CIs and *P* values for testing null correlations) of spirometric variables with clinical variables using PACT baseline data

	FEV ₁ % predicted correlations	FEV ₁ % predicted partial correlations	FEV ₁ % predicted partial correlations (partialling out clinical variables)	FEF ₂₅₋₇₅ % predicted correlations	FEF ₂₅₋₇₅ % predicted partial correlations	FEF ₂₅₋₇₅ % predicted partial correlations (partialling out clinical variables)	FEV ₁ /FVC % predicted correlations	FEV ₁ /FVC % predicted partial correlations	FEV ₁ /FVC % predicted partial correlations (partialling out clinical variables)
Clinical outcomes									
Diary symptoms (cough and wheeze)	−0.02 (−0.15 to 0.10), <i>P</i> = .7140	0.00 (−0.14 to 0.14), <i>P</i> = .97	0.01 (−0.14 to 0.16), <i>P</i> = .86	−0.05 (−0.17 to 0.07), <i>P</i> = .44	−0.05 (−0.19 to 0.09), <i>P</i> = .50	−0.08 (−0.23 to 0.07), <i>P</i> = .28	−0.06 (−0.20 to 0.08), <i>P</i> = .43	0.03 (−0.11 to 0.17), <i>P</i> = .66	0.09 (−0.06 to 0.24), <i>P</i> = .25
Diary rescue albuterol use	−0.14 (−0.26 to −0.02), <i>P</i> = .0218	−0.07 (−0.21 to 0.07), <i>P</i> = .35	−0.09 (−0.24 to 0.06), <i>P</i> = .25	−0.16 (−0.28 to −0.04), <i>P</i> = .01	−0.03 (−0.17 to 0.11), <i>P</i> = .71	0.01 (−0.14 to 0.16), <i>P</i> = .89	−0.23 (−0.36 to −0.09), <i>P</i> = .001	−0.04 (−0.18 to 0.10), <i>P</i> = .54	−0.06 (−0.21 to 0.02), <i>P</i> = .41
ACQ score	−0.20 (−0.32 to −0.08), <i>P</i> = .0012	−0.17 (−0.30 to −0.03), <i>P</i> = .02	−0.15 (−0.29 to 0.00), <i>P</i> = .05	−0.15 (−0.27 to −0.03), <i>P</i> = .02	0.11 (−0.03 to 0.24), <i>P</i> = .14	0.06 (−0.09 to 0.21), <i>P</i> = .44	−0.24 (−0.37 to −0.11), <i>P</i> = .001	−0.16 (−0.30 to −0.02), <i>P</i> = .02	−0.11 (−0.26 to 0.04), <i>P</i> = .14
Prior hospitalizations	−0.04 (−0.16 to 0.08), <i>P</i> = .5215	0.07 (−0.07 to 0.21), <i>P</i> = .35	0.05 (−0.11 to 0.20), <i>P</i> = .55	−0.03 (−0.16 to 0.09), <i>P</i> = .58	−0.08 (−0.22 to 0.06), <i>P</i> = .25	−0.06 (−0.21 to 0.10), <i>P</i> = .47	0.02 (−0.12 to 0.16), <i>P</i> = .78	0.08 (−0.06 to 0.22), <i>P</i> = .28	0.04 (−0.11 to 0.19), <i>P</i> = .60
Physiological outcomes									
Diary morning PEF % pre- dicted	0.33 (0.21 to 0.43), <i>P</i> < .0001	0.26 (0.12 to 0.39), <i>P</i> = .0002	0.28 (0.14 to 0.42), <i>P</i> = .0002	0.26 (0.15 to 0.37), <i>P</i> < .0001	−0.12 (−0.26 to 0.02), <i>P</i> = .09	−0.13 (−0.27 to 0.02), <i>P</i> = .09	0.32 (0.19 to 0.44), <i>P</i> < .0001	0.18 (−0.04 to 0.31), <i>P</i> = .01	0.16 (0.01 to 0.30), <i>P</i> = .05
Diary evening PEF % predicted	0.30 (0.18 to 0.41), <i>P</i> < .0001	0.26 (0.12 to 0.38), <i>P</i> = .0002	0.28 (0.13 to 0.41), <i>P</i> = .0002	0.22 (0.10 to 0.33), <i>P</i> = .001	−0.14 (−0.28 to −0.00), <i>P</i> = .04	−0.14 (−0.28 to 0.01), <i>P</i> = .07	0.27 (0.14 to 0.40), <i>P</i> = .0001	0.18 (0.04 to −0.32), <i>P</i> = .01	0.15 (0.00 to −0.29), <i>P</i> = .05
Maximal BD response (% Change in FEV ₁)	−0.46 (−0.56 to −0.36), <i>P</i> < .0001	0.13 (−0.00 to 0.27), <i>P</i> = .05	0.11 (−0.04 to 0.26), <i>P</i> = .14	−0.46 (−0.56 to −0.36), <i>P</i> < .0001	−0.23 (−0.36 to −0.09), <i>P</i> = .001	−0.16 (−0.30 to −0.01), <i>P</i> = .04	−0.42 (−0.53 to −0.30), <i>P</i> < .0001	0.01 (−0.13 to 0.15), <i>P</i> = .90	−0.06 (−0.21 to 0.09), <i>P</i> = .42
Log ₂ (PC ₂₀ methacholine)	0.35 (0.23 to 0.46), <i>P</i> < .0001	0.12 (−0.03 to 0.27), <i>P</i> = .10	0.12 (−0.03 to 0.22), <i>P</i> = .13	0.35 (0.23 to 0.46), <i>P</i> < .0001	0.06 (−0.09 to 0.21), <i>P</i> = .40	0.05 (−0.10 to 0.20), <i>P</i> = .51	0.40 (0.26 to 0.52), <i>P</i> < .0001	0.06 (−0.09 to 0.21), <i>P</i> = .42	0.06 (−0.10 to 0.21), <i>P</i> = .47
Log ₁₀ (FeNO)	−0.23 (−0.35 to −0.11), <i>P</i> = .0002	0.02 (−0.12 to 0.16), <i>P</i> = .79	0.04 (−0.11 to 0.19), <i>P</i> = .57	−0.23 (−0.35 to −0.11), <i>P</i> = .0002	−0.07 (−0.21 to 0.07), <i>P</i> = .32	−0.01 (−0.16 to 0.14), <i>P</i> = .86	−0.27 (−0.40 to −0.14), <i>P</i> < .0001	−0.05 (−0.19 to 0.09), <i>P</i> = .49	−0.09 (−0.24 to 0.06), <i>P</i> = .22

TABLE E5. Canonical correlation analysis between spirometric variables and clinical variables using CLIC baseline data

CLIC canonical variate pairs: Standardized coefficients			
	Variate pair 1	Variate pair 2	Variate pair 3
Diary morning PEF % predicted	0.15	1.19	0.99
Diary evening PEF % predicted	0.12	−0.71	−1.75
Maximal BD response (% change in FEV ₁)	−0.90	0.50	−0.04
Log ₂ (PC ₂₀)	0.30	0.51	0.56
Diary symptoms (cough and wheeze)	0.06	0.26	−0.08
Diary rescue albuterol use	0.25	−0.13	0.08
Log ₁₀ (FeNO)	0.06	0.15	0.06
ACQ score	−0.07	−0.13	0.34
Prior hospitalizations	−0.03	0.28	0.34
FEV ₁ % predicted	0.05	0.68	−1.11
FEF ₂₅₋₇₅ % predicted	1.07	−0.67	−0.05
FEV ₁ /FVC % predicted	−0.17	0.71	1.19
Canonical correlation	0.84, $P < .0001$	0.53, $P = .002$	0.50, $P = .01$

ACQ, Asthma Control Questionnaire; BD, bronchodilator.

TABLE E6. Canonical correlation analysis between spirometric variables and clinical variables using PACT baseline data

PACT canonical variate pairs: Standardized coefficients			
	Variate pair 1	Variate pair 2	Variate pair 3
Diary morning PEF % predicted	0.64	0.26	0.29
Diary evening PEF % predicted	−0.15	0.39	−0.42
Maximal BD response (% change in FEV ₁)	−0.37	0.82	−0.03
Log ₂ (PC ₂₀)	0.39	0.07	0.53
Diary symptoms (cough and wheeze)	0.17	0.29	−0.86
Diary rescue albuterol use	−0.10	0.03	0.05
Log ₁₀ (FeNO)	−0.02	0.20	0.62
ACQ score	−0.32	−0.38	0.41
Prior hospitalizations	0.10	−0.05	−0.17
FEV ₁ % predicted	0.56	1.64	−0.27
FEF ₂₅₋₇₅ % predicted	−0.12	−2.08	2.44
FEV ₁ /FVC % predicted	0.70	0.60	−2.28
Canonical correlation	0.61, $P < .0001$	0.36, $P = .03$	0.20, $P = .47$

ACQ, Asthma Control Questionnaire; BD, bronchodilator.