

Risk Factors for Onset of Asthma*

A 12-Year Prospective Follow-up Study

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Background: Asthma development and prognosis have been studied extensively in at-risk populations, but knowledge of the natural history of asthma in the general population is limited. **Objective:** To describe the incidence and remission of asthma and its predictors, data from a 12-year follow-up study of a random population sample (n = 291; age range, 7 to 17 years) at enrollment, were analyzed.

Methods: The sample was examined in 1986 and in 1998. A case history, including data on asthma, allergic diseases, and lifestyle factors, was obtained by questionnaire and interview. Airway hyperresponsiveness (AHR) to histamine, lung function, and skin-prick test reactivity to a standard panel of 10 aeroallergens were measured.

Results: The point prevalence of asthma increased from 4.1% at the first survey to 11.7% at follow-up, at which point 19.6% of the sample had ever experienced asthma symptoms. Of the subjects with ever-asthma, 40% had remitted at follow-up. Asthma developed in 45 subjects (16.1%) during the follow-up period, which was predicted by the following factors: wheezing in childhood (odds ratio [OR], 3.61; 95% confidence interval [CI], 1.34 to 9.75), AHR (OR, 4.94; 95% CI, 2.42 to 10.08), allergic sensitization to house dust mites (OR, 3.23; 95% CI, 1.00 to 10.40), and dermatitis (OR, 2.94; 95% CI, 1.22 to 7.11). The simultaneous presence of more than one of these risk factors was associated with a high probability of developing asthma at follow-up (61.5%). In subjects without any risk factors, such as AHR, allergic sensitization, rhinitis, dermatitis or wheezing in childhood; paternal/maternal allergy, or asthma, asthma developed in only 4% during follow-up.

Conclusion: The presence of AHR and concomitant atopic manifestations in childhood increase the risk of developing asthma in adulthood, and should be recognized as markers of prognostic significance, whereas the absence of these manifestations predicts a very low risk of future asthma. (CHEST 2006; 129:309–316)

Key words: allergy; asthma; bronchial reactivity; epidemiology (pulmonary)

Abbreviations: AHR = airway hyperresponsiveness; CI = confidence interval; EF = etiologic fraction; HDM = house dust mite; OR = odds ratio; RR = relative risk; SPT = skin prick test

Many risk factors for asthma development have been identified, particularly in “high-risk” populations, but the natural history of asthma incidence and remission, and its determinants in the general

population have been described less well, as only few prospective studies^{1–5} of asthma in random population samples have been published.

Asthma has been linked to the presence of airway

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hyperresponsiveness (AHR), atopy, and rhinitis in cross-sectional studies,^{4–10} but our knowledge about the impact of these factors on asthma development over time is limited. Increasing evidence for the interaction between upper and lower airways in the development and severity of asthma and rhinitis has led to the suggestion of the term *united airways*, where upper and lower airways are seen as an immunopathologic entity.¹¹

Knowledge of the prognostic significance of concomitant atopic manifestations is at present limited, although some evidence has suggested that the presence of more than one atopic manifestation strongly increases the risk of having asthma in adulthood.⁶ But whether more than one atopic manifestation in nonasthmatic persons increases the risk of developing new asthma during adolescence and adulthood is at this time not known.

In a clinical setting, knowledge of the relative impact of the presence of AHR and other atopic manifestations on the risk of developing asthma is essential in aiding decision making about therapeutic and prophylactic interventions. Based on data from a longitudinal study of a random population sample, we have examined the incidence and remission of asthma from childhood to adulthood, and have evaluated predictive factors for incident asthma.

MATERIALS AND METHODS

A random sample of 983 children and adolescents (mean age, 12 years; age range, 7 to 17 years) living in Copenhagen, Denmark, was drawn from the civil registration list in 1986, and these subjects were invited to participate in the present study. All subjects were invited to a survey in 1986 and 1998 by letter. Of the 983 subjects, 527 (54%) participated in the first survey and 633 (64%) participated in the second survey. A total of 291 subjects (30%) participated in both surveys. Only data for these 291 subjects are included in the present analysis. Risk factors obtained in 1986 were used in the logistic regression model to predict the onset of new asthma during follow-up.

Responders and nonresponders were compared with regard to the prevalence of asthma, asthma-related factors, and potential risk factors associated with asthma at baseline in order to describe any potential bias introduced by the low response rate, a subject that has also been addressed in a previous article.¹² No significant differences were found between responders and nonresponders with regard to anthropometric data, pulmonary function, AHR, and allergic diseases, indicating that the subjects in the present analysis are representative of the entire sample.

Exclusion Criteria

In case the participants were receiving medication for the treatment of asthma and allergy, they were asked not to use theophylline or an antihistamine for at least 24 h, or astemizole for 6 weeks. Therapy with short-acting inhaled bronchodilators should be discontinued for 12 h, and long-acting bronchodilators

for 24 h. Participants were allowed to continue the use of any inhaled or oral corticosteroid they had been taking.

Case History

All participants were examined in the study clinic at both surveys. The participants and, if present, their parents, were interviewed about respiratory and allergic symptoms as related to themselves and their parents, current and former smoking habits, drinking habits, pet keeping, education, present job, family size, and physical activities.

Furthermore, all participants filled out a questionnaire about asthmatic (see below) and allergic symptoms, *ie*, rhinitis (sneezing, running or blocked nose not associated with a cold) and eczema (an itchy dry rash on face, arms or legs). Wheezy bronchitis was defined as a history of breathing difficulties triggered by a respiratory tract infection before the age of 2 years.

The questionnaire concerning respiratory symptoms and the definition of asthma were adopted from studies by the American Thoracic Society, the Division of Lung Disease of the National Heart, Lung, and Blood Institute,^{13,14} and Hopp et al.^{15,16} Asthma was defined on the basis of positive responses to one of the following questions: (1) does your breathing ever sound wheezy or whistling?; (2) do you have attacks of shortness of breath with wheezing?; (3) do you experience wheezing, chest tightness, cough, and breathlessness at rest, with exertion, with emotional stress, with exposure to cold air, or with chest infections or head cold?; and (4) do you experience wheezing after exposure to dust, fumes, mold, pollen, food, pets or drugs? Current asthma was defined as symptoms of asthma within the preceding 12 months.¹⁶

The data on asthma incidence and prevalence used in the present analysis were obtained in 1986 and 1998, where all participants were asked about current and previous asthma symptoms. From this information, the number of new cases as well as the number of remitted cases during follow-up were determined.

Skin-Prick Test

All participants had a skin-prick test (SPT) performed with a standard panel of the following 10 common aeroallergens in Denmark: birch; grass; mugwort; horse; dog; cat; house dust mite (HDM) [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*]; *Cladosporium herbarium*; and *Alternaria iridis* (ALK-Abello; Hørsholm, Denmark). A wheal diameter (calculated as $[d1 + d2]/2$) of at least 3 mm was recorded as a positive response. Identical allergens and procedures were used at each of the three surveys, and atopy was defined as a positive SPT response to at least 1 of the 10 allergens.

Pulmonary Function Test

The FEV₁ and FVC were measured using a 7-L dry wedge spirometer (Vitalograph; Buckingham, UK), which was calibrated weekly. Each measurement consisted of at least three maximal expiratory maneuvers from total lung capacity to residual volume with a variation of < 5%. The highest FEV₁ and FVC values were used in the analysis.

Histamine Challenge Test

Airway responsiveness to inhaled histamine was measured using the method described by Cockcroft et al.¹⁷ at all three examinations. Aerosols of the test solution were generated by a Wright nebulizer (Aerosol Products Ltd; London, UK). The first aerosol was a saline solution (0.9%), followed by increasing

concentrations of histamine (0.075 to 8.0 mg/mL in the first survey, and up to 16.0 mg/mL in the second and third surveys). The test was terminated when a decline of $\geq 20\%$ in FEV₁ occurred or after inhalation of the highest concentration. The histamine concentration provoking a decrease in FEV₁ of exactly 20% from baseline was calculated by linear interpolation from the individual log-dose response curve.¹⁵ A positive test was defined as a decrease in FEV₁ of exactly 20% from baseline of < 8 mg/mL in the first survey of smaller children, and < 16.0 mg/mL histamine (*ie*, AHR) in the second survey. Pregnant and lactating women were excluded from the histamine challenge test.

Statistical Analysis

The data were analyzed using a statistical software package (SPSS, version 10.1; SPSS; Chicago, IL). Differences between responders and nonresponders with regard to the prevalence of asthma and risk factors were tested using χ^2 analysis. Furthermore, χ^2 analysis was used to assess significant differences between the frequencies of risk factors in subjects with asthma vs subjects without asthma during follow-up.

In an analysis of risk factors for new asthma during follow-up, only data for the 279 subjects who were without signs or symptoms of asthma at baseline were used. Each risk factor was primarily assessed separately in a univariate analysis. Risk factors found to be significant in the univariate analysis ($p < 0.05$) were subsequently compared two-by-two in χ^2 tests, where no statistically significant interactions were found. In order to test for any significant effect modifications between the effect of any included variable and that of any other included variable on the outcome, we performed formal statistical tests for primary interaction by generating interaction terms (*eg*, AHR/allergy to HDM; AHR/wheezing in childhood; AHR/dermatitis; and allergy to HDM/wheezing in childhood) and using them as covariates in addition to the main effects (*ie*, AHR, wheezing in childhood, allergy to HDM, and dermatitis) on the independent variable (*ie*, new asthma during follow-up). No modification was observed between the effect of any included variable and that of any other included variable on the outcome.

To identify those variables that were independent predictors of new asthma, significant variables ($p < 0.05$) were subsequently assessed simultaneously in a multivariable logistic regression analysis using backward elimination. To investigate the impact of the simultaneous presence of more than one risk factor that was found to be statistically significant in the multivariate analysis, we created an index describing the number of risk factors present in a subject, where 0 indicated no risk factors, 1 indicated one risk factor, and 2 indicated two or more risk factors. Logistic regression analysis was used to calculate the odds ratios (ORs) for new asthma according to the number of risk factors. The etiologic fraction (EF) [*ie*, attributable risk; the number of cases that can be explained by the presence of a given risk factor] was calculated for the risk factors found to be statistically significant in the multivariable analysis, using the following equation: $EF = (E + [RR - 1]) / (E + [RR - 1] + 1)$, where RR is the relative risk for each risk factor and E+ is the fraction of subjects in the population with the given risk factor. The RRs used for this analysis were calculated from the OR obtained in the regression analysis, by using the following equation described by Zhang and Ju¹⁹: $RR = OR / ([1 - P_0] + [P_0 \times OR])$, where P₀ is the incidence of asthma among subjects who did not have a given risk factor at baseline. As an example of this calculation, the RR for asthma in subjects with AHR as calculated from the adjusted OR was 3.49 (*ie*, $4.9 / ([1 - 0.104] + [0.104 \times 4.9])$). Accordingly, the adjusted EF was 0.37 (*ie*, $[(0.237(3.49 - 1)) / (0.237(3.49 - 1) + 1)]$).

RESULTS

Population Characteristics

Complete data were available for 291 subjects, of whom 57% were women. No significant differences were observed in the baseline characteristics of responders and nonresponders (Table 1).

Table 2 depicts the presence of potential risk factors for asthma in the entire population as well as according to asthma status at follow-up. The group in which asthma developed during follow-up had a higher frequency of wheezing during childhood as well as AHR, atopy to HDMs, and dermatitis at baseline compared to the group in which asthma did not develop (Table 2). Furthermore, 93% of new asthmatic patients (42 of 45 patients) compared to 48% of never-asthmatic patients (112 of 234 patients) had one or more of the following characteristics at baseline: AHR; allergic sensitization; rhinitis; dermatitis or wheezing in childhood; and paternal or maternal allergy or asthma.

Prevalence, Incidence, and Remission of Asthma

In the 291 subjects who participated in both surveys, the point prevalence of asthma was 4.1% ($n = 12$) at baseline and increased to 11.6% ($n = 34$) at follow-up, at which point 19.6% of subjects ($n = 57$) had experienced asthma symptoms at some time. Forty-five new cases of asthma (16.1%) developed during the follow-up period. In some of these subjects ($n = 21$), as well as in two of the subjects with asthma at baseline, asthma symptoms had remitted at follow-up, resulting in 23 cases of remitted asthma at follow-up. This was equivalent to 40% of all asthma cases (23 of 57 subjects) and 7.9% of all 291 subjects (23 of 291 subjects).

Table 1—Baseline Characteristics in a Random Population Sample of 527 Subjects, According to Responder Status at a 12-yr Follow-up*

Variables	Responders (n = 291)	Nonresponders (n = 236)	p Value
Female gender	57.0	49.6	0.21
Age, yr	12.4 (2.9)	12.6 (3.1)	0.67
BMI, kg/m ²	17.6(2.7)	18.9(3.2)	0.45
Wheezing in early childhood	10.1	7.2	0.11
AHR	23.7	21.6	0.59
FEV ₁ , % predicted	90.3 (10.6)	91.4 (9.4)	0.66
Asthma	4.1	4.4	0.68
Positive SPT response†	24.7	30.0	0.09
Rhinitis (ever)	13.1	10.2	0.16
Dermatitis (ever)	5.8	8.2	0.19

*Values are given as % or mean (SD), unless otherwise indicated.

†A positive SPT response to at least 1 of 10 aeroallergens in a standard test panel.

Table 2—Baseline Characteristics in 279 Nonasthmatic Subjects Observed From Age 7 to 17 yr to 19 to 29 yr According to Asthma Status at Follow-up*

Variables	New Asthma, % (n = 45)	Never-Asthma, % (n = 234)	p Value
Female gender	66.7	55.1	0.15
Passive smoking in childhood	75.6	62.8	0.10
Parental allergy	14.3	19.7	0.43
Parental asthma	15.6	12.8	0.62
Wheezing in childhood	17.8	6.5	0.01
AHR	48.9	15.4	0.000
Pets in childhood	71.1	66.7	0.56
Rhinitis (ever)	17.8	11.5	0.25
Positive SPT response†	33.3	20.5	0.06
HDM atopy	24.4	9.0	0.003
Dermatitis (ever)	13.3	3.8	0.01

*Values are given as %, unless otherwise indicated.

†See Table 1 for a definition.

The asthma prevalence was comparable in responders and nonresponders: At baseline, the asthma prevalence was 4.4% of the 236 subjects (10 subjects) who had dropped out of the study at follow-up, and 4.2% of the entire group of 527 subjects (22 subjects) who participated at this survey. At follow-up, the prevalence of asthma was 9.9% of the 342 subjects (34 subjects) who only participated in 1998 and 10.7% of the entire group of 624 subjects (68 subjects) who participated in 1998.

Risk Factors for New Asthma During Follow-up

Potential risk factors for developing asthma during follow-up were primarily analyzed separately in a univariate logistic regression analysis. To determine

the independent effect of each risk factor, a multivariable analysis including all four factors found to be statistically significant in the univariate analysis was subsequently performed (Table 3). Prior to this, any potential confounding or mediating effect introduced by correlations between these risk factors was tested and excluded.

The multivariable analysis showed that among subjects without asthma at baseline, wheezing in early childhood increased the risk of the development of asthma during follow-up (OR, 3.6; 95% confidence interval [CI], 1.3 to 9.8). Subjects with AHR at baseline had a 4.9 times (95% CI, 2.4 to 10.1) increased risk of the subsequent development of asthma compared to subjects without AHR. Dermatitis as well as allergic sensitization to HDMs also increased the risk of asthma developing (dermatitis: OR, 3.2; 95% CI, 1.0 to 10.4; allergic sensitization: OR, 2.9; 95% CI, 1.2 to 7.1).

At least one of these factors was found in 99 of the 279 subjects (36%) without asthma at the time of study inclusion, and asthma developed in 30 of these 99 subjects (30%) during follow-up. Accordingly, 30 of the 45 subjects with new cases of asthma (67%) had at least one of these four risk factors prior to the development of asthma.

Impact of Concomitant Risk Factors on the Risk of Asthma Development

In order to assess the impact of the simultaneous presence of significant risk factors on the risk of the development of new asthma during follow-up, an index for the number of risk factors present in the same subject (*ie*, AHR, atopy to HDMs, dermatitis, and wheezing in childhood) was created. In subjects

Table 3—Risk Factors for New Asthma Development at 12-yr of Follow-up in 279 Nonasthmatic Subjects With Univariate and Multivariable Logistic Regression Analysis

Variables	Univariate Analysis				Multivariable Analysis*		
	% (No.)†	OR	95% CI	p Value	OR	95% CI	p Value
Male gender	12.5 (15/120)	0.6	0.3–1.2	0.15			
Age < 13 yr‡	17.5 (24/137)	1.2	0.7–2.0	0.62			
Passive smoking in childhood	18.8 (34/181)	1.8	0.9–3.8	0.10			
Parental allergy	11.9 (5/42)	0.7	0.3–1.9	0.45			
Parental asthma	18.9 (7/37)	1.3	0.5–3.1	0.62			
Wheezing in childhood	38.8 (8/23)	3.1	1.2–7.9	0.01	3.6	1.3–9.8	0.01
AHR	37.9 (22/58)	5.3	2.7–10.4	0.00	4.9	2.4–10.1	0.00
Pets in childhood	18.1 (39/215)	2.1	0.9–5.3	0.07			
Rhinitis (ever)	22.9 (8/35)	1.7	0.7–3.9	0.25			
Positive SPT response	23.6 (15/63)	1.9	1.0–3.9	0.06			
HDM atopy	34.4 (11/32)	3.3	1.5–7.4	0.00	2.9	1.2–7.1	0.02
Dermatitis (ever)	40 (6/15)	3.9	1.3–11.4	0.01	3.2	1.2–10.5	0.05

*Only factors with p values < 0.05 were included in the multivariable analysis.

†Values are given as % with new asthma during follow-up (No. of new asthma cases/No. of exposed cases).

‡At study inclusion.

with two or more of any of the assessed risk factors, asthma developed in 61.5% of subjects during follow-up compared to 8.4% of subjects with none of these risk factors (OR, 17.4; 95% CI, 6.7 to 45.0; $p = 0.000$).

In comparison, asthma developed in 18.7% of subjects with one of the assessed risk factors during follow-up (OR, 2.5; 95% CI, 1.1 to 5.5; $p = 0.02$). As no significant interactions were observed among the four risk factors, the OR for two or more risk factors represents an additive effect rather than a multiplicative effect.

The data presented in Table 2 show that the risk factors of interest (*eg*, AHR) were also relatively common in the group of subjects who had never experienced asthma at the time of follow-up. However, the negative predictive value of the absence of these factors was high. Of the 279 subjects without asthma at baseline, 77 subjects did not have any of the following conditions: parental allergy; parental asthma; wheezing in early childhood; AHR; allergic sensitization; and symptoms of rhinitis or dermatitis. In these 77 subjects, only 3 (4%) had experienced asthma during follow-up.

EF

In order to estimate the number of cases attributable to the significant risk factors, the EFs were calculated for each of these factors: The presence of AHR at baseline accounted for 37% of new asthma cases at follow-up (EF, 0.37), whereas wheezing in childhood accounted for 13% of new cases (EF, 0.13), allergy to HDMs accounted for 13% (EF, 0.13), and dermatitis accounted for 8% (EF, 0.08) of new asthma cases.

DISCUSSION

Major Findings

In this unselected population sample of children and adolescents, one of five individuals had asthma at some point over a 12-year follow-up period from 7 to 17 years of age to 19 to 29 years of age, of whom 40% were in remission at the latest follow-up. New-onset asthma during follow-up was independently predicted by the presence of AHR, allergic sensitization to HDMs, and dermatitis at baseline, as well as by reported wheezing in early childhood. Furthermore, asthma developed in two thirds of subjects who reported more than one of these factors. The absence of a family history of asthma or allergy, wheezing in early childhood, and AHR, allergic sensitization, rhinitis, or dermatitis at baseline predicted a very low risk of subsequent asthma.

Strengths and Limitations

Relatively few prospective follow-up studies of asthma from childhood and adolescence into adulthood in random population samples have been performed, as most existing data describe the development and prognosis of asthma in populations with an expected increased risk of asthma, such as children of asthmatic or atopic parents.^{1–10,20} Furthermore, some of these studies have not differentiated between new asthma cases and persistent asthma cases at follow-up, as the outcome used in some of these studies has been asthma prevalence at follow-up rather than the number of incident cases during follow-up.^{6,20} In order to predict factors of importance for the future development of asthma in an individual, it is essential to analyze factors that were present before the development of asthma symptoms. In the present study, we analyzed predictors of new cases of asthma during follow-up. The findings of the present study describe the natural history of asthma development in a random population sample of children and adolescents followed up for a period of 12 years and gives an indication of the predictive value of risk factors such as AHR, allergic sensitization, rhinitis, and dermatitis on the development of asthma over time in a general population.

A limitation of the present study may be the relatively high dropout rate from the first to the subsequent surveys, which could lead to an underestimation of the true incidence of asthma. However, the asthma prevalence was similar between subjects participating in both surveys, and subjects participating in only one of the surveys, indicating that this was not the case. Likewise, the presence of the assessed risk factors was similar in subjects participating in both surveys compared to dropouts. Another limitation of the study was the relatively low sample size resulting from the high dropout rate, thus reducing the statistical power to show a significant impact of potential risk factors.

Risk Factors for Asthma Development

Wheezing: Asthma developed during follow-up in a substantial proportion of subjects (35%) who wheezed in early childhood (*ie*, before the age of 2 years), but who were asymptomatic between 7 and 17 years of age. Our findings indicate that subjects who wheeze as infants, but who are subsequently asymptomatic in later childhood, are still at an increased risk of asthma development at some point.

Prospective evidence on early wheezing as a risk factor for adult asthma is sparse. The British Birth Cohort study⁴ assessed wheezing in childhood retrospectively in subjects at 7 years of age, and subsequently found that in adult wheezers who had

wheezed during childhood a large proportion (57%) had been asymptomatic during a large proportion of adolescence, suggesting that a propensity to wheeze is probably a lifelong characteristic in asthmatic persons that may be intermittently expressed.

The Tucson studies⁵ prospectively showed that approximately two thirds of early wheezers subsequently remit, as these “transient wheezers” were asymptomatic at the age of 16 years. We found that at the ages of 19 to 29 years 50% of all early wheezers had experienced asthma symptoms later in life, suggesting that the prognosis of transient wheezing is possibly less benign than has been indicated by childhood studies. Furthermore, it is interesting that almost half of the cases of asthma that developed in early wheezers occurred after the age range of 7 to 17 years. Although wheezing in early childhood increased the risk of subsequent asthma in adulthood, only 13% of new asthma cases during follow-up could be ascribed to early wheezing.

AHR: Asymptomatic AHR to direct agents such as methacholine has previously been shown to predict onset of wheezing later in life. In the New Zealand birth cohort,² 67% of children with asymptomatic AHR to methacholine reported wheezing at the age of 26 years. In the Belmont cohort⁶ of 718 school children, AHR was an independent predictor of current wheezing in adulthood in a sample of school-children who were followed up from ages 8 to 10 years to ages 23 to 25 years. However, when analyzing new cases of asthma during follow-up, AHR in childhood did not predict the late onset of wheezing.³

Still, it is a matter of some controversy whether testing for AHR should be used to screen for subjects who are at risk for asthma. An often-used argument against using AHR for screening has been that AHR is rarely present before the onset of symptoms, but also that asthma symptoms never develop in a substantial number of subjects with AHR. Furthermore, it is still unclear which characteristics define subjects who are at increased risk of the development of asthma in a population with asymptomatic AHR.²¹ We found that AHR was present in one of two subjects prior to the development of asthma, and that asthma developed during the 12-year follow-up period in 40% of subjects with asymptomatic AHR at baseline. Furthermore, we found that in the present population, more than one third of new cases of asthma could be attributed to AHR. In the New Zealand birth cohort,² 95.2% of subjects with AHR at 9 years of age had experienced wheezing at some point during the subsequent 17 years, suggesting that asthma symptoms will occur in most subjects with AHR given a long enough period of observation.

AHR is frequently observed in subjects with allergic rhinitis, and it is a matter of controversy whether AHR is a characteristic of upper airway allergy or a marker of increased risk of asthma in these subjects. One study²² observed 28 children with allergic rhinitis for 7 years and found that AHR to methacholine did not increase the risk of asthma development in this particular group of subjects. From these findings, it was concluded that the high prevalence of AHR seen in allergic patients is not a predictor of asthma development.²² Our findings suggest the opposite, as both AHR and allergy to HDMs were independent predictors of asthma. Furthermore, the presence of AHR in subjects with allergy to HDMs further increased the risk of developing asthma compared with the presence of only one of these two factors. We would therefore argue that AHR in allergic subjects is indeed a marker of an increased risk of developing asthma, and that the effect of AHR in allergy is additive, resulting in a high risk of the development of asthma in subjects with both features.

Atopy to HDM: The presence of atopy has previously been associated with subsequent asthma development in children and adolescents.^{3,23–26} In the Belmont study,³ having atopy at 8 to 12 years of age was a significant risk factor for the onset of wheeze by 16 to 18 years of age. Sensitization to perennial allergens in particular seems to be associated with asthma development.²⁷ In the present study, allergy to HDMs predicted subsequent asthma symptoms, albeit with a relatively low EF. Allergy to any one of 10 aeroallergens in a standard panel tended to increase the risk of asthma only during follow-up, which was possibly due to the limited power of the low sample size.

Dermatitis: The longitudinal association between dermatitis and subsequent asthma is in keeping with previous observations from the British Birth Cohort.⁴ Although 40% of subjects with “dermatitis ever” at baseline had experienced asthma during follow-up, only 9% of new asthma cases during follow-up could be attributed to the presence of dermatitis at baseline, suggesting that dermatitis is a relatively uncommon predictor of asthma.

Concomitant Atopic Manifestations

Toelle et al⁶ addressed the question of whether the concomitant presence of several atopic manifestations increases the risk of asthma more than the presence of a single factor. They⁶ found a strong additive effect of atopy, rhinitis, AHR, and airway obstruction in childhood on the risk of current

asthma symptoms in adulthood in subjects with and without asthma in childhood.

We found a similar additive effect of atopic manifestations and AHR on the risk of developing new asthma, suggesting that high-risk individuals may be identified by the presence of more than one of these factors before the onset of asthma symptoms. As an example of the clinical applicability of this finding, it might be relevant to test for AHR in subjects with a positive SPT response to determine the need for interventional measures such as immunotherapy, although evidence on the preventive effect of intervention on asthma development in these subjects is still sparse.²⁸

Subjects without any of the assessed potential predictors of asthma, such as a family history of asthma, atopic manifestations, or AHR, had a very low risk for the development of asthma, suggesting that some sign of a tendency toward atopic disease will be apparent in late childhood or in the teenage years in most subjects in whom asthma develops, and that in those subjects in whom there are no such signs the development of asthma in subsequent years is a very rare occurrence.

Our findings confirm the longitudinal relationship between the manifestations of atopic disorders in different organ systems and asthma development. If atopic disorders such as allergic sensitization, asthma, rhinitis, and dermatitis were indeed different manifestations of the same systemic disease, it could explain how the combined presence of these manifestations seems to be an indication of more severe disease and of a higher risk of developing further manifestations such as asthma. Furthermore, the predictive values of AHR as well as that of atopic manifestations for the subsequent development of asthma were remarkably high, indicating that a more intensive interventional approach is required in this group of patients.

In conclusion, wheezing in early childhood, AHR, allergic sensitization to HDMs, and a history of atopic dermatitis all independently increase the risk of the development of asthma in adulthood. In particular, the presence of more than one of these factors in the same subjects should be recognized as markers of prognostic significance. The absence of any of these manifestations furthermore predicts a very low risk of future asthma.

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