

Mechanisms of allergic diseases

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Long-term outcomes of early-onset wheeze and asthma

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Evidence from longitudinal cohort studies demonstrates that wheezing that begins in early life and continues into the school years generally persists into adulthood. This persistent wheezing is associated with lung function deficits and airways hyperresponsiveness that appear to be established in the first few years of life. Allergic sensitization early in life, early-life infection with rhinovirus, or colonization with any of a number of bacteria have been associated with increased risk of persistent wheeze. Early life, whether *in utero* or in the first few years of life, presents a window of vulnerability during which airway injury results in persistent airways dysfunction. Available data further suggest that a second such window of vulnerability might be present in the preadolescent and adolescent years. Lung function growth patterns established by age 6 years generally continue into early adulthood to middle adulthood, typically leaving groups of subjects with wheezing that persists into or relapses during adulthood with a mean FEV₁ of about 10% of predicted value less than their peers who do not wheeze. Subgroups of patients with persistent asthma, however, can have progressive decreases in lung function and enter adulthood with even lower lung function. The concern exists that these deficits in lung function apparent in early adulthood might put subjects at risk for the later development of chronic obstructive pulmonary disease. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Asthma, wheezing, lung function, airways hyperresponsiveness, atopy, outcomes, infancy, childhood, early onset

In recent years, evidence has accumulated that much chronic persistent asthma begins in childhood and that respiratory

Abbreviations used

AHR:	Airways hyperresponsiveness
ALSPAC:	Avon Longitudinal Study of Parents and Children
CAMP:	Childhood Asthma Management Program
COPD:	Chronic obstructive pulmonary disease
CRS:	(Tucson) Children's Respiratory Study
FVC:	Forced vital capacity
HDM:	House dust mite
LRTI:	Lower respiratory tract illness
PIAMA:	Prevention and Incidence of Asthma and Mite Allergy
RTI:	Respiratory tract infection
SPT:	Skin prick test
V'maxFRC:	Maximal flow at functional residual capacity

outcomes later in life can be traced to events in early life.^{1,2} Through longitudinal studies, various patterns of wheezing have been brought to light, with symptoms emerging at various times in childhood. In several of these studies, respiratory data collection began in middle to late childhood, with retrospective determination of early-life events.³⁻¹⁹ In 2 studies outcomes to middle adulthood have been determined,³⁻⁹ and 1 study has concentrated exclusively on a large number of subjects with diagnosed asthma.¹²⁻¹⁶ In other longitudinal studies subjects have been followed from birth, allowing for prospective assessment of the development of patterns of wheeze²⁰⁻⁴²; however, most of these cohorts have been assembled fairly recently, with follow-up to early adulthood reported in only 2 cohorts.^{20-22,28,29,32} Strikingly, the findings from these longitudinal studies from birth have helped to explain patterns of lung function and clinical outcomes observed in those with data collection beginning in middle to late childhood.

The purpose of this review is to summarize what is known about the outcomes of early-onset wheezing, with special emphasis on lung function outcomes. Our working definition of early-onset wheezing was wheezing that begins during infancy or the preschool years. The articles included in this review were identified through a search of the PubMed database using a variety of search terms in combination, including "wheeze," "asthma," "early onset," "longitudinal," "birth cohort," "lung function," and "outcomes." Additional references were identified from citations in the articles that were reviewed, as well as from further PubMed searches using author's names or study titles as key words. The studies selected for review included those with data collected during childhood, as well as those with long-term follow-up, with special focus on serial lung function data. Shorter-term studies that appeared to fill in knowledge gaps were also included. Although there is still much to be learned, our review of the literature suggests that the seeds of chronic airways dysfunction are sown in early life.

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TABLE I. Lung function outcomes in early to middle adulthood grouped by wheezing/asthma groups in several population cohorts followed from birth or childhood

Study	Reference	Subjects	Age (y)	FEV ₁	FEV ₁ /FVC ratio
Melbourne Asthma Study	5	Asthma age 7 y	42	95% predicted*	75%*
	5	Severe asthma	42	85% predicted*	70%*
	5	Wheezy bronchitis age 7 y	42	102% predicted	79%
	5	Control	42	104% predicted	80%
British National Child Development Study	8	Wheeze at age 35y; onset at age 0-7 y	35	90.1% control mean*	77%*
	8	Wheeze at age 35 y; onset at age 8-16 y	35	90.9%* control mean	76%*
	8	Wheeze at age 35 y; onset at 17-23 y	35	92.9% control mean*	78%*
	8	Wheeze at age 35 y; wheeze onset at age 24-35 y	35	97.4% control mean	81%
	8	No wheeze at age 35 y; wheeze onset at age 0-7 y	35	97.8% control mean	81%
	8	No wheeze at age 35 y; wheeze onset at age 8-16 y	35	99.8% control mean	81%
	8	No wheeze at age 35 y; wheeze onset at age 17-23 y	35	97.4% control mean	81%
	8	No wheeze at age 35 y; wheeze onset at age 24-35 y	35	96.2% control mean	80%
Dunedin Multidisciplinary Health and Development Study	8	Control (never wheeze)	35		82%
	10	Persistent wheeze from onset	26	96.6% predicted	78%
	10	Relapse	26	95.7% predicted	79.1%
	10	Never wheezed	26	105.6% predicted†	83.7%†
Tucson CRS	29	Chronic asthma	22		−0.37 (z score)‡
	29	Newly diagnosed	22		−0.49 (z score)§
	29	Inactive	22		0.09 (z score)
	29	No asthma	22		0.10 (z score)

The FEV₁ data from Strachan et al⁸ were expressed in the original article as percentages of the mean control values and are listed here as such. The FEV₁/FVC ratio data were similarly expressed in the original article, but based on their data from Table 4 of that article,⁸ the actual ratios of the groups were calculated and are presented here.

**P* < .001 compared with control subjects.

†*P* < .001 for trend.

‡*P* = .004 compared with no asthma.

§*P* = .005 compared with no asthma.

PROSPECTIVE COHORTS ENROLLED FROM CHILDHOOD

Several long-term studies following cohorts of children into adulthood have yielded insights into the natural history and outcomes of childhood asthma. The Melbourne Asthma Study has followed a group of children from a 1957 birth cohort, from which several groups of children with wheezing and a control group without wheezing were randomly selected at age 7 years and an additional group with severe wheezing at age 10 years was added.^{3,4} Five groups were followed longitudinally: the control group, a group with “mild wheezy bronchitis” (<5 episodes of wheezing associated with respiratory tract infection [RTI]), a group with “wheezy bronchitis” (≥5 wheezy RTIs), a group with asthma (wheeze unassociated with RTI), and a group with “severe asthma” (persistent symptoms, barrel chest deformity, and an FEV₁/forced vital capacity [FVC] ratio of ≤50%). Of interest, the authors note that the severe asthma group was characterized by onset of symptoms before age 3 years.

The last published examinations of this cohort occurred in 1999 and 2003, both of which detailed data from the subjects at age 42 years.^{4,5} Of the original wheezy bronchitis group, 60% were wheeze free, and only 5% had persistent asthma. Of the original asthma group, 70% still had symptoms, as did 90% of the severe asthma group, almost half of whom had persistent wheeze. As shown in Table I,^{5,8,10,29} lung function as assessed on the basis of FEV₁ and FEV₁/FVC ratio was no different in the wheezy

bronchitis groups compared with that seen in the control group. Subjects who had childhood asthma had an approximately 10% reduction in FEV₁ and a 5% reduction in FEV₁/FVC ratio relative to those who did not have childhood asthma, and the lowest lung function indices (20% reduction in FEV₁ and 10% reduction in FEV₁/FVC ratio) were exhibited by those in the severe asthma group. The magnitude of the differences between the groups was well established by age 10 years and, despite report of ongoing symptoms, did not worsen through age 42 years. Very few of the subjects received anti-inflammatory therapy. The probability of severe asthma in adult life was increased in the presence of other atopic disease or skin prick test (SPT) reactivity to house dust mite (HDM) or rye grass.

The lessons from this study are clear. Outcomes were generally quite good in children with small numbers of wheezing episodes associated with viral illness; however, frequent and severe symptoms in childhood were associated with a high probability of their continuing into adult life. Furthermore, lower levels of lung function in children with persistent asthma were already present by age 7 to 10 years, without further relative decrease to middle adulthood.⁴

The British National Child Development Study followed all children born in England, Scotland, and Wales during the week of March 3 to 9, 1958, as well as immigrants sharing the same birth week. A nested substudy examined the development and natural history of asthma and atopic diseases. The cohort was followed at

age 7, 11, 16, 23, 33, and 42 years, at which time they were asked about wheezing and asthma, as well as hay fever, allergic rhinitis, and eczema. A subgroup of subjects underwent spirometry at age 35 and 45 years, and an additional subgroup had total and specific IgE levels to dust, cat, and grass measured at age 45 years. By age 7 years, 18.3% of the subjects had experienced wheezing. One half of these children were still wheezing at age 7 years, but by age 11 years, two thirds were wheeze free.⁶ Strikingly, among those who had no reports of wheezing at the age 23- and 33-year surveys, those who had a history of childhood wheeze were significantly more likely to wheeze at age 42 years than those without such a history, an association that remained significant after adjustment for smoking history, atopy, sex, and total IgE level.⁷

The prebronchodilator spirometric data from the subjects at age 35 years are shown in Table I; active wheezing at age 35 years coupled with wheeze onset before age 23 years was associated with an up to 10% reduction in FEV₁ and a 5% to 6% reduction in FEV₁/FVC ratio.⁸ Early-life wheezing before age 7 or 16 years did not affect the rate of decrease in lung function at the ages of 35 to 45 years relative to those who did not have this history of early-life wheeze.⁹

Thus adding to the findings from the Melbourne Asthma Study, this study confirmed that although many with childhood wheezing have good outcomes, much wheezing in adult life, even that which might appear to be new-onset wheeze, is associated with antecedent wheeze in childhood. Furthermore, this study provided additional evidence that lung function patterns are established before adulthood and that those with persistent or relapsing wheeze enter adulthood with relative deficits in lung function.

The Dunedin Multidisciplinary Health and Development Study enrolled the 1139 children born in Dunedin, New Zealand, between April 1972 and March 1973. Also nested in this study was a substudy looking at asthma symptoms, lung function, and atopy. Questionnaires were administered at 2- to 5-year intervals between 9 and 26 years of age; airways hyperresponsiveness (AHR) to methacholine was assessed 5 times between the ages of 9 and 21 years; atopy was assessed at age 11, 13, and 21 years; and bronchodilator responsiveness was assessed at age 18 and 26 years. Respiratory events between birth and age 9 years were assessed retrospectively at age 9 years. Of the original sample, 613 (59% of the original cohort) provided complete respiratory data.

In 14.5% of subjects, wheezing persisted either from age 9 years or from the time of first wheeze, whereas 12.4% had a remission followed by a relapse by age 26 years. Increased AHR (methacholine PC₂₀ ≤ 8 mg/mL) or greater than 10% bronchodilator responsiveness at age 9 years was associated with a 4-fold increased odds of persistence and a 7-fold increased odds of relapse of wheezing by age 26 years. A positive SPT response to HDM at age 13 years was associated with a 2-fold odds of persistence and relapse. Additionally, smoking at age 21 years and female sex were each associated with a 2-fold odds of persistence of wheeze. Younger age at onset of wheezing was associated with wheezing relapse at age 26 years. Subjects with persistent wheezing and relapse had consistently lower FEV₁/FVC ratios than those who never reported wheezing, but the slopes for the change in FEV₁/FVC ratio did not differ between the wheezing groups and those who did not report wheezing. As shown in Table I, at age 26 years, subjects with persistent or relapsed

wheezing exhibited about a 10% reduction in FEV₁ and a 5% reduction in FEV₁/FVC ratio in comparison with those who had never wheezed.¹⁰

Thus the Dunedin study reiterated the finding from the Melbourne and British studies that although much childhood wheezing appears to remit, some wheezing, particularly that associated with AHR, atopy, or smoking, persists into or relapses in early adulthood. Furthermore, this study provided yet more evidence for the concept that lung function patterns are established by school age and that those with persistent or relapsing wheezing enter adulthood with lung function deficits.

Risk factors for hospital admission for asthma were also examined in the Dunedin cohort. Subjects with more allergy, as assessed by a greater number of positive SPT responses, positive results to HDM and cat, higher total IgE levels, and greater eosinophilia, were at greater risk for hospitalization. Subjects with earlier age at onset (mean, 4.3 years), higher frequency of symptoms, lower lung function at age 9 years (mean FEV₁, 92% vs 98% of predicted value; mean FEV₁/FVC ratio, 83% vs 88%), and a greater likelihood of AHR at age 9 years were at increased risk. Subjects with multiple admissions had even earlier age at onset (mean, 2.7 years), more allergy, and greater lung function decrements at age 9 years than those with only 1 admission (mean FEV₁, 86% vs 94% of predicted value; mean FEV₁/FVC, 78% vs 84%). The slopes for change in FEV₁/FVC ratios were not different between hospitalization groups. Of note, the biggest effect of age of onset on hospitalizations was noted in those admissions occurring at age 9 years or earlier.¹¹

The Childhood Asthma Management Program (CAMP) began as a multicenter, randomized, double-masked clinical trial to compare the long-term safety and efficacy of 3 approaches to the management of mild-to-moderate childhood asthma: budesonide and albuterol, nedocromil and albuterol, and placebo and albuterol. The study enrolled 1041 children, all with mild or moderate asthma and aged 5 to 12 years. The treatment phase was 4 to 6 years, followed by a 5-year follow-up observational phase at the end of which 941 (90%) of the original cohort were still being followed. Longer duration of disease before enrollment, ascertained retrospectively at the outset of the study, was associated with lower prebronchodilator and postbronchodilator FEV₁ (mean prebronchodilator FEV₁, 93.9% of predicted value with −0.907% of predicted value per year of duration; mean postbronchodilator FEV₁, 102.8% of predicted value with −0.625% of predicted value per year of duration), FEV₁/FVC ratio (mean prebronchodilator FEV₁/FVC ratio, 79.7% with −0.729% per year of duration), and methacholine AHR (mean PC₂₀, 2.08 mg/mL; mean ln PC₂₀, 0.11 with −0.05 per year of duration, indicating a greater degree of hyperresponsiveness with longer duration). Additionally, longer asthma duration was associated with more use of asthma medications before enrollment, a greater likelihood of being assessed as having moderately severe asthma, exercise-induced symptoms, and higher asthma symptom scores during the run-in phase. Although several markers of atopy (serum IgE level, number of positive SPT responses, and peripheral blood eosinophilia) were also associated with disease duration, they did not confound the relationship between disease duration and lung function, although male sex and markers of atopy were associated with lower lung function.¹² The link between asthma duration and asthma severity, as assessed based on lung function and symptoms, might have been mediated by increased methacholine responsiveness, but the associations were modest at best.¹³

Immediately after the treatment phase of the study, the CAMP investigators noted that 25.6% of the participants experienced a 1% or greater reduction in postbronchodilator FEV₁ per year over the course of that phase of the study, which was unaffected by the treatment assignment (mean FEV₁, 97.4% vs 105.7% of predicted value).¹⁴ Those who experienced this reduction in lung function were younger, smaller, male, and had an asthma diagnosis made at an earlier age but had a shorter duration of disease, less atopy (defined by SPT responsiveness and serum IgE level), better lung function at the outset, and lower percentage of hospitalization than those who did not experience this decrease. On the other hand, among those who did experience this reduction in lung function, better baseline FEV₁ predicted a less steep slope of decrease. Despite the lower degree of atopy at the outset of the study, subjects with a more rapid decrease in lung function exhibited more sputum eosinophils after the washout from the treatment phase of the study (mean, 4.6% vs 2.1%).¹⁴

Followed beyond the end of the treatment phase and into late adolescence, CAMP participants exhibited progressively increased magnitude of airways obstruction relative to a historical longitudinal cohort of children without asthma (most consistently exhibited by progressive reductions in FEV₁/FVC ratio: by age 18 years, male CAMP subjects had a mean FEV₁/FVC ratio of 76.5% vs 86.3% in the nonasthma cohort; the ratio in the CAMP female subjects was 79.4% vs 89.5%) but without indication of the effect of age at onset or duration of disease on this outcome.¹⁵ However, as Martinez¹ points out, in the CAMP population much of the difference in FEV₁/FVC ratio relative to that seen in nonasthmatic subjects was already present by age 6 years. Remission of asthma in the CAMP cohort was infrequent (6%) and associated with milder disease, less atopy, better lung function (mean prebronchodilator FEV₁, 95.9% vs 91.3%; mean FEV₁/FVC ratio, 82.6% vs 77.9%), and less AHR (geometric mean methacholine FEV₁ PC₂₀, 1.8 vs 0.8 mg/mL) at entry into the study.¹⁶

The Childhood Asthma Study was a smaller study of subjects with moderate-to-severe persistent asthma who were initially enrolled in a study of immunotherapy for childhood atopic asthma. The study population initially consisted of 121 subjects aged 5 to 12 years at randomization, of whom 85 were re-evaluated as young adults (age 17-30 years). Of these 85 subjects, 13 (15.3%) were in remission, with a mean prebronchodilator FEV₁ of 94.3% of predicted value; 19 (22.4%) had mild intermittent disease, with a mean FEV₁ of 91.9% of predicted value; 12 (14.1%) had mild persistent disease, with a mean FEV₁ of 87.9% of predicted value; 25 (29.4%) had moderate persistent disease, with a mean FEV₁ of 79.6% of predicted value; and 16 (18.8%) had severe persistent disease, with a mean FEV₁ of 66% of predicted value. Bronchodilator reversibility was greatest in those with moderate and severe persistent disease, yet FEV₁ did not normalize. Although they exhibited significant atopy, subjects who experienced remission had lower mean IgE levels (412 ng/mL vs 1136 ng/mL vs 968 ng/mL) and a lower number of positive SPT responses (7 vs 9 vs 10) than their peers with intermittent and persistent asthma at follow-up. Additionally, subjects who experienced remission used fewer asthma medications during the initial trial than their peers who exhibited ongoing disease. Of note, lung function and methacholine responsiveness at initial randomization did not predict remission; all 3 groups had randomization mean FEV₁ values less than one would expect for a healthy school-aged child (range, 86.7% to 93.2% of predicted value) and were severely hyperresponsive (mean PC₂₀

range, 0.22-0.14).¹⁷ Strikingly, 48% of the subjects in the study exhibited abnormal lung function as adults, and of the subgroup that consented to a steroid trial, three fourths did not improve. Longer duration of asthma, heightened methacholine responsiveness in childhood (PC₂₀, 0.11 vs 0.18 mg/mL), and premature birth at 34 weeks' gestation or less were associated with these abnormalities.¹⁸

Considered collectively, these studies and others¹⁹ demonstrate that wheezing illness in childhood, particularly more persistent disease, is associated with ongoing persistence into adulthood or, in the case of those who experience remission, an increased likelihood of relapse in young to middle adulthood. This disease pattern is associated with atopy and aggravated by smoking. Finally, lung function changes associated with this disease are established before middle to late childhood, and wheezing that persists from childhood into adulthood or that relapses in adulthood is consistently associated with at least a 10% reduction in percent predicted FEV₁ in these adults relative to those who never wheeze. The rate of decrease in lung function on the whole is similar between groups with wheeze and groups that remain asymptomatic, although there might be groups of asthmatic subjects with progressive decreases in lung function. Although the data are inconsistent, these studies suggest that earlier onset in childhood is associated with more severe and persistent disease and lower lung function.

PROSPECTIVE BIRTH COHORTS

One of the major drawbacks in studies beginning in middle to late childhood in which asthma onset is determined retrospectively is the lack of accuracy and precision in the detection of the timing of the first symptoms of asthma. An additional issue is the high probability of ascertainment bias, namely that subjects with more severe disease are likely to be overrepresented among those whose parents report earlier onset of asthma. Also, recall bias can be a major limitation in studies relating clinical phenotype, lung function, or both to early-life events because those who remain ill are more likely have parents who would remember that they were ill as infants or toddlers. To address this, several longitudinal cohort studies have been carried out in which subjects have been followed prospectively from birth, allowing for prospective evaluation of the development of asthma during infancy and childhood and the effect of early-onset disease on long-term outcomes.

The earliest prospective observational birth cohort is the Tucson Children's Respiratory Study (CRS).^{20,21} Offspring of parents enrolled in a large health maintenance organization were recruited shortly after birth between May 1980 and October 1984, and a total of 1246 newborns were initially included. The cohort reflected a general population sample and was not specifically selected for a history of asthma or atopy in the family. Questionnaires were obtained at baseline from the parents, detailing their histories of respiratory illness, smoking habits, and education. The children were seen by their primary care pediatricians when they had signs and symptoms of lower respiratory tract illness (LRTI), and the pediatricians in turn recorded detailed histories and physical examinations to characterize these illnesses. In addition, the parents completed questionnaires when the children were 1.6 and 6 years of age in which they provided further wheezing history, as well as histories of rhinitis and eczema. Serum IgE levels were ascertained in cord blood (n = 750), as well as in specimens obtained at 9 months (n = 672) and 6 years (n = 460) of

life. SPTs were done at age 6 years ($n = 629$). In addition, in 125 subjects pulmonary function testing was assessed at age 2.4 months, before the occurrence of any LRTI, by obtaining partial expiratory flow-volume curves through chest compression. The maximal flow at functional residual capacity ($V'_{\max FRC}$) was used as the marker to reflect the size of the intrapulmonary airways. At age 6 years, partial flow-volume curves were obtained in 526 subjects, and $V'_{\max FRC}$ values were calculated again.

At age 6 years, 826 children had complete data on LRTI in the first 3 years along with completed questionnaires at that time. At age 6 years, subjects were designated as having never wheezed ($n = 403$, 51.5% of the total), having at least 1 wheezing LRTI in the first 3 years of life but no wheezing at age 6 years (transient early wheezing; $n = 147$, 19.9% of the total), having no wheezing LRTI in the first 3 years of life but wheezing at age 6 years (late-onset wheezing; $n = 112$, 15% of the total), and having at least 1 wheezing LRTI by age 3 years and wheezing at age 6 years (persistent wheezing; $n = 100$, 13.7% of the total).²² Transient early wheezing was associated with maternal smoking. Late-onset wheezing was associated with maternal asthma, male sex, and early-onset (year 1) rhinitis. At age 6 years, increased serum IgE levels and SPT reactivity were more frequent in this group than in the transient early or never wheezers. Persistent wheezing was associated with maternal asthma, increased frequency of wheezing, likelihood of being given a diagnosis of asthma, higher serum IgE levels at 9 months and 6 years of age, and SPT reactivity at age 6 years. As depicted in Fig 1, before the onset of wheezing, subjects with transient early wheeze had maximal flow at functional residual capacity ($V'_{\max FRC}$) levels that were less than those of their peers in all other groups (who did not differ from each other). By age 6 years, these transient early wheezers still had lower $V'_{\max FRC}$ values than those who had never wheezed, but those in the persistent wheeze group had the lowest lung function of all of the groups, suggesting that their airways grew more slowly relative to their peers. Lung function in the late-onset wheezers did not significantly differ from that seen in those who did not wheeze. The data thus suggested that those with more frequent persistent disease begin with symptoms very early in life and have an atopic tendency that is expressed in the first year of life, perhaps during a critical time of rapid lung growth. Although their airways are of normal caliber at birth, there is evidence of loss of lung function (reduced growth in airway conductance) relative to their peers by age 6 years, which is consistent with other studies demonstrating that the lung function changes in subjects with persistent asthma were already established by middle childhood.²²

Data from 4-year-old subjects participating in a prospective birth cohort study in Antwerp, Belgium who underwent lung function measurement by means of forced oscillation at age 4 years support the findings from the Tucson CRS cohort. Those children with transient early wheezing and those with persistent wheezing had airways resistance that was greater than that seen in children who had never wheezed. Those with persistent wheezing had a greater degree of atopy and a better response to bronchodilator.²³ Lung function from infancy was not reported in that cohort.

In contrast to the Tucson CRS data, it is important to mention that some studies from birth have reported low lung function shortly after birth as a risk factor for asthma in later childhood.^{24,25} One group of studies deserves particular mention. Investigators in Perth, Australia, recruited a cohort of 243 infants before birth and obtained lung function and AHR data at 1 month,

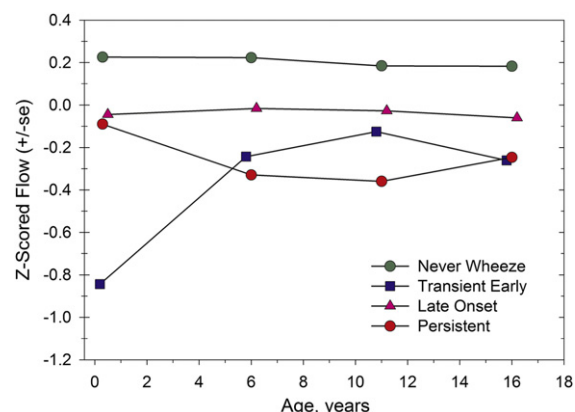


FIG 1. Cross-sectional z scores of height-adjusted maximal expiratory flows at the ages of 2.4 months and 6, 11, and 16 years for the preschool wheezing groups in the Tucson CRS. The z score indicates how many SDs from the mean a subject's value lies. This figure shows that those with persistent wheezing begin life with flows that do not differ from those of their peers with late-onset wheeze or those who never wheeze but demonstrate decreases in flow relative to these other groups by age 6 years. In contrast, those with transient early wheezing demonstrate early and persistent reductions in flow. Reprinted from Morgan et al²⁸ with permission of the American Thoracic Society. Copyright © 2005 American Thoracic Society.

TABLE II. Changes in airway hyperresponsiveness in infancy grouped by wheezing outcomes at age 11 years from the Perth cohort²⁷

	Wheezing at age 11 y	No wheezing at age 11 y	P value
Histamine PC ₄₀ at 1 mo (mg/mL)	0.69	0.89	.274
Histamine PC ₄₀ at 6 mo (mg/mL)	0.90	1.68	.162
Histamine PC ₄₀ at 12 mo (mg/mL)	1.67	3.12	.016

This table was constructed from the data in the body of the article by Turner et al.²⁷

6 months, and 12 months of age, with follow-up to 11 years of age. The lung function index used was $V'_{\max FRC}$, measurement of which was carried out with the same technique as used in Tucson. In that cohort decreased $V'_{\max FRC}$ values at 1 month (z score, -0.59 adjusted SDs from the mean) were associated with persistent but not transient wheeze. Again, the highest risk of an asthma diagnosis at age 11 years was associated with the persistent wheeze group. It was not clear why the pulmonary function findings in Perth diverged from those in Tucson.²⁵ In other cohorts transient early wheezing has been associated with normal lung function in middle childhood, findings that also deviate from those in the Tucson CRS cohort.²⁶ As shown in Table II, the degree of AHR to histamine at 1 month did not differ between those with and without wheeze at age 11 years. Throughout the first year of life, all of the subjects in the Perth cohort gradually became less responsive to histamine, but those who did not wheeze at age 11 years lost their responsiveness to a much greater extent than did those who wheezed at age 11 years. This difference was significant at 12 months of age and was labeled by the investigators "persistence of increased airway responsiveness."²⁷

As regards wheezing in adolescence and early adulthood, the birth cohort studies have demonstrated findings similar to those of cohorts begun in later childhood. Wheezing patterns established in the first 6 years of life were found to persist at age 16 years in the

Tucson CRS cohort.²⁸ Thus those who were wheezing at age 6 years were more likely to have continued wheezing at age 16 years. Furthermore, the increased prevalence of atopy in the 6-year-old subjects with wheezing also persisted into adolescence. These patterns were persistent regardless of whether they had begun before or after age 3 years. Strikingly, the lung function patterns established by age 6 years persisted to age 16 years; that is, transient early wheezers and persistent wheezers continued to have lung function that was diminished relative to that of their peers with late-onset wheeze or no wheeze in the first 6 years of life (Fig 1). Late-onset wheezers had lung function that was slightly but not significantly diminished compared with that of never wheezers.²⁸

The CRS cohort was reassessed at age 22 years, with an emphasis on diagnosed asthma and wheeze. By age 22 years, 30% of the cohort had at one point in their lives received a physician's diagnosis of asthma, 21.3% of the cohort had active asthma, and 19.2% reported wheezing without a formal asthma diagnosis. Subjects with wheezing at age 6 years, either persistent or late onset; smokers; those with parental asthma; those sensitized to *Alternaria* species; and those with low V'maxFRC values or hyperresponsiveness to cold air at age 6 years were more likely to have current asthma or wheeze at age 22 years. Asthmatic subjects at age 22 years were grouped into the categories of newly diagnosed asthma (no report of asthma between the ages of 2 and 16 years but a diagnosis and symptoms at age 22 years), inactive asthma (diagnosis and symptoms between the ages of 2 and 16 years but no symptoms at age 22 years), and chronic asthma (diagnosis and symptoms between the ages of 2 and 16 years and symptoms at age 22 years).²⁹

As shown in Table I, lung function as assessed on the basis of FEV₁/FVC ratio was reduced in both the newly diagnosed and chronic asthma groups. Subjects with chronic or inactive asthma at age 22 years were grouped into 3 categories relative to their age at diagnosis: 2 to 6 years, 8 to 11 years, and 13 to 16 years. After adjustment for asthma status and sex, age at diagnosis was significantly and linearly related to FEV₁/FVC ratio; that is, later diagnosis was associated with better lung function. Newly diagnosed asthma at age 22 years was associated with female sex, parental asthma, late-onset and persistent wheezing at age 6 years, low lung function (lowest quartile of V'maxFRC), and cold air hyperresponsiveness at age 6 years. Interestingly, the FEV₁/FVC ratio in the newly diagnosed asthma group was consistent with that in asthmatic subjects with a past diagnosis who had received their diagnosis earliest. In more than 63% of cases of newly diagnosed asthma at age 22 years, episodes of wheezing occurred during the first 3 years of life or were reported by the parents by age 6 years. Although newly diagnosed asthma was associated with SPT response positivity at age 22 years, it was not associated with sensitization at age 6 years. Thus airway dysfunction was present early in life, but allergic sensitization came later in this group of subjects. Interestingly, bronchodilator response was reduced in subjects with newly diagnosed asthma but not in those with chronic disease, and this coupled with the relatively low FEV₁/FVC ratio suggests the potential for progressive airways dysfunction in this group.²⁹

More recently, studies have been underway of larger birth cohorts, and a statistical technique called latent class analysis has been applied to the data to ascertain patterns of early-life wheeze. On the basis of the pattern of responses over time to questions about wheezing, subjects are assigned to a number of phenotypes called latent classes.³⁰ Through this type of analysis on large numbers of subjects, additional patterns of early-life wheeze have

emerged. In the Avon Longitudinal Study of Parents and Children (ALSPAC) study examining 6265 subjects born in Avon, United Kingdom, 6 phenotypes were identified, and in the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study examining 2810 subjects from multiple centers in The Netherlands, 5 phenotypes emerged.^{30,31} The 1 newly characterized phenotype in common between both studies is the intermediate-onset phenotype, which is characterized by little to no wheeze until 18 to 24 months and then an increase to high prevalence by 42 to 48 months. The subjects in both studies have been followed to 8 years. In both cohorts intermediate-onset wheeze was associated with a diagnosis of asthma by age 8 years, as were persistent wheeze and late-onset wheeze. Intermediate-onset, along with late-onset and persistent wheeze, were all associated with atopy. At 8 years, decreases in lung function were noted in both studies. In the ALSPAC cohort the greatest decreases in FEV₁ were seen in the intermediate-onset and persistent wheeze groups, along with those in a sixth group, prolonged early wheeze, whereas AHR was highest in the intermediate- and late-onset phenotypes.³⁰ In the PIAMA cohort the greatest deficit in FEV₁ at age 8 years was in the persistent wheeze group, whereas increased AHR was seen in the persistent, intermediate-onset, and late-onset phenotypes.³¹ The ongoing prevalence of wheeze at age 7.5 to 8 years was higher among the persistent wheezing and intermediate-onset wheezing groups in ALSPAC than in the PIAMA study. Longer-term outcomes of the intermediate-onset phenotype await ongoing follow-up of these cohorts. Also of note, early-life lung function is not reported for these cohorts.

Numerous longitudinal studies have established early-life allergic sensitization, particularly to perennial allergens, as a major risk factor for persistence of wheeze.³²⁻³⁸ Latent class analysis on a population-based birth cohort in Manchester, England, demonstrated an association between early sensitization to multiple allergens, persistent wheeze, asthma prevalence, and severity.³⁹

In addition to allergic sensitization, data are emerging suggesting that early-life colonization or infection with specific organisms is associated with persistent wheeze and asthma. Although early-life virus-induced wheezing is common early in the development of asthma, data from a population in Madison, Wisconsin, at increased risk for asthma suggest that, of all of the respiratory viruses, rhinovirus-induced wheezing infections presenting in the outpatient setting in infancy and early childhood are the most significant predictors of subsequent asthma and reduced lung function (age 8 years mean FEV₁, 96% of predicted value in those with early rhinovirus-induced wheezing vs 102% in those without).⁴⁰ Lung function was not measured in this cohort before the onset of illness, and therefore it is unclear whether diminished lung function is a cause rather than an effect of the wheezing associated with these rhinovirus infections.^{36,40}

Fecal colonization with *Clostridium difficile* at age 1 month was associated with asthma, wheeze, and atopy at age 6 to 7 years.⁴¹ In infants born to mothers with asthma, colonization at 1 month of age with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, or a combination of these organisms was associated with persistent wheezing, acute severe wheeze, asthma, and bronchodilator reversibility at age 5 years.⁴²

DISCUSSION

The available data agree on the major point that wheeze that begins in early life and persists beyond the third year of age

generally persists into adulthood. In those with what appears to be a new onset of wheeze in adulthood, the likelihood is high that there was an antecedent wheeze in childhood. Those who wheeze in early life are much more likely to have persistent wheeze if they have concomitant atopy. Relapsing wheezing is also more likely in the presence of atopy; furthermore, asthma that is newly diagnosed in early adulthood is associated with new sensitization during adolescence. Smoking and female sex likewise increase the risk of wheeze relapse. There is some disagreement among the studies as to whether subjects with persistent wheeze start life with normal or reduced lung function but general agreement that by school age the lung function patterns are established and track in parallel through at least early to middle adulthood, with persistent wheezers and relapsers demonstrating ongoing decreases in lung function along with heightened AHR.

The cause of asthma is poorly understood. Because the disease we call asthma reflects a number of different wheezing phenotypes, it is likely that there is also a heterogeneity of causes. Given the multiplicity of findings in subjects with early-onset persistent wheezing (ie, some born with normal lung function and some with abnormal lung function), it is probable that even early-life persistent wheezing reflects a heterogeneity of phenotypes with differing causes.

In those with persistent wheeze, airways dysfunction develops either before birth or shortly thereafter. The data from the Tucson CRS suggest that changes occur between birth and age 6 years. The added data from Antwerp suggest that these changes are already evident by age 4 years. Indeed, reticular basement membrane thickening and eosinophilic inflammation have been documented in preschoolers aged 1 to 3 years with chronic wheezing⁴³ and have been documented in individuals as young as 10 months of age.⁴⁴ Although the data from Perth and Tucson diverge with regard to initial lung function in those with persistent wheeze, both studies point to events that play out in the first year of life, setting the stage for persistent wheezing. In the Tucson cohort total IgE levels, which were not increased in cord blood, were increased by 9 months in persistent wheezers. Furthermore, those with persistent wheeze had diminished IFN- γ production in mitogen-stimulated PBMCs obtained at 9 months of age.⁴⁵ Finally, relative eosinophilia accompanied the first wheezy LRTI in those with persistent wheezing.⁴⁶ In the Perth cohort the persistence of increased AHR did not become apparent until 12 months of age. Although the Perth investigators did not note increased atopy at the 12-month mark, they examined skin test reactivity rather than IgE levels.²⁷ Thus considering the Tucson and Perth cohorts collectively, developments occurred in the first year of life affecting airway function and atopy, which appeared to set the stage for persistent wheezing.

Although atopy and airway dysfunction appear to both set the stage for the development of persistent wheeze, they do not appear to be controlled by the same genes.^{47,48} It is possible that when atopy develops at a particular window of vulnerability in the growth of the airway, perhaps in conjunction with specific microbial illnesses or colonizations, persistent wheeze and asthma ensue. In most subjects this window of vulnerability appears to manifest itself in the first year of life. Considering the subjects in the Tucson CRS cohort with new-onset asthma at age 22 years who were sensitized late, it is intriguing to consider that new sensitization during adolescence, a time of rapid growth velocity of the airways,¹⁵ might have also occurred during a second window of vulnerability, leading to the relatively late development of

asthma. The association of asthma in the teenage and early adult years with active smoking^{10,29,49} and the association of new-onset adolescent wheezing, increased peak flow variability, and albuterol responsiveness independent of atopy in girls who become overweight or obese during the school years⁵⁰ lend further credence to the concept of a second window of vulnerability during late childhood and adolescence for airway injury to occur and wheeze and asthma ensue. Finally, childhood-onset asthma as distinct from later-onset asthma appears to be associated with its own unique genes.^{49,51} The risk of wheeze and asthma sequelae from airway injuries at particular windows of vulnerability might therefore be genetically determined, a concept supported by recent evidence of genetic variants associated with early-onset asthma, low lung function, and heightened disease severity.⁵¹

Most of the studies suggest that once lung function patterns are established in subjects with wheezing by the early school-age years, further losses relative to their nonwheezing peers do not occur in most patients. However, the finding of a roughly 10% decrease in FEV₁ and a 5% decrease in FEV₁/FVC ratio during early to middle adulthood in those with persistent or relapsed wheezing is strikingly consistent among the studies. Although the mean values of FEV₁ in these groups fall within the range of what clinicians would consider “normal,” one might speculate that because they do not attain maximal lung function, as those with persistent or relapsing wheezing age, they will be more likely to manifest severe chronic airways disease as their lung function decreases to less than the threshold for chronic obstructive pulmonary disease (COPD).¹ It is important also to consider the progressive loss of lung function noted in participants in the CAMP study, which was not noted in the longitudinal population-based studies.^{14,15} Although the participants in CAMP had mild-to-moderate persistent asthma, they still manifested disease that was much more severe than in those in the population-based cohorts. Subjects with severe persistent asthma might lose lung function at an even more accelerated pace, as evidenced especially by those subjects in the Childhood Asthma Study who entered adult life with a mean FEV₁ of 66% of predicted value.¹⁷ Thus one might further speculate that smaller subgroups of subjects with persistent asthma might indeed be at heightened risk for even more severe COPD, possibly caused by coinheritance of genes coding for severe early-onset asthma, severe AHR, and severe atopy.

Although our understanding of the natural history of asthma has advanced considerably over the past 30 years, there is still much to be learned. Cohort sizes have been relatively small, and the emergence of new wheezing phenotypes from larger cohorts illustrates the tremendous value of larger sample sizes. Pooling of data, such as that occurring in the Global Allergy and Asthma European Network initiative,⁵² should help, but lack of standardization of study protocols can hamper the effort. Subjects who are most at risk, namely inner-city minorities, are woefully underrepresented in longitudinal cohort studies, although a new study is examining the development of asthma in these groups as well.⁵³ Asthma that is clinically significant is not very frequent in population studies, thus necessitating very large cohorts, such as exist in the US National Children's Study,⁵⁴ to detect and have power to examine risk factors for severe disease. There is a need to gather more data on *in utero* exposures. Additionally, premorbid lung function data are relatively sparse and difficult to obtain. New techniques, such as the lung clearance index, which measures the washout of inert gas and detects airways obstruction, can

facilitate obtaining data on larger numbers of infants, who can then be followed through the preschool years, childhood, adolescence, and adulthood.⁵⁵ Finally, existing cohorts that were assembled at birth or during childhood have been followed only to middle adulthood, and thus any association of their childhood disease with later COPD remains a matter of speculation.

In summary, subjects with persistent and relapsing wheezing in early to middle adulthood exhibit abnormalities in lung function that have their roots in infancy and childhood. Furthermore, it would appear that there are 2 postnatal windows of vulnerability during which the growing airway is at risk for injury, leading to wheeze and asthma: during the first few years in combination with allergic sensitization and possibly infection and during adolescence in combination with allergic sensitization but also with weight gain and smoking. The primary prevention of early-onset persistent wheeze and asthma rests on an improved understanding of the events leading to its inception. Realizing that goal will require large collaborative efforts on a global scale. The rewards of such efforts should affect countless lifetimes.

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Key messages

- Early-onset wheeze with atopy is associated with lung function deficit in adolescence/early adulthood.
- Atopy with high IgE levels, eosinophilia, or SPT response positivity is associated with increased risk of persistent wheeze.
- Airway infections in early life with rhinovirus or colonization with *S pneumoniae*, *M catarrhalis*, and *H influenzae* are associated with persistent wheeze and asthma.
- Most deficits in lung function appear to be established as early as birth but certainly within the first 6 years of life.
- About 25% of patients with clinically diagnosed asthma are at risk for accelerated decreases in lung function.
- Adolescence might represent a second window of vulnerability for the development of persistent wheeze and asthma.

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