

Review article

Asthma: from childhood to adulthood

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Asthma is one of the most common chronic and potentially disabling diseases in childhood and young adulthood. Parents of children with asthma frequently ask, "Will my child 'outgrow' his or her asthma?" And often, the physician wants to comfort the parents with the assurance that most children do "outgrow" their asthma. But is this true? And, if so, there remains the question of what determines this favorable outcome of asthma. In spite of advances in our understanding of the pathophysiology of asthma, the natural history of the disease is still unclear. Moreover, it is not known whether early recognition and optimal treatment of asthma have any influence on its outcome later in life.

In the last 50 years, several investigators have attempted to assess the prognosis of asthma from childhood to adulthood. There are, however, several problems with the results of these studies. First of all, the diagnosis of asthma has not been clearly defined in many studies, a fact which makes it difficult to interpret the conclusions. Various terms have been used such as "asthma", "asthmatic bronchitis", "wheezy bronchitis", "allergic asthma", "bacterial asthma", and "wheezing", further hampering clear interpretation of the results. In this review, we have defined asthma as a syndrome characterized by variable and often reversible air-

ways obstruction, airways inflammation, and bronchial responsiveness. Subjects with asthma have episodes of wheeze and/or breathlessness, with intervals of relative or complete freedom from symptoms. These attacks of breathlessness can be elicited by several stimuli, such as exercise, viral infection, and specific (allergic) and nonspecific irritants; e.g., cold, fog, and smoke.

Another problem in assessing factors determining the prognosis of asthma from available publications is their differences in patient selection and study design. The outcome of asthma may be different in epidemiologic and clinical studies, and ranges in severity of the disease and age at the start of the study may affect the prognosis as well. A third problem is variation in duration of follow-up. This is an important factor because remission may often occur during puberty, whereas relapses are not rare and become more frequent with increasing age (1).

To facilitate comparison of the available studies on the outcome of asthma, one has to consider what defines a positive or negative outcome of the disease. For the patient, the absence of symptoms and satisfactory quality of life are probably the most important factors. For the clinician, stable disease is characterized not only by absence of symptoms and satisfactory quality of life, but also

by normal lung function and absence of bronchial responsiveness and airway inflammation.

This paper aims to give an overview of the results of published follow-up studies on the outcome of asthma.

Methods

We have searched MEDLINE (1966–95), Dimdi, and Current Contents, using “follow-up”, “prognosis”, “childhood”, “adulthood”, “lung-function tests”, and the names of a number of authors as key words. The following criteria for inclusion in this review were used

- 1) follow-up studies on the prognosis of childhood and adulthood asthma
- 2) articles written and published in English
- 3) articles published 1945–96
- 4) prospective, patient- or population-based studies including objective measurements.

We made this selection because published studies relying only on questionnaires are generally retrospective in nature. Therefore, the risk of “recall bias” exists in these studies. Patients with current respiratory symptoms usually recall past respiratory symptoms better than those without current symptoms. Another problem is that different questionnaires have been used, making comparison between studies difficult, since subjective data are more difficult to compare than objective measurements. A third reason is that studies which are based only on questionnaires are likely to miss patients with mild to moderate asthma because of the lack of correlation between objective measurements and symptoms in this type of patient. For the sake of completeness, an overview is given in the form of two tables with all available follow-up studies based on questionnaires only, retrospective and prospective studies, as well as studies with objective measurements (Tables 1 and 2). Articles dealing with risk factors for the development, and not the progression, of asthma have been excluded.

We have specifically addressed the effect of age at onset of symptoms, severity of symptoms, allergy, bronchial responsiveness, lung function, viral infections, eczema, sex, active and passive smoking, and therapy on the long-term outcome of the disease, since these factors have been considered important for the prognosis of childhood and adulthood asthma.

Age at onset of symptoms

Most follow-up studies from childhood to adulthood have shown that roughly 50% of children do “outgrow” their asthma (18, 41, 47, 55, 56). One aspect related to outcome is age at onset of respi-

ratory symptoms. The literature relating to this aspect is complex and contradictory. Several studies have shown that onset of wheeze at an early age, usually defined as wheeze before the age of 2 years, correlates with a negative outcome (28, 50, 59). Other investigators, however, found no effect of age at onset of wheeze on the outcome of asthma (32, 47, 54), or even an association with a positive outcome (38, 49, 61). One reason for these contradictions is that most of the follow-up studies recruited their subjects at the age of 7 years or older (28, 39, 45, 47, 55, 56, 59) and are therefore susceptible to “recall bias”, even if they were prospective in nature. By the time the children were 7 years old, some parents might have forgotten minor episodes of wheeze; therefore, studies may have underestimated the percentage of children with an early onset of wheezing who continued to wheeze as adults.

Another possible explanation of the contradictory results is that the group of symptomatic young children can be divided into two subsets, the first being the “happy wheezer”. In this group, the wheezing syndrome is mainly associated with lower airway caliber, but not with bronchial responsiveness, and has a good prognosis. The second group comprises children with early expression of impending asthma. Here the wheezing syndrome is associated with increased prevalence of allergic markers, bronchial responsiveness, and significant impairment of lung function during the first 6 years of life. At present, we have no clinical criteria for recognition of the group to which a young child with wheezing-associated, viral, lower-respiratory-tract illnesses belongs.

Martinez et al. (62) tried to solve this problem. In their study, the association between wheezing-associated, viral, lower-respiratory-tract illnesses in the first 3 years of life and wheezing at 6 years of age was assessed in relation to lung function and IgE levels. IgE levels have been measured in cord blood, as well as during the first year of life and at 6 years of age. The only characteristic of children who wheezed early in life and stopped wheezing before the age of 6 years was their poor lung function early in life and at the age of 6 years. The poor lung function already existed before the children experienced their first lower-respiratory-tract infection. Subjects who wheezed early in life and were still wheezing by the age of 6 years had normal lung function but significantly elevated levels of IgE during their first year of life and had more symptoms during the first year of life than those with transient early wheezing. The former group also had elevated levels of IgE at the age of 6 years, and at that time their lung function was below that of subjects who never wheezed. Thus,

Table 1. Studies on natural history and prognosis of childhood asthma (questionnaire-based studies)

Author(s) (reference)	Year	Study design		n	Follow-up		Ages at survey (years)	End points	Symptom-free (%)	Remarks
		Prospective	Patient group		%	Year				
Flensburg (2)	1945	—	+	338	88	?	Start: ? End: ?	Age of onset, sex difference, duration of disease	40	Hospitalized children
Rackemann & Edwards (3)	1952	—	+	449	94	20	Start: < 13	Symptoms, development of other allergic disorders	31	Private patients First visit after age 13; more serious form of disease
		—	+	239	94	20	End: > 20–33 Start: > 13 End: > 20		22	
Unger et al. (4)	1952	—	—	366	84	1–30	Start: < 13 End: ?	Symptoms, allergy, sex, treatment	34 average: 32	Paroxysmal asthma group Chronic asthma group
Dees (5)	1956	+	+	269	87	2, 10, 15	Start: ? End: ?	Symptoms	44	
Ryssing (6)	1959	—	+	283	99	18–31	Start: ? End: > 18	Symptoms, attacks of asthma	36	298 subjects of study of Flensburg (1945): without specific treatment
Buffum (7)	1959	+	+	87	100	> 2	Start: ? End: 3.5–36 (mean 9)	Wheezing	55	
Ogilvie (8)	1962	—	+	1000	96	3–33 (mean 11)	Start: ? End: ?	Age of onset, clinical type, incidence of bronchitis, allergy, symptoms, sex	48	
Ryssing & Flensburg (9)	1963	—	+	503	98	?	Start: ? End: > 15	Symptoms, dyspnea, asthma	37	
Wilken-Jensen (10)	1963	—	+	781	80	?	Start: ? End: ?	Symptoms, allergy	65	
Kraepelien (11)	1963	—	+	601	88	2–13	Start: ?	Symptoms	29	Hyposensitization
	1963	—	+	100	?	8–10	End: 15–20		12	
Aas (12)	1963	—	+	655 346	? ?	? ?	Start: ? End: ? Start: ? End: ?	Severity, symptoms	44	
Barr & Logan (13)	1964	—	+	767	44	17–27 (mean 22)	Start: ? End: ?	Associated symptoms, wheezing	52	
Buffum & Settipane (14)	1966	—	+	722	72	10	Start: ?	Symptoms, effect of eczema, positive egg skin test, early onset	41	
				136	26	20	Average 5.6 End: ?		55	
Johnstone (15)	1968	+	+	104	61	14	Start: ? End: 16	Number of asthma attacks, number of days wheezing	22	Pediatric allergic clinic: placebo injections
Johnstone & Dutton (16)	1969	+	+	210	62	14	Start: ? End: 16	Age of onset, severity of asthma, effect of treatment	72 22	Hyposensitized children Treatment with placebo injections
Mukoyama et al. (17)	1975	—	+	2300	44	5–15	Start: ? End: ?	Symptoms	36	Seen in hospital
Blair (18)	1977	—	+	417	50	22–28	Start: < 12	Atopy, age of onset, severity of asthma at onset, family history, breast- feeding	52	Seen in hospital Private practice
				267	91	(mean 20) 20–24 (mean 20)	End: > 20 Start: < 12 End: > 20			
Cserhati et al. (19)	1984	—	+	522	85	?	Start: ? End: 14–36	Symptoms	57	
Linna (20)	1985	+	+	512	40	4–6 (mean 4.8)	Start: 4–10 End: 8–16	Symptoms, atopy, eczema, attack rate, family history of atopy	26	Outpatient clinic
Park et al. (21)	1986	+	—	2702	87	10	Start: 0 End: 10	Age at onset, frequency of attacks, number of hospital admissions	80	Children with wheezing attacks Asthmatics
									50	

Table 1 cont. Studies on natural history and prognosis of childhood asthma (questionnaire-based studies)

Author(s) (reference)	Year	Study design		n	Follow-up		Ages at survey (years)	End points	Symptom-free (%)	Remarks
		Prospective	Patient group		%	Year				
Jönsson et al. (22)	1987	–	+	119	98	23–31	Start: 5–15 End: 26–43	Age at onset, severity of asthma, eczema, respiratory tract infections, family history	55	
Strachan et al. (23)	1988	+	–	10 557	72	16	Start: 7 End: 23	Cough, phlegm	96	
Tuchinda (24)	1990	+	+	247	100	?	Start: <12 End: 15	Severity of illness, sex difference, skin tests	37	
Åberg & Engström (25)	1990	–	–	1335	89	?	Start: ? End: 14	Age of onset, association with eczema, allergic rhinitis, family history	55 69 45	Without other allergic symptoms With other allergic symptoms
Ross et al. (26)	1992	–	–	455	81	25	Start: 7 End: 30–40	Education, employment, housing, social class	38	
Jenkins et al. (27)	1994	+	–	1723	87	25	Start: 7 End: 29–32	Current asthma, current atopic asthma, frequent asthma	75	

first of all, factors other than abnormal lung function may cause early wheezing in infants in whom episodes of wheezing persist up to the age of 6 years, and, secondly, there is a direct relation between the risk of persistent wheezing and serum IgE levels in the first year of life. No relation was found between the risk of persistent wheezing and cord-serum IgE levels. According to the authors, this suggests that some form of IgE-mediated sensitization may occur during the first year of life in children with persistent wheezing. This clearly demonstrates that follow-up studies must begin early in life and that suitable markers must be developed to establish factors predicting the outcome of the disease.

Severity of symptoms

Follow-up studies assessing the impact of severity of symptoms or frequency of wheezing at the time of onset showed that more severe symptoms correlate with a negative outcome (32, 41, 47, 54, 59, 63). However, it is important to realize that there are asymptomatic subjects who have bronchial responsiveness, but do not perceive induced bronchial obstruction during histamine provocation (64). The same is true of asthmatic subjects, some reporting little discomfort with severe airway obstruction, whereas others experience marked

discomfort with small increases in airway obstruction. If perception of symptoms is low, this can be a risk factor for worsening severe asthma because of delay in giving adequate therapy (65). Rubinfield & Pain (66) found in their study of 82 patients, of whom 61 were asthmatic and 21 had occupational asthma, that poor perceivers of airway obstruction were detected by measurement of lung function only and could not be predicted by age, sex, or previous history of asthma. Thus, assessing the severity of asthma only by symptoms may result in underestimation and undertreatment of the disease.

Sex

Most studies have reported a higher prevalence of asthma in boys during infancy and childhood (28, 67–69). The cause of this higher prevalence is still unknown. It is not yet clear whether a difference in sex affects the outcome of asthma. Ten prospective studies with objective measurements have investigated the role of sex in the prognosis of asthma. Seven of these studies did not find a difference in outcome (1, 28, 47, 50, 58–60), another one found women to have a better prognosis than men (41), and two found female sex to be associated with a poor outcome (32, 55).

In the Melbourne study, which started in 1964, 401 children were randomly selected from 30 000

Table 2. Studies on natural history and prognosis of childhood asthma with objective measurements

Author(s) (reference)	Year	Study design		n	Follow-up		Ages at survey (years)	End points	Symptom-free (%)	Remarks
		Prospective	Patient group		%	Year				
Williams & McNicol (28)	1969	+	—	295 106 controls	94 89	3	Start: 7 End: 10	Age of onset of wheezing, symptoms, skin sensitivity	68	Random sample of 7-year-old primary schoolchildren
McNicol & Williams (29–31)	1973	+	—	378 106 controls	83 77	4–7	Start: 7, 10 End: 14	Frequency and severity of wheezing, time since last episode, age at last episode	3–80	Dependency on group difference, new group of 83 children added with severe asthma
Martin et al. (32)	1980	+	—	378 106 controls	73 61	11–14	Start: 7, 10 End: 21	Pulmonary function and BHR, exercise labiality		
Martin et al. (33–37)	1980	+	—	378	88	11–14	Start 7, 10 End: 21	Frequency of wheezing, progress in grade, age of onset, sex	50	Group of infrequent wheezing in childhood Group of frequent wheezing in childhood
	1981			106	73				20	
	1982			controls						
Foucard & Sjöberg et al. (38)	1984	+	+	81	99	12	Start: 0–5 End: 12–17	Family history, allergy, serum IgE, age of onset, wheezing	78	
Giles et al. (39)	1984	+	—	851	26	7	Start: 13 End: 20	Symptoms, wheezing	78	
Schachter et al. (40)	1984	+	—	73	?	6	Start: 7–45 End: 13–51	Symptoms, FEV ₁ , Vmax ₅₀ , environmental influences	68	
Bronniman & Burrows (1)	1986	+	—	136	100	9	Start: <10–79 End: ?	Frequency of asthma attacks, attacks of breathlessness with wheeze, FEV ₁ % pred., chronic productive cough	22	
Kelly et al. (41)	1987	+	—	378 106 controls	85 45	18–21	Start: 7, 10 End: 28	Symptoms, progress in grade, sex	73	Group of infrequent wheezing in childhood
									32	Group of frequent wheezing in childhood
Nishima et al. (42)	1987	—	+	89	100	5–9	Start: ? End: ?	Serum IgE	33	Hospitalized children
Kelly et al. (43)	1988	+	—	378 106 controls	65 36	18–21	Start: 7, 10 End: 28	Pulmonary function, BHR	73	Group of infrequent wheezing in childhood
									32	Group of frequent wheezing in childhood
Friberg et al. (44–45)	1988	+	+	20 males	100	14	Start: 11 End: 25	Pulmonary function, height, symptoms, work capacity, pulmonary gas exchange	45	Improved
	1989									
Østergaard (46)	1988	+	+	72 59 controls	93	6	Start: <12 End: 11–18 (mean: 13.5 girls, 14.1 boys)	Pulmonary function, serum IgE and blood eosinophils	?	Intrinsic asthma
Gerritsen et al. (47)	1989	+	+	119	85	16	Start: 6–14 End: 22–31	Symptoms, pulmonary function, BHR, allergy	57	

Table 2 cont. Studies on natural history and prognosis of childhood asthma with objective measurements

Author(s) (reference)	Year	Study design		n	Follow-up		Ages at survey (years)	End points	Symptom-free (%)	Remarks
		Prospective	Patient group		%	Year				
Kelly et al. (48)	1990	+	—	378 106 controls	85 45	18–21	Start: 7.10 End: 28	Skin tests, blood eosinophils, serum IgE, relation of atopic illness and BHR		
Sporik et al. (49)	1991	+	—	67	67	11	Start: 0 End: 11	Atopy, wheezing, BHR	76	Start wheezing before 2 years of age
									19	Start wheezing after 2 years of age
Croner & Kjellman (50)	1992	+	—	89	66	11.5–14.5	Start: 0 End: 11.5–14.5	Pulmonary function, BHR, allergy, family history, cord-blood IgE	42	
Almind et al. (51)	1992	+	+	343	62	7	Start: 18–80 End: 25–87	Pulmonary function, mortality, morbidity, allergic vs nonallergic	42	Nonallergic asthma. No chronic cough;
									72	allergic asthma: no chronic cough
Ulrik et al. (52)	1992	+	+	180	79	10 (9–12)	Start: 31 extrinsic, 43.5 intrinsic End: 41/53.5	Pulmonary function, BHR, skin test, RAST, mortality rate	4	Intrinsic and extrinsic asthma group
Ulrik et al. (53)	1992	+	+	213	82	10 (9–12)	Start: 31 extrinsic, 43.5 intrinsic End: 41/53.5	Pulmonary function, BHR, skin test, RAST, mortality rate, difference between intrinsic and extrinsic asthma	4	Intrinsic and extrinsic asthma group
Kokkonen & Linna (54)	1993	+	+	131	82	?	Start: < 16 End: 20–24	Pulmonary function, BHR, symptoms, skin test	28	
Roorda et al. (55)	1993	+	+	406	85 70 (lung function)	11–19 (mean 14.5)	Start: 8–12 End: 21–29	Symptoms, BHR, pulmonary function	24	
de Gooijer et al. (56)	1993	+	—	60	85	27	Start: 8–11 End: 34–37	Symptoms, atopy, blood eosinophils, IgE, BHR, pulmonary function	47	
Oswald et al. (57)	1994	+	—	378 106 controls	? (mean 84%) 80	25–28	Start: 7, 10 End: 35	Symptoms, tobacco smoking	65 30 10	Mild wheezy group Asthma group Severe asthma group
Godden et al. (58)	1994	+	—	121 167	80 60 spirometry 78 56 spirometry	25	Start: 9–15 End: 34–40	Pulmonary function, BHR, symptoms, peak flow	39	
					97					
Kjellman & Hesselmar (59)	1994	+	+	58	97	15	Start: 9 (5–14) End: 24	Symptoms, pulmonary function, skin tests, need for medication	16	
Panhuysen et al. (60)	1996	+	+	426	44	25	Start: 24 (13–44) End: 49	Pulmonary function, symptoms, IgE, skin tests, BHR	?	

BHR: bronchial hyperresponsiveness.

7-year-old schoolchildren. They comprised a control group of 106 children, a group of 75 children with mild wheezy bronchitis, a group of 107 children with moderate wheezy bronchitis, and a group of 113 children with asthma. The selection of children was based on the parents' answers to a questionnaire. These children were followed up from age 7 to age 35 and were studied at age 10, 14, 21, 28, and 35. A sample of more severely affected asthmatic children was added from the same age stratum in 1967, when they were aged 10 years. In this study, Kelly et al. (41) found that 28% of males aged 21–28 suffered a worsening of their symptoms in comparison with 19% of females. This contrasts with the findings of Martin et al. (32) in the same study, when the subjects were 14–21 years of age. At that age, a smaller degree of improvement of symptoms in females than in males was observed. This could be interpreted as an age effect, females becoming less symptomatic at a later age.

However, Roorda et al. (55) could not support this hypothesis. They followed 406 children, aged 8–12 years, with a doctor's diagnosis of asthma, for a mean period of 14.8 years. In this study, women had more symptoms than men at the age of 21–29 years, an age range comparable to that in the study of Kelly et al. (41). The study of Godden et al. (58) is one of the investigations in which sex was not found to affect the outcome. In 1964, they started a prospective community survey in 455 children having either asthma ($n=121$), wheeze in the presence of infection ($n=167$), or no respiratory symptoms ($n=167$). This selection was made both by questionnaire and by clinical assessment. After a follow-up of 25 years, at age 34–40, they found no influence of sex on prognosis in relation to symptoms of wheeze, cough, phlegm production, or peak-flow variation, yet they found more severe bronchial responsiveness in women.

One study investigated 72 nonatopic asthmatic children aged 11–18 years (46), finding that more nonatopic asthmatic boys developed atopic asthma than girls. Nonatopic asthma in girls appeared to have a negative outcome in that fixed or declining lung function occurred, as well as signs of pulmonary hyperinflation and lung fibrosis. Thus, in this study, girls seemed to have a worse prognosis than boys.

With regard to a causal relationship of sex and prognosis of asthma, we emphasize the problems in interpreting the differences in health outcomes. In general, it is extremely difficult to separate the effects of biologic and physiologic differences from those related to social influences (70). New follow-up studies are needed which carefully take sex; social, environmental development; and/or

progression of lung-function impairment and hormonal development into account to clarify this matter.

Eczema

Atopic dermatitis is a chronic, relapsing, pruritic dermatitis that usually occurs in patients with a personal or family history of atopy. In most patients, atopic dermatitis begins during infancy. It has been estimated that 65% of patients with atopic dermatitis develop it during their first year of life, and 90% before the age of 5 (71). Research into a link between eczema as a risk factor for the progression of asthma is complicated by the fact that eczema is generally defined as imprecisely as asthma itself. A further problem is that many studies did not include a physical examination to establish the presence of eczema, but based their findings on questionnaires only (28, 32, 41, 47, 55). Because eczema is a disease that changes in severity within hours or days, it is difficult to determine its role in the persistence and severity of asthma. Nonetheless, it has been clearly established that the prevalence of eczema is higher in asthmatics than among the general population. Kokkonen & Linna (54) re-examined a group of 108 subjects, aged 20–24 years, who had had asthma in childhood. They found that atopic dermatitis in childhood was a factor which predicted a high attack rate of symptoms in adulthood (>50 attacks per year). However, whether persistent eczema is associated with worse asthma with regard to its long-term outcome is not known.

Viral infection

Several retrospective and prospective studies have investigated the role of viral infections (72, 73). Mild wheezing in association with viral respiratory tract infections occurs in 10–20% of all infants and children and has an excellent prognosis (29, 38, 62). The prognosis for viral exacerbation in atopic asthma at school age has not been studied. Because asthma severity is determined by lumping episodes together with interval symptoms, it is impossible to distinguish the outcome for episodes alone. Although episodes often seem to be more severe, prolonged, or frequent in those with more troublesome interval symptoms, this is by no means always the case. Some children with severe chronic symptoms seem to be unaffected by viral infection. This suggests that viral responsiveness is to some extent independent of the two main associates of later asthma: bronchial responsiveness and atopy (74). However, it is clear that in most of the asthmatic patients and even in healthy subjects, viral infections increase

bronchial responsiveness and cause temporary deterioration of lung function. Whether these viral infections affect the long-term outcome of asthma remains to be established. One may assume that viral infections, like allergen exposure, do affect the long-term outcome, since both may induce acute changes in inflammation in the airways. Given the relation of airway inflammation to airway remodeling and hence the possibility of irreversible changes in airway walls and lung tissue, frequent exacerbation may ultimately result in a worsened outcome of asthma. But however likely this may seem, it has not been prospectively investigated.

Atopy

There are various expressions of atopy, e.g., rhinitis, dermatitis, and asthma, on exposure to allergens. Most patients with asthma have clinical and serologic evidence of atopy. The results of studies examining the relationship of allergy to the outcome of asthma from childhood to adulthood are conflicting: some investigators found no effect on the outcome (32, 75–77), whereas others did (39, 41, 48, 56, 78, 79). The studies which have shown an effect all point to a negative association of atopy with the outcome of asthma. Within the group of atopic asthmatics, the most severe cases also tend to have the most extensive allergic features (hay fever, eczema) (32, 41).

Atopy has also been proposed as a risk factor for decline in lung function in an epidemiologic setting independent of the presence of clinical asthma (43, 80). However, in a patient-based prospective study, Ulrik et al. (52) showed that the decline in lung function was more rapid in non-atopic asthmatic adults than in atopic asthmatic adults. In contrast, Almind et al. (51) found no difference between nonatopic and atopic asthmatic adults in annual decline in lung function. The explanation of these discrepant findings could be the difference in patient selection. Although the duration of follow-up (10 and 7 years) and the age of the patients were approximately the same in both studies, a significant finding of median age at the start of the study of Ulrik et al., being 43.5 years for the nonatopic asthmatics and 31.0 years for the atopic asthmatics, might explain differences in lung-function decline between the groups. In the study of Almind et al. (51), the mean age of the nonatopic asthmatics was also significantly higher than that of the atopic asthmatics, i.e., 52 years and 36 years. Thus, the difference in age between non-atopic and atopic asthmatics cannot be the reason for the difference found in annual decline in lung function in both studies, given the observation that the age difference was similar in both studies.

However, the duration of asthma at the start of the study was approximately 10 years longer in the study of Ulrik et al. Only 20% of the asthmatics were smokers in this study, whereas 83% of the nonatopic and 71% of the atopic asthmatics were smokers in the study of Almind et al. Thus, smoking may have obscured the difference in FEV₁ decline between atopic and nonatopic asthmatics in the latter study. Another reason for finding a difference between the two studies is that in Almind et al.'s study allergic status was verified at the end of follow-up and investigated with skin tests only, whereas it was verified at the start of the study by means of skin tests and radioallergosorbent test in Ulrik et al.'s study. As the expression of allergy may decline with age (60), this may have affected the results. A final possible contributory factor is therapy, because 66% of nonatopic asthmatics and 47% of atopic asthmatics were treated with inhaled corticosteroids in the study of Ulrik et al. If this therapy affects the outcome of asthma positively, nonatopics would fare worse. Since the studies of both Ulrik et al. and Almind et al. were not designed to investigate the role of therapy prospectively, no conclusions can be made on this point.

Many studies have shown that house-dust-mite allergens are a major risk factor for children having abnormal airway function or symptoms of asthma, and that a high density of house-dust mite increases the risk of acute attacks and of hospitalization for asthma (81, 82).

Many studies are underway to find out whether allergen avoidance from birth has a positive effect on the long-term outcome of asthma. Since an increase in allergen exposure has been shown to be associated with more severe bronchial responsiveness (83) and larger PEF variability (82), as well as more symptoms, and allergen avoidance has been shown to improve asthma (68), it seems likely that allergen avoidance may improve the outcome of asthma.

Bronchial responsiveness

Increased nonspecific bronchial responsiveness is a central feature in the diagnosis of asthma (84). This increased responsiveness may precede the development of asthma (85). This has been observed not only in children or young adults (85, 86), but also in middle-aged men with asthma, chronic bronchitis or chronic sinusitis being excluded (87). Bronchial responsiveness persists in children with symptoms of asthma (88) and it generally improves in young asthmatic subjects with a better clinical course of the disease (56, 89). This has been confirmed in several other studies showing that

more severe bronchial responsiveness is associated with more respiratory symptoms, a higher frequency of wheezing (41, 80, 90–92), and a steeper fall in FEV₁ (80, 91) in asthmatic children and adults. Peat et al. found that the combination of wheeze and bronchial reactivity distinguishes the asthmatic group with ongoing significant respiratory impairment (91).

One study (93) in 71 mild asthmatic patients, who were part of a larger group of 182 adults with mild asthma ($n=71$) and chronic obstructive pulmonary disease ($n=111$) completed a 2-year, randomized, controlled intervention study with bronchodilators. They used no corticosteroids during the study period. This study has shown an interaction between bronchial responsiveness and atopy with regard to their effect in the decline in lung function. Atopic patients with asthma had a larger decrease in FEV₁ at follow-up when they had more severe bronchial responsiveness. This suggests that such patients are thus at risk of developing progressive airways obstruction.

In a multicenter trial, Kerstjens et al. (94) compared three inhalation regimens in which a β_2 -agonist was combined with a corticosteroid, an anticholinergic bronchodilator, or placebo. Patients, aged 18–60 years, with bronchial responsiveness and obstruction ($n=274$) were followed for 2.5 years. The greatest improvements in FEV₁ were found in younger patients, nonsmoking patients, patients with allergy, and patients with more severe bronchial responsiveness. The severity of bronchial responsiveness defined patients with a better overall response to inhaled corticosteroids, since improvement in PC₂₀ with corticosteroids was also more pronounced in younger patients with less airways obstruction and more easily reversible airway obstruction. Long-term treatment with inhaled corticosteroids may diminish the number and activation state of inflammatory cells in the airways dramatically; nevertheless, it does not normalize bronchial responsiveness (94–96), or does so only in a few patients with mild asthma.

Finally, Kondo (89) showed an improvement in bronchial responsiveness in non-steroid-dependent asthmatic patients during preadolescence and adolescence. He suggests that this improvement may be one of the underlying mechanisms in the “outgrowing” of asthma. In one study, the outcome of childhood asthma was determined by both bronchial responsiveness and bronchial obstruction (47), although another study did not find this association (55).

It is still unclear to what extent control of bronchial responsiveness, e.g., by medication and allergen avoidance, may affect the long-term outcome of the disease.

Level of lung function

In both children and adults, a low level of FEV₁ appears to be predictive of continuation of wheezing and of a low level of lung function in adulthood, as well as of more rapid decline of FEV₁ (32, 41). In their population-based, follow-up study of 401 children, Martin et al. (33) found that subjects with chronic asthma had a large vital capacity (VC) relative to body size at 14 years of age, but this abnormality was no longer present at 21 years of age. They also found that subjects who had minor wheeze in childhood and who had been wheeze-free for at least 3 years at the age of 21 were, as a group, indistinguishable from the control group in lung function. This contrasts with the finding of Borsboom et al. (99), who performed a 7-year longitudinal survey of two cohorts of 404 adolescents, aged 11–19 at the first measurement. They found that adolescents with a positive history of prepubertal respiratory symptoms, even if they lose their symptoms, remain at a disadvantage with respect to lung function when they reach adulthood. Adolescents with a positive history of prepubertal respiratory symptoms exhibited lung growth parallel to asymptomatic subjects, but at a lower level. A possible explanation of this contrast could be differences in the severity of symptoms between both studies. In the study of Borsboom et al., childhood symptoms often would not have been classified as asthma but might, for example, have been attributed to respiratory infections, whereas in the study of Martin et al. the symptoms were specifically related to asthma. Thus, it could be postulated that the effect of childhood asthma on lung function is reversible, whereas the effect of childhood respiratory infection is not, or not completely.

However, there is growing concern that, despite increased use of prophylactic treatment, some children may have a persistently high functional residual capacity (FRC), putting them at risk of irreversible lung-function impairment in later life (100). However, they are, as yet, not distinguishable from those who react with normalization of FRC and of spirometry.

Smoking

Parental smoking affects the development of asthma. Tager et al. (101) found that cigarette smoke exposure *in utero* contributes to reduced airway size and/or changes in respiratory mechanics, especially in girls. Murray & Morrison (102) found that although passive smoking may cause asthma only in children with atopic dermatitis, it aggravates the disease in both those who have and

who have not had atopic dermatitis. Another study found an increased prevalence of bronchial reactivity in children of smoking parents, especially in boys and children with a history of asthma (103). However, in a study concerning asthma and wheezing in the first 6 years of life, Martinez et al. (62) showed that maternal smoking was the only risk factor common to a group of early wheezers who ceased wheezing before the age of 6 and a group of persistent wheezers, suggesting that exposure to tobacco smoke may have effects other than those on airway growth *in utero*. Finally, in one study, parental smoking had progressive, more serious, and clinically significant effects on FEV₁/VC values among wheezing adolescents of both sexes. In nonwheezing subjects, parental smoking was associated only with a mild and nonprogressive, but persistent impairment of the FEV₁/VC ratio in boys (104).

However, smoking itself hardly ever appears as a risk factor for progressive airflow limitation when asthma is present. This may be the result of the "healthy smoker effect", in that those with more susceptible airways do not take up smoking or quit at an early stage. Thus, a negative effect may not become apparent. The observation that active smoking during adolescence is associated with shortening of the plateau phase of FEV₁ that generally occurs between 20 and 35 years of age (101) suggests that there is an overall negative effect of smoking in adolescence which may also be present in asthmatic subjects. Further observations have shown that cessation of smoking during adolescence had a positive impact on lung growth (106).

Therapy

There are numerous problems in studying the "natural history" of asthma. One of the characteristic features of the disease is its responsiveness to therapy. But the influence of treatment on the long-term course of the disease may be difficult or even impossible to determine, because of changes in therapy regimens over the years. Other problems are the lack of therapy compliance, especially during puberty, and the inherent variability of the disease regardless of therapy. Double-blind, placebo-controlled, long-term studies are needed to elucidate the effect of therapy on long-term outcome of asthma. One such study was by Haahtela et al. (96). In a double-blind study, they compared the effect of an inhaled corticosteroid with that of an inhaled β_2 -agonist in a long-term treatment of 2 years of 103 newly detected patients with mild to moderate asthma. The conclusion of this study was that

the early use of an inhaled corticosteroid in the treatment of newly detected asthmatics results in a greater improvement in objective variables, such as PEF and bronchial responsiveness, and in subjective variables such as symptoms, than does regular treatment with a β_2 -agonist. Thus, if early introduction of inhaled corticosteroids leads to sustained control of airway inflammation and bronchial responsiveness, it may improve the overall outcome of the disease.

The same result was found in another "open" study (106) in 105 patients with mild to moderate asthma not earlier treated with inhaled corticosteroids, but needing an inhaled bronchodilator of three or more doses a week and/or having asthma symptoms. These asthmatics were treated with an inhaled corticosteroid for 2 years. According to the symptoms, they were divided into six groups; duration of symptoms ranged from less than 6 months up to more than 10 years. A significant negative correlation was found between duration of symptoms and maximum increases in PEF and FEV₁. The authors concluded that early treatment of asthma with an inhaled steroid may prevent patients from developing chronic airway obstruction. In a later publication of the same study group, Haahtela et al. (107) showed that a reduction of the dose from 1200 μ g for 2 years to 400 μ g of inhaled corticosteroids for 1 year was feasible without deterioration of lung function and bronchial responsiveness in most asthmatic subjects. However, discontinuation of treatment with inhaled corticosteroids often led to exacerbation of the disease. The same result was shown by Waalkens et al. (108), who performed a study with 28 children, aged 11–18 years, who had completed 28–36 months of treatment with inhaled corticosteroid and inhaled β_2 -agonist. In a double-blind study, they were randomized either to continue inhaled steroids or to join the tapering-off followed by placebo group, for a period of 6 months. In the cessation group, symptoms and additional bronchodilator use increased, and both FEV₁ and PD₂₀ histamine decreased, whereas these all remained unchanged in the group that continued treatment with inhaled corticosteroid (Fig. 1). Thus, we can conclude that inhaled corticosteroids suppress the underlying mechanisms of asthma, but cannot cure the disease.

Some studies suggest that regular use of β_2 -agonists may actually worsen asthma (109, 110) and is a risk factor for (near) death from asthma (111). Irrespective of presence or absence of symptoms, regular bronchodilator use may negatively affect lung function (112). This has been attributed to the lack of effect in reducing

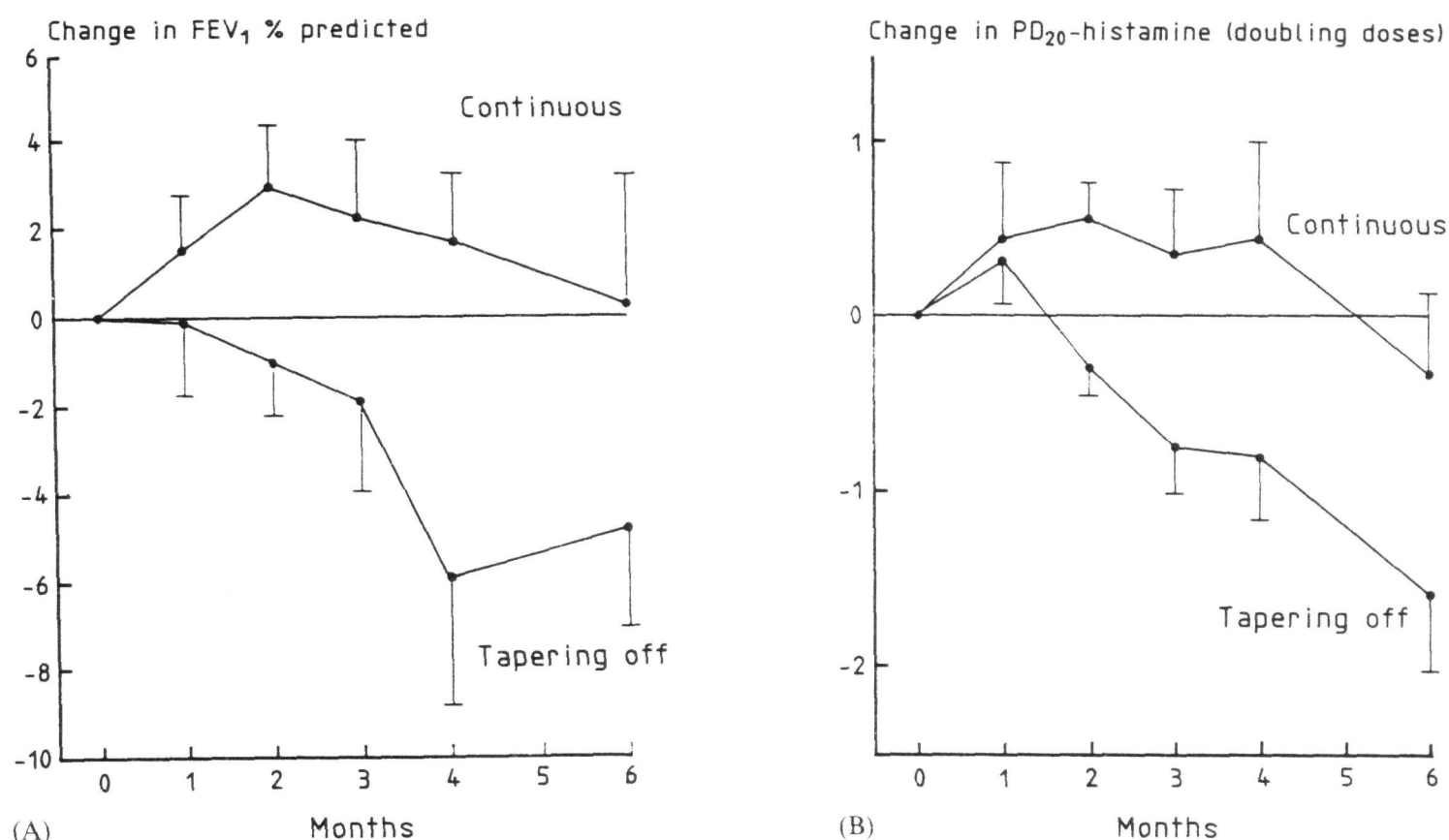


Fig. 1. Effect of gradual reduction of inhaled steroids on FEV₁ (A) and airway responsiveness (B) in asthmatic children (from Waalkens et al. [108] with permission).

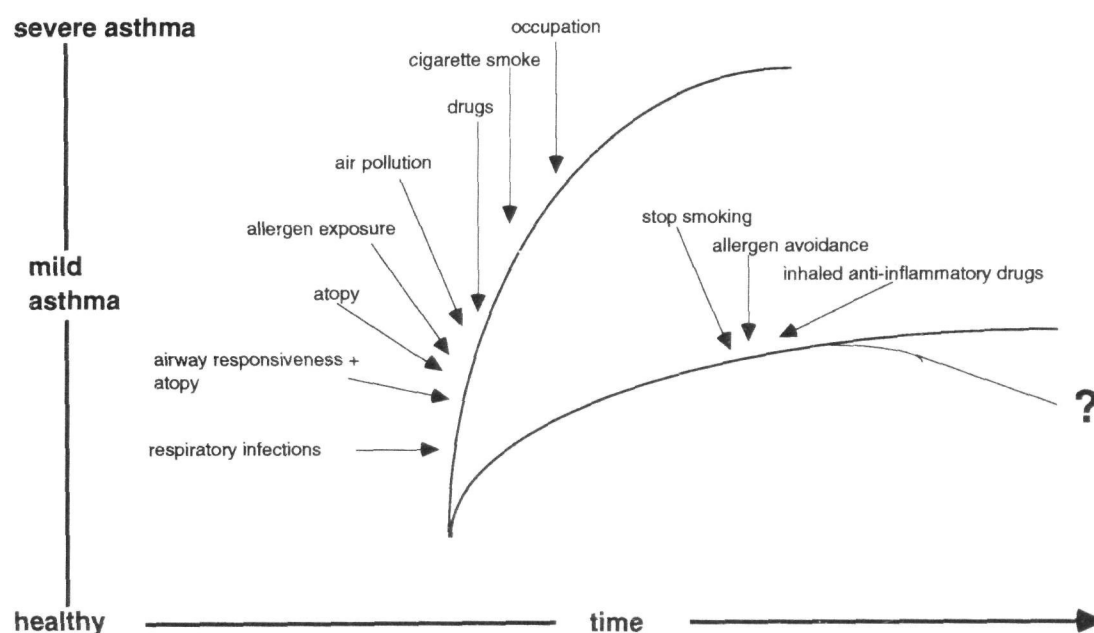


Fig. 2. Effect of various factors on progression of asthma.

inflammation, masking of the ongoing lung-function deterioration by relieving symptoms almost continuously, and, possibly, increase in exposure to allergens and environmental toxins. Other short-term studies show worsening of bronchial responsiveness, a result which is the opposite of the improvement in bronchial responsiveness with inhaled corticosteroids (113, 114). If these studies relate to clinical practice, they suggest that prolonged treatment with β_2 -agonists may affect the outcome of asthma negatively. However, van Schayck et al. (115) performed a follow-up study

of 4 years with 83 mildly asthmatic patients and patients with chronic bronchitis. These subjects, with a mean age of 52 years, were randomly assigned to receive either continuous or on-demand β_2 -agonists. The authors found no difference between the group who received β_2 -agonists continuously and the group who received β_2 -agonist on demand after 4 years of follow-up, with respect to annual decline in lung function (49 and 51 ml), mean morning peak-flow rate, diurnal (and week-to-week) variation in peak-flow rate, bronchial responsiveness, exacerbation rate,

and reported health. It must be determined whether these findings can be reproduced. Nevertheless, it seems reasonable to accept that anti-inflammatory therapy is the first step in treatment of asthma, from a very low age onward.

Concluding remarks

Little is known about the long-term outcome of asthma. One reason for this is the impossibility of performing a perfectly designed follow-up study, i.e., a population-based study from birth to adulthood and senescence, including all important measurements, which is large enough to analyze. Another reason that little is known about the prognosis of asthma is the differences in study design that make results seem contradictory at first sight.

Some key conclusions can be made:

- 1) Asthma is generally a benign disease with a good prognosis.
- 2) Persistent wheeze suggests a deterioration in lung function.
- 3) Disappearance of symptoms in adults does not indicate remission or cure of asthma.
- 4) A better FEV₁ and level of bronchial responsiveness in childhood are important factors in determining that a patient will outgrow asthma.
- 5) Delay in administration of anti-inflammatory drugs may result in irreversible damage of the airways.
- 6) Next to optimal anti-inflammatory drugs, optimal allergen, environmental toxin, and tobacco smoke avoidance may improve the course of asthma (Fig. 2).

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