Irreversible lung function deficits in young adults with a history of childhood asthma

Susan L. Limb, MD,[a] Kathryn C. Brown, MD,[a] Robert A. Wood, MD,[b] Robert A. Wise, MD,[c] Peyton A. Eggleston, MD,[b] James Tonascia, PhD,[d] and N. Franklin Adkinson, Jr, MD[a] *Baltimore, Md*

Background: Asthma, traditionally characterized as reversible airway obstruction, might lead to structural changes and permanent impairment.
Objective: We sought to study the frequency, severity, and reversibility of pulmonary deficits in adults with a history of moderate-to-severe childhood allergic asthma.
Methods: Subjects (n = 121) previously enrolled in a randomized trial of immunotherapy for childhood asthma were recalled. Eighty-four young adults (age, 17-30 years; 78% male) were reevaluated by means of spirometry. Subjects with a postbronchodilator FEV_1, forced vital capacity, or FEV_1/forced vital capacity ratio less than or equal to the 5th percentile or 2 or more indices less than or equal to the 10th percentile (National Health and Nutrition Examination Survey III normative data) were invited to undergo complete pulmonary function testing, physical examination, and chest radiography after 1 week of 1 mg/kg daily prednisone.
Results: Of 84 subjects reevaluated, 40 (48%) had one or more spirometric indices less than or equal to the 5th and 10th percentiles ($P < .0001$). Twenty-eight of the 40 subjects were reassessed after prednisone treatment, of whom 21 (75%) did not improve. Adult and childhood (age 5-12 years) spirometric results were positively correlated ($r = 0.49$-0.72, $P < .001$). Abnormal adult spirometric results were associated with a longer duration of asthma at enrollment in the original trial (4.6 vs 6 years, $P = .02$), increased childhood methacholine sensitivity (PC_{20}, 0.11 vs 0.18 mg/mL; $P = .01$), and birth prematurity (adjusted odds ratio, 10.7; 95% CI, 1.4-84.5). Immunotherapy status was unrelated to adult lung function.
Conclusions: Many adults with a history of moderate-to-severe allergic asthma in childhood have irreversible lung function deficits. Childhood spirometry, duration of asthma, methacholine sensitivity, and birth prematurity might identify such individuals at a young age. (J Allergy Clin Immunol 2005;116:1213-9.)

Key words: *Childhood asthma, pulmonary function test, spirometry, methacholine sensitivity*

Clinical observation and new concepts of airway remodeling challenge the notion of asthma as a disease of reversible obstruction. Several longitudinal studies have indicated that individuals with wheezing and self-reported asthma might have decreased lung function later in life. Lange et al[1] tracked 17,506 Danish adults and noted that the 1095 subjects with self-identified asthma had steeper decreases in FEV_1 over a 15-year period. Similarly, Sears et al[2] studied a general pediatric cohort and found that 89 subjects with chronic self-reported wheezing had lower prebronchodilator lung function as adults. Whether these decreases in adult lung function are reversible either spontaneously or with bronchodilators and steroids remains unclear.

To address this issue, we recalled 121 prior participants in a placebo-controlled trial of immunotherapy for childhood asthma conducted from 1984 through 1994.[3] All subjects had asthma diagnosed by a physician and had moderate-to-severe asthma on the basis of medication use and symptom frequency. We now report pulmonary function outcomes and associated findings from this well-characterized cohort.

METHODS

Study participants

The Childhood Asthma Study (CAS; December 1984 through July 1994) was a double-blind, randomized, placebo-controlled trial of immunotherapy as an adjunct treatment of allergic asthma.[3] The 121 original subjects, ages 5 to 12 years at randomization, had physician-diagnosed asthma requiring daily medications for at least 1 year before enrollment. Evaluations performed during the original study included daily medication-symptom diaries, home visits, allergy skin testing, and methacholine challenges with associated spirometry. The cohort included a range of socioeconomic status, sex, and ethnicity. The primary study outcome was the daily medication usage score as a measure of disease severity. The original CAS showed no significant differences between the placebo and active immunotherapy groups; both groups' medication use and methacholine sensitivity decreased similarly during the trial period.[3]

An attempt was made to evaluate all 121 of the original subjects between November 2001 and September 2003. Reasons for nonparticipation included inability to locate or contact the subject (n = 10), incarceration (n = 3), and death (n = 1). Twenty-two additional CAS subjects did not respond or refused for unknown reasons. Exclusion criteria for the current study included other medical conditions known to affect pulmonary function. One patient was excluded because of severe kyphoscoliosis under these criteria.

From [a]the Division of Allergy and Clinical Immunology, [b]the Department of Pediatrics, and [c]the Divisions of Pulmonology and Critical Care Medicine, Johns Hopkins School of Medicine, and [d]the Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University.

Supported by the Philip Morris External Research Program and National Institutes of Health, National Center for Research Resources, grant no. 5M01RR02719 to The Johns Hopkins Bayview General Clinical Research Center.

Received for publication August 8, 2005; revised September 13, 2005; accepted for publication September 19, 2005.

Available online November 8, 2005.

Reprint requests: N. Franklin Adkinson, Jr, MD, JHAAC Rm 2A.62, 5501 Hopkins Bayview Circle, Baltimore, MD 21224. E-mail: fadkinso@jhmi.edu.

0091-6749/$30.00

doi:10.1016/j.jaci.2005.09.024

TABLE I. Demographics and childhood characteristics of subjects in the original CAS clinical trial who were and were not evaluated in young adulthood

	Evaluated (n = 84)	Not evaluated (n = 37)	*P* value
Age at recall, y (mean [range])	24 (18-31)	25 (19-31)	.10
Sex (% male)	62 (73.8%)	27 (73.8%)	.59
Race			
White	46 (54.8%)	19 (51.4%)	.74
African American	37 (44.0%)	18 (48.6%)	
Other	1 (1.2%)	–	
Prior immunotherapy (% active treatment)	42 (50.0%)	19 (51.4%)	.52
Average asthma medication score (range 0-7)*†	3.8 ± 2.6	3.6 ± 2.6	.58
Average % trial days with inhaled steroid use	32.4%	32.2%	.98
Average peak flow rate, % predicted (mean ± SD)*	83.4 ± 11.6	85.3 ± 11.9	.44
Prebronchodilator FEV_1, % predicted (mean ± SD), at end of trial	86.9 ± 10.4	87.0 ± 11.6	.95
Total serum IgE (ng/mL) at randomization‡	876 (686-1119)	930 (637-1359)	.70
Methacholine FEV_1 PC_{20} at end of trial (mg/mL)‡	0.14 (0.12-0.17)	0.13 (0.10-0.19)	.96

*Averaged over 2.8 years of the childhood clinical trial period.
†Daily medication usage score, as previously described,[3] averaged over the trial period.
‡Geometric mean (95% CI).

Abbreviations used
CAMP: Childhood Asthma Management Program
CAS: Childhood Asthma Study
FVC: Forced vital capacity
OR: Odds ratio

Written informed consent was obtained from the 84 subjects subsequently enrolled under a protocol approved by the Johns Hopkins Institutional Review Board. Subjects continued their usual medication regimens.

Study design

During the initial adult evaluation, subjects underwent spirometry, inhalant allergy skin testing, and interviews regarding interim medical history and symptoms. Asthma exacerbation, oral corticosteroid use in the past 30 days, or active pulmonary symptoms were criteria for exclusion from testing on any given day. Individuals with postbronchodilator FEV_1, forced vital capacity (FVC), or FEV_1/FVC ratios of less than or equal to the 5th percentile or at least 2 of these spirometric measures less than or equal to the 10th percentile (adjusted for age, sex, height, and ethnicity according to National Health and Nutrition Examination Survey III population norms[4]) were categorized as abnormal. Subjects with abnormal postbronchodilator results were prescribed 1 mg/kg daily oral prednisone (maximum dose, 70 mg/d) for the 7 days before complete pulmonary function testing, physical examination, and chest radiography to assess the steroid responsiveness of lung deficits.

Pulmonary function tests

Childhood prebronchodilator spirometry was performed in conjunction with methacholine challenges by using a Collins water-sealed spirometer (WE Collins, Braintree, Mass). Initial adult postbronchodilator spirometry was performed 20 minutes after 2 puffs of albuterol (90 μg per actuation) with a Collins dry-sealed spirometer (WE Collins). Full pulmonary function tests according to American Thoracic Society guidelines[5] were performed by using a dry rolling-seal spirometer (Sensormedics 2800, Yorba Linda, Calif). Spirometric measurements from both devices were tested and confirmed for equivalence. Spirometric measures in both childhood and young adulthood were converted to percentages of the predicted value or the percentile for the measure by using norms for nonasthmatic subjects from the National Health and Nutrition Examination Survey III national sample.[4]

Skin testing

Skin testing was performed as previously described[3] with a panel of 18 common perennial and seasonal allergens (ALK-Abello, Round Rock, Tex): dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), molds (*Cladosporium*, *Penicillium*, *Aspergillus*, and *Alternaria* species and *Mucor racemosus*), pollens (*Quercus Alba*, *Cynodon dactylon*, *Aspidistra eliator*, *Plantago* species, and rye/orchard/timothy grass mix), and epidermals (cat, dog, American-German cockroach, mouse, and guinea pig).

Statistical analyses

Statistical analyses were performed with SPSS 10.1 (Chicago, Ill) and Stata 8.0 (College Station, Tex) software as follows: Student and paired *t* tests for continuous variables, Wilcoxon rank sum test for skewed variables, and χ^2 test for categoric variables and comparison of observed and expected rates. The Spearman rank-order correlation was used to summarize the relationship between childhood and adult spirometric results. Logistic regression analysis was used to evaluate the odds of abnormal adult spirometric results in relation to childhood exposures and family history risk factors. Similar analysis was used to evaluate the risk of abnormal spirometric results in relation to asthma and atopy status in young adulthood. The Hosmer-Lemeshow χ^2 test was used to assess the adequacy of fit of the multiple logistic models. All *P* values are reported as 2 sided, and values of less than .05 were considered statistically significant.

RESULTS

Demographics

Eighty-four of the 121 subjects from the original study were evaluated (mean follow-up, 10.8 years; range, 8-15.6 years). Demographic features and childhood characteristics of the subjects who were and were not

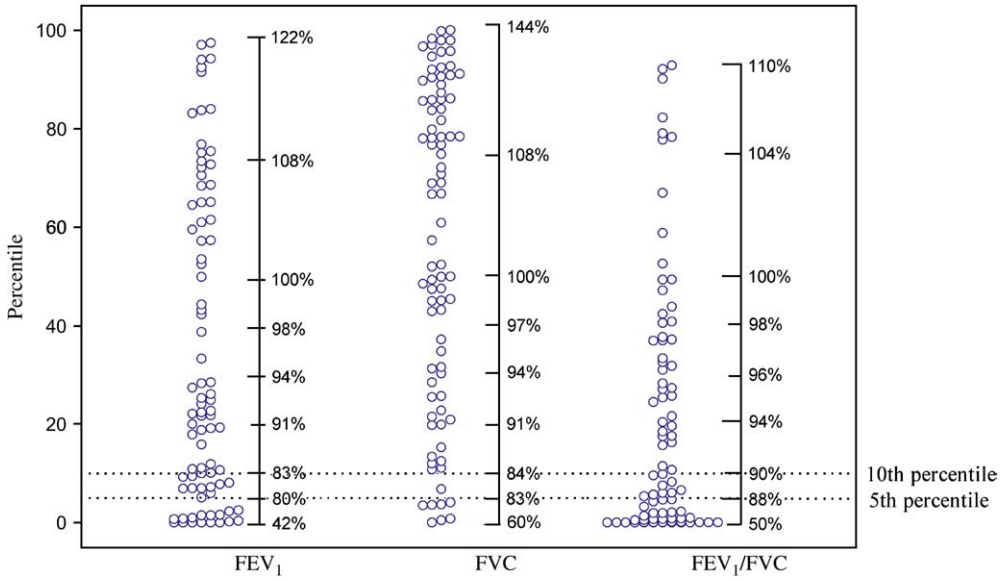

FIG 1. Percentiles based on National Health and Nutrition Examination Survey III normative data and percent predicted values for postbronchodilator spirometric measures at initial adult evaluation (n = 84). Axes for estimated corresponding percent predicted values are displayed as insets (exact correspondence of measures varies with age, sex, height, and ethnicity). Mean FEV_1 percent predicted = 91.2%; mean FVC = 102.8%; mean FEV_1/FVC ratio = 88.6%.

reevaluated are summarized in Table I. No significant differences were noted in mean age at recall, sex, ethnicity, childhood lung function, medication use, or socioeconomic status[6] (data not shown).

Adult spirometric evaluation at visit 1

Forty (47.6%) subjects were defined as abnormal on the basis of a postbronchodilator FEV_1, FVC, or FEV_1/FVC ratio of less than or equal to the 5th percentile or at least 2 of these spirometric measures of less than or equal to the 10th percentile ($P < .0001$, χ^2 test; Fig 1). Deficits in FEV_1 and FEV_1/FVC ratio predominated, which is consistent with pulmonary obstruction (Table II). Sixteen subjects had an FEV_1 of less than or equal to the 5th percentile, and 11 others had values between the 5th and 10th percentiles. Similarly, 34 subjects had an FEV_1/FVC ratio of less than or equal to the 5th percentile, and an additional 9 were between the 5th and 10th percentiles. None of the 8 subjects with an FVC of less than or equal to the 10th percentile shown in Table II qualified as having abnormal spirometric results by this measurement alone; all 8 had other deficits in FEV_1 or FEV_1/FVC ratio. Bronchodilator response was greater in the group with abnormal spirometric results (12.8% vs 7.5% change from prebronchodilator FEV_1, $P = .02$).

Groups with normal and abnormal spirometric results did not differ in terms of sex, ethnicity, total serum IgE level, or prior immunotherapy status (Table III). However, the group with abnormal spirometric results was older (24 vs 22 years, $P = .01$) and had a longer duration of asthma symptoms (21 vs 19 y, $P = .01$), defined as the time from onset of first symptoms to current age. Age at asthma onset did not differ ($P = .6$), but differences in asthma duration existed even in childhood (4.6 vs 6.0 years at childhood enrollment, $P = .02$). A significant negative correlation was observed between asthma duration and FEV_1 at randomization ($r = -0.62$, $P < .001$). The abnormal group also displayed lower average peak expiratory flows and FEV_1, increased inhaled corticosteroid use, and increased methacholine sensitivity in childhood.

As shown in Fig 2, adult prebronchodilator FEV_1 percent predicted correlated with childhood values ($r = 0.48$, $P < .001$), as did FEV_1/FVC ratio ($r = 0.48$, $P < .001$). The relationship between adult and childhood FVC was even more pronounced ($r = 0.72$, $P < .001$). Comparison between prebronchodilator peak flows at baseline in childhood versus adulthood revealed a similar relationship ($r = 0.421$, $P < .001$). Similar correlations were found between adult postbronchodilator indices and childhood values as well (data not shown). Mean percent predicted and percentile spirometric data from childhood are available in Table E1 in the Online Repository in the online version of this article at www.jacionline.org. Comparison of childhood and adult percent predicted prebronchodilator values across the whole cohort showed statistically significant decreases over time in FEV_1 (95.5% vs 83.6%, $P < .001$) and FEV_1/FVC ratio (92.4% vs 82.1%, $P < .001$) but not FVC (101.6% vs 101.5%, $P = .97$). Postbronchodilator measurements from childhood were unavailable for comparison.

Analysis of various early childhood exposures and potential risk factors showed an increased risk associated with prematurity (≤34 weeks' gestation; odds ratio [OR], 10.7; 95% CI, 1.4-84.5; $P = .02$; Table IV). No significant associations were detected for factors such as breast-feeding, childhood secondhand tobacco smoke

TABLE II. Postbronchodilator spirometric results in young adulthood

	Normal (n = 44)	Abnormal (n = 40)	*P* value	Percentile* ≤5th	Percentile* ≤10th
FEV_1	101.3 ± 10.5	80.1 ± 14.9	<.001	16	27
FVC	104.2 ± 10.4	101.3 ± 17.3	.37	7	8
FEV_1/FVC ratio	96.6 ± 5.6	84.5 ± 13.8	<.001	34	43
% Δ FEV_1 after albuterol	7.5 ± 4.1	12.8 ± 13.9	.02	–	–

All values are reported as mean percent predicted ± SD.
Abnormal spirometric results are defined as either FEV_1, FVC, or FEV_1/FVC ratio of less than the 5th percentile or at least 2 pulmonary function test indices less than the 10th percentile on the basis of National Health and Nutrition Examination Survey III spirometric norms.[4]
*Numbers in columns represent the number of subjects in each percentile category.

TABLE III. Demographics, asthma, and atopy in childhood of subjects with normal and abnormal spirometric results in young adulthood

	Normal (n = 44)	Abnormal (n = 40)	*P* value
Age, y (mean, range)			
At adult reevaluation	22 (17-28)	24 (18-30)	.02
At asthma onset	3 (1-8)	3 (0-8)	.6
At childhood enrollment	7 (4-12)	9 (5-13)	.01
Duration of asthma symptoms, y (range)			
At childhood enrollment	4 (0-9)	6 (1-11)	.02
At adult follow-up	19 (13-25)	21 (16-28)	.01
Sex (% male)	35 (79.5%)	27 (67.5%)	.21
Race			
White	23 (52.3%)	23 (57.5%)	.48
African American	21 (47.7%)	16 (40.0%)	
Other	–	1 (2.5%)	
Prior immunotherapy (% active treatment)	21 (47.7%)	21 (52.5%)	.66
Average asthma medication score (range, 0-7)*†	3.4 ± 2.5	3.9 ± 2.6	.16
Average % trial days with inhaled steroids	23.4%	42.8%	.01
Average peak flow rate*	86.4 ± 11.0	80.2 ± 11.6	.01
Prebronchodilator FEV_1, % predicted (mean ± SD), at randomization	100.0 ± 17.3	90.5 ± 8.9	.02
Total serum IgE (ng/mL) at randomization‡	881 (649-1196)	870 (581-1302)	.73
Methacholine FEV_1 PC_{20} at end of trial (mg/mL)‡	0.18 (0.15-0.21)	0.11 (0.08-0.15)	.01
Mean ± SD no. of positive readings from panel of 18 prick-puncture allergy skin tests	9 ± 4	9 ± 3	.44

*Mean ± SD averaged over 2.8 years of childhood clinical trial period.
†Daily medication usage score, as previously described,[3] averaged over trial period.
‡Geometric mean (95% CI).

exposure, number of children in the household or pet exposure before age 1 year, or family history of asthma.

Analysis of current symptoms and asthma medication use showed a significant association of abnormal spirometric results with regular use of inhaled steroids (adjusted OR, 4.8; 95% CI, 1.0-22.4; $P = .04$) and daily medications other than steroids (adjusted OR, 24.8; 95% CI, 1.9-321; $P = .01$; Table V). No significant associations were observed for smoking, number of emergency department visits in the past year, allergy skin tests, active eczema or rhinitis, and total serum IgE levels.

Adult pulmonary function test evaluation at visit 2 after corticosteroids

Forty of 84 subjects had abnormal postbronchodilator spirometric results and qualified for prednisone on the basis of initial abnormal spirometric results. Twenty-eight (70%) of 40 received 7 days of 1 mg/kg oral prednisone and were reevaluated. Of the remaining 11 subjects, 5 refused corticosteroids, and 6 did not return, despite repeated scheduling.

Seven (25%) of the 28 subjects retested after corticosteroid therapy had sufficient (but not statistically significant) improvement to meet normal spirometric criteria (Table VI). In this steroid-responsive group the mean FEV_1 percent predicted improved from 84.1% to 96.7% ($P = .14$), and the FEV_1/FVC ratio improved from 80.4% to 89.6% ($P = .11$). The remaining 21 subjects did not show improvement in these variables. Improvement with prednisone was not associated with lower FEV_1 at initial adult evaluation ($P = .62$). Other pulmonary function test indices, including residual volume, total lung capacity, and diffusing capacity of lung for carbon monoxide, and chest radiographs were normal or consistent with asthma;

no restrictive patterns or diminished diffusion capacities were observed.

DISCUSSION

In this study we found a large number of lung deficits resistant to albuterol and high-dose prednisone in young adults with a history of moderate-to-severe childhood asthma. More than two thirds of the original asthma cohort returned for evaluation, and those returning appeared to be representative of the total group. Nearly half (40/84) of the recalled cohort members had abnormal spirometric results according to American Thoracic Society guidelines,[5] despite bronchodilator administration.

The high proportion with abnormal and adult postbronchodilator spirometric results might reflect selection of moderately severe, physician-diagnosed asthma in the original pediatric cohort in contrast to other studies based on self-reports of wheezing and asthma and a milder range of disease. Individuals with more severe asthma might be more likely to have permanent airway changes that lead to bronchodilator-resistant airflow limitation.[7] This statement might oversimplify the issue, however, because several studies have suggested that lung function does not always correlate with the extent of histopathologic changes.[8,9]

Subjects with abnormal spirometric results received a week of high-dose oral prednisone to minimize subclinical asthmatic inflammation. Despite corticosteroid therapy, 22 of 29 subjects examined had persistent obstructive deficits that kept them below the 5th and 10th percentiles for a normal population. Even for subjects who reverted to normal postbronchodilator spirometric results with prednisone, improvement was modest and incomplete when compared with those with initially normal results. The apparent steroid resistance of these functional deficits suggests the presence of postinflammatory structural alterations. However, we do acknowledge possible limiting factors to this conclusion. Subjects who qualified but declined steroids might differ from those who received steroids and underwent complete pulmonary function testing. Comparison of these subjects in terms of their baseline adult and childhood spirometric results, demographics, and childhood and adult medication use revealed no significant differences (data not shown), but other differences might exist that we cannot ascertain. Other factors include the adequacy of the steroid dose, which was relatively high by clinical standards but might have been insufficient in dose or duration to reverse the deficits observed.

Across the cohort, adult and childhood lung function correlated significantly (Fig 2), suggesting that lung impairment begins early in life and that individuals at risk might be identifiable at a young age. Other studies have noted similar correlations. Rasmussen et al[10] reported that subjects with low postbronchodilator FEV_1/FVC ratios at age 18 years tended to have had low ratios at age 9 years. Similarly, Grol et al[11] found lower lung function and increased bronchial reactivity in childhood to be independent risk factors for a lower FEV_1 in early adulthood.

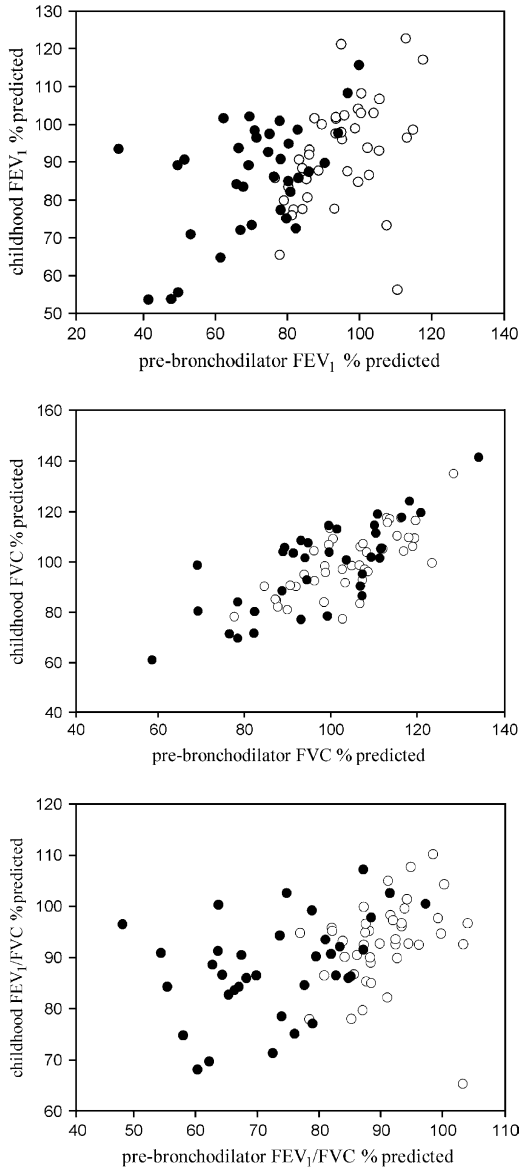

FIG 2. Correlations between childhood and young adult prebronchodilator spirometric results: normal (*open circles*) and abnormal (*filled circles*) categorization on the basis of spirometry in young adulthood.

Unfortunately, we do not have postbronchodilator spirometric results from childhood available for a more direct comparison of childhood and adult lung function, although analysis of prebronchodilator spirometric results suggests that early impairment followed by ongoing disease progression might occur in a subset of asthmatic individuals (see Table E1 in the Online Repository in the online version of this article at www.jacionline.org).

The longer duration of asthma associated with abnormal spirometric results might correspond to a critical period of disease development in early childhood. These results are also consistent with prior studies implicating duration of disease with severity. Jenkins et al[12] reported that asthma severity correlates with disease duration in children and

TABLE IV. Logistic regression analysis of abnormal spirometric results in young adulthood in relation to childhood exposures and family history risk factors

	Normal, n (%)	Abnormal, n (%)	OR (95% CI)*	*P* value	Adjusted OR (95% CI)*	*P* value
Prematurity (≤34 weeks' gestation)	2 (4.8)	7 (17.9)	4.4 (0.8-22.5)	.08	10.7 (1.4-84.5)	.02
Breathing problems as newborn	10 (30.3)	6 (18.2)	0.6 (0.2-1.8)	.37	0.3 (0.1-1.1)	.08
Breast-fed	23 (53.5)	23 (59.0)	1.2 (0.5-3.0)	.62	1.4 (0.5-3.7)	.54
Other children in household during first year of life	16 (37.2)	17 (43.6)	1.3 (0.5-3.2)	.56	1.5 (0.6-4.2)	.38
Secondhand tobacco smoke at home	20 (46.5)	13 (33.3)	0.6 (0.2-1.4)	.23	0.6 (0.2-1.6)	.28
Cat during first year	5 (11.6)	6 (18.2)	1.4 (0.4-4.9)	.56	1.4 (0.3-5.9)	.64
Dog during first year	9 (20.9)	9 (30.0)	1.1 (0.4-3.2)	.82	1.0 (0.3-3.1)	.97
Any first-degree relatives with asthma	27 (62.8)	29 (72.5)	1.6 (0.6-4.0)	.35	1.6 (0.6-4.6)	.35

*The OR indicates the risk for each factor alone; the adjusted OR indicates the risk for each factor adjusted for the other factors in a logistic regression model. The logistic regression analyses were performed on 80 to 84 subjects, with the difference in n accounted for by missing data values. Hosmer-Lemeshow adequacy-of-fit test ($df = 3$): $\chi^2 = 0.23$, $P = .97$.

TABLE V. Logistic regression analysis of abnormal spirometric results in young adulthood in relation to current asthma and atopy status

Risk factors	Normal, n (%)	Abnormal, n (%)	OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
Current medication						
No medication	10 (22.7)	5 (12.5)	–	–	–	–
As-needed albuterol only†	23 (52.3)	12 (30.0)	1.0 (0.3-3.8)	.95	1.2 (0.3-5.3)	.76
Inhaled steroids ± other medications†	10 (22.7)	16 (40.0)	3.2 (0.8-12.1)	.09	4.8 (1.0-22.4)	.04
Daily medications other than steroids†	1 (2.3)	7 (17.5)	14.0 (1.3-147)	.03	24.8 (1.9-321)	.01
Current smoking	9 (20.4)	10 (25.0)	1.2 (0.4-3.4)	.70	1.5 (0.4-5.4)	.52
≥1 ED visit in past year	6 (13.6)	8 (20.0)	1.6 (0.5-5.0)	.44	2.7 (0.7-11.1)	.17
Eczema in past year	11 (25.0)	7 (17.5)	0.6 (0.2-1.8)	.40	0.9 (0.3-3.0)	.85
Rhinitis in past year	40 (90.9)	35 (87.5)	0.7 (0.2-2.8)	.62	0.5 (0.1-2.5)	.44
Current total serum IgE, high vs low‡	22 (50.0)	19 (48.7)	1.0 (0.4-2.2)	.91	0.8 (0.3-2.2)	.60
Skin test positivity, high vs low§	20 (45.5)	17 (44.7)	1.0 (0.4-2.3)	.95	0.6 (0.2-1.7)	.32

ED, Emergency department.
*The OR indicates the risk for each factor alone; the adjusted OR indicates the risk for each factor adjusted for the other factors in a logistic regression model. The logistic regression analyses were performed on 79 to 84 subjects, with the difference in n accounted for by missing data values. Hosmer-Lemeshow adequacy-of-fit test ($df = 3$): $\chi^2 = 2.96$, $P = .40$.
†Odds ratio for abnormal spirometry in relation to "no medication" group.
‡High total serum IgE level is defined as greater than 768 ng/mL (median value).
§High skin test positivity is defined as more than 8 positive readings (median value) from a panel of 18 prick-puncture allergy skin tests.

TABLE VI. Pulmonary function indices before and after prednisone in steroid-responsive and steroid-nonresponsive young adults with abnormal postbronchodilator spirometric results

	Before prednisone			After prednisone		
	Total (n = 28)	Steroid responsive (n = 7)	Steroid nonresponsive (n = 21)	Total (n = 28)	Steroid responsive (n = 7)	Steroid nonresponsive (n = 21)
FEV_1*	80.9 ± 14.5	84.1 ± 20.4	79.9 ± 12.5	84.5 ± 13.8	96.7 ± 11.7	80.4 ± 12.2
FVC	102.9 ± 17.2	103.6 ± 15.3	102.6 ± 18.1	105.2 ± 16.2	108.0 ± 14.4	104.2 ± 16.9
FEV_1/FVC ratio	79.1 ± 15.7	80.4 ± 13.7	78.6 ± 9.3	80.7 ± 9.9	89.6 ± 1.5	77.7 ± 9.7
% Δ FEV_1 after albuterol	14.9 ± 15.7	12.6 ± 8.5	15.7 ± 17.5	13.2 ± 12.8	8.2 ± 5.5	14.8 ± 14.1
RV	–	–	–	116.3± 39.4	93.5 ± 14.4	123.9 ± 42.3
TLC	–	–	–	102.5 ± 13.2	99.3 ± 7.9	103.6 ± 14.5
FRC	–	–	–	91.1 ± 25.0	79.3 ± 21.6	95.1 ± 25.3
D_{LCO}	–	–	–	114.0 ± 20.0	106.1 ± 15.1	116.6 ± 21.0

RV, Residual volume; *TLC*, total lung capacity; *FRC*, functional residual capacity; D_{LCO}, diffusing capacity of lung for carbon monoxide.
Dosage: 1 mg/kg prednisone (maximum dose, 70 mg) per day for 7 days.
Steroid responsive is defined by an increase in pulmonary function test values sufficient to meet the criteria for normal spirometry (FEV_1, FVC, and FEV_1/FVC ratio >5th percentile and at least 2 indices >10th percentile).
*All pulmonary function test indices are reported as mean percent predicted ± SD.

adults with a history of childhood asthma but not in patients with adult-onset asthma. Similar observations have been made in the Childhood Asthma Management Program (CAMP) study of mild-to-moderate childhood asthma.[13]

Analysis of early risk factors indicated an increased risk of irreversible obstructive lung disease among subjects born prematurely, although the strength of this finding is limited by sample size and accuracy of subjects' self-reports. In a British cross-sectional study of 5573 children (age, 5-11 years), prematurity was associated with increased risk of wheeze and cough on awakening later in life.[14] In a more recent longitudinal study of 454 children, Raby et al[15] observed that prematurity was a predictor of asthma at age 6 years. Altered lung growth or damage in the perinatal period might set the stage for airway remodeling and obstructive lung disease.[16] Allergens, infections, and other environmental factors, such as pet exposure, might modulate this vulnerability. The development of irreversible obstructive lung disease is likely a multifactorial process that varies between individuals, with both genetic factors and early exposures playing a role.[17,18]

Our results extend observations that airway hyperresponsiveness in childhood might indicate not only current asthma severity but might also predict future lung deficits. Weiss et al[19] reported a positive correlation between methacholine PC_{20} and prebronchodilator FEV_1 among subjects (age, 5-13 years) in the CAMP study. Among our subjects childhood methacholine sensitivity was associated with abnormal adult lung function as well. The group with abnormal spirometric results also had increased bronchodilator responses (13% vs 7%), suggesting suboptimal disease control. Despite increased reversibility, postbronchodilator spirometric results remained low, indicating only a partial β-agonist response. In a longitudinal study of asthmatic adults, Ulrik and Backer[20] reported that subjects with increased bronchodilator reversibility at enrollment were more likely to have nonreversible airway obstruction 10 years later. They hypothesized that more aggressive asthma treatment early on might prevent later lung obstruction. Notably, in our study regular inhaled corticosteroids were used more frequently by subjects with abnormal spirometric results both in childhood and currently. This observation might reflect underlying asthma severity, rather than a lack of steroid efficacy or steroid-induced harm, although findings from the CAMP study and the Steroid Treatment as Regular Therapy trial in mild-to-moderate disease indicate that inhaled steroids are not a panacea for asthma-associated lung function decrease.[21,22]

The main objective of this study was to assess pulmonary function outcomes and characterize the deficits that might be associated with chronic childhood asthma. Our results suggest that childhood allergic asthma is associated with airway obstruction that is not easily reversed with bronchodilators or steroids in a substantial subset of asthmatic patients, and this subset might be identified early in life. Further study is necessary to explore the genetic factors and early exposures that initiate these airway changes to facilitate better treatment and prevention.

REFERENCES

1. Lange P, Parner J, Vestbo J, Schnohr P, Jensen J. A 15-year follow-up study of ventilatory function in adults with asthma. N Eng J Med 1998; 339:1194-200.
2. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.
3. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31.
4. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87.
5. American Thoracic Society Lung function testing: selection of reference values and interpretational strategies. A statement of the American Thoracic Society. Am Rev Respir Dis 1991;144:1202-18.
6. Sarpong SB, Hamilton RG, Eggleston PA, Adkinson NF Jr. Socioeconomic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. J Allergy Clin Immunol 1996; 97:1393-401.
7. Jeffery PK. Remodeling in asthma and chronic obstructive lung disease. Am J Respir Crit Care Med 2001;164(suppl):S28-38.
8. Payne DN, Rogers AV, Adelroth E, Bandi V, Kalpalatha K, Guntupalli KK, et al. Early thickening of the reticular basement membrane in children with difficult asthma. Am J Respir Crit Care Med 2003;167: 78-82.
9. Jenkins HA, Cool C, Szefler SJ, Covar R, Brugman S, Gelfand EW, et al. Histopathology of severe childhood asthma: a case series. Chest 2003; 124:32-41.
10. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, et al. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV_1/vital capacity ratio: a longitudinal population study from childhood to adulthood. Am J Respir Crit Care Med 2002;165:1480-8.
11. Grol MH, Gerritsen J, Vonk JM, Schouten JP, Koeter GH, Rijcken B, et al. Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. A 30-year follow-up study. Am J Respir Crit Care Med 1999;160:1830-7.
12. Jenkins HA, Cherniack R, Szefler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. Chest 2003;124:1318-24.
13. Bacharier LB, Dawson C, Bloomberg GR, Bender B, Wilson L, Strunk RC, et al. Hospitalization for asthma: atopic, pulmonary function, and psychological correlates among participants in the Childhood Asthma Management Program. Pediatrics 2003;112:e85-92.
14. Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. BMJ 1993; 306:817-20.
15. Raby BA, Celedon JC, Litonjua AA, Phipatanakul W, Sredl D, Oken E, et al. Low-normal gestational age as a predictor of asthma at 6 years of age. Pediatrics 2004;114:e327-32.
16. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. J Allergy Clin Immunol 2005;116:16-24.
17. Van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature 2002;418:426-30.
18. Busse WW, Rosenwasser LJ. Mechanisms of asthma. J Allergy Clin Immunol 2003;111(suppl):S799-804.
19. Weiss ST, Van Natta ML, Zeiger RS. Relationship between increased airway responsiveness and asthma severity in the Childhood Asthma Management Program. Am J Respir Crit Care Med 2000;162:50-6.
20. Ulrik CS, Backer V. Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. Eur Respir J 1999;14: 892-6.
21. Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the Childhood Asthma Management Program. Am J Respir Crit Care Med 2004;170:234-41.
22. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen Y, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomized, double-blind trial. Lancet 2003;361:1071-6.