

The pattern of atopic sensitization is associated with the development of asthma in childhood

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Background: Even though atopic sensitization has been shown to be strongly associated with childhood asthma, asthma eventually develops in only one third of atopic children.

Objective: The aim of this study was to prospectively investigate the pattern of atopic sensitization typically associated with the development of asthma in childhood.

Methods: The German Multicenter Allergy Study followed 1314 children from birth to the age of 7 years. Parental questionnaires on asthma and asthmatic symptoms were completed 6 times up to the age of 2 years and from then on yearly. Determination of specific IgE to 9 food and inhalant allergens was performed yearly, and at the age of 7 years, a bronchial histamine challenge was conducted.

Results: Onset of atopic sensitization in atopic children with current asthma at the age of 7 years was significantly earlier than in atopic children without current asthma (39.4% before age 1 year vs 21.0%, $P = .015$). Early atopic sensitization without any sensitization to inhalant allergens at the age of 7 years conferred no increased risk for asthma at this age. Only those children sensitized to any allergen early in life and sensitized to inhalant allergens by the age of 7 years were at a significantly increased risk of being asthmatic at this age (odds ratio, 10.12; 95% CI, 3.81-26.88). However, even in this group of persistently sensitized children, the risk of being asthmatic at the age of 7 years was only increased if a positive parental history of asthma or atopy was present (odds ratio, 15.56; 95% CI, 5.78-41.83), with the effect being strongest for maternal asthma.

Conclusion: Our results indicate that an underlying factor pertaining to asthma and maternal transmission may determine both a certain pattern of sensitization and the expression of asthma. (J Allergy Clin Immunol 2001;108:709-14.)

Key words: Early and persistent sensitization, asthma, childhood, atopic family history

Abbreviations used

BHR: Bronchial hyperresponsiveness

MAS: Multicenter Allergy Study

OR: Odds ratio

Atopic sensitization plays a major role in the development of asthma. Approximately two thirds of asthmatic subjects are sensitized to at least one inhalant allergen. However, even though up to 40% of children are sensitized to inhalant allergens by early school age,¹ only 25% to 30% of these will eventually have asthma. It is still unclear why this subgroup of atopic children will become asthmatic, whereas others either remain asymptomatic or even lose their atopic sensitization.

The longitudinal German Multicenter Allergy Study (MAS) is a birth cohort study with regular assessment of asthma and asthmatic symptoms and measurements of specific IgE from age 1 year up to age 7 years and thus offers the ideal data for the analysis of the association of atopic sensitization and the development of asthma in childhood in an observational, prospective setting. The aim of this study was to characterize the typical course of atopic sensitization in the development of childhood asthma and to identify factors that influence and drive the atopic march from atopic sensitization to asthma.

METHODS

Study population

The German MAS, a prospective birth cohort study, recruited 1314 newborns in 5 German cities during 1990. A detailed description of study subjects and methods is given elsewhere.² Briefly, 499 newborns with risk factors for atopy (elevated 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 study. The cohort children were followed up at the age of 1, 3, 6, 12, and 18 months and from then on yearly within 3 months of the child's birthday up to the age of 7 years. The study was approved by the local ethics committee.

Parental questionnaires

At each follow-up visit, parents gave structured interviews to a study doctor on the development of their child. Greatest interest was paid to asthmatic and atopic symptoms and diseases. At the age of 7 years, children were considered as "currently wheezing" if the parents reported at least one episode of wheezing in the past 12

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months. Furthermore, at the age of 7 years, parents were asked whether their child had ever had a doctor's diagnosis of asthma. This was defined as "diagnosis asthma ever." "Current asthma" was defined as a doctor's diagnosis of asthma and current wheeze at the age of 7 years. Assessed environmental factors comprised, among others, parental education, pet ownership, breast-feeding, and environmental tobacco-smoke exposure.

In a detailed questionnaire at the time of birth, atopic family history and prenatal characteristics were assessed. Of the questionnaire items, 11 screening conditions were chosen to define parental atopic and asthmatic status on the basis of a validation study in a subsample of parents.³ Parents were regarded as atopic if they reported diagnoses or relevant symptoms of atopic eczema, allergic rhinitis, or food allergy. Parents were regarded as asthmatic if they reported a diagnosis or relevant symptoms of asthma. Furthermore, parental smoking history was assessed.

Specific IgE

At the age of 1, 2, 3, 5, 6, and 7 years, the parents were asked to consent to blood sampling of their children. Specific IgE antibodies to food allergens (cow's milk, egg white, soy bean, and wheat) and inhalant allergens (the house dust mite *Dermatophagoides pteronyssinus*, cat and dog dander, and mixed grass and birch pollen) were determined by using 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. A child was defined as atopic, if he or she was sensitized to any of the allergens at any time point. Early sensitization was defined as a positive response up to the age of 2 years to any one of the tested allergens, and late inhalant sensitization was defined as a positive response to any one of the tested inhalant allergens at the age of 7 years; if a child had not participated in blood sampling at age 7 years, the result at age 6 years was used. Combining these 2 phenotypes, a child was defined as: (1) never sensitized, if neither was present; (2) transiently sensitized, if early sensitization to any allergen and no late sensitization to inhalant allergens was present; (3) late-onset sensitized, if late sensitization to inhalant allergens and no early sensitization to any allergens was present; or (4) persistently sensitized, if both early sensitization to any allergen and late sensitization to inhalant allergens were present.

Bronchial histamine challenge

At the age of 7 years, bronchial challenge was performed, starting with 0.5 mg/mL and increasing up to 8.0 mg/mL histamine according to a standard procedure.⁴ The 90th percentile of the distribution of PC₂₀FEV₁ in a healthy subsample equaled 0.85 mg/mL.⁵ Bronchial hyperresponsiveness (BHR) was defined as a PC₂₀FEV₁ of greater than this value.

Statistical analyses

χ^2 tests were used to compare prevalences between groups. Wilcoxon rank sum tests were used for the analysis of continuous variables. Logistic-regression models were calculated to analyze the association between the different patterns of sensitization and the outcome of asthma at the age of 7 years. These models were also used for the analysis of the influence of various potential risk factors (eg, maternal smoking and parental atopy) on the different sensitization patterns, as well as on the outcome of asthma. SAS software (version 6.12) was used for all statistical analyses.

RESULTS

Response rates

Of the 1314 children in the MAS birth cohort, 1120

(85.2%) participated in the follow-up survey at age 1 year, and 939 (71.5%) children participated in the final follow-up survey at the age of 7 years (Fig 1). The participation rates for blood sampling and for bronchial challenge at age 7 years were slightly lower.

Children were compared with respect to the number of absolved follow-up visits on the basis of data collected at birth to assess potential participation bias. Children with a parental history of atopy ($P < .001$ for trend), a higher level of parental education ($P < .001$), or no parental smoke exposure ($P < .001$) participated significantly more often than children without the respective characteristics. No significant differences were found with respect to sex, cord-blood IgE levels, or number of older siblings (data not shown).

Atopic sensitization and asthma

A total of 1062 (80.8%) children participated in at least one blood sampling for determination of specific IgE levels; 736 (69.3%) of these children were sensitized at any time point to at least one of the 9 tested allergens. Of these atopic children, 7.3% had current asthma at the age of 7 years.

The most prevalent type of atopic sensitization before the age of 2 years to any single allergen was to hen's egg (16.4%), followed by cow's milk (13.1%). Sensitization to inhalant allergens before the age of 2 years was less prevalent (grass pollen, 6.2%; house dust mites, 3.0%). Food sensitization at this age, either without (odds ratio [OR], 2.21; 95% CI, 0.78-6.29) or with (OR, 11.10; 95% CI, 4.73-26.07) concurrent inhalant sensitization was a strong predictor for the development of asthma until school age. In contrast, inhalant sensitization before the age of 2 years without concurrent food sensitization conferred no increased risk for the development of asthma (OR, 0.85; 95% CI, 0.11-6.51).

At the age of 7 years, the most prevalent type of atopic sensitization to any single allergen was to grass pollen (23.3%), followed by house dust mites (15.7%). Sensitization to food allergens at the age of 7 years was less prevalent (cow's milk, 13.6%; wheat, 11.4%) and conferred no increased risk for asthma at school age if no concurrent inhalant sensitization was present (OR, 1.24; 95% CI, 0.15-10.35 compared with no sensitization). A child was only at an increased risk of having asthma if he or she was sensitized to inhalant allergens at this age, either without (OR, 3.44; 95% CI, 1.18-10.01) or with (OR, 9.43; 95% CI, 3.77-23.57) concurrent food sensitization. This effect was strongest for perennial inhalant allergens compared with seasonal inhalant allergens.

When comparing the total quantity of specific IgE between atopic subjects with current asthma and nonasthmatic atopic subjects (ie, the total sum of allergen-specific IgE to the various tested allergens), atopic subjects with current asthma had significantly higher levels than nonasthmatic atopic subjects ($P = .0005$). Similarly, total IgE levels were significantly higher in atopic subjects with current asthma than in nonasthmatic atopic subjects ($P = .018$).

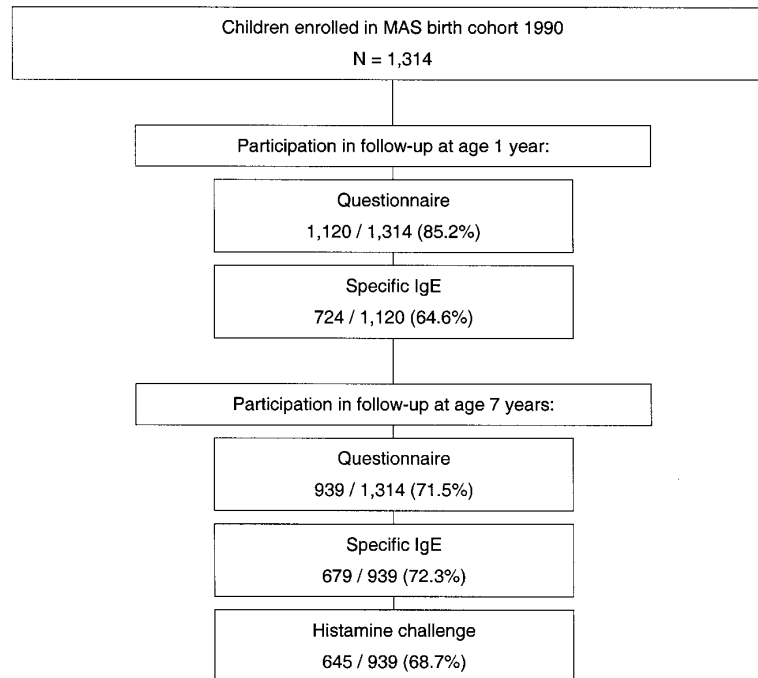


FIG 1. Response rates.

Age at initial sensitization

When comparing atopic children with and without current asthma, a significant age difference was seen with respect to initial atopic sensitization. Fig 2 shows the age at which atopic children first showed a positive response to any one of the allergens tested, stratified for current asthma at the age of 7 years. Of the atopic children with current asthma at the age of 7 years, 39.4% had already been sensitized at the age of 1 year compared with only 21% of the atopic children without current asthma ($P = .015$). This difference remained significant up to the age of 2 years. Similar results were seen when comparing atopic children with and without BHR at the age of 7 years. Thirty-three percent of the atopic subjects with BHR had been sensitized as early as age 1 year compared with only 18% in the group of atopic subjects without BHR ($P = .006$).

Furthermore, the younger the age at which a child first showed an atopic sensitization to one of the tested allergens, the higher both the total sum of allergen-specific IgE to the various tested allergens and the total IgE ($P < .0001$).

Transient and persistent sensitization

Transient sensitization, as defined in the "Methods" section, conferred no increased risk for asthma at the age of 7 years (Fig 3). Only persistently sensitized children (ie, children who were sensitized to any allergen early in life and who were sensitized to inhalant allergens by the age of 7 years) were at a significantly increased risk of being asthmatic at the age of 7 years (OR, 10.12; 95% CI, 3.81-26.88 compared with never being sensitized).

Risk factors for persistent sensitization compared with

those for transient early sensitization were a positive parental history of asthma or atopy (OR, 3.24; 95% CI, 1.75-6.00), with the effect of maternal atopy being stronger than that of paternal atopy (maternal atopy: OR, 4.50; 95% CI, 2.01-10.07; paternal atopy: OR, 1.36; 95% CI, 0.62-2.97), as well as maternal smoking during pregnancy (OR, 2.27; 95% CI, 1.14-4.52), which was also a significant risk factor for asthma at school age (OR, 2.46; 95% CI, 1.28-4.73).

Interaction of persistent sensitization and parental history of asthma or atopy

However, not all persistently sensitized children showed an increased risk for asthma. Persistent sensitization without a parental history of asthma or atopy conferred no increased risk for asthma at the age of 7 years (Fig 4). Only those persistently sensitized children who had a positive parental history of asthma or atopy were at significantly increased risk of being asthmatic at the age of 7 years (OR, 15.56; 95% CI, 5.78-41.83 compared with never being sensitized). When analyzing the influence of maternal and paternal asthma and atopy on children's asthma at the age of 7 years separately, persistently sensitized children with an asthmatic mother were at 10 times the risk of having current asthma at the age of 7 years compared with persistently sensitized children with no asthmatic mother (Table I). Asthma or atopy of the father showed no significant effect nor did atopy of the mother.

DISCUSSION

We observed that the sensitization pattern typically associated with asthma in childhood is best characterized

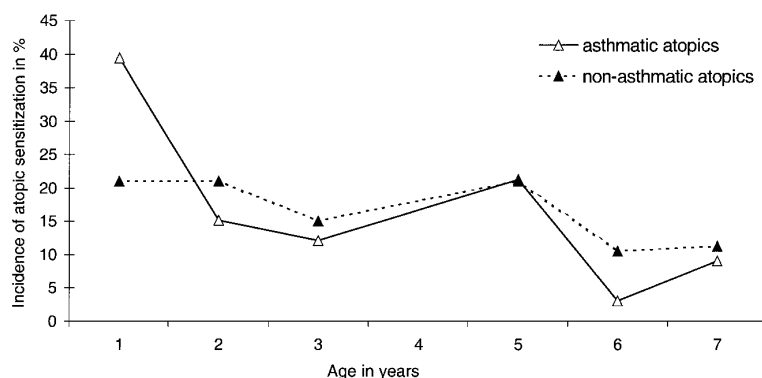


FIG 2. Age at onset of atopic sensitization in atopic children, stratified for current asthma at the age of 7 years.

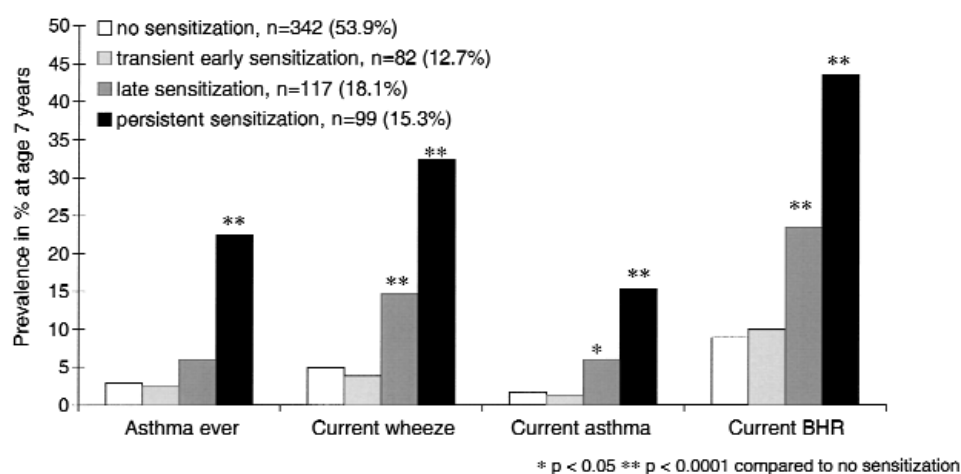


FIG 3. Prevalence of asthma and asthmatic symptoms at the age of 7 years, stratified for sensitization pattern.

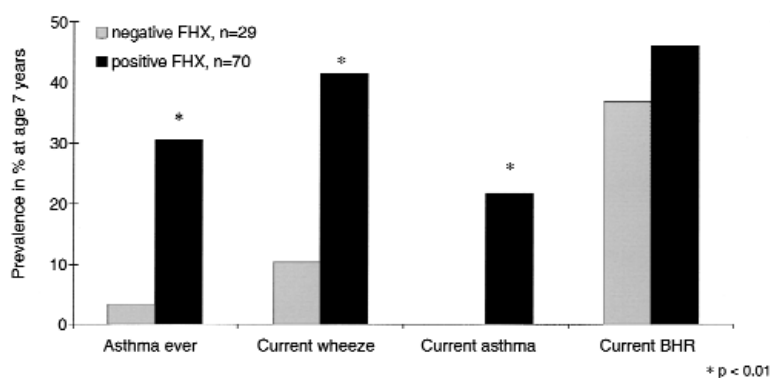


FIG 4. Prevalence of asthma and asthmatic symptoms at the age of 7 years in children with early and late sensitization (persistent sensitization), stratified for atopic family history. *FHX*, Family history of atopy or asthma.

by an early beginning of sensitization, as well as by the persistence of sensitization. However, only persistently sensitized children with a positive family history of asthma or atopy were at an increased risk of being asthmatic at the age of 7 years. This effect was strongest for a maternal history of asthma, indicating that an underlying factor pertaining to asthma and maternal transmission

may determine both a certain pattern of sensitization and the expression of asthma. This maternal link between atopy and asthma is further supported by the effect of maternal smoking, which was a risk factor both for persistent sensitization and asthma. All results remained basically unchanged when defining current asthma as a doctor's diagnosis of asthma plus current BHR.

TABLE I. Risk factors for asthma and asthmatic symptoms at the age of 7 years in children with persistent sensitization

	Asthma ever	Current wheeze	Current asthma	Current BHR
Atopy				
Maternal	1.76 (0.53-5.77)	1.88 (0.67-5.30)	1.84 (0.40-8.47)	0.58 (0.20-1.69)
Paternal	0.70 (0.20-2.49)	1.82 (0.62-5.37)	0.77 (0.16-3.61)	1.54 (0.51-4.71)
Asthma				
Maternal	4.80 (1.24-18.59)	9.53 (2.17-41.90)	9.61 (2.16-42.78)	3.18 (0.45-22.49)
Paternal	2.94 (0.69-12.51)	1.46 (0.39-5.50)	3.72 (0.67-20.53)	1.44 (0.33-6.28)

Data are given as adjusted ORs (95% CIs) for all other variables in the table.

The positive association of an early onset of atopic sensitization and the development of asthma is in line with findings from several other studies. However, the understanding of what may be defined as early sensitization varies greatly with respect to the time of onset of atopic sensitization.

Two prospective studies defined early-onset atopy as sensitization to inhalant allergens before the age of 8 years and observed a significant positive association of early-onset sensitization with asthma, whereas children with late-onset sensitization (after age 8 years) showed no increased prevalence of asthma.^{6,7} However, the age of 8 years might be too late to investigate the link between atopy and asthma because specific IgE antibodies can already be detected at birth.⁸

Atopic sensitization to food allergens, particularly to egg and cow's milk, are first observed during the course of atopic sensitization,⁹ with specific IgE antibodies to food allergens being detectable in up to 10% of 1-year-old children.¹⁰ Sensitization to hen's egg at the age of 1 year has been shown to be positively associated with subsequent inhalant sensitization^{11,12} and the development of asthma up to school age.¹²⁻¹⁴

Interestingly, when analyzing the type of sensitization associated with the development of asthma, different priorities were seen for sensitization in infancy and at school age in the data presented here. At age 7 years, food sensitization without concurrent inhalant sensitization conferred no increased risk for asthma at school age. A child was only at an increased risk of having asthma if he or she was sensitized to inhalant allergens at this age, either with or without concurrent food sensitization. These observations are in line with results from various cross-sectional studies in school-aged children that have found inhalant sensitization to be strongly associated with asthma, possibly indicating the importance of a local immune reaction of the airway mucosa.¹⁵⁻¹⁷

However, prospective studies starting at the age of 1 year or earlier have observed that food sensitization occurring very early in life was significantly associated with asthma at school age.^{12,13} In our data food sensitization before the age of 2 years, either with or without concurrent inhalant sensitization, was a strong predictor for the development of asthma until school age. In contrast, inhalant sensitization before the age of 2 years without concurrent food sensitization conferred no increased risk for the development of asthma.

The current understanding of the development of childhood asthma is the notion of a progressive atopic march: It starts with early atopic sensitization to food allergens, which is understood as a risk factor for subsequent inhalant sensitization, which in turn is regarded as a risk factor for the development of asthma. Hence primary prevention strategies for asthma have focused on allergen-avoidance measures early in life to avoid primary sensitization to both food and inhalant allergens.

However, recent epidemiologic studies and intervention trials on the association of allergen exposure and the outcome of atopy and asthma in childhood, even though observing a reduced prevalence of sensitization to the respective allergen, showed neither a consistent protective effect of reduced food^{13,18} or reduced food and inhalant allergens¹⁹ nor any conclusive positive effect of increased inhalant allergen levels²⁰ on the development of asthma.

These findings indicate that atopic sensitization may be merely an intermediate step in the development of asthma and not a causal risk factor necessarily resulting in asthma.

Our data support this notion. Even if a child was sensitized to any allergen as early as the age of 1 year and sensitized to inhalant allergens at the age of 7 years, an increased risk for asthma at the age of 7 years was only observed if a family history of asthma was present. These findings suggest that atopy in itself is not related to asthma unless an underlying condition drives both a certain pattern of sensitization and the development of childhood asthma. Alternatively, an underlying condition very early in life might determine the development of asthma, which in turn induces sensitization to certain allergens at a specific age. This would explain why allergen-avoidance strategies have thus far failed to prevent asthma in childhood.

When distinguishing between maternal and paternal influences, the maternal effect was strongest. This was seen both for the transition from early sensitization to persistent sensitization and for the development of asthma in persistently sensitized children. This increased maternal influence has repeatedly been observed, both in epidemiologic studies with objective measurements of atopy in both parents and the child and in genetic linkage studies.²¹ The association of maternal smoking with persistent atopic sensitization and asthma seen in our study indicates that the maternal effect on the development of atopy in the child may not solely be based on genetic

influences but also on environmental influences in utero.

Hence our study might provide the missing link between atopy and asthma in childhood, in that an underlying factor pertaining to asthma and maternal transmission may determine both a certain pattern of sensitization and the expression of asthma. These data support the hypothesis that the development of childhood asthma and atopy run parallel if certain perinatal or hereditary influences prevail, rather than being subsequent stepping stones in a progressive atopic march. Alternatively, it may be the asthma that determines the pattern and the level of atopic sensitization.

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