

Atopic diseases in infancy. The German multicenter atopy study (MAS-90)

Bergmann RL, Bergmann KE, Lau-Schadensdorf S, Luck W, Dannemann A, Bauer CP, Dorsch W, Forster J, Schmidt E, Schulz J, Wahn U. Atopic diseases in infancy. The German multicenter atopy study (MAS-90). *Pediatr Allergy Immunol* 1994; 5 (Suppl 1): 19–25. © Munksgaard 1994.

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Atopic diseases are complex multifactorial in origin (1). A genetic background predisposes vulnerable individuals to develop IgE-mediated reactions to environmental allergens. Since the classical work by Croner et al. (2) many studies have shown that atopic vulnerability can be recognized at birth and atopic disease predicted by family history and cord blood IgE values (3). However, the predictive value especially of cord blood IgE has been questioned recently (4–8).

The rising public concern about environmental pollution and many reports of the increasing prevalence of atopic diseases in affluent societies have initiated a new series of investigations on the predictability and early prevention of atopic disorders.

Effective prevention and early intervention strategies are priority research objectives. However, our knowledge about the relative contribution of genetic and environmental factors for the manifestation, severity, duration and impact of atopic diseases is still unsatisfactory.

The German Multicenter Atopy Study (MAS-90) was initiated to evaluate the predictive value of various clinical and immunological parameters as well as the significance of early environmental exposures to allergens and trigger factors for the development of atopic diseases in early childhood.

Methods

5 German cities and 6 obstetric departments (Berlin Düsseldorf, Freiburg, Mainz, München) were the catchment area for the recruitment of newborns to a

prospective study. A family questionnaire on atopic diseases, relevant symptoms, and tests as well as sociodemographic variables was distributed in the delivery wards to the parents of 7,609 infants born at the study centers between 1.1. and 31.12. 1990.

A total of 6,019 parents filled in the questionnaire. In 78% of families, mother and father answered the questions concerning their own diseases either together or each one for himself, 22% of mothers filled in the questionnaire for the father. Of the questionnaire items 11 validated screening conditions were chosen to indicate atopic status of the family member. These items were validated by the results of a Phadiatop test in a subsample of parents (9).

Cord blood IgE values were determined by CAP-Rast-Feia. Detection limit was set at 0.35 kU/l. Contamination with maternal blood was avoided by puncture of cord vessels and also controlled for by exclusion of samples with an IgA value above 32 µg/ml (10). Cotinine values in cord blood were determined by gaschromatography.

A cohort of 1314 newborns was recruited for the prospective study, 499 infants (38%) were selected as being at high risk with at least two atopic family members and/or a cord blood-IgE value above 0.9 kU/l. The control group of 815 infants (62%) was chosen at random from the remaining newborns (one or no atopic family member and cord blood IgE value less than 0.9 kU/l) (Fig. 1).

The cohort infants came regularly with their parents to follow-up visits at the ages 1, 3, 6, 12, 18, 24 months and continue to do so every year. Parents filled in a questionnaire and gave a structured in-

STUDY BASE

6 Study Centers in 5 German Cities

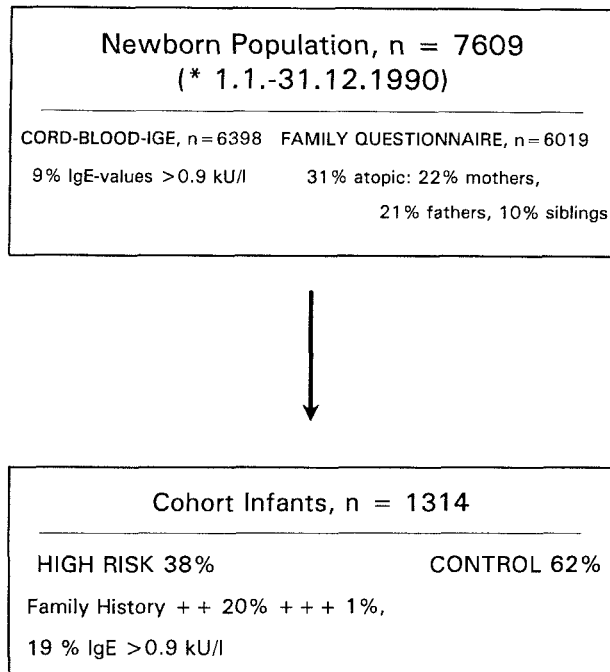


Fig. 1. Study Base of the MAS-90 cohort.

interview about their infants' diseases, relevant atopic symptoms, nutrition and development, about environmental factors, housing conditions, psychological problems and demographic features. To keep reporting bias low, the parents kept a diary, in which details of the infant's diet, diseases and important events were recorded. The infants had a standardized physical examination by a physician with special emphasis on skin conditions. Carpet dust samples were analyzed for major indoor allergens, i.e. house dust mites, cat and dog dander at 6, 18 and 36 months of age. Blood samples were taken at 12 and 24 months for determining total IgE and for CAP values against 9 common food and inhalant allergens. Also, spot urine samples for cotinine determinations by gaschromatography, were collected at 12 and 24 months of age.

Clinical manifestations of atopic diseases and atopic sensitisation were treated separately: The diagnosis of the family physician, of the examining doctor and additionally, a statistical analysis of the relevant symptoms or signs were used to define an obvious or probable atopic manifestation in the first 24 months of life. Obvious asthma required at least two wheezing episodes with shortness of breath, obvious atopic eczema a combination of at least three typical morphological features at three typical

sites. From symptoms and signs only a probable diagnosis could be given for atopic rhinocconjunctivitis. Consistent vomiting, diarrhea and colic, without infection, after consumption of allergenic foods, were regarded as symptoms and signs for food intolerance. The child was considered sensitized, when the IgE antibody concentration against at least 1 of 9 common allergens was higher than 0.35 kU/l (= CAP class 1). Statistical analyses were performed using SPSS/PC.

Results

Risk factors at birth

Of all infants born in 1990 in the 6 study centers, only 58% did not have any atopy risk at birth. 9% of the 6398 cord blood-IgE values were above 0.9 kU/l, 31% of 6019 newborns had at least one atopic family member (22% mothers, 21% fathers and 10% siblings), Fig. 1; 7.4% had at least two atopic family members, and only 0.8% had an elevated IgE value and two atopic family members.

The cord blood IgE values had a skewed distribution: The 75. percentile had the value of 0.35 kU/l (i.e. just above the detection limit), the 90. percentile of 0.79 kU/l, the 95. percentile of 1.36 kU/l and the 97. percentile of 2.03 kU/l (Fig. 2).

Prevalence and distribution of risk factors in early childhood

Infants were exposed to food allergens early. While in the newborn nursery, 92% of mothers started breastfeeding, 49% of infants received supplements during the first days of life, in 36% of cases this was cow's milk-based formula. In the first three months of life, 53% of infants were fed at least some solid foods.

Feeding habits in the first 3 months of life were different in atopic and non-atopic families. When infants of atopic families needed a breastmilk substitute in the newborn nursery, they received hydrolyzed cow's milk formulae rather than adapted

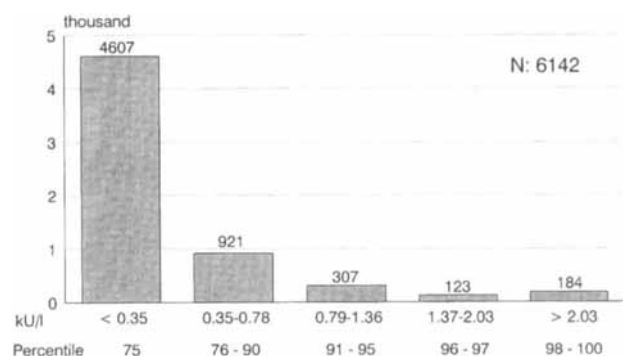


Fig. 2. Distribution of cord blood IgE values in the MAS-90 newborn population.

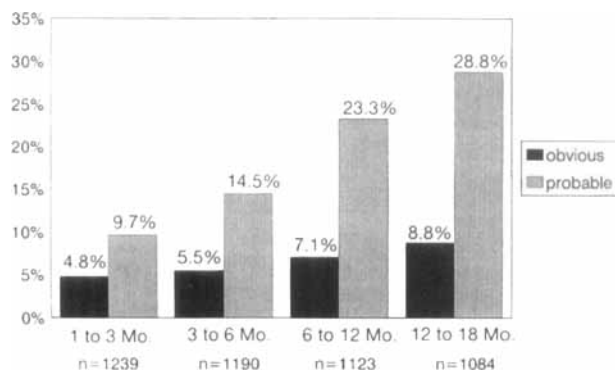


Fig. 3. Period prevalences of obvious and probable eczema in the first 18 months of life.

cow's milk-based products. During the first three months of life atopic parents introduced solid foods later than non-atopic parents.

There were regional differences in indoor allergen concentrations. The highest median value for mite allergen concentration in carpet dust was found in Freiburg (798 ng/g), the lowest value in Berlin (72.5 ng/g). The median value for all centers was 190 ng/g. In 25% of households mite allergen concentrations were above the critical value of 2000 ng/g. Floor level below 2nd, living in a one family house as opposed to an apartment, and a high number of persons living in the apartment were risk factors for high mite allergen concentrations in the dust samples. Neither the age of the building or mattress, nor the type of heating correlated significantly with mite allergen exposure.

Of all families, 31% owned pets, mostly cats; these were evenly distributed between atopic and non-atopic families. Only atopic families with a member complaining of symptoms caused by animals had less frequently pets. Also, families with higher levels of education had pets in their homes less frequently. There was no correlation between cat and mite allergen exposure.

By history, in about 50% of households, there was at least one smoker in the family. Nearly the same proportion of passive smoke exposure was found by an objective method: 51% of 671 urine samples had a relevant cotinine concentration of 30 ng/mg creatinine at one year of age. During pregnancy 23% of mothers smoked according to questionnaire data, and 27% of the newborns had a relevant cotinine concentration above 5 ng/ml in cord blood. Less cigarettes were smoked in the household, when the fathers had an atopy ($p < 0.001$), but cotinine values in urine samples were found to be significantly lower only when the mothers and siblings had an atopy ($p < 0.005$).

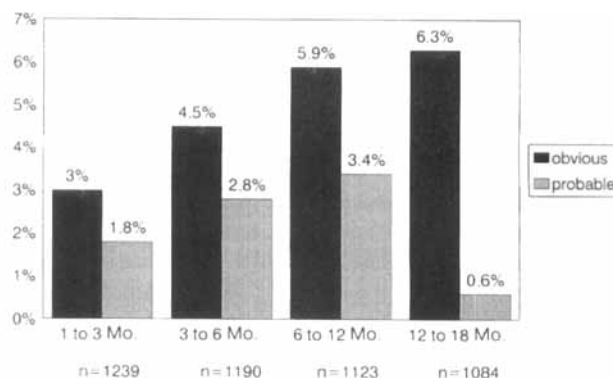


Fig. 4. Period prevalences of obvious and probable asthma in the first 18 months of life.

Prevalence and incidence of atopic manifestations

The period prevalence of an atopic manifestation describes the proportion of infants who had the disease in the interval preceding a follow-up visit. Period lengths in the MAS-90 study were of different durations, i.e. increasing from 1 month to 6 months. The period prevalence of an obvious atopic eczema was rising from 4.8% at 3 months to 8.8% at 24 months. The period prevalence for a probable atopic eczema was higher, rising from 9.7% at 3 months to 24.7% at 24 months (Fig. 3). In contrast, the period prevalence for obvious asthma was higher than for probable asthma, reaching a peak at 12 months of age, and declining thereafter (Fig. 4).

Food intolerance was reported in 1.7% of infants before 3 months of age. This level for period prevalence was about maintained during the first two years. Additional 8% of children could probably also have a food intolerance during any interval in the first two years. The period prevalences for atopic rhinitis and conjunctivitis in infants where in the range of 0.5%.

The lifetime prevalence (or cumulated incidence during life time), i.e. the frequency of children who ever had an obvious atopic eczema was 12% in the first year, and 18% in the first two years of life. The

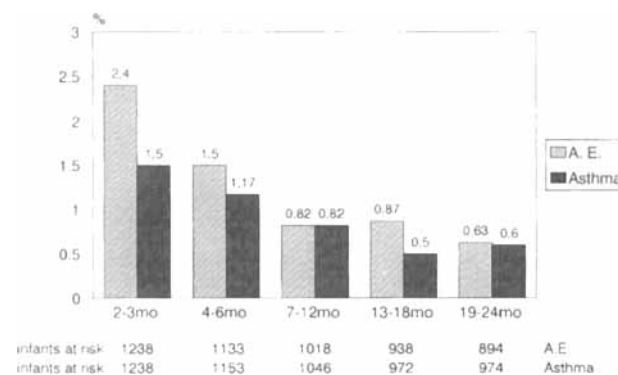


Fig. 5. Risk per month of new cases of atopic eczema or asthma during each period.

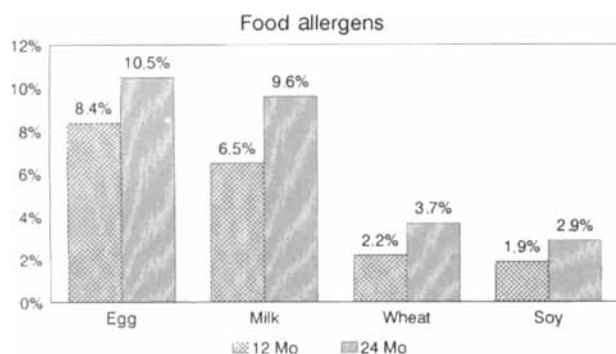


Fig. 6. Prevalences of sensitization against food allergens at 12 and 24 months of age.

respective numbers for obvious asthma were 10% and 15%, and for food intolerance 3.0% and 4.5%. The lifetime prevalence (cumulated incidence) of all obvious atopic diseases during the first year of life was 25%, and during the first two years 34%.

The risk of eczema and asthma per period (or cumulated incidence of newly diagnosed cases per period) – standardized for period length – was highest in the period two to three months of age and declined thereafter (Fig. 5).

Prevalence of atopic sensitisation

At 12 months of age 16% of the children were sensitized against at least one of nine common allergens, and at 24 months of age 24% of children were sensitized. Specific sensitization occurred predominantly against food, whereas sensitization against indoor and outdoor allergens became not remarkable before 24 months of age (Figs 6, 7). Percentage of infants sensitized against food allergens was rising with the severity and duration of eczema in the infants (Fig. 8).

Prediction of atopic disease at birth

The period prevalences of atopic diseases during the first 12 as well as 24 months of life were significantly higher in infants of atopic than in non-atopic

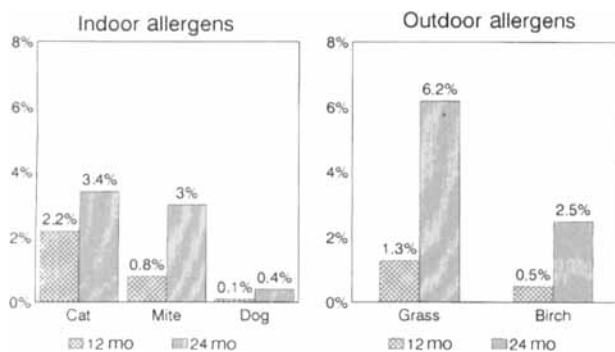


Fig. 7. Prevalences of sensitization against outdoor allergens at 12 and 24 months of age.

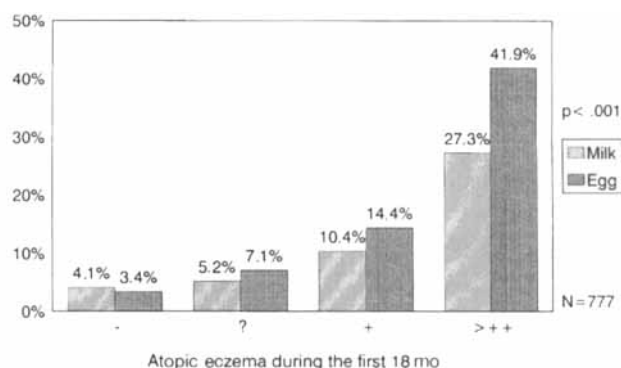


Fig. 8. Percent of infants with atopic eczema sensitized against milk and egg protein according to severity and duration of eczema: – no, ? probable, + during one period, >+ during at least 2 periods.

families. Infants of families with two atopic first degree relatives had nearly twice the prevalence of atopic eczema as infants with only one atopic family member (Fig. 9). The risk to have an eczema for the first time was higher during the first three months of life, and also elevated by an atopic family history (Fig. 10). The influence of the atopic family history decreased with age (Fig. 10).

Of the risk factors at birth, family history of atopic disease (i.e. no, one or two close relatives atopic) was significantly related to obvious atopic manifestations of the infants at one year ($p < 0.00005$), and at two years ($p < 0.00001$), while cord blood IgE percentiles were significantly related to sensitization of the infants at one year ($p < 0.00001$) and at two years ($p < 0.0001$). Cord blood-IgE was not a predictor of atopic manifestations of the infants neither at the age of one, nor at the age of two years.

Discussion

The distribution of risk factors in over 6000 infants screened at birth for the MAS-90 study is similar to many other population based studies. Cord blood IgE values were skewed to the right, and irrespective

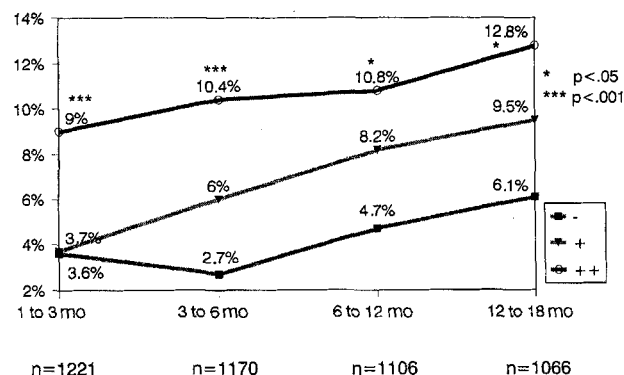


Fig. 9. Period prevalences of obvious atopic eczema, profiles according to atopic history of first degree relatives: – no family atopy, + one atopic relative, ++ two or more atopic relatives.

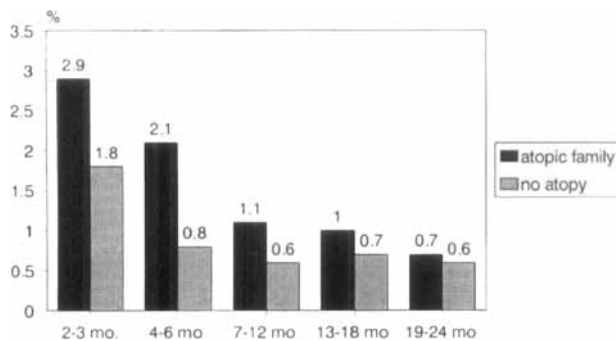


Fig. 10. Risk per month of new cases of atopic eczema according to atopic history of first degree relatives.

of the techniques used, most of the samples were below detection limits (10–12, 6). Proportions of elevated values (differently defined) ranged from 3% above 1.0 kU/l (10) to 13% above 0.5 kU/l (12); 9% of elevated values in the MAS-90 study is within this range of observations.

The percentage of close family members of newborns being atopic, as obtained by history, was slightly lower in the MAS study (31%) compared to others, e.g. 32% (13), 36% (11), 39–45% (14) and 57% (6). This could be due either to an underestimation by recall of the prevalence of atopic diseases in the parents or to a lower true prevalence in Germany. Because the parents were not only asked for diagnoses but also for atopy-specific symptoms, underestimation was somewhat controlled for. This is confirmed by the results of the Phadiatop test, which identified the same proportion of atopic parents as the questionnaire did (9).

In most of the prospective cohort studies on the prediction of atopic diseases in early childhood the infants were non-selected, while the MAS-90 cohort is enriched with high risk infants. A higher prevalence of atopy is therefore expected in the MAS-90 infants at follow-up. Also, a true increase of atopic diseases in infants of recent birth cohorts has to be considered. In all these studies different criteria for atopic diseases were used. In the MAS-90 study manifestation and sensitization were treated separately in order to study the etiology. Although atopic diseases are IgE mediated, clinical manifestations often precede or are observed without a positive test for a specific sensitization, or vice versa.

While lifetime prevalence of obvious atopic eczema in the MAS-90 study was 12% in the first year and 18% in the first two years of life, it was usually less in non-selected cohorts: eczema was observed in 11% of infants during the first year and also in nearly 11% of infants during the second year of life (15, 6). In the first 18 months of life only 6% of Swedish infants, born in 1974–75, were reported to having (had) eczema (2), and 8% of infants from a recent study in the USA (17). In contrast, 15% of

infants in the Danish study, whose cohort was enriched with infants with elevated cord blood IgE values, had atopic eczema in the first 18 months of life (12). A high rate was also found in unselected infants born in 1977 in New Zealand: 17% of these infants had eczema in the first two years of life (16).

The lifetime prevalence of asthma in the first year and in the first two years was 10% and 15%, respectively, in the MAS-90 study. In the non-selected cohort studies, about 10% of infants had asthma in the first year and 11% in the second year in Great Britain (6, 15). There were only 1.7% of Swedish infants with asthma in the first 18 months (2). In the USA, 19% of infants in the first year had a lower respiratory tract infection with wheeze (17), which is not quite comparable to the asthma definitions of the MAS-90 study. In the Danish study 10% had a wheezy bronchitis in the first 18 months (14), which is similar to the prevalence in the MAS-90 study.

Food intolerance was observed in 2.9% of infants during the first 18 months of life in Denmark (17), which is close to the values in the MAS-90 study of 3%, while the prevalence of food reactions was higher in other studies. Except for the British study, most prospective studies find a very low prevalence of allergic rhinitis and conjunctivitis.

The lifetime prevalence of obvious atopy in the MAS-90 study was 25% in the first year, and 34% in the first two years. In other studies, different atopic disorders were included in this overall diagnosis, and there was no selection of infants with a high family risk. Prevalences therefore were slightly lower, e.g. 19% of definite atopic disorders during the first 18 months in Denmark (14) and 23% of atopic manifestations in the first year and also in the second year of life in the British study (6, 15).

One of the clues in differential diagnosis between atopic eczema and seborrheic dermatitis is thought to be the age at onset. In contrast to the course of the disease assumed by many authors, in this study the highest rate of new cases of atopic eczema was observed before three months of age. This would be in line with the observations of Yates et al. (18), who did not find a significant difference in the age at onset between both skin diseases. Bonifazi and Meneghini (19) even observed that of 2320 children with eczema studied, in 51% the disease began during the first 3 months of life.

The high incidence of wheezing in the first 3 months of life in this study reflects the susceptibility of small infants to lower respiratory tract infections, which is declining with age. Although some of the early wheezers will develop asthma later in life, most of the children who wheezed before their second birthday, never wheezed again (20). The follow-up of the MAS-90 study will prove who of the wheezing infants will develop atopic asthma.

Sensitization has been defined in the MAS-90 study as a CAP-value above 0.35 kU/l against at least 1 allergen. This cut-off value is rather low, and the prevalence of sensitized infants is higher in the MAS-90 cohort than in other studies: 16% of infants were sensitized at one year of age and 24% at two years of age. At 2 years of age only 5% of the population based British study infants had a positive SPT, most frequently against housedust, cat and egg (15), and at 18 months of age 8.5% and 12% of the infants in the two study centers in Denmark had a positive RAST against at least one allergen, predominantly against milk and egg (21). In the MAS-90 study sensitization against aeroallergens increased from age 1 to age 2 years, which is in line with experiences of others. In a longitudinal study in France, e.g. 29 infants with severe atopic eczema were followed up through 3 years of age. While all these infants were sensitized against food antigens and none against aeroallergens at 4 months of age, at 3 years of age 79% were sensitized against aeroallergens (22).

Exclusive breastfeeding through the first 6 months of life is rare in Germany (23). A high proportion of infants in this study was exposed to cow's milk proteins already in the first days of life, and to a diversity of solid foods in the first three months of life. Although atopic parents were more reserved regarding these adverse feeding habits, still a high proportion adhered to the customary rules which might be influenced by the availability and attractivity of commercial foods rather than by necessity and appropriateness of supplements.

From analyses of the family questionnaire data for all newborns we concluded, that there were less smokers in those parents who had atopic symptoms; this phenomenon was called 'the healthy smoker effect' (5). The follow-up data of the cohort point to the same direction: In apartments with atopic fathers less cigarettes were smoked than with non-atopic fathers. But there was no difference in passive smoke exposure between both groups, whereas when the mothers or the siblings suffered from an atopic disease, all family members were probably urged to smoke in the absence of the infant or to stop smoking: Urine cotinine values were significantly lower in those infants. Pregnancy, on the other hand, did not prevent mothers from smoking: 22% of mothers in the MAS-90 study smoked in pregnancy, which is nearly the same prevalence as in the follow-up questionnaire, and comparable to the frequency of 26% in the USA (24).

The major importance of two perennial indoor allergens for the risk of atopic airway disease has been shown in previous studies. Mite allergen concentrations are lower in the MAS-households than in many other European areas or in the USA (25, 26).

But still 25% of households had mite allergen concentrations above the critical value for sensitization, i.e. 2000 ng/g carpet dust (27). The prevalence of furred pets in the homes of the MAS-study, i.e. 31%, is quite high, but probably lower than in the German population and lower than in other countries, where cats and dogs were found in over 50% of homes (28).

As with early feeding habits and with parental smoking, a family history of atopy influences the style of living, especially in people with acute complaints from the offending allergen. Therefore, confounding, and interactions of, factors will have to be controlled for when causal inferences will be drawn from the results of the MAS-90 study.

The detailed analysis and discussion on the prediction of the atopic manifestation and sensitization by the family history and by the cord blood IgE value has been presented elsewhere (29).

Acknowledgement

Supported by the German Ministry of Research and Technology Grant No. 070 156 33.

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