

FEV₁ is associated with risk of asthma attacks in a pediatric population

Anne L. Fuhlbrigge, MD, MS,^a Barrett T. Kitch, MD, MPH,^a A. David Paltiel, PhD,^b
Karen M. Kuntz, ScD,^c Peter J. Neumann, ScD,^c Douglas W. Dockery, PhD,^d and
Scott T. Weiss, MD, MS^a *Boston, Mass, and New Haven, Conn*

Background: FEV₁ is endorsed by the National Asthma Education and Prevention Program as a means for grading asthma severity. However, few data exist on the relationship between FEV₁ and asthma outcomes during long-term follow-up.

Objective: We explored the relationship between the percent predicted FEV₁ (FEV₁%) and subsequent asthma attacks in a longitudinal study of pediatric lung health.

Methods: A retrospective cohort of 13,842 children (100,292 observations) seen annually over a 15-year interval was analyzed for measurement of pulmonary function, and a respiratory questionnaire was completed. Up to grade 9, a standard questionnaire was completed by a parent or guardian; thereafter it was completed by the patient. For each observation, the report of an attack during the past year was paired with FEV₁ recorded at the field survey 1 year earlier.

Results: A progressive decrease in the proportion of individuals reporting an attack was associated with increasing decile of FEV₁%. Two categorization schemes for FEV₁% were examined: a scheme based on the National Asthma Education and Prevention Program recommendations (<60%, 60%-80%, and >80%), and an alternative scheme (<80%, 80%-100%, and >100%). In multivariate models, FEV₁% was an independent predictor of attacks: among the parental report group, the odds ratios were 2.1 (95% CI, 1.3-3.4) and 1.4 (95% CI, 1.2-1.6) for FEV₁% < 60% and FEV₁% of 60% to 80% compared with FEV₁% > 80%, respectively; and among the self-report group, odds ratios were 5.3 (95% CI, 2.2-12.9) and 1.4 (95% CI, 1.2-1.7) for FEV₁% < 60% and FEV₁% of 60% to 80% compared with FEV₁% > 80%, respectively. With the alternative classification scheme, the relationship was similar, but the difference in risk between categories of FEV₁% decreased.

Conclusion: The strong association between FEV₁% and risk of asthma attack over the subsequent year supports an emphasis on objective measures of lung function in assessment of risk for adverse asthma outcomes. (*J Allergy Clin Immunol* 2001;107:61-7.)

Key words: Asthma, FEV₁, percent predicted FEV₁, severity, attack, outcome

Abbreviations used

ETS: Environmental tobacco smoke

FEV₁ %: Percent predicted FEV₁

NAEPP: National Asthma Education and Prevention Program

OR: Odds ratio

PEFR: Peak expiratory flow rate

Asthma is a chronic inflammatory disease with clinical manifestations that result from variable airflow obstruction. Spirometric measures, principally FEV₁, have long been used as markers of the degree of airflow obstruction. FEV₁ is endorsed by the National Asthma Education and Prevention Program (NAEPP) as an important means for grading asthma severity.¹

The endorsement of FEV₁ is based on the observation that both patients and physicians are imperfect at assessing the degree of airway obstruction without objective means²⁻⁶ and the belief that the severity of disease as assessed by FEV₁ or peak expiratory flow rate (PEFR) predicts important disease outcomes, such as exacerbations, disease progression, and functional impairment or quality of life.

In the area of asthma outcomes, research has been limited by the lack of a gold standard that allows for stratification for asthma severity. In a disease process as complex as asthma, no single measure can be expected to completely describe the severity of disease. However, when the goal is less to describe "what is" and more to predict "what will be," the challenge is to define a simple severity classification scheme that takes current clinical information, assigns patients to a particular severity class, and then uses that measure to predict likely downstream outcomes, such as the frequency and severity of future clinical events, resource utilization patterns, and long-term patient quality of life.

No consensus exists as to what such a scheme should measure. The NAEPP has developed a classification scheme that has been widely disseminated. A central component of this scheme is the objective measure of lung function (FEV₁ or PEFR). Although PEFR is considered a useful clinical measure, the variability of PEFR is twice that of FEV₁,^{7,8} and PEFR may be less reliable in children with asthma.^{9,10} Our analysis is focused on FEV₁. No distinction has been made between the classification schemes proposed for pediatric compared with adult populations. The use of the same categories for

From ^aChanning Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ^bYale School of Medicine and Yale School of Management, New Haven; ^cCenter for Risk Analysis, Harvard School of Public Health, Boston; and ^dDepartment of Environmental Health, Harvard School of Public Health, Boston.

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Reprint requests: Anne L. Fuhlbrigge, MD, MS, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115-5805.

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TABLE I. Characteristics of analysis population*

Characteristic	Observation
Female sex, n (%)	12,076 (49)
White race, n (%)	22,279 (90.4)
FEV ₁ %, n (%)	
≤60%	77 (0.3)
>60%-80%	1,350 (5.5)
>80%-100%	12,555 (50.9)
>100%	10,654 (43.3)
Total observations, n (%)	24,636 (3,452)
Mean age,† y	13.0

*Values given are for the total number of observations available for analysis, not unique individuals.

†Mean of observations analyzed.

FEV₁ classification among adults and children is based on expert opinion because there is little information in the literature addressing this issue.

This study was motivated by the search for components of an asthma classification scheme that could be used for the purposes of prediction and planning, one that allows identification of mutually exclusive states. We sought to explore whether a relationship could be observed between FEV₁ and subsequent asthma attacks within a pediatric population.

METHODS

Study population

We performed a retrospective cohort analysis of subjects from a longitudinal study; details of the study design have been published.¹¹ In brief, this study enrolled 13,842 subjects (100,292 observations) from schools in 6 US states (Watertown, Mass; Kingston and Harriman, Tenn; Steubenville and Mingo Junction, Ohio; a geographically defined section of St Louis, Mo; Portage, Pardeeville, Rio, and Wyocena, Wis; and Topeka, Kan) between 1974 and 1979. The sample included all first- and second-grade children in both the public and private schools within each of the study communities. In addition, new first graders were added to the sample each year until approximately 1500 to 2000 children were enrolled in each community. Children were followed up for a maximum of 15 years. At the initial and subsequent annual examinations, children were seen in their schools for measurement of height, weight, and pulmonary function.

To include a large population of potentially asthmatic children, we defined our analysis population as all children who reported 1 or more asthma attacks at any time during follow-up. We subsequently repeated the analysis and restricted the population to children who reported ever having asthma.

Questionnaire

At each visit, up to grade 9 (approximately age 14 years), each child took home a standard questionnaire to be completed by a parent or guardian (parental report). Thereafter, in most cases the questionnaire was completed by the child (self-report). For 377 children the questionnaire was completed, at least once, by the parent despite the child's being aged 15 years or older.

Previous evaluation of the Six Cities population has documented differences in the information obtained from parental compared with self-report.¹² In addition, different information regarding potential confounders (tobacco exposure) was obtained from the 2 respondent

(age) groups: the parental questionnaire ascertained information on environmental tobacco smoke (ETS), whereas information on personal tobacco exposure ("In the past year have you smoked 5 or more tobacco cigarettes?") was obtained from the self-report questionnaire. Because of the differences in the type of response and the information available, all analyses were stratified by respondent identity.

The questionnaire also requested information about demographic data, respiratory illness, history of asthma, and respiratory symptoms. A history of asthma was defined as a positive response to the question "Does this child have the following: asthma, hay fever?" (among the parental report group) and a positive response to "Have you ever had asthma?" (among the self-report group). An asthma attack was defined as an affirmative response to the question "Have you had an attack of wheezing and shortness of breath in the past year?"

Pulmonary function

Standard height and weight in stocking feet were measured. Forced expiratory maneuvers were performed on a recording 8-L Stead-Wells survey spirometer (Warren E. Collins, Braintree, Mass) while the subject was sitting with free mobility and without a nose-clip. Each child performed at least 5 forced expiration maneuvers, but not more than 8. From the acceptable expirations determined by the examiner, forced vital capacity and FEV₁ were measured. The mean of the best 3 efforts was calculated after correction for body temperature and pressure saturated.¹³

We were interested in lung function as a predictor of subsequent asthma attack. For each observation, the report of an attack in the past year was paired with the FEV₁ value recorded at the field survey 1 year earlier. Observations for which the interval between FEV₁ measurement and questionnaire response was greater than 1 year were excluded. FEV₁ was analyzed as the percentage of the FEV₁ predicted (FEV₁%) for a given height, age, race, and sex, based on published equations.¹⁴ Equations were available for children of black and white race only. We initially divided FEV₁% into decile categories. For multivariate models FEV₁% was grouped into 3 discrete categories. We evaluated 2 different categorization schemes. The initial scheme (FEV₁ for group 1: 3 categories of <60%, 60%-80%, and >80%) was based on the NAEPP recommendations. An alternative categorization (FEV₁ for group 2: 3 categories of <80%, 80%-100%, and >100%) was derived to allow a better distribution of subjects among the 3 categories.

Statistical methods

Multiple logistic regression was used to obtain the adjusted odds ratio (OR) of asthma attack for the categories of FEV₁% evaluated. Multiple observations of FEV₁ and report of asthma attack were available in subjects. To account for correlation between observations from the same individual, we used methods developed by Zeger and Liang¹⁵ using generalized estimating equations for the logistic case to evaluate the relationship between the dependent and independent variables. All analyses were performed with the statistical software package SAS version 6.12 (SAS Institute, Cary, NC). Nested models were compared by the contrast option available in SAS version 7.0.

RESULTS

The original Six Cities cohort contained 13,842 subjects examined annually during a 15-year interval (100,292 observations). The study population was limited to 3626 black and white children (31,075 observations) who reported an asthma attack at some time during follow-up. This analysis was further restricted to 3452 subjects for whom questionnaire data could be paired with FEV₁ val-

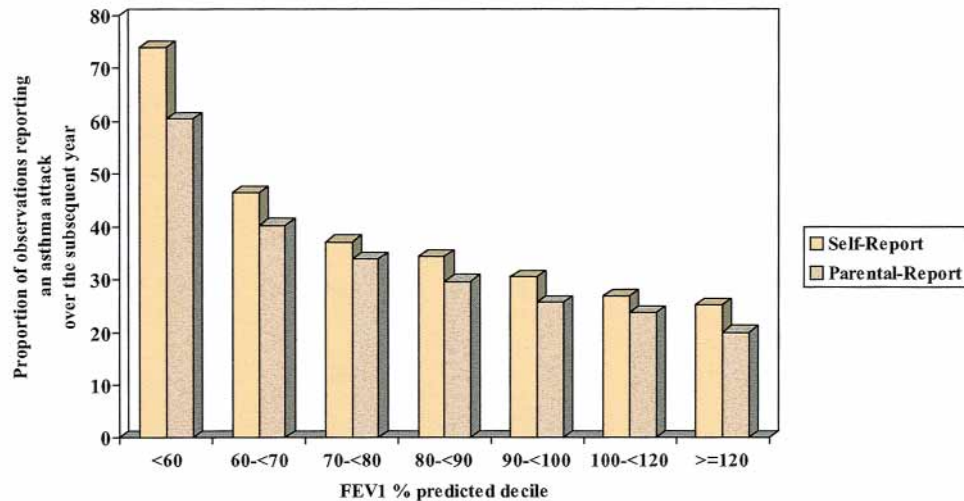


FIG 1. Proportion of observations reporting an asthma attack during the subsequent year by FEV₁%. FEV₁ is classified into deciles of FEV₁%. Observations are stratified by the source of questionnaire information: parental versus self-report.

TABLE II. Risk of asthma attack over a 1-year period: Comparison of FEV₁% classification schemes

Population	Risk of subsequent attack, OR (95% CI)					
	NAEPP classification			Alternative classification		
	>80%	60%-80%	<60%	>100%	80%-100%	<80%
Parental report						
Unadjusted	—	1.3 (1.1-1.4)	1.9 (1.4-2.6)	—	1.1 (1.1-1.2)	1.4 (1.2-1.6)
Adjusted*	—	1.4 (1.2-1.6)	2.2 (1.5-3.2)	—	1.1 (1.0-1.2)	1.5 (1.3-1.8)
Self report						
Unadjusted	—	1.3 (1.1-1.6)	4.6 (2.0-10.7)	—	1.2 (1.1-1.4)	1.6 (1.3-1.9)
Adjusted†	—	1.4 (1.2-1.7)	5.3 (2.2-12.9)	—	1.3 (1.1-1.4)	1.7 (1.4-2.1)

*Multivariable analysis, adjusted for previous attack, sex, and age.

†Multivariable analysis, adjusted for previous attack, sex, age, and smoking.

ues 1 year earlier (24,636 observations). The number of observations per subject ranged from 1 to 12. Most (60.4%) had between 7 and 11 observations. The sex distribution for the observations was essentially equal (49% female); 90.4% were white. The mean age of observations evaluated was 13.0 years. Overall, an asthma attack was reported at 6644 (27%) of the observations. The distribution of FEV₁% is shown in Table I. There was no difference in the distribution of age, sex, or race between the baseline cohort and the analysis population (data not shown). The demographics of the population stratified by respondent group were similar except for a difference in the mean age of the parental group compared with self-report group, 11.3 years and 16.5 years, respectively.

FEV₁% was significantly associated with risk of an asthma attack during the year after its measurement. We observed a progressive decrease in the proportion of individuals reporting an asthma attack in association with increasing FEV₁%. The proportion of individuals reporting an asthma attack was consistently higher in the self-report (older) group than in the parental report (younger)

group, but the pattern of response was similar (Fig 1).

The distribution of the population within each of the 2 alternative categorizations based on FEV₁% is shown (Table II). An association between FEV₁% category and asthma attack was shown with either classification scheme (Fig 2). With the NAEPP scheme, within the parental report group, 60.4% of observations with FEV₁% < 60 reported an attack compared with only 25.4% of observations with FEV₁% > 80%. A similar pattern was seen among the self-report group, with 73.9% and 29.4% reporting an attack in observations with FEV₁% < 60% and FEV₁% > 80%, respectively. The alternative classification scheme demonstrated a similar relationship between FEV₁% and attack, but the magnitude of the difference among categories of FEV₁% was smaller (Table II).

The risk of asthma attack was strongly associated with report of a previous attack. However, the effect of a previous attack was more pronounced among the parental report (younger) than the self-report (older) group, OR 4.3 (CI, 3.9-4.9) and OR 1.55 (CI, 1.39-1.73), respectively. Personal smoking was associated with an increased

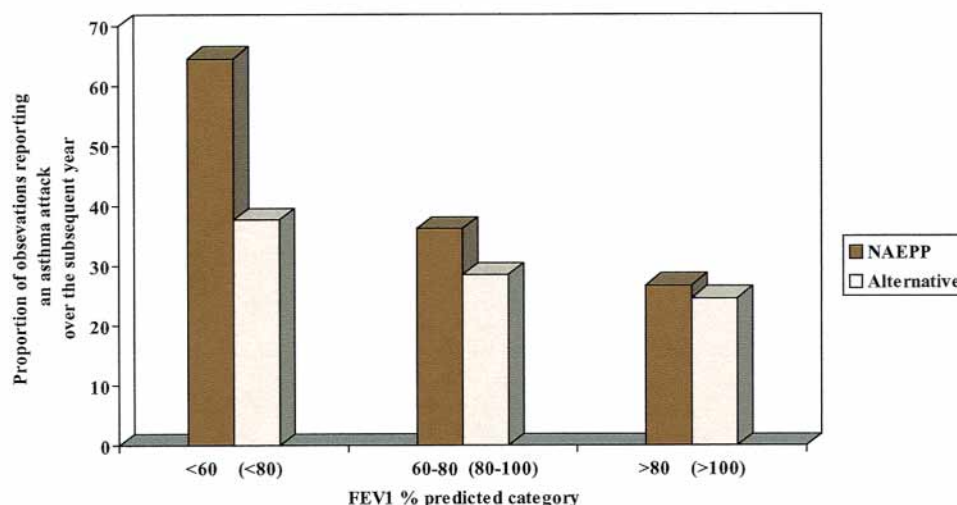


FIG 2. Proportion of observations reporting an asthma attack during the subsequent year by FEV₁%. FEV₁ classified with 2 schemes on the basis of FEV₁%, the NAEPP scheme (<60%, 60%-80%, and >80%) and an alternative scheme (<80%, 80%-100%, and >100%).

TABLE III. Association of FEV₁% and asthma attack: Comparison of subjects identified by history of asthma versus subjects identified by asthma attack history

Population	Risk of subsequent attack, OR (95% CI)					
	NAEPP classification			Alternative classification		
	> 80%	60%-80%	< 60%	> 100%	80%-100%	< 80%
Parental report*						
History of attack	—	1.4 (1.2-1.6)	2.2 (1.5-3.2)	—	1.1 (1.0-1.2)	1.5 (1.3-1.8)
History of asthma	—	1.5 (1.2-1.9)	3.4 (2.0-5.8)	—	1.0 (0.9-1.2)	1.6 (1.2-2.0)
Self report†						
History of attack	—	1.4 (1.2-1.7)	5.3 (2.2-12.9)	—	1.3 (1.1-1.4)	1.7 (1.4-2.1)
History of asthma	—	1.5 (1.1-2.0)	4.0 (1.2-13.6)	—	1.2 (1.0-1.4)	1.7 (1.3-2.3)

*Multivariable analysis, adjusted for previous attack, sex, and age.

†Multivariable analysis, adjusted for previous attack, sex, age, and smoking.

risk of attack among the self-report group, although ETS was not associated with an increased risk of attack among the parental report group, OR 1.38 (CI, 1.25-1.54) and OR 1.03 (CI, 0.93-1.15), respectively. Increasing age and male gender were associated with a decreased risk of attack among both reporting groups, OR 0.63 (CI, 0.57-0.72) and OR 0.87 (CI, 0.83-0.90), respectively. Black race was not associated with an increased risk of attack in either reporting group, OR 1.10 (CI, 0.90-1.35).

Multivariable models examined the association of FEV₁% and subsequent asthma attack, controlling for these potential confounding variables. As was true in the unadjusted analyses, the risk of asthma attack increased as FEV₁% category decreased (Table II). The magnitude of the association between FEV₁% and risk of asthma attack was modified by respondent (age) category. In the multivariable models, among observations with a FEV₁% < 60%, the OR for the self-report (older) group was more than twice that for the parental report (younger) group within the same category of FEV₁%.

When categorized as recommended in the NAEPP

guidelines, FEV₁% remained a significant predictor of subsequent asthma attack among both respondent (age) groups (Table II). For the alternative classification scheme, FEV₁% < 80% was still significantly associated with an increased risk of attack compared with the reference category (FEV₁% > 100%). However, for the intermediate category (FEV₁% 80%-100%) compared with the reference category (FEV₁% > 100%), the lower confidence bound equaled 1, OR 1.09 (CI, 1.0-1.19). When nested models were examined to identify the most parsimonious model, the removal of FEV₁% was associated with a significant loss of information regarding the risk of attack ($P = 0.003$).

Finally, we restricted our analysis to individuals who reported a history of asthma at any time during follow-up. For the NAEPP classification, FEV₁% continued to be strongly associated with the risk of attack (Table III). For the alternative classification, the pattern of the association was similar to that in the less restricted population. Compared with observations with an FEV₁% > 100%, observations with FEV₁% < 80% had an

increased risk of attack. However, for observations with FEV₁% between 80% and 100%, the lower bound of the CI crossed 1 for both reporting groups (Table III).

DISCUSSION

We have shown that a single measure of FEV₁% can predict the risk of an asthma attack during the subsequent year of follow-up. The NAEPP has endorsed the use of objective measures of lung function in classifying asthma severity.¹ A fundamental goal of a severity classification is to create categories that capture differences in risk that can be used to guide asthma therapy. Our study provides important data on the long-term relationship between FEV₁% and risk of asthma outcomes within a pediatric population.

We examined the FEV₁% cutoffs disseminated by the NAEPP (<60%, 60%-80%, and >80%) and an alternative scheme (<80%, 80%-100%, >100%). We thought it important to examine the differing classification schemes for 2 reasons. First, to our knowledge no previous analysis had evaluated the specific cutoffs presented within the NAEPP guidelines in a pediatric population. Second, in our general population sample, a small proportion of the pediatric population had an FEV₁% < 60%.

In our population both of the 3-category schemes captured variation in risk and were informative in predicting risk of attack. The NAEPP categorization exhibited greater differences between the levels of FEV₁% and maintained a stronger association with risk of attack within all the subgroups evaluated. This classification scheme is widely used clinically.

For the purposes of prediction and planning, it is useful to find a simple objective measure of severity, such as underlying lung dysfunction, to predict subsequent outcomes such as asthma symptoms or morbidity. We do not propose that asthma severity can be fully described by measurement of FEV₁%. Most definitions for asthma severity, including the NAEPP definition, include information about asthma symptoms, morbidity, and medication use in addition to measures of lung function. However, the disadvantage of such definitions is that they do not allow identification of mutually exclusive groups.

An advantage of FEV₁% as a marker of asthma severity is its objectivity and reproducibility.^{16,17} It is frequently acquired in clinical trials, and the efficacy of new therapies is often expressed in terms of impact on FEV₁%. In addition, review of the clinical trials literature examining asthma therapies suggests that improvements in FEV₁ parallel improvements in other asthma outcomes such as exacerbations,¹⁸⁻²⁰ health care utilization,^{21,22} symptoms,^{19,23-25} health-related quality of life,^{20,26} and rescue medication use.²⁵ Because many downstream consequences of asthma are the direct result of airway obstruction, it makes sense to use a test that measures baseline obstruction level.

We observed a difference in the magnitude of the association between FEV₁% and risk of asthma attack between the two reporting groups. The relative risk among the self-report (older) group with a FEV₁% < 60% was approxi-

mately twice that of parental report (younger) group within the same category of FEV₁%. The differences in our analysis were of magnitude and direction similar to those documented by Demokosh et al¹² in this population. They observed a difference in the report of wheeze depending on the identity of the respondent. Self-reported wheeze rates were 2.4 times higher (95% CI, 1.2-4.8) than parent-reported wheeze rates. Braun-Fahrlander et al²⁶ noted similar results, with adolescents reporting higher rates of current symptoms and of ever asthma than their parents (relative risk of wheeze, 1.6). Parents may be less aware of occasional symptomatic episodes and report only more serious events. Children may also interpret the questions differently than adults.²⁷ Whether the differences between the respondent (age) groups are the result of reporting bias is difficult to discern from the current analysis. Parental report was primarily used among younger children, whereas self-report was used among the older children; true biologic differences are possible between young children (age 6-13 years) and adolescents (age > 14 years).

Personal smoking was a significant predictor of asthma attacks among the self-report (older) group, whereas ETS was not associated with attacks among the parental report (younger) group. Personal smoking is associated with asthma morbidity,²⁸⁻³⁰ consistent with our findings. An association between ETS and lower respiratory tract infections in young children has been reported.³¹ However, this was seen in children younger than 2 years; among children aged 3 to 6 years, the association was no longer significant, OR 1.25 (95% CI, 0.99-1.78). The minimum age of children in our analysis was 5.7 years. In addition, a relationship between ETS and symptoms among patients with asthma has not been consistently demonstrated.^{29,32,33} Our definition of ETS included low-level exposure and may have contributed to the lack of an association.

Several limitations of this study should be discussed. We examined self-reported asthma attacks. Other outcomes, such as quality of life, need for rescue medication use, and hospitalizations for asthma, are obviously of interest, although they are likely to be correlated with occurrence of asthma attacks. A number of factors other than FEV₁ have been postulated to influence risk of hospitalization, such as allergen exposure, race or ethnicity, socioeconomic status, area of residence, and access to care.³⁴⁻³⁷ None of these variables was examined in our analysis. In addition, we did not control for asthma medication use within this analysis. Recall bias also must be considered. We observed that 25% of observations with FEV₁% < 60% were not associated with a report of an attack. Recall of events over a 1-year period and differences in interpretation among subjects as to what constitutes an attack may be responsible for this result. Not all questionnaire responses (4.7%) could be paired with appropriate FEV₁ values. A common cause for missing FEV₁ data was inability to perform acceptable spirometry. Although unacceptable spirometry is associated with age (younger children have more difficulty performing the maneuver), no association with any of the reported respiratory symptoms was observed within the Six Cities cohort.³⁸

Finally, our analysis included individuals who reported a history of asthma attack but did not report a history of asthma. Asthma is frequently underdiagnosed, especially in children.³⁹ In addition, several studies have supported the use of asthma symptoms to identify subjects with asthma.⁴⁰⁻⁴³ In the Tasmanian Long Term Health Survey, investigators evaluated the association between self-report of asthma attacks or wheezy breathing during the past 12 months and a diagnosis of asthma by a respiratory physician. They found a sensitivity of 0.8 (0.58-0.93), specificity 0.97 (0.90-0.99), positive predictive value 0.89 (0.68-0.98), and negative predictive value 0.94 (0.86-0.98). In a pediatric cohort (the International Study of Asthma and Allergy in Childhood), investigators reported similar results. Panhuysen et al⁴⁴ reported that the presence of 1 symptom group in subjects younger than 16 years or 2 in subjects older than 16 years is compatible with asthma and that a clear history of recurrent asthma attacks is considered strong evidence of asthma. This literature supports inclusion of subjects with a surrogate diagnosis of asthma (a history of an attack) in our analysis population. When we restricted our current analysis to children with a history of asthma, the results were similar.

CONCLUSIONS

A strong association exists between FEV₁% and risk of asthma attacks during the subsequent year. Further research is needed to explore the predictive accuracy of FEV₁ over various time horizons and over a broad range of outcomes, such as resource utilization, quality of life, and symptoms. Nonetheless, these data support an emphasis on objective measures of lung function in assessment of risk for adverse asthma outcomes.

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