

Natural course of sensitization to food and inhalant allergens during the first 6 years of life

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Background: Specific IgE antibody responses to alimentary and environmental allergens are one of the hallmarks of atopic diseases. The knowledge of the time course of allergic sensitization during early life may facilitate measures for preventive interventions.

Objective: In a prospective birth cohort study (the Multicenter Allergy Study [MAS]) we investigated annual incidence and prevalence rates of sensitization to food and inhalant allergens during the first 6 years of life.

Methods: For 216 children of a prospective birth cohort (MAS), a complete follow-up of specific IgE measurements to 9 food and inhalant allergens was available at 1, 2, 3, 5, and 6 years of age. On the basis of these measurements, sensitization rates were estimated for the reference population of 4082 children by weighted analysis.

Results: Annual incidence rates of sensitization to food allergens decreased from 10% at 1 year of age to 3% at the 6 years of age. Incidences of sensitization to inhalant allergen, however, increased with age (from 1.5% at 1 year to 8% at 6 years). Point prevalences of allergic sensitization to at least 1 of the 9 tested allergens increased from 11% at 1 year up to 30% at 6 years. This increase was due to markedly increasing sensitization rates to inhalant allergens (1.5% to at least 1 inhalant allergen at 1 year and 26% at 6 years of age), whereas sensitization rates to food allergens remained stable during the first 6 years of life (10%).

Conclusion: The earliest serologic marker for atopic immunoreactivity in infancy is the presence of IgE antibodies to egg, followed by milk. The development of sensitization to inhalant allergens occurs mostly after infancy. Beyond the third birthday annual incidence and prevalence increase markedly with age. Rates for outdoor allergens are twice those for indoor allergens. (*J Allergy Clin Immunol* 1999;103:1173-9.)

Key words: Specific sensitization, prevalence, incidence, natural course of allergic sensitization, children

Abbreviations used

CB-IgE: Cord blood IgE

95% CI: 95% confidence interval

MAS: Multicenter Allergy Study

sIgE: Specific IgE

One of the characteristics of atopic individuals is their capacity to mount IgE-mediated immune responses on exposure to minute amounts of naturally occurring allergens. Many of these sensitized subjects have been shown to later have allergic symptoms. Therefore early detection of risk markers, such as the presence of serum IgE antibodies to allergens, could facilitate allergy prevention in children. Studies such as the International Study of Asthma and Allergies in Childhood (ISAAC) have provided valid data about the prevalence of allergic symptoms. Up to now, however, there has been a lack of such data for IgE-mediated allergic sensitization, especially in young children and in large population-based samples. Little is known about the prevalence of specific sensitization and in particular about the natural course of allergic sensitization. Previous studies with follow-up of the same children over about 4 years included only a selected group of subjects: either children at risk for atopy (ie, at least 1 atopic parent)¹⁻³ and/or children undergoing prophylactic treatment in interventional studies.^{2,3} In addition to children at risk, some investigations included unselected subjects.⁴⁻⁶ However, there were methodological limitations in study design because specific sensitization was only determined once (ie, the natural course of sensitization cannot be described), and sensitization was assessed only in children in whom atopic disorders had already developed.^{4,5} Moreover, sample sizes were mostly smaller than in our cohort, consisting of a complete follow-up of annual specific IgE measurements from over 200 children.^{1-3,5,6}

Data from cross-sectional studies and small cohorts, in general between 50 and 100 subjects in the respective age groups, provide information about incidence and prevalence rates mainly for school-age children and rarely provide a description of the time course of allergic sensitization.⁶⁻¹⁵

As part of a prospective German birth cohort study

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Received for publication Sept 2, 1998; revised Dec 29, 1998; accepted for publication Dec 30, 1998.

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0091-6749/99 \$8.00 + 0 1/1/96778

TABLE I. Characteristics of newborns in the analyzed subsample and the population sample

	Population sample (n = 4082)	Subsample (n = 216)
Atopic family history		
None	60%	44%
One atopic family member	32%	36%
≥2 atopic family members	8%	20%
CB-IgE ≥0.9 kU/L	8%	16%
Elevated CB-IgE (≥0.9 kU/L) in combination with atopic family history		
No atopic family member	7%	36%
One atopic family member	9%	57%
≥2 atopic family members	10%	6%
Sex (male)	51%	52%
Parental educational level		
Middle school	52%	59%
High school	16%	12%
Higher education	32%	29%
Age of mother, y (mean)	28.8	28.8
Gestational age, wk (mean)	39.8	39.9
Birth weight (mean)	3371 g	3380 g
Number of older siblings of study child		
None	51%	51%
One	37%	39%
Two or more	12%	10%
Smoking mother (at birth)	27%	22%
Smoking father (at birth)	46%	41%

Atopic family history and elevated CB-IgE levels were used as weights in the analysis.

(the Multicenter Allergy Study [MAS]), specific (s)IgE to food and inhalant allergens was determined annually in more than 200 consecutively followed children. On the basis of these measurements and weighting for atopic risk factors in a large population-based sample of 4082 children, we estimate prevalence and incidence rates of allergic sensitization during the first 6 years of life for all 4082 children.

METHODS

Study population

Subjects in this study were participants of the MAS. A detailed description of the 1314 study subjects and methods is presented elsewhere.¹⁶ Briefly, in 1990 all 7609 newborns were enrolled in 6 obstetric departments in 5 German cities. For 5051 children, data about atopic family history and cord blood IgE (CB-IgE) was available. There were no significant differences between the total sample and the 5051 children with respect to the main characteristics given in Table I. Of these subjects, 499 eligible newborns with elevated CB-IgE levels (≥0.9 kU/L) and/or at least 2 close atopic family members participated in our birth cohort. Of the remaining subjects, 815 randomly selected newborns with none of these atopic risk factors present were also included (see flow diagram of participants in Fig 1). At each follow-up visit, parents filled out questionnaires and gave structured interviews about atopic symptoms and diseases of their children, about atopic family history (mothers and fathers were

TABLE II. Characteristics of the analyzed subsample (n = 216) and the remaining children of the overall MAS birth cohort (n = 1098 at start of follow-up)

	Analyzed subsample (n = 216)	Remaining subjects of MAS cohort (n = 1098)*	P value†
Sex (male)	52	52	.95
Parental educational level			.13
Secondary school	59	54	
High school	12	15	
Higher education	29	31	
Parental atopy			
Atopic mother	32	36	.25
Atopic father	32	30	.59
Detectable CB-IgE (≥0.35 kU/L)	35	36	.77
Season of birth			.24
Spring/Autumn (Mar-May, Sep-Oct)	32	34	
Summer (May-August)	42	37	
Winter (Nov-Feb)	26	29	
Duration of breast feeding			.06
Up to 1 month	24	31	
1-6 months	48	43	
More than 6 months	28	26	
Number of siblings at birth			.15
None	51	57	
1	39	32	
2 or more	10	11	
Parental smoking habit			
Mother smoking during pregnancy	23	26	.43
Mother and/or father smoking (at 3 years)	47	48	.68
Pets in household (at 18 months)	29	30	.53
Cat allergen exposure by 18 months (median)	64 ng/g	64 ng/g	.72
Mite allergen exposure by 18 months (median)	270 ng/g	231 ng/g	.12

*Because of missing information for some characteristics and loss to follow-up until 6 years of age, number of subjects varies between 1098 and 839.

†Chi-square test for differences in the 2 samples.

considered separately and defined as atopic if at least 1 of the following conditions were present: asthma, hay fever, atopic eczema, or food allergy), and parental educational level (highest level in parents). Blood samples were obtained at 1, 2, 3, 5, and 6 years of age. The study was approved by the local ethics committee, and informed parental consent was obtained. Participation rate of the total MAS cohort was 73% (n = 962 of 1314 subjects) until the sixth birthday.

Inclusion criterion for this study was a complete follow-up of annual specific IgE measurements at the ages of 1, 2, 3, 5, and 6 years to assess true incidence and prevalence rates. These 216 children with a complete follow-up of blood exams until the sixth birthday did not differ substantially from the overall MAS cohort in terms of sex, season of birth, parental atopy status, maternal smoking during pregnancy, and other characteristics (Table II).

No children of Mediterranean or non-European origin were among the 216 subjects with the complete series of sIgE measurements. Thus for the description of the natural course of sensitization

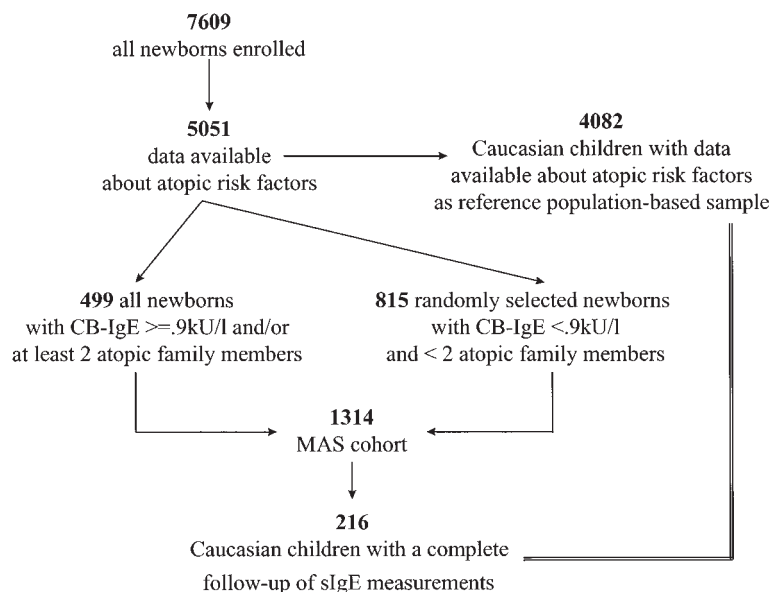


FIG 1. Flow diagram of participants.

to food and inhalant allergens of the population-based sample, families of Mediterranean and non-European origin were excluded. Four thousand eighty-two children of the population-based sample remained in the analysis. On the basis of the specific serum IgE measurements of those 216 cohort children, incidence and prevalence rates were estimated for the 4082 subjects of the population-based sample as described in the statistics section.

Specific serum IgE measurements

CB-IgE and sIgE antibodies to hen's egg, cow's milk, soy and wheat, mixed grasses, birch pollen, house dust mite, and cat dander were determined annually and also at 3, 5, and 6 years of age to dog by CAP-RAST-FEIA (Pharmacia). A child was defined as sensitized if sIgE levels were equal or greater than 0.7 kU/L (CAP class 2). This limit was chosen to exclude possibly ambiguous or transient events of sensitization caused by variations in measurement sensitivity over the study period.

Statistics

To estimate prevalence and incidence rates of allergic sensitization for a population-based sample, the analyzed subsample of MAS cohort children had to correspond to the original population sample of newborns in 6 obstetric departments in 1990. Thus subjects of our cohort were weighted¹⁷ by the 2 atopic risk factors on which the selection procedure for the MAS cohort was based (ie, atopic family history and elevated CB-IgE levels). After this adjustment for the differences between the MAS cohort subsample and the population-based sample, sIgE measurements of our study sample were used to calculate prevalence and incidence rates for the population-based sample of 4082 children. The distribution of the 2 weighting factors and other perinatal characteristics are given in Table I for the population-based sample and the analyzed MAS cohort.

Prevalence rate of allergic sensitization is defined as the proportion of sensitized children (sIgE ≥ 0.7 kU/L) in the total group at the respective time point. Incidence rate of allergic sensitization is defined as the proportion of children with sensitization (sIgE ≥ 0.7 kU/L) in the group of children at risk (ie, children originally free of sensitization in whom it could have developed during the period) within the respective time period. The 95% confidence intervals

(95% CIs) around the rates were computed with the standard formula:

$$\text{rate} \pm 1.96 \sqrt{\text{rate}(1 - \text{rate})/N}.$$

Differences in specific IgE levels to food and inhalant allergens were assessed by the Wilcoxon test. Statistical analysis was performed by using spss/pc (SPSS Inc).

RESULTS

A description of the population-based sample and the analyzed subsample with regard to the weighting factors and other perinatal characteristics available for both samples are given in Table I. The differences in respect to the 2 atopic risk factors (atopic family history and elevated CB-IgE level) were due to the study design but were adjusted for in the analysis. The subsample corresponded to the population-based sample with regard to the other characteristics.

We were unable to detect sIgE to any of the allergens tested in any of the cord blood samples. Point prevalences of allergic sensitization to at least 1 of the tested allergens increased from 11% (95% CI: 7%-15%) at 1 year of age up to 30% (95% CI: 24%-36%) at 6 years of age. This increase was due to markedly increasing sensitization rates to inhalant allergens (1.5% [95% CI: 0%-3%] to at least 1 inhalant allergen at 1 year of age and 26% [95% CI: 20%-32%] at 6 years of age), whereas sensitization rates to food allergens remained stable during the first 6 years of life (10% [95% CI: 6%-14%]) to at least 1 food allergen at 1 and 6 years of age). Annual incidence rates of sensitization to at least 1 of the 4 food allergens decreased from 10% (95% CI: 6%-14%) at 1 year of age to 3% (95% CI: 1%-5%) at 6 years of age. Despite annual incidences of food sensitization greater than zero during the first years of life, the prevalence rate of food sensitization at 6 years of age did not exceed the rates at earlier time points because of frequent occurrence of transient sensitization. Incidences of sensitiza-

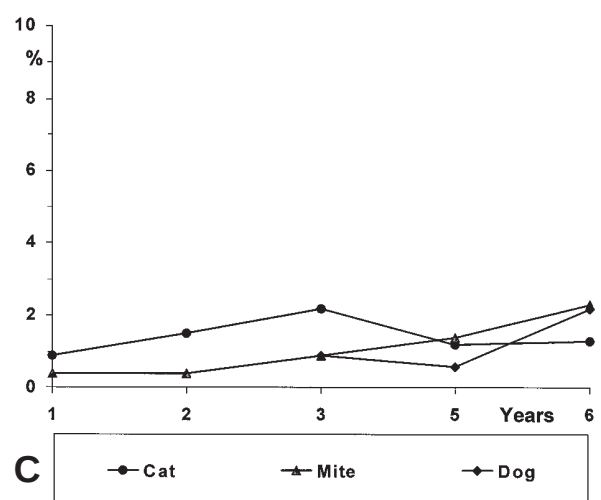
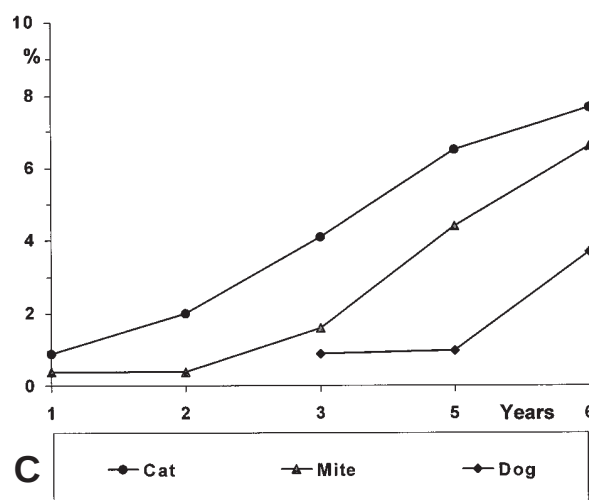
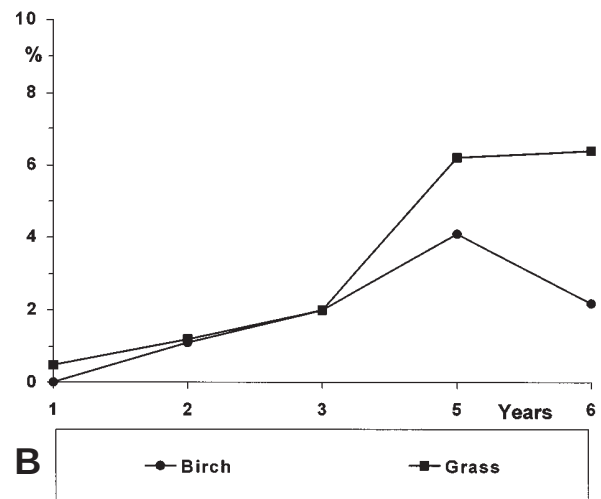
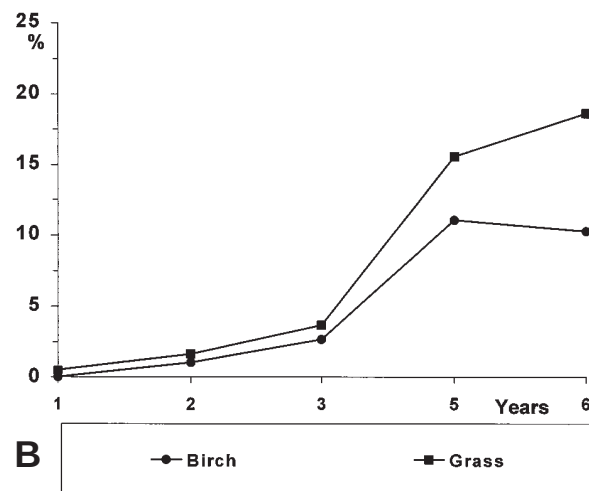
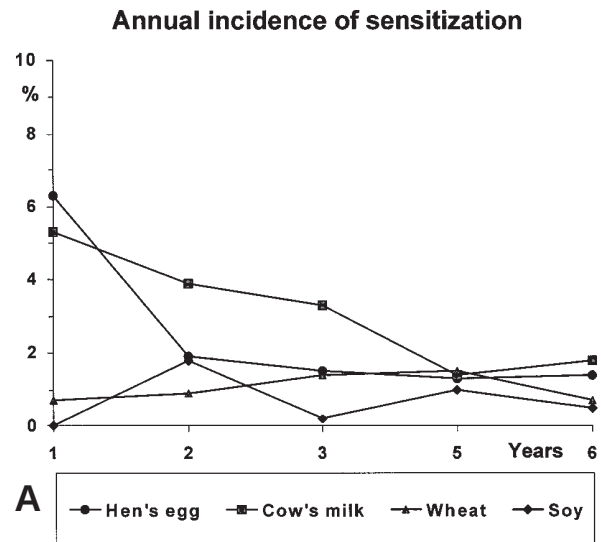
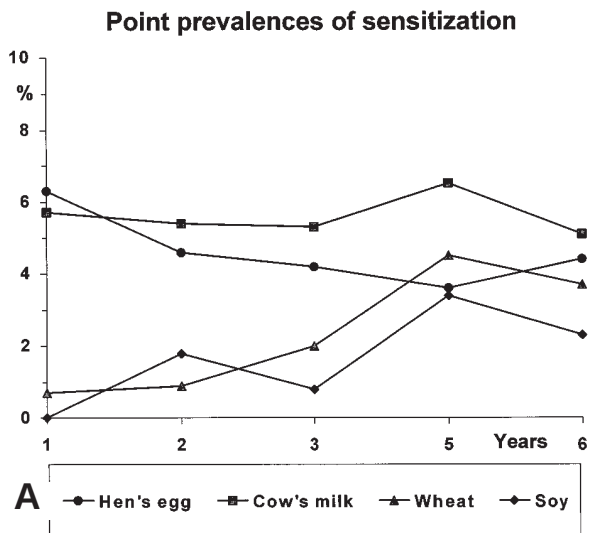


FIG 2. Prevalences of sensitization to food (**A**) and inhalant (**B** and **C**) allergens by 6 years of age (cutoff level: ≥ 0.7 kU/L [CAP class 2]; estimates for the original population-based sample of 4082 children).

FIG 3. Annual incidence rates of sensitization to food (**A**) and inhalant (**B** and **C**) allergens by 6 years of age (cutoff level: ≥ 0.7 kU/L [CAP class 2]; estimates for the original population-based sample of 4082 children).

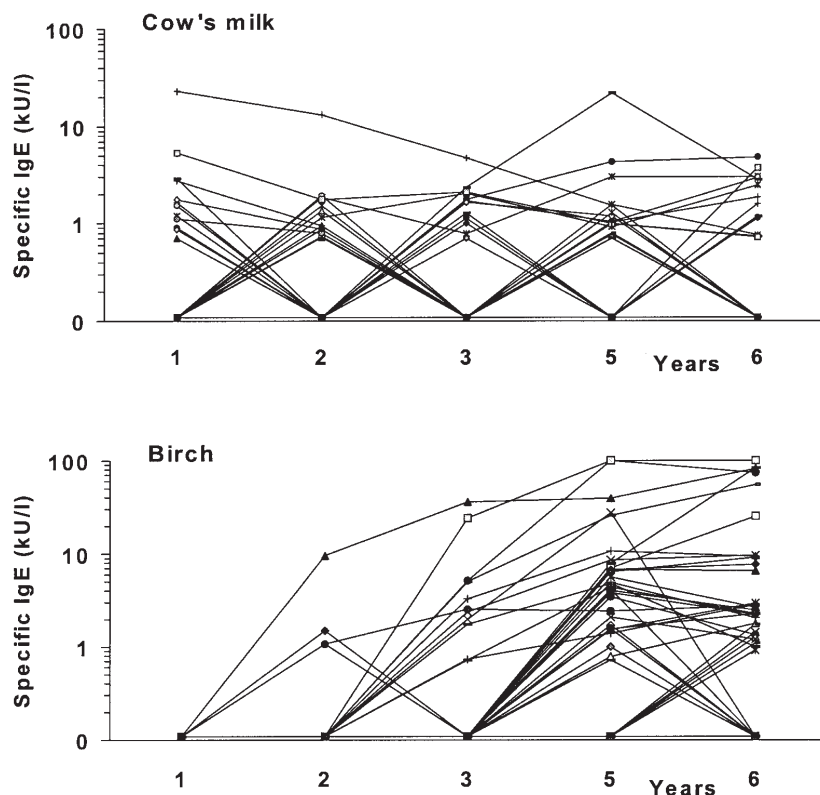


FIG 4. Natural course of sIgE concentrations to milk and birch by 6 years of age. Each line represents an individual subject distinguished by different patterns. In 83% of children sIgE to milk and in 84% of children sIgE to birch was less than 0.7 kU/L at each year of age; cases were not weighted.

tion to at least 1 inhalant allergen, however, increased with age (from 1.5% [95% CI: 0%-3%] at 1 year to 8% [95% CI: 4%-12%] at 6 years).

Point prevalences and annual incidences of sensitization to the single allergens are summarized in Figs 2 and 3. Whereas for hen's egg and, to a lesser extent, for cow's milk the highest incidence and prevalence rates were observed at 1 year of age (about 6%), prevalences for other food allergens (soy and wheat) showed a peak at 5 years of age. As expected, during early childhood children were mainly sensitized to food allergens. At 5 and 6 years of age sensitization rates to each of the 4 tested food allergens were about 4% to 5%, with a tendency to lower rates at 6 years of age. With respect to inhalant allergens, prevalences of sensitization were below 2% during the first 2 years of life, steadily increasing in later years. By the age of 6 years, sensitization to outdoor allergens was observed twice as often (birch: 10% [95% CI: 6%-14%]; grass: 19% [95% CI: 14%-24%]) as that to indoor allergens (4% [95% CI: 1%-7%] to 7% [95% CI: 4%-10%]). The annual incidence increased markedly after the third birthday for birch (up to 4% [95% CI: 1%-7%]) and for grass (>6% [95% CI: 3%-9%]), whereas the annual incidence for sensitization to indoor allergens increased slowly up to about 2% (95% CI: 0%-4%) after 3 years of age.

From the third birthday on, sIgE levels to inhalant allergens were significantly higher than sIgE levels to food allergens in children of the same age ($P < .006$). Median sIgE values to inhalant allergens increased up to a peak at the fifth birthday and then decreased during the sixth year of life. sIgE levels to soy and wheat showed the same pattern, whereas sIgE concentrations to egg and milk, allergens that children are exposed to very early, already showed a peak in infancy.

In respect to the natural course of sensitization in individuals, the occurrence of sIgE was a dynamic process with events of transient sensitization. Not only the occurrence of sIgE to food allergens varied from year to year. Transient specific sensitizations defined as sIgE below the detection limit after allergic sensitization in previous measurement(s) were observed in 72% of children sensitized to cow's milk and in 81% sensitized to hen's egg. Also in some children previously sensitized to an inhalant allergen, sIgE was no longer detectable in 1 or more later measurements. Such transient specific sensitizations were observed in 5% of children sensitized to mite, in 10% each sensitized to cat or grass, and in 19% sensitized to birch. As an example, for the 216 children, the course of sIgE measurements to milk and birch by 6 years of age is shown in Fig 4. The occurrence of transient allergic sensitization did not depend on age but was observed at each

year of life. Transient sensitization to outdoor allergens, however, occurred more often after the third birthday, corresponding to the increasing incidence of that type of sensitization. sIgE concentrations in transiently sensitized children were lower than in consistently sensitized children at each year of occurrence. Significant differences ($P < .05$), however, were not found at any age.

DISCUSSION

To our knowledge, this is the first study with a complete and consecutive follow-up of sIgE measurements of over 200 children from birth to 6 years of age that allows estimates for a large population-based sample. Previous reports regarding specific allergic sensitization often relied on small sample sizes in the respective age groups, on selected groups of subjects (eg, children at risk for atopy), or both.^{1,3-7,18-20} Reports of prevalence rates were mostly based on cross-sectional studies, and sIgE measurements were rarely available for precise years of age, especially in young children.^{2,8-15}

An important question of our study design concerns the representativeness of the results in respect to the development of allergic sensitization during childhood and the transferability to the general population. The analyzed subcohort did not differ significantly from the total MAS cohort regarding characteristics considered relevant for the development of atopy. Thus there seemed to be no selection bias because of different participation rates in blood examinations. The MAS cohort is atopy enriched because the inclusion for a part of the birth cohort was based on the presence of 2 atopic risk factors (elevated CB-IgE level and positive atopic family history). We controlled for this selection by the adjustment of the subset for the distribution of these 2 criteria in the original population-based sample. In respect to other characteristics (Table I), we observed no differences between the analyzed subset and the population-based sample that would indicate a reason for a possible overestimation or underestimation of our results. For other factors possibly influencing the rates, such as breast feeding or pets in the home, we cannot compare the distributions between the cohort and the population-based sample because those data were not gathered for the population-based sample. We assume that families participating in the MAS cohort tended to avoid possible risk factors more often than families of the population sample (ie, increased awareness because of study participation). Thus the estimated rates are underestimations rather than overestimations. However, the educational level of the families of the original sample of 4082 children seems to be higher than in the average German population (high school or higher education: 48% vs 36%).²¹ Although all families of all healthy newborns in 6 hospitals in 1990 were questioned, the higher parental educational level may be due to different admission patterns to the obstetric departments of the chosen hospitals. We conclude that the subjects of our weighted analysis correspond sufficiently to the population-based sample and that our results are reliable esti-

mates for the German population, even though a possible selection bias cannot be entirely excluded.

For comparisons with other studies, differences in study design and subjects have to be taken into consideration. Almost all studies investigating prevalence of allergic sensitization used skin prick tests for outcome determination. Findings should be comparable to determination of sensitization by specific serum IgE measurements, but skin prick tests may be more susceptible to variation and errors in measurement techniques.²² Incidence and prevalence rates for the population-based sample, however, can hardly be compared with other findings because virtually no results are available about the prevalence and incidence of specific sensitization and the natural course of sensitization in large population-based samples of children. Our observed sensitization rates to inhalant allergens at 6 years of age are comparable to figures of prevalence studies in schoolchildren 6 to 16 years old.^{10-13,15} Those similar and more or less stable rates for children from the sixth birthday on indicate that the development of allergic sensitization mainly occurs during the first years of life. For younger age groups, reported figures in the literature vary to a greater extent because the study groups differ in respect to atopic risk factors and other selection criteria. During the first 3 years of life, prevalence and incidence rates were slightly higher for sensitization to indoor allergens. After the third birthday, however, the annual incidence increased markedly for outdoor allergens, and prevalence rates were observed about twice as often as indoor allergens. It is well known that allergen exposure varies from country to country and from continent to continent, resulting in differing sensitization rates to indoor and outdoor allergens. In Scandinavia, for example, very high cat allergen exposure levels were observed, whereas in Germany outdoor allergens such as birch and grass play a great role in the development of allergic sensitization. Our data can only reflect sensitization patterns in Germany respective to central Europe (ie, depending on the types of allergen exposures in these regions), with obviously high sensitization rates to outdoor allergens as Kuehr^{10,11} and von Mutius¹³ previously reported in schoolchildren.

Transient sensitization to food allergens is a common and known phenomenon in childhood,^{18,19} and transiently sensitized children seem to have lower risks for later allergic disease than permanently sensitized children.²³ Whereas transient sensitization to inhalant allergens is regarded as a very rare event by many pediatric allergists and is not well studied, we observed such transient events in up to 19% of children sensitized to inhalant allergens during the first 6 years of life. It seemed that transient sensitizations occurred more likely in children with lower specific serum IgE levels. Because the limit of sIgE measurements used in our study was relatively high (CAP class 2), these findings are not due to variations in measurement sensitivity. Whether this phenomenon vanishes in older children or is relevant with regard to different prediction probabilities of atopy in those 2 groups of sensitized individuals remains unsolved.

This study provides epidemiologic data to describe the natural course of specific sensitization, including the occurrence of transient sensitization in childhood. The reported prevalence and incidence rates can be used as basic figures to determine time trends and the extent of a possible increase in allergic sensitization in children. For predictive purposes, the knowledge of the natural history of specific sensitization is a prerequisite for estimating the development of allergic diseases and for allergy prevention in childhood.

This study reports reliable estimates of prevalence and incidence rates of sensitization to food and inhalant allergens and describes the natural course of allergic sensitization during the first 6 years of life. The earliest serologic marker for atopic immunoreactivity in infancy is the presence of IgE to egg, followed by milk. The development of sensitization to inhalant allergens occurs mostly after infancy. Beyond the third birthday, annual incidence and prevalence increases markedly with age. Rates for outdoor allergens were twice those for indoor allergens.

We thank C. P. Bauer, F. Bieber, G. Edenharter, J. Forster, C. Genzel, M. Goetz, M. Groeger, B. Hampel, G. Leskosek, R. Mayrl, C. Sommerfeld, and P. Wagner for their contributions to the MAS-90 study.

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