The natural course of atopic dermatitis from birth to age 7 years and the association with asthma

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Background: Atopic dermatitis (AD) is considered to be one of the first manifestations in the atopic march. However, few prospective studies on AD and its association with childhood asthma exist.

Objective: The aim of this study was to prospectively investigate the natural course of AD to determine factors influencing its prognosis and to analyze the relationship of AD with childhood asthma.

Methods: The Multicenter Allergy Study, a German birth cohort, followed 1314 children from birth to age 7 years. Physical examinations, parental interviews on atopic symptoms and diagnoses, and determination of specific IgE levels were performed regularly.

Results: The cumulative prevalence of AD in the first 2 years of life was 21.5%. Of these children with early AD, 43.2% were in complete remission by age 3 years, 38.3% had an intermittent pattern of disease, and 18.7% had symptoms of AD every year. Severity (adjusted cumulative odds ratio, 5.86; 95% CI, 3.04-11.29) and atopic sensitization (adjusted cumulative odds ratio, 2.76; 95% CI, 1.29-5.91) were major determinants of prognosis. Early wheeze and a specific sensitization pattern were significant predictors for wheezing at school age, irrespective of AD. Early AD without these cofactors constituted no increased risk of subsequent wheeze (adjusted odds ratio, 1.11; 95% CI, 0.56-2.20) or bronchial hyperreactivity.

Conclusion: AD is a common condition in infancy but disappears around age 3 years in a significant proportion of children. The prognosis is mostly determined by the severity and the presence of atopic sensitization. Early AD is associated with asthma at school age, but in many of these asthmatic children, wheezing manifests before or with the onset of AD. Children with AD and wheeze have a marked loss in lung function, suggesting a distinct phenotype rather than a progressive development from AD to asthma. (J Allergy Clin Immunol 2004;113:925-31.)

Key words: *Atopic dermatitis, natural course, prognosis, asthma, sensitization, childhood, atopic march*

Atopic dermatitis (AD) is the most common inflammatory skin disease in childhood, often manifesting in early infancy and with a natural course varying considerably over time.[1] Early manifestation of AD has been observed to be associated with an increased risk of asthma[2,3] and is thus regarded as one of the first steps in the atopic march. However, because only few prospective studies exist that start at birth and have sufficient follow-up, little is known about the natural course of AD and the potential succession of atopic phenotypes in childhood.

The aim of this study was to investigate the natural course of early AD from birth to school age to determine factors influencing its prognosis and to analyze the association of AD with the development of asthma in a prospective birth cohort.

METHODS

Study population

The German Multicenter Atopy Study (MAS), a prospective observational birth cohort, recruited 1314 of 7609 infants born in 1990 in 6 German delivery wards in 5 German cities. A detailed description of the stratified sampling scheme and study subjects is given elsewhere.[4] Briefly, 499 newborns with risk factors for atopy (increased cord blood IgE [≥0.9 kU/L], at least 2 atopic family members, or both) and 815 newborns with none of these risk factors were included in the cohort. These children were followed up at the age of 1, 3, 6, 12, 18, and 24 months and from then on yearly within 4 weeks of the child's birthday up to the age of 7 years. Only those children who attended at least one follow-up in each of the first 2 years of life, not counting the visit at age 1 month, were included in the present analysis. The study was approved by the local ethics committee.

Parental questionnaires and interviews

In a questionnaire administered at the time of birth, atopic family history was assessed, as was the parental level of education and the child's parity. Of the questionnaire items, 11 screening conditions were chosen to define parental atopic status on the basis of a validation study in a subsample of parents.[5] Parents were regarded as atopic if they reported diagnoses or relevant symptoms of AD, asthma, allergic rhinitis, or food allergy. Parents were defined as having a higher level of education if schooling of at least one parent lasted 13 years or longer.

At each follow-up visit, parents gave structured interviews to a study physician. Foremost interest was on atopic symptoms and

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Abbreviations used
AD: Atopic dermatitis
BHR: Bronchial hyperreactivity
COR: Cumulative odds ratio
MAS: Multicenter Allergy Study
OR: Odds ratio

diseases. Furthermore, symptoms and diagnoses of other illnesses were assessed at every follow-up, as was maternal breast-feeding and feeding practices up to age 2 years. Parental smoking habits were assessed at age 1 month, and pet keeping was assessed at age 3 months. Early wheeze was defined as any wheezing in the first 3 years of life. Current wheeze at age 7 years was defined as any wheezing in the past 12 months. Infectious diseases in the first 2 years of life were categorized as lower respiratory tract infections (irrespective of the infectious agent), viral infections, bacterial infections, fungal infections, gastrointestinal infections, and fever of unknown origin.[6]

Cord blood, total, and specific IgE

Serum samples were obtained from the children at birth and at 1, 2, 3, 5, 6, and 7 years of age. Cord blood IgE, total IgE, and specific IgE antibodies to food allergens (cow's milk, egg white, soy bean, and wheat) and inhalant allergens (house dust mite [*Dermatophagoides pteronyssinus*], cat dander, mixed grass, and birch pollen) were determined by using the CAP-RAST FEIA (Pharmacia & Upjohn, Freiburg, Germany). Sensitization to a specific allergen was defined as a concentration of 0.35 kU/L or greater of the respective specific IgE (CAP I). Increased cord blood IgE was defined as a concentration of 0.9 kU/L or greater, and increased total IgE at age 2 years was defined as a concentration of 30.0 kU/L or greater.

Assessment of indoor allergen exposure

At the age of 6 months, Der p 1, Der f 1, and Fel d 1 were extracted from dust samples collected by the parents from the carpet and analyzed with a sandwich ELISA (ALK, Copenhagen, Denmark), as previously described.[7]

Lung function and bronchial histamine challenge

At the age of 7 years, lung function was measured in a subsample of 800 children by using a body plethysmograph (Master-Lab, E. Jaeger, Würzburg, Germany). In 647 of these children, a bronchial challenge was performed, starting with 0.5 to 8.0 mg/mL histamine according to a standard procedure.[8] The 90th percentile of the distribution of $PC_{20}FEV_1$ in a healthy subsample equaled 0.85 mg/mL. Bronchial hyperreactivity (BHR) was defined as a $PC_{20}FEV_1$ of greater than this value.

Definition of AD (also see e-text in the Journal's Online Repository at www.mosby.com/jaci)

AD was defined as present if at least one of the following applied: (1) reported diagnosis by the family physician, (2) parental reporting of symptoms of AD, and (3) visible AD at the time of follow-up. Early manifestation of AD was defined as onset of disease in the first 2 years of life, and severity of early AD was assessed on the basis of parental reporting of the frequency of child's scratching. An ordinal variable combining early AD and the frequency of scratching was used as the outcome variable. Furthermore, an objective severity score was assessed during the skin examination at age 2 years. At age 7 years, children with early AD were grouped into 3 disease patterns: the group with complete remission after age 2 years comprised those children who showed no AD after the age of 2 years; children with AD at every follow-up until age 7 years were categorized as having persistent AD; and all children with early AD fulfilling neither of these criteria were categorized as having intermittent AD.

Statistical analysis (see e-text in the Journal's Online Repository at www.mosby.com/jaci)

χ^2 Tests were used to compare prevalences between groups, Welch ANOVA was used to analyze the severity score, and *t* tests were used to analyze lung function. The effects of early childhood factors on early AD and on the prognosis of early AD were analyzed by using cumulative logistic regression analyses; results are expressed as crude and adjusted cumulative odds ratios (CORs). The proportional odds assumption was tested and found to be tenable in most cases. If the assumption was not tenable, a binary logistic regression model was calculated for the dichotomous outcome variable of disease versus no disease. For statistical analysis, allergen exposure, age at introduction of solid food, and the number of infections were categorized according to the quartiles in the total MAS population. Furthermore, unadjusted and adjusted logistic regression models were calculated to evaluate the independent role of early AD, early wheeze, and type of atopic sensitization on the outcome of wheeze and BHR at age 7 years. SAS software (version 8.02) was used for all statistical analyses.

RESULTS

Response rates (see e-text in the Journal's Online Repository at www.mosby.com/jaci)

Of the 1314 children in the MAS birth cohort, 1123 (85.5%) children participated in at least one follow-up in each of the first 2 years of life. Of these 1123 children, 665 (59.2%) participated in blood sampling at age 2 years, and 858 (76.4%) had complete data on the course of AD up to the age of 7 years (ie, participated in every follow-up).

Early manifestation of AD

Of the 1123 MAS children included in the present analyses, 13.4% had AD in the first year of life. By age 2 years, the lifetime prevalence amounted to 21.5% (241/1123). Of these 241 children with early manifestation of AD, 35.3% reported no concurrent scratching, 31.5% reported infrequent scratching, and 33.2% reported frequent or very frequent scratching. Parental reporting of scratching as a measure of the period prevalence of disease severity in the first 2 years of life correlated well with the severity score at the 2-year follow-up (mean ± SD: 1.9 ± 5.8, 4.8 ± 9.4, and 14.4 ± 14.5 for no, infrequent, and frequent scratching, respectively; $P < .001$).

Parental atopy was significantly associated with the manifestation and severity of early AD, with the effect being strongest for parental AD (Table I). Furthermore, increased total and specific IgE levels at the age of 2 years showed a strong positive association with early AD, especially with the more severe form. The association of atopic sensitization and early AD was strongest for onset of sensitization in the first year of life: whereas 48 (41.0%) of 117 children with sensitization at age 1 year showed

TABLE I. Manifestation of AD in the first 2 years of life: distribution of risk factors (column percent), unadjusted and adjusted* CORs, and 95% CIs for early AD

	No AD (n = 882)	AD + no scratching (n = 85)	AD + infrequent scratching (n = 76)	AD + frequent scratching (n = 80)	COR (95% CI)	Adjusted COR* (95% CI)
Family history						
≥2 Atopic family members	171/880 (19.4%)	17/85 (20.0%)	18/75 (24.0%)	29/80 (36.2%)	1.59 (1.15-2.20)	1.43 (0.99-2.08)
Parental AD	86/873 (9.8%)	10/84 (11.9%)	11/73 (15.1%)	22/80 (27.5%)	2.20 (1.50-3.24)	1.94 (1.23-3.05)
Parental hay fever	364/880 (41.4%)	41/85 (48.2%)	36/75 (48.0%)	43/80 (53.7%)	1.43 (1.07-1.90)	1.46 (1.07-2.00)
Parental asthma	192/881 (21.8%)	19/85 (22.3%)	13/75 (17.3%)	25/80 (31.2%)	1.15 (0.82-1.60)	1.10 (0.76-1.59)
Cord blood and total IgE at age 2 y						
Increased cord blood IgE (≥0.9 kU/L)	170/848 (20.0%)	16/84 (19.0%)	13/69 (18.8%)	6/76 (7.9%)	0.69 (0.47-1.03)	0.63 (0.40-0.99)
Increased total IgE (≥30 kU/L)	188/527 (35.7%)	22/53 (41.5%)	16/40 (40.0%)	33/55 (60.0%)	1.73 (1.20-2.50)	1.93 (1.29-2.90)
Atopic sensitization at age 2 y (CAP I)						
Any sensitization	112/516 (21.7%)	11/52 (21.1%)	18/39 (46.1%)	30/53 (56.6%)	2.50 (1.69-3.71)†	2.52 (1.62-3.90)†
Any food sensitization	79/519 (15.2%)	7/52 (13.5%)	10/40 (25.0%)	23/54 (42.6%)	2.10 (1.36-3.25)†	2.28 (1.40-3.70)†
Any inhalant sensitization	55/516 (10.7%)	5/51 (9.8%)	11/39 (28.2%)	22/54 (40.7%)	3.00 (1.89-4.78)†	2.58 (1.52-4.37)†
Early wheeze	239/747 (32.0%)	25/76 (32.9%)	32/64 (50.0%)	30/70 (42.9%)	1.54 (1.13-2.10)	1.45 (1.05-2.00)

*Adjusted for 2 or more atopic family members, increased cord blood IgE, and early wheeze (excluding the respective risk factor of interest).
†Binary logistic regression model (OR/adjusted OR) was calculated for AD versus no AD because of nontenable proportional odds assumption.

early AD, this was the case in only 15 (22.7%) of 66 children with onset of sensitization in the second year of life (P = .012). In contrast to total and specific IgE, increased cord blood IgE was inversely associated with the manifestation and severity of early AD.

All other analyzed early life factors (ie, sex, breast-feeding, age at introduction of solid foods, pet keeping, level of mite and cat allergen exposure, parental smoking, maternal smoking during pregnancy, older siblings, parental education, and number of infectious diseases) did not show a significant association with the manifestation and severity of early AD (data not shown).

Prognosis of early AD (also see e-text in the Journal's Online Repository at www.mosby.com/jaci)

Of the 192 children with early manifestation of AD and complete data on the course of AD, 43.2% were in complete remission after age 2 years (Fig 1). Of these 83 children, 55.4% only had had symptoms in the first year of life. Almost one fifth (18.7%) of all children with early AD had symptoms of AD every year up to age 7 years and were thus categorized as having persistent AD. An intermittent pattern of AD up to age 7 years was observed in 38.0% of the children with early AD.

The strongest risk factor for a poor prognosis of early AD was the severity (Table II): 72.2% of the children with persistent AD reported frequent scratching with early AD, whereas this was the case in only 35.6% of the children with an intermittent pattern and in only 14.5% of the children with complete remission after age 2 years (adjusted COR, 5.86; 95% CI, 3.04-11.29).

Furthermore, early atopic sensitization played a major role for the prognosis of AD. Sensitization to food allergens, especially the less prevalent types, such as wheat (adjusted COR, 7.43; 95% CI, 2.21-25.02) and soy bean (adjusted COR, 4.46; 95% CI, 1.34-14.87) sensitization, showed the strongest associations. The magnitude of early atopic sensitization (ie, the sum of the measured concentrations of specific IgE) was strongly associated with the prognosis of AD; however, no cutoff achieved a satisfactory positive or negative predictive value for a sufficiently accurate prognosis (data not shown).

A parental history of AD was associated with the prognosis of AD, although not quite reaching statistical significance. However, a strong atopic family history, defined as 2 or more atopic family members, remained a significant predictor of poor prognosis, even in the adjusted model (adjusted COR, 2.40; 95% CI, 1.29-4.48). Furthermore, children with concomitant early wheeze had a significantly poorer prognosis. A cat in the home in early childhood increased the risk of persistent AD, although not significantly so (adjusted COR, 2.33; 95% CI, 0.85-6.38). However, when analyzing the level of cat allergen in the children's homes, no association of cat exposure and pattern of AD was observed (adjusted COR, 1.23; 95% CI, 0.44-3.39, for highest vs lowest quartile). None of the other analyzed early life factors (ie, sex, older siblings, breast-feeding, age at introduction of solid foods, dog keeping, level of mite allergen exposure, parental smoking, maternal smoking during pregnancy, parental level of education, and number of infectious diseases) showed a significant association with the prognosis of early AD (data not shown).

Children with a manifestation of disease in the first year of life did not have a poorer prognosis than children with a manifestation of disease in the second year of life: equal proportions of children with onset in the first and in the second year had complete remission, intermittent AD, and persistent AD (43.3%, 35.0%, and 21.7% with onset in the first year of life and 43.1%, 43.1%, and 13.9% with onset in the second year of life, respectively; P = .50).

Early AD and asthma

Early wheezing was fairly common in this cohort: 35.6% of all children wheezed in the first 3 years of life. As

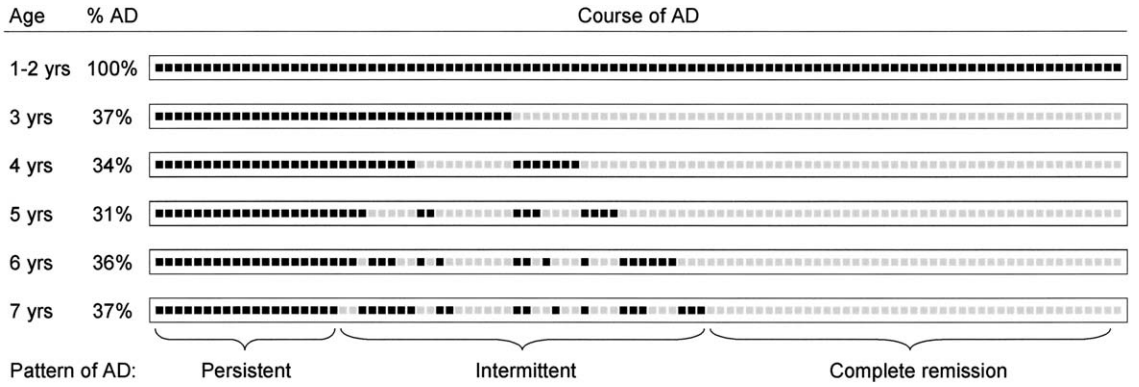

FIG 1. Natural course of AD up to age 7 years in children with early manifestation of disease (≤2 years). Each symbol represents 1% of the children with early AD, and the natural course of each 1% subsample can be traced vertically. *Filled squares* represent subjects with AD in the respective time period.

shown in Table I, the prevalence of early wheeze was significantly increased in children with early AD and infrequent or frequent scratching compared with no AD or AD without scratching (46.3% vs 32.1%, $P = .001$), potentially indicating an early comanifestation of asthmatic symptoms in individuals with moderate to severe AD. This group of children with early AD and wheeze showed a specific sensitization pattern characterized by sensitization to wheat, cat, mite, soy, or birch (ie, the less prevalent sensitization types at age 2 years; Fig E1 in the Journal's Online Repository at www.mosby.com/jaci). The notion of a distinct disease entity is further supported by the fact that children with early AD and concomitant early wheeze had significantly reduced lung function at the age of 7 years compared with children with no early AD or no early wheeze (Fig E2 in the Journal's Online Repository at www.mosby.com/jaci).

These children with early AD and concomitant wheeze were at almost 3 times the risk of having current wheeze at age 7 years as children with no early AD (adjusted odds ratio [OR], 2.84; 95% CI, 1.54-5.24). This risk was even higher in those 44.2% (23/52) of the children with early AD and concomitant wheeze who showed any of the less prevalent sensitization types at age 2 years (adjusted OR, 9.13; 95% CI 3.61-23.10 compared with no early AD). Interestingly, this effect was independent of concurrent sensitization to egg or milk. A similar, although somewhat smaller, effect of the less prevalent sensitization types was observed in nonwheezing children: those few children with AD and no concomitant wheeze who showed any of the less prevalent sensitization types (11/76) were at significantly increased risk of wheezing at age 7 years (adjusted OR, 6.68; 95% CI, 1.90-23.50 compared with no early AD). However, the majority of children with early AD and no concomitant wheeze showed no increased risk of wheezing at age 7 years compared with children with no early AD (adjusted OR, 1.11; 95%, CI 0.56-2.20). All results remained essentially unchanged when using BHR at age 7 years as the outcome.

In a multivariate regression analysis modeling the association of early life factors and asthma at age 7 years in the total study population, only the sensitization pattern and early wheeze showed a significant effect on current wheeze and BHR (Table III). Early AD, a significant independent factor in the unadjusted analysis, was no longer a significant predictor of asthma when adjusting for sensitization pattern and early wheeze. When including severity of early AD in these multivariate models, the results remained essentially unchanged: severity of AD showed no significant association with wheeze or BHR when adjusted for early wheezing, the sensitization pattern, and multiple atopic family history (data not shown).

DISCUSSION

In a large, observational, population-based birth cohort, we assessed and analyzed the manifestation and natural course of AD. Early AD, defined as onset of disease in the first 2 years of life, was a frequent phenomenon with a prevalence of 21.5%. Almost half (43.2%) of these children, however, were in remission after their second birthday. Major determinants of the prognosis of early AD were severity of disease and early atopic sensitization. Early AD was significantly associated with wheeze and BHR at age 7 years. However, the majority of children with early AD and asthmatic symptoms at age 7 years already wheezed in early childhood, indicating an early comanifestation of these atopic phenotypes rather than a progressive atopic march.

We used cumulative logistic regression analyses to analyze the data. This is important to keep in mind because the COR summarizes the effect of a specific risk factor on the ordinal outcome in one single measure. A major advantage of this method is that complex outcome variables, such as AD, need not be strictly dichotomized into diseased versus nondiseased groups but can be graduated into groups on the basis of severity of disease (ie, no, mild, moderate, and severe disease), which has the benefit of allowing for a separate category of potentially questionable cases (eg, the children with mild or intermittent AD).

TABLE II. Prognosis of early AD up to age 7 years: Distribution of risk factors (column percentage), unadjusted and adjusted* CORs, and 95% CIs for the pattern of AD

	Complete remission (n = 83)	Intermittent AD (n = 73)	Persistent AD (n = 36)	COR (95% CI)	Adjusted COR* (95% CI)
Disease severity of early AD					
Severity score at age 2 y (mean ± SD)	1.62 ± 5.57	7.64 ± 11.18	17.89 ± 14.04	1.10 (1.07-1.13)	1.10 (1.07-1.14)
Frequent scratching with early AD	12/83 (14.5%)	26/73 (35.6%)	26/36 (72.2%)	6.44 (3.45-12.02)	5.86 (3.04-11.29)
Family history					
≥2 Atopic family members	16/83 (19.3%)	23/72 (31.9%)	18/36 (50.0%)	2.73 (1.51-4.92)	2.40 (1.29-4.48)
Parental AD	9/81 (11.1%)	13/71 (18.3%)	9/36 (25.0%)	2.02 (0.99-4.15)	1.93 (0.89-4.18)
Parental hay fever	38/83 (45.8%)	41/72 (56.9%)	20/36 (55.6%)	1.43 (0.84-2.43)	1.38 (0.78-2.42)
Parental asthma	19/83 (22.9%)	14/72 (19.4%)	12/36 (33.3%)	1.29 (0.69-2.41)	1.19 (0.63-2.27)
Cord blood IgE and total IgE at age 2 y					
Increased cord blood IgE (≥0.9 kU/L)	11/80 (13.7%)	13/68 (19.1%)	2/34 (5.9%)	0.83 (0.38-1.82)	1.29 (0.52-3.19)
Increased total IgE (≥30 kU/L)	20/53 (37.7%)	24/44 (54.5%)	11/22 (50.0%)	1.63 (0.83-3.22)	1.54 (0.75-3.17)
Atopic sensitization at age 2 y (CAP I)					
Any sensitization	13/52 (25.0%)	21/42 (50.0%)	13/22 (59.1%)	3.08 (1.50-6.32)	2.76 (1.29-5.91)
Any food sensitization	7/52 (13.5%)	16/43 (37.2%)	8/22 (36.4%)	2.72 (1.24-5.93)	2.87 (1.27-6.48)
Any inhalant sensitization	8/52 (15.4%)	14/43 (32.6%)	9/22 (40.9%)	2.68 (1.23-5.84)	1.68 (0.70-4.01)
Early wheeze	24/77 (31.2%)	28/66 (42.4%)	17/32 (53.1%)	1.91 (1.08-3.39)	1.80 (1.01-3.23)

*Adjusted for 2 or more atopic family members and early wheeze (excluding the respective risk factor of interest).

The variability of the distribution of symptoms and morphology, the variability of the time course of disease, and the lack of a diagnostic test for AD constitute a major problem in defining AD. Several studies relied on objective symptoms at the time of follow-up as assessed by the study physician, whereas others used complex definitions of AD on the basis of validated diagnostic criteria (eg, by Hanifin and Rajka[9]). No matter which definition is used, drawbacks exist. One major drawback of the former is that assessment of AD at a specific time point does not take the variable time course into account, thus potentially underestimating the true prevalence. A major drawback of the latter is that several of the diagnostic criteria are not applicable in young children, whereas others are themselves factors of interest in the analysis of disease (eg, age at onset, personal history of other atopic diseases, and parental atopy).

We chose a complex definition for AD on the basis of parental reporting of symptoms and previous physician diagnoses and visible AD at the physical examination, as defined by a computer algorithm in accordance with the morphologic criteria given by Hanifin and Rajka.[9] This definition was also used in previous MAS publications on AD,[4,10,11] thus maintaining internal validity. Atopic sensitization and family history of atopy were purposely not included in the definition of AD to enable the analysis of the association of these factors with the clinical manifestation and prognosis of disease in the child. We believe this approach to be most appropriate for the study question because 40.4% of the children with early AD had no parental atopy and 59.4% had no early atopic sensitization and would have otherwise been excluded from the analysis.

To describe the course of AD after age 2 years, we defined 3 distinct disease patterns: complete remission, intermittent AD, and persistent AD. The intermittent disease pattern was defined through exclusion criteria (ie, as those children not in remission after age 2 years and not showing or reporting AD at every follow-up visit), thus comprising a wide range of disease patterns, as can be seen in Fig 1. This definition is to some extent arbitrary. However, when the prognosis of AD was studied by using the age at remission as a continuous variable, the findings remained unchanged. Significant predictors for a poor prognosis of early AD were severity of disease, atopic sensitization, early wheeze, and a strong family history, as observed in other studies.[12,13] None of the other analyzed early life factors had a significant effect on the prognosis of early AD.

Of the children with manifestation of AD in the first 2 years of life, 43.2% were in complete remission after their second birthday. This percentage is somewhat larger than that observed in a previous study by Wüthrich,[12] indicating a better prognosis than previously assumed. This might, however, be the result of 2 reasons pertaining to the definition of AD and the length of follow-up. We defined AD fairly broadly, thus including a large number of mild cases with a good prognosis, as shown by the association of severity and prognosis of disease. Other studies used more stringent definitions for AD, thus resulting in a poorer prognosis for the course of AD. Furthermore, our cohort was followed from birth to school age, whereas Wüthrich[12] presents data until adulthood. We have no information on a potential relapse of disease in adulthood for those children in remission in our cohort, and hence the prognosis in the group of children in remission by age 7 years in our cohort remains to be seen.

Our definition of early AD was based on onset of AD within the first 2 years of life because this is a frequently used time span for the definition of early manifestation of

TABLE III. Prognosis of asthma: Unadjusted and adjusted* ORs and 95% CIs for current wheeze and BHR at age 7 years

	Current wheeze (age 7 y)		BHR (age 7 y)	
	OR (95% CI)	Adjusted OR* (95% CI)	OR (95% CI)	Adjusted OR* (95% CI)
Early AD	1.93 (1.22-3.06)	1.46 (0.73-2.90)	1.61 (1.01-2.58)	1.22 (0.63-2.35)
Early wheeze	2.86 (1.81-4.51)	2.07 (1.11-3.85)	1.90 (1.20-3.00)	1.93 (1.09-3.39)
Type of atopic sensitization† (age 2 y)				
No less prevalent type + no frequent type	1.00	1.00	1.00	1.00
No less prevalent type + any frequent type	0.79 (0.27-2.32)	1.03 (0.34-3.09)	1.10 (0.50-2.39)	1.48 (0.66-3.31)
Any less prevalent type + no frequent type	5.93 (2.49-14.10)	4.50 (1.64-12.32)	4.53 (1.63-12.52)	3.53 (1.15-10.80)
Any less prevalent type + any frequent type	8.71 (4.26-17.79)	6.32 (2.83-14.10)	4.67 (2.13-10.21)	4.05 (1.71-9.57)

*Adjusted for the other variables in the table and for 2 or more atopic family members.
†Frequent types of sensitization = egg, milk, or grass; less prevalent types of sensitization = wheat, cat, mite, soy, or birch.

AD and comprises the age group with the peak incidence of AD in childhood. In contrast, the definition of early wheeze was based on onset of symptoms within the first 3 years of life, according to the definition of wheezing phenotypes by Martinez et al.[14] On the basis of these definitions, we defined early AD with any early wheezing as being concomitant or as a comanifestation of these atopic phenotypes, irrespective of the exact chronologic order of onset of these 2 phenotypes within the first years of life. This resulted in 87 children defined as having concomitant early AD and wheeze. Onset of wheeze occurred after the onset of AD in 56% of these children, onset of wheeze and AD was truly concomitant in 11% of these children, and onset of AD was preceded by the onset of wheezing in 33% of these children. Thus half of the children defined as having a comanifestation had onset of AD before or with wheeze, and half had onset of AD after wheeze. When using equal time spans for the definition of early AD and early wheeze (ie, the first 2 years of life), merely 28% of the resulting 74 children thus defined as having concomitant early AD and wheeze showed an onset of wheeze subsequent to the onset of AD. A similar proportion was observed when defining early AD and early wheeze as the onset of both phenotypes within the first 3 years of life. Thus no clear trend indicating an atopic march from AD to asthma is detectable, irrespective of the time span used for defining early AD or early wheeze.

The proportion of children with a persistent wheezing phenotype was significantly increased in children with early AD compared with children with no early AD (data not shown). In contrast, the transient wheezing phenotype was equally prevalent in both groups, again pointing toward an early comanifestation of AD and asthma. The notion of a distinct disease entity is further supported by the fact that children with early AD and concomitant wheeze differed significantly from children with no early AD or no early wheeze with respect to lung function at age 7 years and the type of atopic sensitization. In contrast, the majority of children with early AD and no concomitant wheeze were not at risk of being asthmatic at age 7 years. Only those nonwheezing children with eczema showing a sensitization pattern similar to that of wheezing children (ie, showing any of the less prevalent sensitization types of wheat, cat, mite, soy, or birch sensitization) were at increased risk of subsequent asthma. This small subgroup (1% of the total MAS study population) might thus constitute a small potential target group for intervention as previously observed in other studies of children with AD and mite sensitization in early childhood.[15,16]

Hence our study might help to clarify the association between AD and childhood asthma: rather than early AD being a risk factor for subsequent asthma in a progressive atopic march, it seems more likely that a certain phenotype exists as a coexpression of asthma and AD characterized in early life by AD plus either wheezing or a specific pattern of atopic sensitization and a more severe course, resulting in significant impairment of lung function.

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