

Persistent airflow obstruction in inner-city children with asthma

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ABSTRACT

Background: Airway remodeling has been shown to be persistent in patients with asthma despite treatment with controller medications. Patients with early airflow obstruction may continue to experience poor lung function despite treatment.

Objectives: To determine whether early airflow obstruction in inner-city children with asthma persists despite guideline-based asthma care.

Methods: In a retrospective study that used a cohort of inner-city children with asthma treated by using an asthma-specific disease management system, the patients were stratified into “low” or “high” lung function groups at the time of the initial visit (high, forced expiratory volume in the first second of expiration [FEV₁] % predicted and FEV₁/forced vital capacity [FVC] $\geq$ 80%; and low, FEV₁% predicted and FEV₁/FVC < 80%). These patients then received National Heart, Lung, and Blood Institute guideline-based asthma treatment at regular follow-up intervals with spirometry performed at these visits as part of regular care. FEV₁% predicted and FEV₁/FVC were followed up for up to 10 years for both the high and low cohorts.

Results: Over 10 years, the patients initially in the “high” group maintained FEV₁% predicted and FEV₁/FVC at values similar to the initial visit (94 to 96% and 87 to 89%, respectively), whereas those in the low group had only slight increases of FEV₁% predicted and FEV₁/FVC over the same time (77 to 82% and 78 to 82%, respectively). Low FEV₁% predicted and FEV₁/FVC at the time of the first visit was significantly associated with an increased risk of low values of these lung functions over the next 3–5 years despite treatment. African American ethnicity and male gender were also associated with lower lung function over time.

Conclusion: Early airflow obstruction in inner city children asthma is associated with poor lung function in later life despite guideline-based asthma care. Current asthma therapy may not affect pathways and leads to airway remodeling in children with asthma.

(Allergy Asthma Proc 42:310–316, 2021; doi: 10.2500/aap.2021.42.210043)

Disruptions in lung development likely results in respiratory repercussions in later life. Infants and young children exposed to various forms of lung injury are at high risk to develop chronic respiratory diseases into later childhood and even adult life. Preterm infants with chronic lung disease have increased early wheezing and persistent asthma.¹ Adults born with extremely low birthweight have abnormal lung function values compared to adults delivered at term.²

Early lower respiratory tract infection with respiratory virus are strong independent predictors of asthma development in later life.³ In the Children’s Respiratory Study (CRS), children diagnosed with pneumonia during the

first 3 weeks of life were twice as likely to develop asthma compared with children not afflicted with an early lung infection.⁴ Analysis of emerging data suggests that early perturbations in lung function from various injuries, such as chronic lung disease, viral infections, and smoking exposure, may result in the development of adult chronic obstructive pulmonary disease (COPD).⁵

Although prevention of early lung injury may reduce the risk of persistent lung dysfunction, it is unclear if treatment of underlying early lung disease, *e.g.*, asthma, will result in normalization of early onset airflow obstruction. The Childhood Asthma Management Program (CAMP) study⁶ showed that long-term treatment with inhaled corticosteroids (ICS) did not alter airway remodeling in children with persistent asthma. Inhaled fluticasone administered to young children with early wheezing and at risk for development of asthma did not alter the respiratory disease burden in later childhood.⁷ Although the results of these studies suggest that early treatment does not alter the natural history of asthma, there is less evidence to show that once lung function has been compromised in the early lives of children with asthma, airflow obstruction persists despite optimal asthma therapy. In this study, we endeavored to determine whether inner-city children with asthma who initially present with

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

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significant airflow obstruction continue to have abnormal lung function values despite guideline-based care.^{8–10}

METHODS

Design and Study Population

This was a retrospective analysis of patients enrolled in the disease-specific asthma management program (Breathmobile) at the Los Angeles County/University of Southern California Medical Center from 1995 to 2014.¹¹ Patients were treated by allergy specialist providers (KYCK, LS) in concordance with national asthma guidelines, with 2–4-month regular follow ups.^{8,9} Spirometry was performed at the initial and follow-up visits by using with American Thoracic Society (ATS) criteria.^{8–10} Spirometry was adjusted for ethnicity. Subjects were excluded if they had fewer than three follow-up appointments per year or had missing baseline asthma severity, asthma control assessments, and lung function data at any visit. This study was approved by the institutional review board at the University of Southern California Health Science Campus. This study was informed consent exempt because it was a retrospective study that used de-identified patient data that was recorded as part of normal patient care.

Outcome Measures

The primary outcome was annual lung function. Specifically, (1) the percentage of predicted of forced expiratory volume in the first second of expiration ($FEV_1\%$), and (2) FEV_1 divided by forced vital capacity (FVC) (FEV_1/FVC) in percentage. We also created two dichotomous outcomes, which indicated high and low lung function by using 80% of $FEV_1\%$ and FEV_1/FVC ratio as the cutoff point.

Predictors

Clinical and demographic characteristics were analyzed to determine whether they were predictors of high and low lung function, with the primary predictor being baseline $FEV_1\%$ and FEV_1/FVC on the diagnosis and entry into the program.

Statistical Analyses

The patient characteristics and baseline statistics were summarized and compared by their baseline $FEV_1\%$ category (high or low). A two-sided t -test was conducted on continuous variables, and the χ^2 test was conducted on categorical variables. To predict the lung function at each visit, we were able to use random-effects models because individual patients were followed up over time. Random-effects models add a random intercept to control for unobserved individual patient-specific factors related to lung function

outcomes, while, at the same time, allowing the estimation of the effects of observed patient characteristics. We conducted a random-effects multivariate linear regression on the continuous outcome of the FEV_1/FVC ratio and $FEV_1\%$ in patient follow-up visits. We also conducted random-effects multivariate logistic regression on the dichotomous outcome of the FEV_1/FVC ratio $\geq 80\%$ and $FEV_1\% \geq 80\%$. Each lung function outcome was aligned with the corresponding baseline lung function measure in these four regression models.

Sensitivity Analyses

To test the robustness of the analyses, we implemented the same analyses by using a smaller, 5-year sample, including all patients who had been followed up for at least 5 years.

RESULTS

Patient Characteristics

There were 1337 unique patients with 4502 visits. The majority of the patients were Hispanic children, with more boys (809) than girls (528). The mean age on entry into the program was 9.4 years. There was a diverse range of baseline asthma severity, with 29% intermittent, 20% mild persistent, 32% moderate persistent, and 19% severe persistent. (Table 1).

Predictors of High versus Low Lung Function. Patients with low $FEV_1\%$ and FEV_1/FVC ($<80\%$) continued to have lower $FEV_1\%$ and FEV_1/FVC during subsequent visits despite guideline-based care. Patients with high values ($\geq 80\%$) at the time of the initial visit maintained these high values during the same period. Random-effects multivariate linear regression results showed that the lung function values at follow-up visits were largely predicted by the baseline lung function (Table 2). An increase of baseline $FEV_1\%$ by 10 percentage points was associated with a 6.72 percentage point increase in follow-up $FEV_1\%$ values. An increase of the baseline FEV_1/FVC ratio by 10 percentage points was associated with a 6.05 percentage point increase in the follow-up FEV_1/FVC ratio. The $FEV_1\%$ value at follow-up visits was positively associated with being Hispanic ($\beta = 0.039$; $p=0.017$). The FEV_1/FVC ratio at follow-up visits was negatively associated with being male ($\beta = -0.012$; $p=0.002$), being black ($\beta = -0.021$; $p=0.01$), and being the age group of 6–9 years ($\beta = -0.017$; $p=0.008$) and of 10–14 years ($\beta = -0.018$; $p=0.008$).

Random-effects multivariate logistic regression results showed that the outcome of high $FEV_1\%$ at follow-up visits was positively associated with high-baseline $FEV_1\%$ (odds ratio [OR] 68.399; $p<0.01$) and being Hispanic (OR 4.628; $p<0.01$) (Table 3). Also, the outcome

Table 1 Characteristics and baseline statistics of the individual patients

	Low Baseline FEV ₁ % (n = 252)	High Baseline FEV ₁ % (n = 1085)*	Total (N = 1337)	p
Sex, n (%)				
Boys	150 (59.5)	659 (60.7)	809 (60.5)	0.723
Girls	102 (40.5)	426 (39.3)	528 (39.5)	
Race or ethnicity, n (%)				<0.001
White	7 (2.8)	14 (1.3)	21 (1.6)	
Black	37 (14.7)	37 (3.4)	74 (5.5)	
Hispanic	197 (78.2)	997 (91.9)	1194 (89.3)	
Asian or Pacific Islander	7 (2.8)	16 (1.5)	23 (1.7)	
Other	4 (1.6)	21 (1.9)	25 (1.9)	
Age at first visit, mean (95% CI), y	9.0 (8.2–9.9)	9.5 (9.3–9.6)	9.4 (9.2–9.6)	0.107
Baseline asthma severity, n (%)				0.012
Mild intermittent	57 (22.6)	328 (30.2)	385 (28.8)	
Mild persistent	42 (16.7)	223 (20.6)	265 (19.8)	
Moderate persistent	97 (38.5)	335 (30.9)	432 (32.3)	
Severe persistent	56 (22.2)	199 (18.3)	255 (19.1)	
Baseline FEV ₁ %, mean (95% CI)	71.5 (70.7–72.4)	95.4 (94.8–96.1)	90.9 (90.2–91.7)	<0.001
Baseline FEV ₁ /FVC ratio, mean (95% CI)	83.8 (82.6–85.0)	88.3 (87.9–88.7)	87.4 (87.1–87.9)	<0.001
Season at first visit, n (%)				0.125
Spring	54 (21.4)	294 (27.1)	348 (26.0)	
Summer	55 (21.8)	213 (19.6)	268 (20.0)	
Fall	87 (34.5)	312 (28.8)	399 (29.8)	
Winter	56 (22.2)	266 (24.5)	322 (24.1)	
Adherence rate, mean (95% CI), %	59.5 (53.4–65.6)	69.3 (66.6–72.1)	67.5 (65.0–70.0)	0.003
Years of follow-up, mean (95% CI)	5.0 (4.7–5.3)	5.0 (4.9–5.1)	5.0 (4.9–5.1)	0.96

FEV₁ = Forced expiratory volume in the first second of expiration; CI = confidence interval; FVC = forced vital capacity.

*High Baseline = FEV₁ ≥ 80% predicted.

Low Baseline = FEV₁ < 80% predicted.

of a high FEV₁/FVC ratio result at follow-up visits was positively associated with a high baseline FEV₁/FVC ratio (OR 64.667; $p < 0.01$) and negatively associated with being male (OR 0.535; $p < 0.01$) and being black (OR 0.174; $p < 0.05$). Over 10 years, the patients' lung function stayed relatively stable. The FEV₁% stayed between 94 and 96% for all years among the patients with a high-baseline FEV₁% and increased slightly, from 77 to 82%, among the patients with low baseline FEV₁%. The FEV₁/FVC ratio stayed between 87 and 89% for all the years among the patients with a high baseline FEV₁/FVC ratio and increased slightly, from 78 to 82%, among the patients with a low baseline FEV₁/FVC ratio (Fig. 1). The age at the first visit, baseline asthma severity, and season at the first visit were not statistically significant predictors in any of the regression results.

DISCUSSION

This study demonstrated that children with asthma who presented with early airflow obstruction continued to have abnormal pulmonary function values despite

guideline-based asthma care. Both baseline FEV₁% and FEV₁/FVC at the time of entry into the Breathmobile program correlated significantly with the follow-up values at subsequent visits (Table 2). The patients with an FEV₁% and FEV₁/FVC ratio ≥ 80% at the first visit (high baseline) had odds of 68.4 and 64.7 of FEV₁% and FEV₁/FVC being ≥ 80% at subsequent visits, respectively (Table 3). Male and African American patients were more likely to have a lower FEV₁/FVC ratio at subsequent visits, regardless of initial baseline values.

Many studies^{1,2,5} show that early life airway insults result in persistent perturbations in airway function throughout life. The CRS first demonstrated that children with early airway obstruction continued to have low persistent reduced pulmonary airflow into adulthood.^{4,5} The Tasmanian Longitudinal Health Study¹² (TAHS) found subjects with a low FEV₁ value during the first 2 decades of life were likely to have persistently low values throughout life and some with accelerated decline in later decades.

Our results were unique because we found two groups of patients with different lung trajectories within a cohort of patients with asthma. Other studies

Table 2 Random-effects multivariate linear regression on lung function at follow-up visits: coefficients

Variable	FEV ₁ % (n = 4502)		FEV ₁ /FVC ratio (n = 4502)	
	Coef.	±SE	Coef.	±SE
Baseline FEV ₁ %	0.672**	0.016		
Baseline FEV ₁ /FVC ratio			0.605**	0.014
Age group (RG, 0–5 y)				
6–9 y	–0.023	0.015	–0.017*	0.008
10–14 y	–0.019	0.016	–0.018*	0.008
15–21 y	0.003	0.017	–0.015	0.009
Sex (RG, girls)				
Boys	0.001	0.004	–0.012**	0.002
Race or ethnicity (RG, white)				
Black	0.010	0.019	–0.021*	0.010
Hispanic	0.039*	0.017	–0.011	0.009
Asian or Pacific Islander	–0.021	0.023	–0.005	0.012
Other	0.023	0.023	–0.010	0.012
Adherence rate, %	0.014**	0.005	0.006*	0.002
Age at first visit	0.000	0.001	0.000	0.000
Baseline asthma severity (RG, mild intermittent)				
Mild persistent	0.004	0.006	–0.002	0.003
Moderate persistent	0.004	0.005	–0.003	0.003
Severe persistent	0.009	0.006	–0.003	0.003
Season at first visit (RG, spring)				
Summer	–0.008	0.006	–0.001	0.003
Fall	–0.008	0.006	0.000	0.003
Winter	–0.000	0.006	0.000	0.003
Years of follow-up	0.000	0.001	–0.001	0.000

FEV₁ = Forced expiratory volume in the first second of expiration; FVC = forced vital capacity; coef. = coefficient; SE = standard error; RG = reference group.

**p* < 0.05.

***p* < 0.01.

examined subjects from the general population. The Melbourne Asthma Study¹³ subjects with and without asthma were stratified into groups with high or low FEV₁ values. A general population-based cohort was used in the Avon Longitudinal Study of Parents and Children (APSLAC) study¹⁴ to lung function trends in patients with differing characteristics, *e.g.*, body mass. The CRS used a nonselected birth cohort of patients born between 1980 and 1984.¹⁵ It is likely that insult to airways during childhood leads to persistent abnormal lung function. The CRS showed that young children who were afflicted with pneumonia before 3 years of age have impaired lung function and asthma compared with similar children without pneumonia.⁴ The subjects in the TAHS,¹² whose mothers smoked or who themselves smoked had lower lung function values and were at risk of COPD.¹² Ongoing atopy and asthma result in diminished lung growth and ongoing

perturbations in lung function in children.¹⁶ Injurious agents likely initiate and facilitate ongoing pulmonary inflammation, which results in abnormal lung development and repair.^{17,18}

Identification of two groups of patients with different lung function trajectories within a cohort of patients with asthma suggested pathology unique to some patients, which led to ongoing low lung function values. There was no significant difference in the baseline asthma severity between the high and the low trajectory groups; therefore, underlying asthma severity was not likely to be such a factor. Severity is a gross proxy of airway inflammation, which suggests that inflammation is not likely a cause of persistent diminished lung function. This is supported by the fact that guideline-based treatment with anti-inflammatory agents failed to increase spirometry in the “low” trajectory group. Pathologic pathways

Table 3 Random-effects multivariate logistic regression on lung function at follow-up visits: odds ratios

Variable	High FEV ₁ % (<i>n</i> = 4502)#		High FEV ₁ /FVC ratio (<i>n</i> = 4502)§	
	OR	±SE	OR	±SE
High baseline FEV ₁ %	68.399**	16.664		
High baseline FEV ₁ /FVC ratio			64.667**	16.437
Age group (RG, 0–5 y)				
6–9 y	0.606	0.465	0.618	0.474
10–14 y	0.742	0.577	0.536	0.419
15–21 y	1.383	1.132	0.365	0.299
Sex (RG, girls)				
Boys	0.911	0.163	0.535**	0.102
Race or ethnicity (RG, white)				
Black	1.557	1.033	0.174*	0.135
Hispanic	4.628**	2.746	0.514	0.364
Asian or Pacific Islander	0.762	0.611	0.430	0.417
Other	3.144	2.762	1.074	1.134
Adherence rate %	1.869**	0.405	1.121	0.244
Age at first visit	1.013	0.023	1.036	0.029
Baseline asthma severity (RG, mild intermittent)				
Mild persistent	1.225	0.322	0.876	0.234
Moderate persistent	1.060	0.238	0.743	0.170
Severe persistent	0.916	0.235	0.830	0.220
Season at first visit (RG, spring)				
Summer	0.946	0.249	0.770	0.204
Fall	0.887	0.211	1.031	0.250
Winter	0.964	0.243	0.971	0.249
Years of follow-up	1.022	0.038	1.047	0.039

FEV₁ = Forced expiratory volume in the first second of expiration; FVC = forced vital capacity; OR = odds ratio; SE = standard error; RG = reference group.

**p* < 0.05.

***p* < 0.01.

#FEV₁% ≥ 80%.

§FEV₁/FVC ratio ≥ 80%.

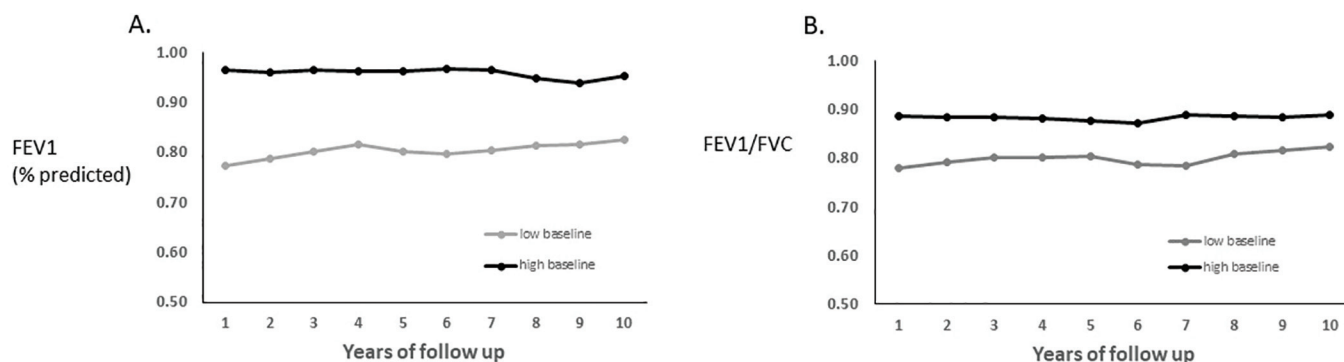


Figure 1. Lung function values of patients over 10 years stratified by “high” and “low” values at the time of the first visit. (A) FEV₁ (% predicted). The patients with FEV₁ > 80% predicted at the first visit continued to be between 94 and 96%; whereas those with FEV₁ < 80% predicted at the time of the first visit increased slightly, from 77 to 82%. (B) FEV₁/FVC ratio. The patients with FEV₁/FVC > 80% predicted at the first visit remained between 87 and 89%, whereas those with FEV₁/FVC < 80% at the first visit had a slight increase, from 78 to 82%. FEV₁ = Forced expiratory volume in the first second of expiration; FVC = forced vital capacity.

involved in a poor spirometry response to anti-inflammatory agents may be similar to those responsible for failure of ICS to attenuate airway remodeling in children with asthma.^{6,7}

Studies have shown an association between various wheezing phenotypes and long-term abnormalities in lung function in children. ALSPAC subjects with early persistent and intermediate onset wheeze had a significantly lower FEV₁/FVC ratio during adolescence compared with those who never or infrequently wheezed.¹⁴ The Melbourne Asthma Study¹³ found that the subjects with never or infrequent and early transiently wheeze had significantly higher lung function values at 12 and 18 years of age compared with those who had early persistent, intermediate, and late onset wheeze.¹⁹

We did not determine whether high or low lung function groups were associated with a specific early wheezing phenotype. It is possible that the patients with low lung function values manifested early persistent and severe disease compared with those with better spirometry values. This was less likely because the mean age of the patients on entry into the program was similar in both groups and the baseline asthma severity assessed before treatment was not different between the two groups. Seasonality of the first visit had no effect on both groups because asthma control among children is worse during the winter and spring when respiratory viruses are prevalent.^{3,8,9} A lack of association of the lung function values at entry and seasonality suggested the existence of an already perturbed pathway in the low lung function group of patients with asthma before the program started. Analysis of these data suggested that, among the patients with persistent asthma was a group of patients with compromised airway function that persisted despite guideline-based care.

African American ethnicity and older age were predictive of low lung function values, which suggested that genetically determined mechanisms contributed toward persistent airway obstruction in patients with persistent asthma. These patients may have predisposed airways, which resulted in more pathologic changes in response to chronic inflammatory insult or an inability to repair damage after diffuse lung injury. This was consistent with evidence that showed that African American patients with asthma have more severe disease and are less responsive to therapeutic agents compared with other ethnicities.²⁰

Results that showed that the male patients with lower long-term lung function values were, in part, congruent with the fact that asthma prevalence was higher among the male patients during childhood. Male patients ages < 15 years have twice the risk of asthma hospitalization compared with female patients.²¹ A recent large meta-analysis showed that male gender was at risk for developing asthma during preschool and early school age.²²

The male patients in our cohort may have had more exacerbations before being treated, thereby experienced long periods of lung damage. Asthma prevalence becomes female predominant during late teenage years and into adulthood. Severity also becomes more severe during this period. It, however, is unclear whether there is any differential response to treatment with standard asthma therapy between the genders at any age.²¹

Children enrolled at a later age had lower long-term lung function values compared with patients who were entered at a younger age. The age of entry in this study was similar to patients in the CAMP study.⁶ Our data were consistent with the findings of the CAMP study⁶ in which ICS treatment did not attenuate airway remodeling. Younger patients in this study showed better lung function, which is in contradistinction to the Prevention of early asthma in kids (PEAK) study, which showed no effect of ICS on the natural history of asthma in preschool children. Patients in the PEAK study had more symptom-free days while taking inhaled fluticasone and only after cessation of the ICS did these parameters return to values similar to placebo.⁷ Younger patients may have worsening lung function if guideline-based care is withdrawn. We previously demonstrated that patients lose asthma control when anti-inflammatory medications are discontinued after achieving asthma control.²³

We did not follow up the patients into late adolescence and early adulthood, so it is unknown whether further therapy may result in improvement of lung function later in life. Results of the Tucson respiratory study strongly suggest that the development of adult COPD is associated with abnormal lung function values during childhood, and there may be certain vulnerable windows wherein pathologic conditions, *e.g.*, asthma, may facilitate this process.⁵ Investigators in the TAHS¹² demonstrated three lung function trajectories associated with development of COPD: early below average, early below average with accelerated decline, and below average. Early life predictors of these included asthma and bronchitis.¹² Early and persistent lung insults likely result in a high risk of adult COPD. Exact mechanisms for these permanent changes are unknown.

There are limitations within this study, and results should be interpreted with these in mind. The patients were treated by up to four unique providers, and some patients may have received different management strategies, which resulted in poor improvements of lung function. Further, the patients received different controllers based on insurance coverage. Patients were recruited over a span of time, wherein three updates on the National Heart, Lung, and Blood Institute asthma guidelines^{8–10} were published with updated treatment recommendations.

These factors were minimized because providers were mandated to treat in accordance with national asthma guidelines.^{8–10} Even if specific asthma controller agents were restricted to different patients, the patients were treated with equivalent asthma medications according to the recommended step therapy per the guidelines. Both initially high and low lung function groups were treated in accordance with the same set of recommended updated guidelines immediately on update.^{8–10} Low and high lung function groups improved over time, which suggested that both received effective treatment. An alternative explanation of the data is that lung function was stable over time, with some regression to the mean.

We rated asthma severity based on the patient's first visit. This may not reflect true baseline disease activity due to inherent patient recall bias and difficulty "estimating" underlying disease activity during the controller naive state. Better assessment of asthma severity would be step therapy required for long-term asthma control. Also, we did not perform pre-/postbronchodilator spirometry on all the patients. The patients with less or no reversibility may respond less to treatment spirometrically even if they have symptomatic improvement. We are confident that a combination of patients' history and physical examination and lung function analysis diagnosed asthma with good specificity; there is a small possibility that some patients with normal lung function values and no reversibility did not actually have asthma.

CONCLUSION

Inner-city children with asthma who presented with low lung function values had persistent airflow obstruction despite guideline-based care compared with similar patients with normal lung function values. Elucidation of responsible pathways will be pivotal in attenuating airway remodeling in these patients.

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