

CME review article

This feature is supported by an unrestricted educational grant from AstraZeneca LP

Determinants of asthma and its clinical course

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Objective: To examine factors that influence the natural history of asthma, such as genetics, atopy, air pollution and environmental tobacco smoke, gastroesophageal reflux, and infection, to promote early identification and treatment of patients at risk for persistent asthma.

Data Sources: Journal articles published in English involving human subjects with asthma.

Study Selection: Studies were selected for their relevance to the discussion of asthma and the factors that contribute to its persistence. Epidemiologic studies were favored in assessing the natural history of asthma from childhood to adulthood.

Results: Major factors that can influence the severity and persistence of asthma are genetics, atopy, pollution, environmental tobacco smoke, gastroesophageal reflux, and respiratory infections. Epidemiologic studies reveal that factors strongly linked to the persistence of childhood asthma into adult life are early age of disease onset with more severe symptoms, atopy, and level of allergen exposure.

Conclusions: Although there is still much research to be done, epidemiologic studies have repeatedly proven that the natural history of asthma is in some ways predictable. Early identification of patients at risk for persistent asthma, combined with early institution of pharmacologic and nonpharmacologic intervention strategies, may lead to better outcomes.

Ann Allergy Asthma Immunol. 2004;93:309–316.

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INTRODUCTION

Asthma is a complex genetic disease. Variable phenotypic expressions lead to a genetic predisposition to develop asthma, and a wide range of allergic and nonallergic factors can modify its persistence and severity (Fig 1). The natural history of asthma thus depends on the interaction between genetic bases and environmental factors and on both the magnitude and timing of exposure to those factors. This review examines the persistence of asthma as determined by genetics, atopy, air pollution and environmental tobacco smoke (ETS), and infection to promote early identification and treatment of patients at risk for persistent asthma. Journal articles published in English involving human subjects with asthma were searched. Studies were selected for their relevance to the discussion of asthma and the factors that con-

tribute to its persistence. Epidemiologic studies were favored in assessing the natural history of asthma from childhood to adulthood.

GENETICS

Multiple candidate genes have been implicated in the development of persistent asthma. Bronchial hyperresponsiveness (BHR) progressively increases with increasing total serum IgE levels.¹⁻⁴ In multiple studies, the genetic regulation of IgE production has been linked to chromosome 5q.⁵ In addition to chromosome 5, other chromosomes have been linked to positive skin prick test (SPT) results, blood eosinophilia, total serum IgE level, and BHR. These include chromosomes 4 (BHR), 6 (IgE, eosinophilia), 7 (IgE, eosinophilia, BHR), 11 (IgE, SPT), 13 (SPT), and 16 (IgE, BHR).⁶

Furthermore, pharmacogenetic studies of polymorphisms of the β_2 -adrenergic receptor (β_2 -AR), 5-lipoxygenase promoter region (5-LO), and glucocorticoid receptors have shown the influence of genetics on disease severity and

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Capitol Allergy and Respiratory Disease Center, Sacramento, California.
Received for publication February 11, 2004.
Accepted for publication in revised form May 12, 2004.

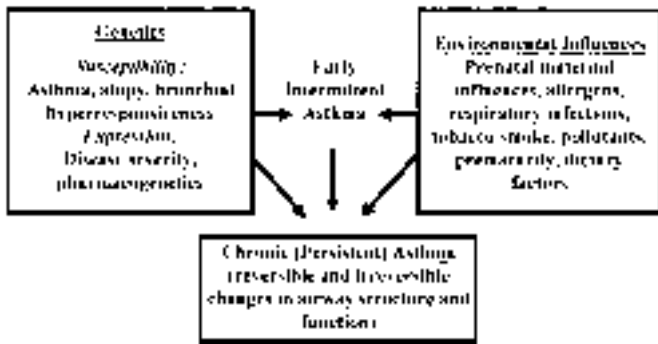


Figure 1. Gene-environment interactions in the development of asthma. Courtesy of E. R. Bleeker, MD.

response to therapy. Israel et al⁷ studied 190 asthmatic patients to determine the effects of regular or as needed albuterol use on peak expiratory flow for more than 16 weeks. Patients homozygous for β_2 -AR arginine 16 (Arg16) polymorphism who used albuterol, 180 μ g, in a metered-dose inhaler 4 times daily had morning peak expiratory flow values of 30.5 ± 12.1 L/min lower than patients with the same genotype who used albuterol only on an as needed basis (Fig 2). In a separate study, Taylor et al⁸ found that patients homozygous for β_2 -AR Arg16 polymorphism had a higher frequency of asthma exacerbation per year: 3.57 for regular treatment with albuterol, 1.9 for placebo treatment, and 0.64 for salmeterol (Fig 3). These data are important, because homozygous β_2 -AR Arg16 polymorphism is found in approximately 15% of the population.⁷ In addition, glucocorticoid receptor β -positive cells are more prevalent in patients who exhibit less sensitivity to steroid treatment.⁹ Alteration of the *GRC* gene may also be linked to fatal asthma.¹⁰ Finally, a polymorphism in the promoter region of 5-LO expression has

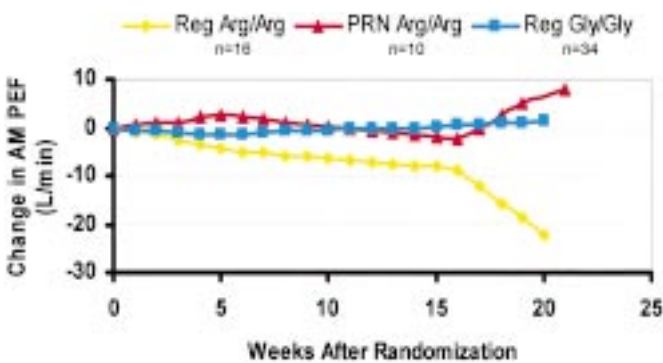


Figure 2. Comparison of response to regular or as needed albuterol use by genotype. AM PEF indicates morning peak expiratory flow rate; PRN Arg/Arg, patients homozygous for α_2 -adrenergic receptor arginine 16 polymorphism who used albuterol as needed; Reg Arg/Arg, patients homozygous for α_2 -adrenergic receptor arginine 16 polymorphism who used albuterol regularly; and Reg Gly/Gly, patients homozygous for α_2 -adrenergic receptor glycine 16 polymorphism who used albuterol regularly. Reprinted with permission from Israel et al.⁷

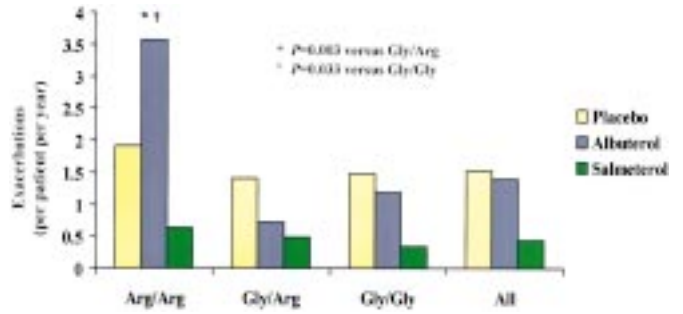


Figure 3. Influence of α_2 -adrenergic receptor polymorphisms on asthma exacerbations. Arg/Arg indicates patients homozygous for arginine at codon 16 of the α_2 -adrenergic receptor; Gly/Arg, patients heterozygous for arginine and glycine at codon 16 of the α_2 -adrenergic receptor; and Gly/Gly, patients homozygous for glycine at codon 16 of the α_2 -adrenergic receptor. Reprinted with permission from Taylor et al.⁸

been linked to a reduced response to 5-LO inhibitor therapy.^{11,12} As this area of research expands, we hope to be able to predict therapy response and regulate doses of pharmacologic agents to obviate adverse effects.

ATOPY

The connection between IgE-mediated sensitivity and asthma is especially strong in asthmatic children, among whom more than 85% show positive SPT results to airborne allergens.¹³ Sensitivity to indoor allergens, such as house dust mites, cockroach, and warm-blooded domestic animals, has been shown to be a risk factor in the development of asthma.¹⁴

In the homes of 311 adults (mean age, 42 years; age range, 10–62 years; average forced expiratory volume in 1 second [FEV₁], 88%; FEV₁ range, 25%–131% predicted), Langley et al¹⁵ tested concentrations of house dust mite (Der p 1), cat (Fel d 1), and dog (Can f 1) in the living room, carpet, and mattress. In patients with the highest level of sensitivity and exposure to these allergens, the FEV₁ was significantly lower (83.7% vs 89.3% predicted). These patients also showed higher levels of exhaled nitric oxide (12.8 vs 8.7 ppb) and more severe BHR (provocative dose of methacholine causing a 20% fall in FEV₁ [PD₂₀], 0.25 vs 0.73 mg) compared with those patients not sensitized or exposed.

In an epidemiologic study performed on the Isle of Wight, Kurukulaaratchy et al¹⁶ followed up 1,456 infants from the age of 10 years. Of this group, 169 (21%) demonstrated BHR at the age of 10 years; 56% of these patients had current wheeze. BHR at 10 years of age (PD₂₀, <4 mg) was associated with atopy (positive SPT result) at 4 years (odds ratio [OR], 4.75) and 10 years (OR, 9.83). Also associated with BHR was a history of maternal asthma (OR, 7.58).

Wolfe et al¹⁷ studied a cohort of 378 asthmatic Australian children from the age of 7 years to 35 years at 7-year intervals. The presence of atopy in childhood as defined by positive SPT results to house dust mite or rye grass was a significant risk factor for moderate-to-severe asthma in later

life (OR, 1.66). The findings of this study show the extent to which asthma is associated with childhood atopic conditions.

The acquisition of IgE-mediated sensitivity to both indoor and outdoor allergens is a major risk factor for the persistence and severity of asthmatic symptoms. Continued research is needed to determine the potential contributions to disease management of specific allergy immunotherapy and treatment with monoclonal anti-IgE antibody.

AIR POLLUTION AND ETS

Air pollution has been shown to increase symptoms in patients with asthma.^{18,19} In early studies, sources of air pollution were primarily identified as sulfur dioxide and particulates generated by coal and oil combustion. These pollutants were shown to cause cough and bronchitis.²⁰ More recent studies have shown increased levels of nitrogen dioxide (NO₂) from sources such as power plants and motor vehicles. This phenomenon has contributed to elevated ozone levels, which result from the action of sunlight on hydrocarbons and NO₂.²¹ Exposure to high ozone levels can cause cough, chest pain, and increased BHR.²² Additionally, diesel exhaust is an important airborne particulate matter, particularly in urban areas. In patients exposed to high levels of diesel exhaust, exaggerated IgE responses may occur.²³

Various studies performed in the United States have evaluated ozone, particulate matter less than 2.5 μm in diameter (PM_{2.5}), NO₂, and organic carbon (OC; a result of emissions from gasoline and diesel vehicles). A New England study, in which 271 children younger than 12 years were followed up for 6 months (April to September 2001), showed that ozone levels but not PM_{2.5} were significantly associated with respiratory symptoms and rescue medication use among asthmatic children using maintenance medication.²⁴ In Southern California, a cohort of 3,535 children (9–16 years old) with no history of asthma was studied from 1996 to 1999. Ozone, NO₂, particulate matter less than 10 μm in diameter, and OC in 12 Southern California areas were monitored for 4 years. There was no overall increased risk of asthma development in either the high- or low-pollution areas. However, in areas with the highest ozone levels, children were more likely to develop asthma if they participated in 3 or more team sports (OR, 3.3).²⁵ Also, McConnell et al²⁶ studied 475 asthmatic children in the same 12 Southern California areas and found a correlation between increase in symptoms and higher concentrations of OC and NO₂.

A study performed in Munich, Germany, involved a cohort of 7,509 school-aged children (5–7 years old and 9–11 years old) enrolled in the International Study of Asthma and Allergies in Children. The children underwent SPTs, radioallergen sorbent tests, pulmonary function tests, and 4.5% hyperosmolar saline challenge. The city's traffic patterns were then analyzed. Daily traffic counts were performed for all streets where it was estimated that more than 4,000 vehicles per day traveled. Additionally, pollutants, including benzene, soot, and NO₂, were measured in 18 heavy traffic sites and 16 low-to-medium traffic sites. To estimate pollution exposure,

a computer program was then used to calculate the total amount of traffic and pollution within a distance of 50 m from each subject's home. The study found that increased cough was associated with higher levels of benzene, soot, and NO₂, current asthma with soot and benzene, and current wheeze with benzene and NO₂. Also, in patients exposed to both high traffic volumes and ETS, there was an increased incidence of positive SPT results.²⁷

ETS during pregnancy has been associated with a higher incidence of physician-diagnosed asthma in the offspring.^{28,29} A recent analysis of 51 publications estimated that ETS exposure increases the risk of acquiring asthma before 6 years of age by 37% and after 6 years of age by 13%.³⁰ In addition, the effects of cigarette smoke—increased elastolysis, airway inflammation, and parenchymal lung damage—may be augmented by increased incidence of allergic diathesis seen in selected subjects exposed to ETS.²⁷

INFECTION

The relationship between infection and the development of childhood asthma is still a matter of hypothesis. Various studies have shown that exposure to respiratory syncytial virus (RSV), a common infection during the first year of life, increases the risk of development of asthma later in childhood. For example, Pullen and Hey³¹ studied 130 children who had been admitted to the hospital with RSV bronchiolitis during infancy and compared them to a control group. During the first 4 years of life, the RSV group showed a higher incidence of wheeze than the control group (38% vs 15%). At the age of 10 years, 6.2% of the RSV group were wheezing compared with 4.5% of the control group. Sigurs et al³² reported similar findings, concluding that RSV bronchiolitis in infancy severe enough to cause hospitalization was highly associated with the development of asthma by the age of 7½ years (OR, 12.7). Other studies have shown that although exposure to early infection is linked to onset of wheezing during early childhood, its effects decline by approximately the age of 13 years. In the Tucson Children's Respiratory Study (TCRS), RSV infection predicted a 4-fold increased risk of persistent wheeze at the age of 6 years, which decreased to no increased relative risk by the age of 13 years. Also in the TCRS, children with either early attendance at day care (beginning at younger than 6 months) or more than 2 siblings at home were found to have a higher incidence of wheezing associated with early viral infection compared with children who had less exposure to other children. However, the relative risk of wheezing decreased significantly after 3 years of age (Fig 4).³³

On the other hand, recent studies have shown that an inverse relationship between respiratory infections and asthma may in fact exist. In a study performed in Boston, MA, Celedón et al³⁴ identified 453 children with a family history of atopy, 238 of whom attended daycare during the first year of life. In children with a maternal history of asthma, daycare in early life increased risk of asthma and recurrent wheeze during the first 6 years of life (Fig 5C). F5

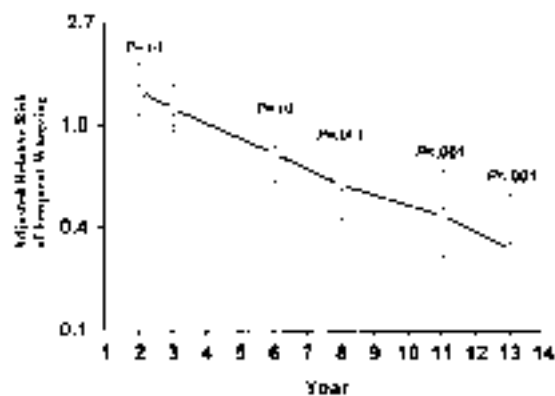


Figure 4. Risk of wheezing in children with 2 or more older siblings or who attended day care during the first year of life. Relative risks were adjusted for sex, history of asthma in the mother or father, the mother's smoking status during the prenatal period, breastfeeding status, the race of the parents, and the mother's level of education. Error bars indicate 95% confidence intervals. The *P* values are for the comparisons between the children with greater exposure to others at home or at day care and those with less exposure. The adjusted relative risks are shown on a natural-log scale. Reprinted with permission from Taussig et al.³³

However, in children without a maternal history of asthma, day care in early life was instead associated with a decreased risk of wheezing at 6 years of age (Fig 5B). Other studies have likewise reported a more complex and potentially protective effect of infections.^{20,35,36}

EPIDEMIOLOGIC STUDIES

A review of a few important epidemiologic studies will help to examine the factors involved in the persistence of asthmatic symptoms or abnormalities in pulmonary function over time. In the Melbourne Asthma Study, Phelan et al³⁷ followed up a group of 7-year-old children with a history of wheezing at 7-year intervals beginning in 1964. The children were grouped as follows: (1) control: no history of wheezing (*n* = 105); (2) mild wheezy bronchitis: fewer than 5 episodes of wheeze associated with infection (*n* = 74); (3) wheezy bronchitis: 5 or more episodes of wheezing associated with infection (*n* = 104); (4) asthma: wheezing unassociated with respiratory infection (*n* = 113); and (5) severe asthma: wheezing that began before 3 years of age, persistent symptoms at 10 years of age, barrel chest, and/or reduction of FEV₁/forced vital capacity less than 50% (*n* = 83). The patients were reviewed at ages 10, 14, 21, 28, 35, and 42 years. At the last review, 87% of the patients who were alive participated. During the study, there were 15 deaths, with 1 attributed to asthma. During the first 25 years of the study, anti-inflammatory therapy using inhaled corticosteroids was not routinely emphasized in the care of persistent asthma.

Most children who had only a few episodes of wheezing associated with infection ceased to wheeze by adult life; those who continued to wheeze did so infrequently and were little troubled by their symptoms. Children with persistent asthma

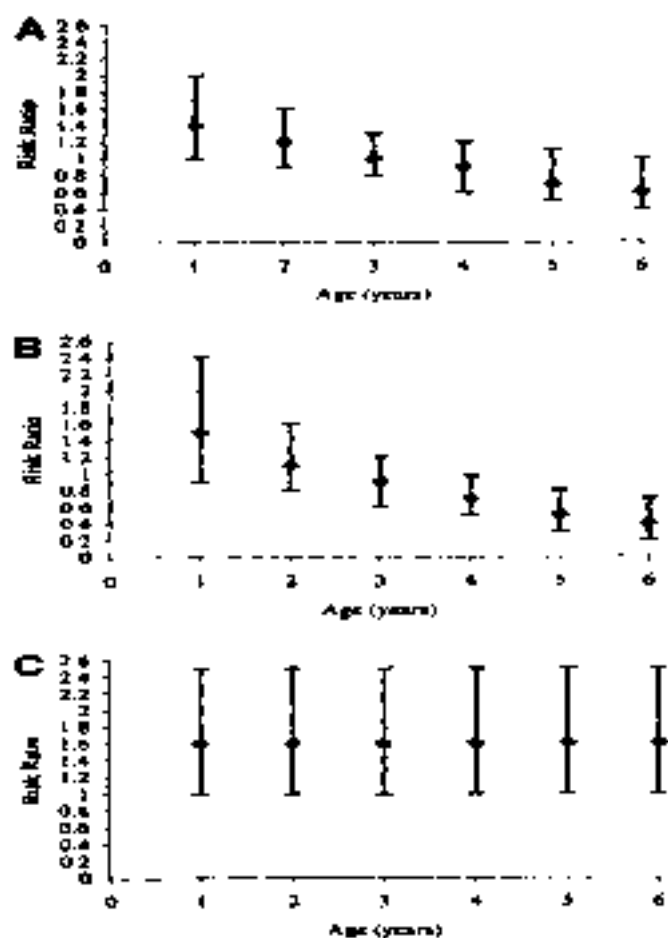


Figure 5. A, Adjusted risk ratio of wheezing between the ages of 1 and 6 years among children who attended day care in the first year of life compared with children without exposure to day care in the first year of life. B, Adjusted risk ratio of wheezing between the ages of 1 and 6 years among children without a maternal history of asthma who attended day care in the first year of life compared with children without a maternal history of asthma without exposure to day care in the first year of life. C, Adjusted risk ratio of wheezing between the ages of 1 and 6 years among children with a maternal history of asthma who attended day care in the first year of life compared with children with a maternal history of asthma without exposure to day care in the first year of life. All risk ratios were adjusted for sex, household income, having a least 1 physician-diagnosed lower respiratory tract illness in the first year of life, and maternal smoking during pregnancy. Error bars indicate 95% confidence intervals. Reprinted with permission from Celedón et al.³⁴

continued wheezing significantly into adult life. There was no significant loss of lung function in those with mild childhood asthma, whereas children with severe asthma had a reduced lung function by 14 years of age, which persisted into adult life but did not continue to deteriorate. Also of note is the male-female ratio of the different groups at age 42 years: 1:1 for infrequent wheezing, 2:1 for frequent wheezing, and 4:1 for persistent asthma.³⁷

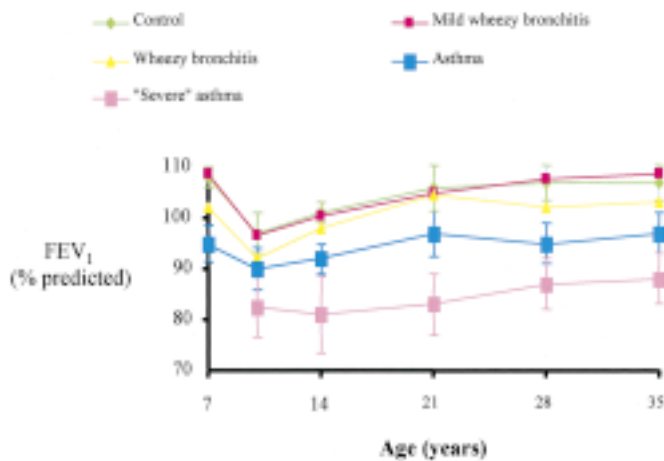


Figure 6. Asthma and wheezing from 7 to 35 years (Melbourne Asthma Study). FEV₁ indicates forced expiratory volume in 1 second. Reprinted with permission from Phelan et al.³⁷

In Dunedin, New Zealand, Sears et al³⁸ studied a cohort of 613 children (52% male) from the age of 9 to 26 years. The patients were seen every 2 years from 3 to 15 years of age and then at 18, 21, and 26 years of age. During the study, 51.4% of the patients reported wheezing for at least 1 study visit. Eighty-nine (15.5%) wheezed persistently from the age of 9 to 26 years; 168 (27.4%) had remission, but 76 (12.4%) relapsed by the age of 26 years. Risk factors that predicted persistent symptoms or relapse included sensitivity to house dust mite, BHR, female sex, smoking, and early age of onset. As in the Melbourne study (Fig 6), pulmonary function test results were consistently lower in patients with persistent or relapsing wheezing than in those with infrequent wheeze.

The TCRS that began in 1980 has followed up 1,246 subjects for 24 years, with a 78% (n = 974) retention rate. At the age of 6 years, 48.5% had had at least 1 episode of wheezing, 19.9% had transient wheeze, 15% had late wheeze (onset after 3 years of age), and 13.7% had persistent wheeze. The TCRS subsequently developed an Asthma Predictive Index, which can be used to predict the risk of asthma development in 2- and 3-year-old patients experiencing frequent wheezing episodes (Fig 7). The study found that 75%

A Clinical Index to Define Risk of Asthma Year 2 and 3

Major Criteria	Minor Criteria
- Parental asthma	- Allergic rhinitis
- Eczema	- Wheezing apart from colds
	- Eosinophilia ($\geq 4\%$)

Figure 7. A clinical index to define risk of asthma at years 2 and 3. Reprinted with permission from Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med.* 2000;162:1403-1406.

of patients who had 1 major criterion or 2 minor criteria had active asthma between 6 and 13 years of age, whereas 68% of patients with a negative index never had asthmatic symptoms during the school years.³³

In the Isle of Wight study, 71% of the original cohort of 1,456 patients attended all 4 study visits. These 1,034 patients were categorized at 10 years of age into 4 groups: (1) non-wheezers; (2) early transient wheezers (wheezing onset before 4 years, which ceased by 10 years); (3) persistent wheezers; and (4) late-onset wheezers (wheezing onset after 5 years and present at 10 years). Of those categorized, 417 (40.3%) had wheezing of some form: 211 had early transient wheezing, 125 had persistent wheezing, and 81 had late-onset wheezing. Major risk factors that predicted wheezing were family history of asthma, positive SPT result at 4 years, and recurrent chest infections at 2 years. Conversely, a significantly reduced risk of wheezing was found in patients with recurrent nasal symptoms at 1 year. These 4 factors were used to create a risk score (0 to 4) for asthma persistence. Of the patients with a risk score of 4, 83% had persistent disease, whereas 80% of those scoring 0 or 1 had only transient disease.³⁹

In the German Multicenter Allergy Study, which began in 1990, Lau et al⁴⁰ have followed up 1,314 children from birth

Table 1. Multivariate Likelihood Ratios (LRs) for Childhood Characteristics Predicting Outcomes in Adulthood*

Childhood characteristics	Asthma symptoms		Troublesome asthma	
	With characteristic, %	LR (95% CI)	With characteristic, %	LR (95% CI)
Atopy	36.7	2.02 (1.54-2.66)	47.6	2.56 (1.77-3.72)
AHR	19.6	2.56 (1.78-3.67)		
Wheeze in last 12 months	19.5	1.92 (1.46-2.53)		
Obstructive spirometry	5.5	2.88 (1.27-6.53)	8.5	4.36 (1.72-11.04)
Female	53.0	1.29 (0.78-2.13)	62.2	1.69 (0.96-2.89)
Hayfever			45.6	2.14 (1.59-2.89)

Abbreviations: AHR, airway hyperresponsiveness; CI, confidence interval.

* Reprinted with permission from Toelle et al.⁴¹

onward. Annual assessments include physical examination and radioallergosorbent tests for food and inhalant allergens. Lung function was measured at 7 years in 800 subjects. At the most recent annual visit, current wheeze (at least 1 episode of wheezing in the past 12 months) was strongly associated with reduced lung function at 7 years. Current wheezers had a higher incidence of sensitization to indoor allergens, atopic family history, and elevated cord blood IgE levels. Transient wheezers showed a slightly reduced expiratory flow at 50% forced vital capacity ($98.9\% \pm 24.2\%$ vs $103.2\% \pm 22.8\%$ in nonwheezers). In this group, lower respiratory tract infections and maternal smoking were associated with reduced FEV₁.

Toelle et al⁴¹ studied a cohort of 575 children in New South Wales, recruited at the age of 8 to 10 years and then reevaluated 15 to 17 years later. At the follow-up visit, asthma symptoms were defined as wheeze, sleep disturbance from asthma, or inhaled corticosteroid use during the previous year. Patients described as having "troublesome asthma symptoms" had urgent physician visits, hospitalization, activity limitation, or sleep disturbance due to asthma during the previous year. The likelihood ratios for asthma symptoms and troublesome asthma in adulthood as determined by childhood characteristics are given in Table 1. The strongest predictors of asthma in adulthood were female sex and the presence, during childhood, of atopy, airway hyperresponsiveness, airway obstruction, and persistent wheeze. In patients with all 5 characteristics, the likelihood ratio of the persistence of childhood asthma into adult life was 36.9.

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CONCLUSION

The studies mentioned herein have found that numerous factors can play a role in predicting the persistence of asthma. Although female sex appears in many studies as a predictive variable of asthma, it has yet to be found that female sex is significantly linked to disease persistence. Further research is needed to clarify this point. Factors strongly linked to the persistence of childhood asthma into adult life are early age of disease onset with more severe symptoms, atopy, and level of allergen exposure. Although there is still much research to be done, epidemiologic studies have repeatedly proven that the natural history of asthma is in some ways predictable. Early identification of patients at risk for persistent asthma, combined with early institution of pharmacologic and non-pharmacologic intervention strategies, may lead to better outcomes.

ACKNOWLEDGMENT

I thank Julia McElvain, BA, for editorial assistance.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Chipps BE. 2004;93:309–316.

Self-Assessment Exam Questions

1. The determinants for persistence of asthma include early life exposure to:
 - a. respiratory infection
 - b. household pets
 - c. high levels of house dust mite
 - d. all of above
2. Genetically determined responses to classes of pharmacologic agents include all but:

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- a. antihistamines
b. glucocorticoid
c. leukotriene-modifying agents
d. β -adrenergic stimulants
3. The role of IgE-mediated sensitivity in childhood asthma occurs in what percentage of patients?
a. 5%
b. 20%
c. 30%
d. 85%
4. A significant factor that causes asthma to remain persistent is:
- a. exposure to diesel fumes
b. development of atopic state
c. in utero exposure to tobacco smoke
d. all of the above
5. Abnormalities of pulmonary function in asthma are the most severe in patients who have:
a. transient wheeze
b. early-onset wheeze with remission
c. persistent wheeze and relapse
d. exercise-induced asthma
- Answers found on page 380.**
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