

Indoor allergen exposure is a risk factor for sensitization during the first three years of life

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Background: The purpose of the study was to investigate the influence of environmental allergen exposure on allergic sensitization in infancy and early childhood.

Methods: A cohort of 1314 newborns was recruited and followed up prospectively at the ages 12, 24, and 36 months. The levels of major mite (Der p 1 and Der f 1) and cat (Fel d 1) allergens were determined from domestic carpet dust samples by sandwich ELISA. Specific serum IgE antibodies to mite and cat allergens were determined by CAP fluoroimmunoassay (Pharmacia). Logistic regression was used to assess the effects of allergen exposure, age, family history, and cord blood IgE simultaneously on the risk of sensitization.

Results: Children, who had been found to be sensitized at least once during the first 3 years of life, were found to be exposed to significantly higher house dust mite (median, 868 ng/gm vs 210 ng/gm; $p = 0.001$) and cat (median, 150 ng/gm vs 64 ng/gm; $p = 0.011$) allergen concentrations in domestic carpet dust compared with the group without sensitization. In homes with low (≤ 25 th percentile) dust concentrations, the risk of sensitization to mite (1.6%) and cat (2.0%) is low, compared with 6.5% for mite and 6.3% for cat if the domestic exposure is above the 75th percentile. The dose-response relationships between allergen levels and sensitization indicate that the increase in sensitization risk at low allergen levels is more pronounced in cat allergy ($p = 0.002$) than in mite allergy ($p = 0.026$). In the group with a positive family history, lower mite and cat allergen concentrations are needed to achieve specific sensitization compared with the group with a negative family history.

Conclusion: Our data indicate that avoidance measures in the domestic environment aimed at the primary prevention of allergen-driven sensitization should be introduced at the earliest possible stage, if possible during infancy. (*J Allergy Clin Immunol* 1997;99:763-9.)

Key words: Atopy, early sensitization, house dust mites, environment, allergy prevention

A number of epidemiologic studies indicate that the prevalence of allergic airway diseases has been increasing over recent decades, especially in western industrialized countries, for reasons that are not yet completely understood.¹⁻³ Changes in lifestyle and an increase in indoor allergen exposure caused by higher indoor temperature and humidity have been suggested as potential determinants, although evidence for both hypotheses is indirect.⁴

Sensitization to indoor allergens has been demonstrated to be one of the major risk factors for the development of asthma in childhood.⁵⁻⁸ Several cross-sectional studies in older children indicate that specific sensitization to house dust mites is related to dust mite allergen concentrations in mattress dust.^{9,10} Exposure threshold levels for several indoor allergens have been proposed, but individuals vary widely in their susceptibility to levels of exposure, and no absolute value that could generally ensure minimum risk has been identified.

During the neonatal period, there is never atopic sensitization to indoor allergens, defined by the presence of specific serum IgE antibodies. However, if it develops, it generally does so in the first decade of life. A full understanding of the relationship between allergen exposure and the time course of sensitization appears to be a prerequisite for strategies to prevent or delay sensitization (primary prevention). This study was designed to assess the role of indoor allergen exposure during the first 3 years of life as a potential risk factor.

METHODS

Patients

In the German Multicenter Atopy Study, 7609 newborns were recruited in five German cities (Berlin, Düsseldorf, Freiburg, Mainz, and Munich). A family questionnaire on atopic diseases, relevant symptoms, diagnostic tests, and socio-demographic variables was filled in by the parents. The details of the study design are reported elsewhere.¹¹

A cohort of 1314 of the newborns was recruited for our prospective study. Four hundred ninety-nine infants (38%) were selected as being at high risk (having at least two atopic first-degree family members and/or a cord blood IgE value above 0.9 kU/L). Eight hundred fifteen infants (62%) were chosen at random from the remaining newborns (one or no atopic family members and cord blood IgE value less than 0.9 kU/L).

The cohort infants were brought to follow-up visits at the

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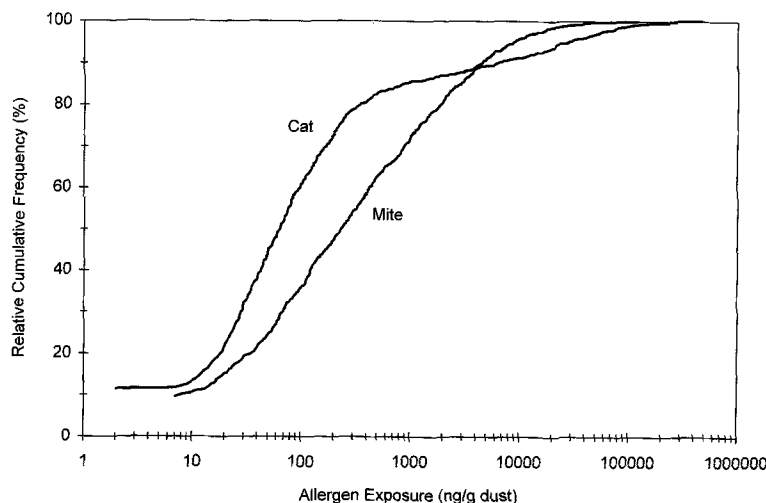


FIG. 1. Relative cumulative frequency distribution of mean concentration of major mite (Der p 1 + Der f 1) and cat (Fel d 1) allergens in carpet dust samples.

ages 1, 3, 6, 12, 18, 24, and 36 months. Parents filled in a questionnaire and gave structured interviews about their infants' diseases and relevant symptoms. Study participation rate at the third birthday of the children was 80%.

In this analysis we included all members of the cohort with available dust and blood samples. The availability of the dust samples was $n = 1051$ for Der p 1 and Der f 1 and $n = 1039$ for Fel d 1. The numbers of children with at least one positive blood sample were 880 for specific IgE to mite allergens and 873 for specific IgE to cat allergens. Both dust and blood samples were available for 764 children with specific IgE to mite and for 746 children with specific IgE to cat.

Serum IgE

Blood samples were taken at 12, 24, and 36 months for the determination of total serum IgE and specific IgE antibodies to *Dermatophagoides pteronyssinus* and cat by using a quantitative fluoroimmunoassay (CAP-FEIA; Kabi Pharmacia Diagnostics, Uppsala, Sweden). For total IgE, the detection limit was 0.35 kU/L. A child was considered sensitized if IgE antibody concentrations were higher than 0.35 kU/L (i.e., CAP class 1), with a kilounit being equal to 2.4 ng of IgE (World Health Organization IgE standard 75/502).

Dust sampling

Carpet dust samples were obtained when children were 6 and 18 months old. The exact date of dust collection varied within a range of ± 1 month. The families were instructed to use their own vacuum cleaners, with a new dust bag, to vacuum 1 m² areas of the carpet in the living room, parents' bedroom, and child's bedroom (carpets were present in all houses) for 3 minutes. The dust bag was put in a plastic bag, mailed to our laboratory, and kept at 4°C until analysis.

Allergen assay

Allergen extraction and analysis of Der p 1, Der f 1, and Fel d 1 were performed as previously described by using a sandwich ELISA (ALK, Copenhagen, Denmark).¹² Assay sensitivity was 2 ng/gm dust. Previous experiments demonstrated an interassay coefficient of variation of 17% to 25% and an intraassay coefficient of variation of 5% to 10%.

The results are expressed in nanograms of major allergen per gram of carpet dust.

When both dust samples were available for a particular child, arithmetic mean values of the samples obtained at the ages of 6 and 18 months were used in further statistical analyses.

Statistical analysis

Allergen exposure levels in sensitized and nonsensitized children were compared by using the Mann-Whitney U test. Because rates of participation in blood sampling varied over the 3 years of observation, cumulative sensitization rates were estimated by the life table method.¹³ If a child had missing data on sensitization to mite or cat allergens at a time point, his or her sensitization status for that time point was interpreted as negative, regardless of whether the child was found to be sensitized at a subsequent examination. Logistic regression¹⁴ was used to assess the effects of allergen exposure, age, family history, and cord blood IgE on the risk of sensitization simultaneously. Positive family history was defined as at least one atopic family member (parent or sibling). To model the dose-response relationship between allergen concentration and sensitization, suitable power transformations of allergen levels were chosen from the set of fractional polynomials.¹⁵ To avoid numerical ambiguities, this analysis was confined to cases with positive allergen exposure. The statistical significance of a potential risk factor is given as p value of the likelihood-ratio test statistic relative to the model without the factor in question.

RESULTS

Carpet dust concentrations of major allergens of mite and cat vary over a wide range (Fig. 1). The results from dust samples obtained at 6 and 18 months (Table I) indicate that the allergen concentrations are of about the same magnitude at both time points within our large field study, in spite of the fact that sampling procedures were only partly standardized. Nine hundred eighty-two children had at least one blood examination during the observation period. The number of children in our cohort who were sensitized to either mite or cat was

TABLE I. Mite and cat allergen exposure (in nanograms per gram of dust) in house dust samples collected from the cohort at 6 and 18 months of age

Exposure to	No. of samples	25th percentile	Median	75th percentile
Der p 1 + Der f 1 (6 mo)	965	33	184	985
Der p 1 + Der f 1 (18 mo)	794	58	223	1306
Fel d 1 (6 mo)	948	15	55	217
Fel d 1 (18 mo)	768	27	60	190

TABLE II. Prevalence and concentration of specific serum IgE antibodies to indoor allergens (mite, cat) among children at 1, 2, and 3 years of age

	Serum IgE measurement					
	<i>D. pteronyssinus</i>			Cat		
	No. of samples	n (%) (detectable)	Median of detectable IgE (kU/L)	No. of samples	n (%) (detectable)	Median of detectable IgE (kU/L)
First year	783	9 (1.1)	15.6	787	20 (2.5)	0.8
Second year	671	22 (3.3)	1.7	670	23 (3.4)	1.7
Third year	620	34 (5.5)	2.3	624	33 (5.3)	3.2

TABLE III. Mite allergen (Der p 1 + Der f 1) concentrations (mean of determination at 6 and 18 months) in children with detectable and undetectable IgE to *D. pteronyssinus* and in children with unknown sensitization status

Specific serum IgE to <i>D. pteronyssinus</i>	n	Der p 1 + Der f 1 exposure (ng/gm dust)		
		25th percentile	Median	75th percentile
One year				
Detectable*	7	1110	1944	4000
Not detectable	697	53	223	1098
Serum samples not available	347	49	268	1310
Two years				
Detectable*	20	160	497	1662
Not detectable	593	51	243	1211
Serum samples not available	438	52	203	1188
Three years				
Detectable*	30	100	706	2538
Not detectable	528	47	202	1085
Serum samples not available	493	57	270	1402
Sensitization up to 3 years of age				
At least once†	41	223	868	3700
Never sensitized†	839	50	210	1113
Unknown	171	48	270	1390

* $\geq$ CAP class 1.

†Difference of allergen exposure between sensitized and nonsensitized children was determined by Mann-Whitney U test ($p = 0.001$).

small at the first birthday. However, the number of children with detectable specific serum IgE increased during the observation period (Table II). From the homes of these 982 children, sufficient dust for analysis was available for 873 Fel d 1 and 880 Der p 1/Der f 1 assays.

When mite allergen exposure was related to the sensitization status of children at 12, 24, and 36 months, the median allergen exposure levels were higher for children with detectable than for those with undetectable serum IgE to mites (Table III). In the homes of

children who had been found to be sensitized at least once to house dust mite, the median carpet dust concentrations were significantly higher than in the homes of the nonsensitized group (median allergen concentrations, 868 ng/gm [$n = 41$] vs 210 ng/gm dust [$n = 839$], $p = 0.001$).

Similar results were found for children sensitized to cats. Regarding sensitization status up to 3 years of age, the median cat allergen concentrations in the group of sensitized children were significantly higher than in the

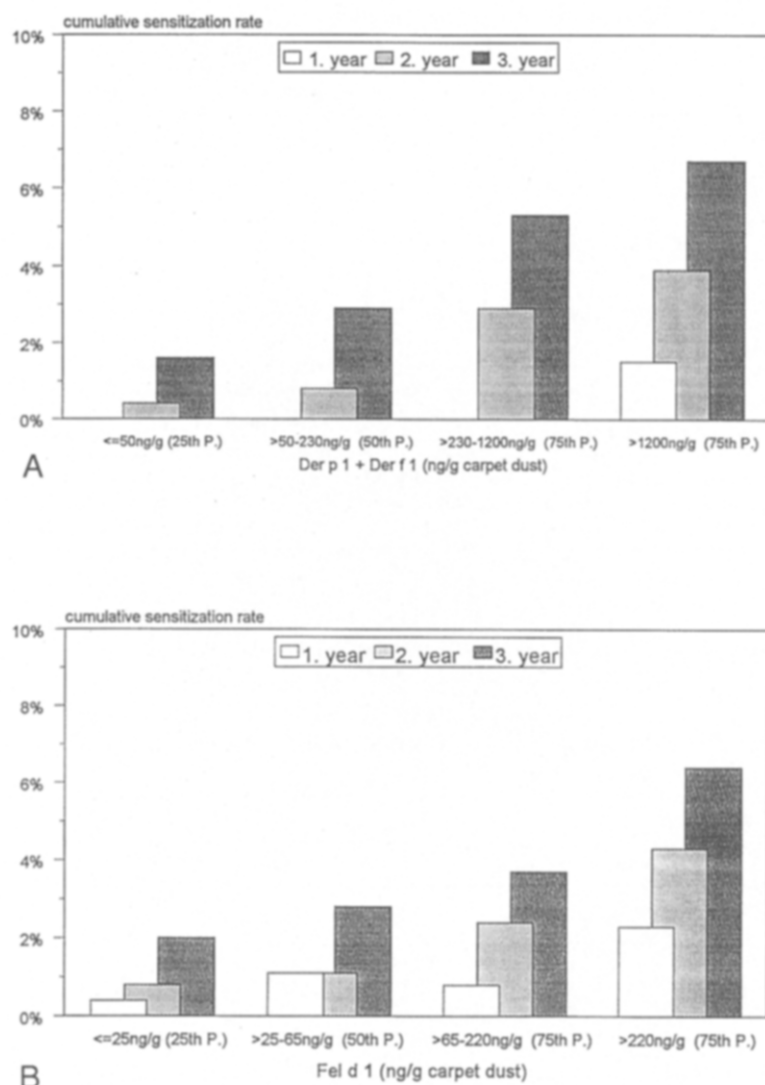


FIG. 2. Mite (A) and cat (B) allergen exposure levels in relation to cumulative percentage of sensitization. Ranges of the four groups were obtained by calculating the 25th, 50th, and 75th percentiles of mite and cat allergen concentrations of all children included in the analysis.

group of nonsensitized children (median allergen concentrations, 150 ng/gm [$n = 37$] vs 64 ng/gm dust [$n = 836$], $p = 0.011$). Although mite and cat allergen concentrations in dust samples, which had been obtained throughout the year, showed some seasonal variations, the incidence of sensitization for both cats and mites was not affected by these changes.

Cumulative rates of sensitization to house dust mites were 0.5%, 1.9%, 3.8%; and to cat allergens, 1.1%, 2.0%, 3.3% in the first 3 years of life. Fig. 2 shows the cumulative sensitization rates in the four quartiles of allergen levels up to the first, second, and third years of life. In homes with very low ($\leq$ 25th percentile) carpet dust concentrations, the risk of sensitization to mite or cat allergens during the first 3 years of life is 1.6% or 2.0%, respectively, increasing to values above 6% if the domestic major allergen exposure is above the 75th

percentile, which is 1200 ng/gm for Der p 1 + Der f 1 and 220 ng/gm for the major cat allergen Fel d 1.

If stratified by atopic family history, the relationship between sensitization and allergen exposure shows different patterns. After the data were ordered according to increasing allergen concentrations, the number of sensitized children up to that allergen concentration was determined (Fig. 3). In the group with a positive family history, a mite allergen exposure below 750 ng/gm is sufficient to result in a 3% sensitization rate. In contrast, an exposure up to 25,000 ng/gm dust is necessary to achieve a sensitization rate of 3% in the group of children with a negative family history. Similar dose-response relationships were found for cat allergen exposure and sensitization rates cumulated over exposure levels in the two subgroups. The steep increase of sensitization risk at low exposure levels is concealed by

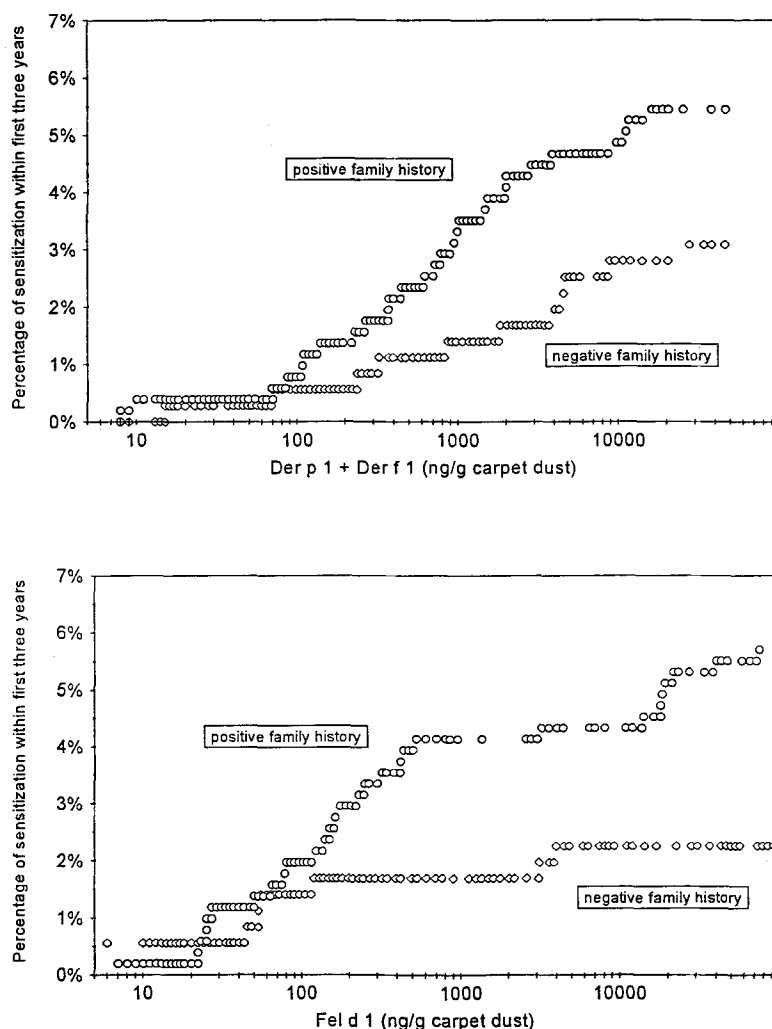


FIG. 3. Sensitization rates to *Dermatophagoides pteronyssinus* and cat up to 3 years of age cumulated over major mite (Der p 1 + Der f 1) and cat allergen (Fel d 1) exposure levels in children with and without a positive family history of atopy.

the logarithmic scaling. Logistic regression analysis (Table IV) shows that the risk of sensitization to mite allergens increases significantly with age (odds ratios: 5.2 for second year and 8.8 for third year vs first year [$p = 0.0001$]). In contrast, the risk of sensitization to cat allergens remains the same ($p = 0.37$) in the second and third years when compared with the already high risk in the first year. Different power transformations proved to be appropriate to model the dose-response relationship between allergen levels and sensitization to mite or cat allergens. For cat allergen exposure, the fit of the $1/\sqrt{x}$ transformation is better than the fit of the log transformation. If log transformation of the cat allergen exposure is used, the association remains significant; however, the odds ratio changes to 1.6 (95% confidence interval [CI]: 1.2 to 2.1, $p = 0.008$). The type of these transformations indicates that the increase in sensitization risk at low allergen levels is more pronounced in cat allergy ($p = 0.002$) than in mite allergy ($p = 0.026$).

Other evaluated covariates were atopic family history, detectable cord blood IgE, gender, and smoking in household (no vs yes). Gender and smoking in household were not considered in the final models because of their absence of effect on sensitization. The association between atopic family history and sensitization was stronger for cat (odds ratio = 3.0) than for mite allergens (odds ratio = 1.8) and was significant only for sensitization to cat allergens ($p = 0.007$). Detectable cord blood IgE doubles the risk of sensitization to both types of indoor allergens ($p < 0.05$).

DISCUSSION

Our findings indicate that the early induction of sensitization to indoor allergens during infancy and early childhood in children with or without a family history of atopy is related to domestic allergen exposure. Our birth cohort study is the first to offer evidence for the time course of the incidence of sensitization over the first 3

TABLE IV. Multiple logistic regression analysis of risk factors for sensitization to mite and cat allergens in children up to 3 years of age (adjusted for study center)

Sensitized/Not sensitized	Sensitization to	
	Mite (n = 35/n = 729)	Cat (n = 31/n = 715)
Second vs first year of life		
Odds ratio (CI)	5.2 (1.5-18.3)	1.0 (0.4-2.5)
Third vs first year of life		
Odds ratio (CI)	8.8 (2.6-30.1)	1.7 (0.7-4.1)
Allergen exposure*		
Odds ratio (CI)	1.2 (1.03-1.5)	2.3 (1.3-3.9)
Cord blood IgE (not detectable vs detectable)		
Odds ratio (CI)	2.1 (1.045-4.1)	2.1 (1.01-4.4)
Family history (non vs at least one atopic family member)		
Odds ratio (CI)	1.8 (0.9-3.8)	3.0 (1.3-7.1)

CI, 95% confidence interval.

*Transformations y used for allergen concentrations x in logistic regression $y_{\text{mite}} = \log(X_{\text{mite}})$, $y_{\text{cat}} = \frac{-10}{\sqrt{X_{\text{cat}}}}$. After transformation of the mean allergen concentrations, odds ratios were computed as the exponent of the respective regression coefficient (e^{β}) and the CI according to the standard formula ($e^{\beta \pm z \cdot \text{se}(\beta)}$).

The following results are found if the log transformation of cat allergen exposure is used: odds ratio: 1.6 (95% CI: 1.2-2.1, $p = 0.008$).

years of life. The incidence of specific sensitization to mites during infancy is low (0.5%) and tends to increase during the second (1.4%) and third (1.9%) years of life. In contrast, no similar trend for the incidence of sensitization to cats (1.1%, 0.9%, 1.3%) could be observed.

The demonstration of a dose-response relationship between exposure to cat and mite allergens and specific sensitization was possible, although sampling procedures used in this study to quantitate allergen load within the individual households could only partly be standardized and—especially for cat allergens—the relationship between allergen levels in the air and from carpet dust is known to be variable.

The demonstration of dose-response effects depends on sampling from a wide range of exposure. In Germany, where the majority of homes and apartments are infested by house dust mites, mite allergens could be demonstrated in 88% and cat allergens in 83% of all carpet dust samples. The concentrations of major allergens from house dust mites or cats ranged over more than 3 orders of magnitude. Although measurement of carpet dust does not indicate the actual amount of allergen entering the airways, reservoir measurements have been accepted as the most appropriate available index of exposure.¹⁶

Cross-sectional¹² and longitudinal¹⁷ studies at school age have led to the conclusion that the risk of sensitization increases with increasing allergen exposure. Recently, several authors have proposed exposure thresh-

olds for sensitization to indoor allergens and allergic symptoms, but there appears to be no absolute value, which could function as a recommended target to provide minimum risk. Our cohort shows that children with a positive family history of atopy are especially susceptible to even very low levels of exposure.

Our results also indicate that although genetically linked markers, which are detectable during the neonatal period (positive family history, elevated cord blood IgE), may increase the risk of early sensitization, the sensitivity to these predictors is too low to use them as neonatal screening parameters or as a basis for early intervention.

The fact that, in contrast to mite allergen, extremely low levels of domestic cat allergen exposure are associated with some risk of early sensitization indicates that cat allergen exposure in places other than the domestic environment may have led to specific IgE responses. Munir et al.¹⁸ have reported higher levels of Fel d 1 in dust samples of Swedish day care centers than in family apartments.

Evidence has been accumulated that most asthmatic illness in childhood is associated with some degree of sensitization, in particular sensitization to indoor allergens.¹⁹⁻²² In Sweden, where house dust mites are found in homes relatively infrequently, the presence of mite allergens has been reported to relate to asthmatic symptoms.²³ For older children, a dose-response effect between exposure and asthmatic symptoms has been difficult to demonstrate because many factors may simultaneously influence the severity of asthma.²⁴ In another birth cohort study, Sporik et al.²⁵ were able to demonstrate that the onset of wheezing in later childhood is related to the amount of Der p 1 in mattress dust samples during infancy. However, the evidence for a dose-response effect between mite allergen exposure and disease severity was indirect and largely circumstantial. In our cohort wheezing during the first 2 years of life was not related to allergic sensitization or a positive family history of atopy. Instead, we were able to describe an association between the prevalence of wheezing during this period and the presence of specific antibodies to respiratory syncytial virus.²⁶

Because specific sensitization to mites and pets appears to be especially important among the various environmental risk factors for childhood asthma, intervention strategies have been developed to address the various sites where mite and pet allergens occur.^{27, 28} In most studies, strategies have been investigated in established diseases, in which sensitization has already occurred (secondary prevention). There is only one study in the literature ("Isle of Wight Study") investigating attempts to prevent or delay mite sensitization of infants at risk for atopic disease.²⁹⁻³¹ Intervention in this study included both reduction of indoor allergen exposure and avoidance of exposure to food allergens in infancy. The authors observed a significant reduction in sensitization to house dust mites between the prophylactic and control groups.

Our data may provide the basis for the study of intervention strategies aimed at primary prevention. Although the time course of atopic sensitization to

indoor allergens is clearly different from the time course of food sensitization and IgE responses to environmental allergens are infrequently observed in infancy, early avoidance during the first year of life seems mandatory. The principles of the control strategies for mite and pet allergens are similar; however, the approach may need to be completely different. Mite allergen elimination is primarily directed toward the major allergen reservoirs such as mattresses and carpets. In addition, countering the biologic factors, which stimulate mite populations and allergen production at different sites (indoor humidity, poor ventilation), seems to be important. Cat allergens remain airborne over a long period, so their elimination may have to include air filtration. Taking into account the data presented in this study, it must be the aim of primary prevention studies to reduce indoor allergens to a minimum.

In summary, our study shows a dose-response relationship for sensitization to indoor allergens during the first 3 years of life. In the future, it remains to be seen how the incidence of allergic airway symptoms, such as rhinitis and asthma, is related to early allergen exposure. It will also be necessary to develop adequately powered, randomized, controlled studies to investigate the potential benefits of low-allergen domestic environments for infants at high risk of developing allergic diseases, because avoidance of primary sensitization in susceptible infants seems possible.

The incidence of sensitization to mites has been described to be related to allergen exposure at school age.¹⁷ Therefore it would seem reasonable to assume that continuous avoidance measures throughout life are necessary to achieve a reduction in long-term sensitization and possibly subsequent atopic disease.

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