

Clinical aspects of allergic disease

Sensitization to mite allergens is a risk factor for early and late onset of asthma and for persistence of asthmatic signs in children

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Background: To describe the natural history of asthma between the ages of 7 and 10 years and to analyze risk factors for prevalences, as well as new onset of asthma-like symptoms, a longitudinal study of 1812 children was conducted.

Methods: In four surveys, each 1 year apart, four asthma-like symptoms and several hypothetical risk factors were ascertained through standardized questionnaires. Sensitization to seven common inhalant allergens was measured by skin prick testing. Exposure to mite allergens (Der p I, Der f I) was assessed by measuring the antigen concentrations in the dust of each child's mattress. Occurrence of more than one asthma-like symptom closely related to the practitioner's diagnoses of bronchial asthma and recurrent wheezy bronchitis was used as the outcome variable.

Results: After an initial prevalence of 14.5%, new onset of symptoms in children unaffected at the beginning was reported in 7.2% during the 3 years. Of the factors explaining prevalence and persistence of asthma-like symptoms (sensitization to mite allergens and animal danders, history of hay fever and eczema, low gestational age, male gender, parental atopy), only sensitization to mite allergens (odds ratio = 2.3, 95% confidence interval = 1.1-4.7) and parental atopy (odds ratio = 2.1, 95% confidence interval = 1.2-3.7) were also significantly associated with new onset. In a relatively small number of sensitized subjects with new onset of symptoms (n = 31), mite antigen concentration did not appear to be associated with incidence of symptoms.

Conclusion: Sensitization to mite allergens antedated the onset of asthma-like symptoms, and no strong effect of allergen exposure on clinical development could be found. Thus the primary focus should be on preventing sensitization to mite allergens by implementing avoidance measures in infancy or at early school age in order to reduce the onset of asthma at a later stage. (*J ALLERGY CLIN IMMUNOL* 1995;95:655-62.)

Key words: Asthma, sensitization, mite, incidence, children, risk factor, population-based

Bronchial asthma in childhood is associated with sensitization to common inhalant allergens.^{1,2} In most affected children, allergic sensitization and onset of asthmatic symptoms, such as wheezing, is

Abbreviations used

95% CI: 95% confidence interval
LGA: Low gestational age
OR: Odds ratio
SPT: Skin prick test

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detectable in infancy.³ However, a proportion of sensitized individuals has no asthmatic complaints at early school age.⁴ Some earlier studies have suggested that sensitization to common inhalant allergens can precede respiratory symptoms by an extended period.^{5,6} Thus onset of complaints

TABLE I. Frequency of potential risk factors under stratification for prevalence of asthma-like symptoms in survey 1 and incidence of symptoms from survey to survey

Factor	Prevalence in survey 1				Incidences from survey to survey					
	Number of symptoms			p	1 to 2		p	2 to 3		p
	0 (n = 1206)	1 (n = 336)	>1 (n = 262)		No (n = 1057)	Yes (n = 26)		No (n = 927)	Yes (n = 25)	
SPT+										
Pollens	9.6	11.7	20.5	≤0.001	9.5	27.3	≤0.01	12.5	4.0	NS
Mites	8.8	9.9	25.9	≤0.001	8.3	27.3	≤0.01	11.1	16.0	NS
Danders	4.9	7.8	22.8	≤0.001	4.8	13.6	NS	5.6	16.0	≤0.05
Any allergen	16.1	19.5	36.6	≤0.001	15.8	40.9	≤0.01	19.8	24.0	NS
History of hay fever	4.0	7.3	12.8	≤0.001	3.5	20.0	≤0.001	5.9	0	NS
History of eczema	13.4	18.9	26.9	≤0.001	14.2	15.4	NS	19.9	28.0	NS
LGA	6.5	8.8	10.8	≤0.01	6.5	15.4	NS	6.1	8.0	NS
Male gender	46.4	50.6	58.0	≤0.01	44.9	73.1	≤0.01	44.7	36.0	NS
Maternal atopy	21.9	26.5	31.0	≤0.001	22.6	46.2	≤0.01	23.7	20.0	NS
Paternal atopy	17.7	23.2	28.2	≤0.001	18.5	42.3	≤0.01	18.8	28.0	NS
Maternal smoking	29.3	31.3	34.5	NS	32.1	15.4	NS	30.0	36.0	NS
Location										
Freiburg	51.9	54.2	45.8		52.0	42.3		51.8	56.0	
Lörrach	27.5	22.9	24.8		27.0	38.5		26.8	16.0	
Kehl	20.7	22.9	29.4	≤0.05	21.0	19.2	NS	21.5	28.0	NS
Educational level										
High	37.0	39.8	35.6		37.2	32.0		37.5	45.8	
Medium	27.9	26.4	33.6		28.4	44.0		28.1	33.3	
Low	35.2	33.8	30.9	NS	34.4	24.0	NS	34.4	20.8	NS

Any incidence is analyzed, but only if no symptom was reported in survey 1. No = 1 or no symptoms; Yes = more than 1 symptom. SPT+, Positive SPT response; NS, not significant.

might also be found at school age. It is still not clear by which factors such a late new onset of asthma can be predicted. By analyzing data from a 3-year follow-up community-based cohort study, this article focuses on the relevance of several risk factors for prevalence and incidence of asthmatic symptoms. In addition to sensitization to inhalant allergens and exposure to mite allergens, the analyses account for gender, parental atopy, maternal smoking, gestational age, and histories of hay fever and eczema.

METHODS

Study population

Data were collected in a longitudinal study designed to assess risk factors for allergy and asthma in a community-based cohort of children.⁷ All parents in three mainly urban areas of Southwestern Germany (Freiburg, Lörrach/Weil, and Kehl) whose children started school in 1989 ($N = 2604$) were invited to participate, and of these, 1812 (70%) took part. Three questionnaires (surveys 1 to 3: 1990, $n = 1812$; 1991, $n = 1626$; and 1992, $n = 1477$) were distributed and completed by the parents. If consent was given, skin prick tests (SPTs) were carried out consecutively, 12 months apart, each in

spring (1990, $n = 1470$; 1991, $n = 1416$; 1992, $n = 1305$). A final questionnaire (survey 4: 1993, $n = 1394$) completed ascertainment of the 3-year follow-up. The first and second exposure assessments refer to household visits between December and March of the respective winters (1990/91 and 1991/92) in which dust samples from each child's mattress were taken. The study was approved by the local ethical committee and also by local school authorities.

Questionnaires

Questions regarding the child's medical history,⁴ which were used in each of the four questionnaires, dealt with yearly prevalence of four asthma-like symptoms (cough after exercise; wheeze [in 1990 survey: lifetime prevalence]; shortness of breath/cough in the night/morning; and attacks of shortness of breath [in 1990 survey: lifetime prevalence]). Other items were asthma (doctor's diagnoses of bronchial asthma or recurrent wheezy bronchitis) and hay fever (doctor's diagnoses of asthma and hay fever: lifetime prevalence in survey 1 and yearly prevalence in surveys 2 to 4); signs of eczema; parental atopy (maternal or paternal history of asthma, hay fever, or eczema); maternal smoking in the preceding 12 months; low gestational age (LGA) (child born at least 3 weeks before term); educational level (highest

Incidences from survey to survey		
3 to 4		
No (n = 856)	Yes (n = 18)	p
16.2	56.3	≤0.001
13.5	56.3	≤0.001
8.5	31.3	≤0.01
23.5	62.5	≤0.001
7.4	0	NS
21.4	22.2	NS
6.4	0	NS
43.9	66.7	NS
23.4	38.9	NS
18.6	38.9	≤0.05
29.1	27.8	NS
51.2	50.0	
27.0	22.2	
21.9	27.8	NS
37.9	44.4	
29.0	27.8	
33.1	27.8	NS

level achieved at school by father or mother); nationality; and gender.

SPT

On each of the three occasions, the SPT was carried out by trained staff members under the supervision of a physician, and the same equipment and technique were used each time.⁷ Seven inhalant allergens (ALK, Hørsholm, Denmark) were applied to each child's forearm with the aid of an uncoated Phazet needle (Pharmacia, Uppsala, Sweden). Extracts from grass pollens (mixture of the six most common species), birch and hazel pollens, *Dermatophagoides pteronyssinus* and *D. farinae*, as well as cat and dog dander, were used (concentration: 10 histamine equivalent units in prick testing). Histamine hydrochloride (10 mg/ml) and sodium chloride (9 gm/L) were applied as control solutions. The reactions were recorded after 15 minutes. The largest and perpendicular diameters of a wheal were measured, and the arithmetic mean was calculated. A reaction to the negative control was subtracted from the allergen value. Sensitization required a wheal reaction to the allergen 2 mm or greater and a ratio (wheal to allergen/wheal to histamine) of 0.5 or greater.

Mite allergen exposure

Dust was collected from the total area of the upper side of the mattress in a standardized manner with the

same device (collector and filter from ALK) and the same type of vacuum cleaner (Miele & CIE., Guetersloh, Germany) with an airflow of 56 L/sec (specified by the manufacturer) for 5 minutes. The sample was transported to the laboratory immediately and stored at -20° C until it was extracted. Extraction (whole sample without removal of larger particles) and quantification by ELISA were performed with species-specific antibodies to *Der p* I and *Der f* I (ALK) according to the method described by Lau et al.⁸ The antigen concentration in the sample was calculated with a standard curve ranging between 1.6 and 400 ng/ml (ALK). The monoclonal antibodies to *Der p* I and *Der f* I used were Nhp5 and Nhf3, respectively. The intraassay ($n = 15$) and interassay ($n = 23$) coefficients of variation ranged between 2.5% and 12% and between 3% and 12%, respectively. Assay sensitivity was 0.004 µg of antigen per gram of dust. Mite allergen concentration is the sum of *Der p* I and *Der f* I divided by the weight of sampled dust in micrograms per gram. More details of the procedure are described elsewhere.⁹

Statistical analysis

Prevalence of asthma-like symptoms is classified into three groups: no symptom, one symptom, more than one symptom. After the description of history, the prevalences and incidences (dependent variables) were analyzed with cross-tabulation together with the chi square test (bivariate analysis) and multivariate models. Logistic analyses of prevalences of symptoms in each of the four surveys compare children with more than one symptom to those with one or no symptoms, which is also done in the longitudinal analysis of prevalences.¹⁰ Analysis of incidence (new onset), including children with no symptoms in survey 1, compares cases with onset of more than one symptom to control subjects with one or no symptoms. Analysis of incidence was carried out with a person-time logistic model.¹¹ The independent variables, gender, LGA, parental atopy, educational level, and location of residence did not change throughout the analyses, whereas information on clinical history (hay fever and eczema, prevalence cumulated from survey to survey) and maternal smoking habit is derived from the preceding and the current questionnaire, respectively. Sensitization to the groups of allergens (at least one of the three kinds of pollens, at least one of the two danders, at least one of the two mite allergens) is specified for each analysis as ascertained in the preceding survey (exception: prevalence of symptoms in survey 1 in which SPT of survey 1 was used). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for risk assessment from the multivariate models.

RESULTS

Of the 1812 children who participated in the first survey, 199 (11%) had been diagnosed with asthma. Among these children, one of the four asthma-like symptoms was reported in 34 (17.1%),

and in 119 (59.8%) more than one symptom had occurred. In contrast, only 8.9% of the nonasthmatic children ($n = 143$) had more than one symptom, and one symptom was observed in 302 of them (18.8%). The yearly prevalences of more than one asthma-like symptom in the following three surveys were lowest in the initial no-symptom subpopulation ($n = 1083$: 1991, 2.4%; 1992, 2.9%; and 1993, 2.8%), moderate in the one-symptom group ($n = 306$: 1991, 9.8%; 1992, 9.6%; and 1993, 5.6%), and highest in the group with more than one symptom ($n = 237$: 1991, 38.0%; 1992, 33.5%; and 1993, 27.9%). Frequencies of at least one symptom in consecutive years are about 60% in the last group, whereas in the one-symptom group in only 30% to 40% did such a persistence of symptoms occur. Of those participants with no initial symptom, 7.2% ($n = 66$) showed an incidence of more than one symptom during the observation period of 3 years.

Bivariate analysis

Regarding prevalence in survey 1, several of the hypothetical factors show an association with more than one asthma-like symptom (Table I). In the following sections, "no or one symptom" (references) is contrasted to "more than one symptom" (cases). Analyses of incidences from survey to survey show associations of onset of symptoms and different sensitizations. Gender, LGA, and histories of eczema and hay fever are not statistically important for incidences in survey 3 and 4.

Multivariate analysis

Multiple logistic regressions for the four cross sections (surveys 1 to 4) demonstrate increased risks of sensitization to mite allergens (OR = 2.2 to 4) and to animal danders (OR = 2.6 to 3.6), whereas for sensitization to pollens in three of four surveys no significant detrimental effect is obvious (OR = 0.5 to 1.9) (Table II). Histories of eczema and hay fever, LGA, male gender, and residence in Kehl are in three and two surveys, respectively, associated with more than one asthma-like symptom, whereas with regard to parental atopy, maternal smoking, and residence in Lörrach, no clear tendency toward an increased risk is obvious. The longitudinal model, which groups the four cross sections together, shows that sensitization to mite and animal allergens, histories of hay fever and eczema, LGA, male gender, and residence in Kehl are significantly associated with the dependent variable (Table II). Regarding persistence of asthma-like symptoms after an initial history of at least

one symptom, the risk for more than one symptom in consecutive surveys is increased in children with sensitization to mite or dander allergens, LGA, and histories of eczema or hay fever (Table II).

Incidence of more than one symptom during the observation period of 3 years after no symptom in the first survey ($n = 57$) was analyzed in a separate person-time logistic model. Sensitization to mite allergens (OR = 2.3, [95% CI] = 1.7-3.3) and parental atopy (OR = 2.1, 95% CI = 1.2-3.7) are the only variables showing significant association with the incidence of asthma-like symptoms. From Fig. 1, it is evident that in survey 1, in children without sensitization to mite allergens, a history of fewer than two asthma-like symptoms is about 20% more frequent than in initially sensitized participants. From these levels, during the course of the study, the frequency of "less-than-two-symptoms" status decreases in 5% to 7% increments in the sensitized group and in 2% to 3% increments in the group without sensitization.

Exposure to mite allergens

To take into account the relevance of exposure to mite allergens for prevalence and incidence of asthma-like symptoms in sensitized individuals, mite allergen concentrations found in the respective groups were compared (Fig. 2). The distributions of mite allergen concentration are similar in the groups with different numbers of symptoms, and no statistical difference was found between them.

DISCUSSION

In a community-based cohort of children, prevalences and incidences of asthma-like symptoms were ascertained in order to describe the natural history of asthma between the ages of 7 and 10 years and to analyze risk factors for prevalences and new onset of symptoms. The number of symptoms was counted, and because presence of more than one symptom is closely related to doctors' diagnoses of asthma, this variable was focused for risk assessment. The study shows an initial prevalence (more than one symptom) of 14.5% and a new onset rate of 7.2% for an observation period of 3 years, giving a crude average incidence of approximately 2.4% per year. Our data suggest that initial prevalence is associated with persistence of complaints and that even in children who are free of symptoms at the age of 7 years an asthmatic outcome can emerge with remarkable frequency. To our knowledge, comparable data from a cohort of children in whom follow-up

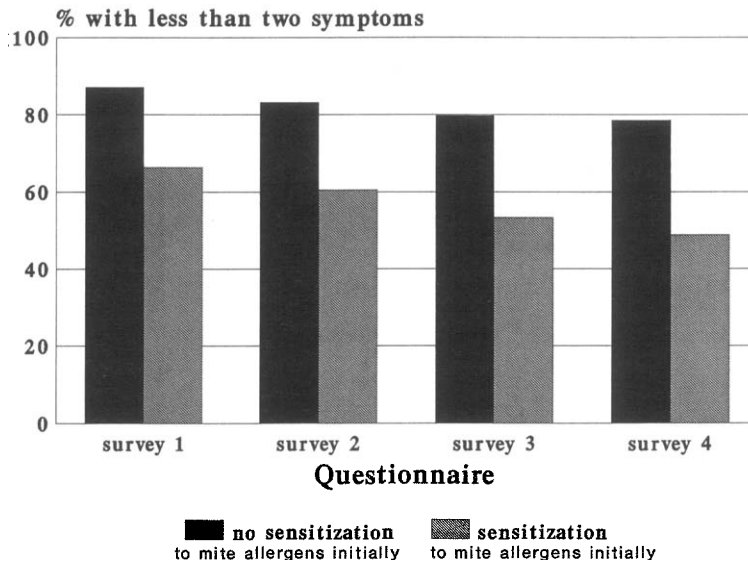


FIG. 1. Decreasing frequency of "less than two asthma-like symptoms" for children with ($n = 172$) and without ($n = 1298$) initial sensitization (SPT results of survey 1) to mite allergens.

TABLE II. Cross-sectional and longitudinal logistic regression analyses (cases with more than 1 symptom vs references with less than 2 symptoms) of prevalences, analysis of persistence, and analysis of incidence

Independent factor	Analyses of prevalence						Analysis of persistence* (n = 457)		Analysis of incidence† (57 cases, 2278 person-years)	
	Cross-sectional				Longitudinal (n = 1486)					
	1 (n = 1330)	2 (n = 1234)	3 (n = 1180)	4 (n = 1097)						
	OR	OR	OR	OR	OR	95% CI	OR	95% CI	OR	95% CI
SPT+ to pollens	0.7	0.7	0.5‡	1.9	0.8	0.5-1.2	1.1	0.5-2.4	1.2	0.5-2.6
SPT+ to mites	2.2§	2.9§	4.0§	2.2‡	2.4§	1.7-3.3	2.6	1.4-4.8	2.3‡	1.1-4.7
SPT+ to danders	3.1§	3.6§	2.6	3.0§	2.9§	1.9-4.3	3.0	1.5-6.3	1.8	0.8-4.4
History of hay fever	2.5	3.6§	1.9‡	1.3	1.9	1.3-3.0	2.3‡	1.0-5.2	1.1	0.4-3.1
History of eczema	1.6‡	1.2	1.5	2.0	1.4‡	1.0-1.8	1.8‡	1.1-3.0	1.0	0.5-1.9
LGA	1.3	2.3	2.9§	1.9	1.9	1.3-3.0	2.4‡	1.1-5.1	1.1	0.4-3.2
Male gender	1.5‡	1.6‡	1.2	1.7	1.5	1.1-1.9	1.3	0.9-2.1	1.4	0.8-2.5
Parental atopy	1.3	1.4	1.1	1.3	1.3	1.0-1.7	1.3	0.8-2.0	2.1	1.2-3.7
Maternal smoking	1.3	0.9	1.4	1.0	1.2	0.9-1.6	0.8	0.5-1.2	1.0	0.5-1.8
Location Lörrach	1.0	1.1	0.9	1.9‡	1.1	0.8-1.5	0.9	0.5-1.7	1.0	0.5-2.0
Location Kehl	1.7	1.2	1.8‡	2.3	1.6	1.2-2.3	1.6	0.9-2.7	1.5	0.7-3.0

All analyses are controlled for educational level and nationality.

SPT+, Positive SPT response.

*At least one symptom in survey 1, then: persistence (≥ 2 symptoms in at least one consecutive survey, $n = 145$) versus reversion (< 2 symptoms in each consecutive survey, $n = 312$).

†Any incidence is analyzed, but only if no symptom was reported in survey 1.

‡ $p \leq 0.05$.

|| $p \leq 0.01$.

§ $p \leq 0.001$.

Absence of symbol indicates $p > 0.05$.

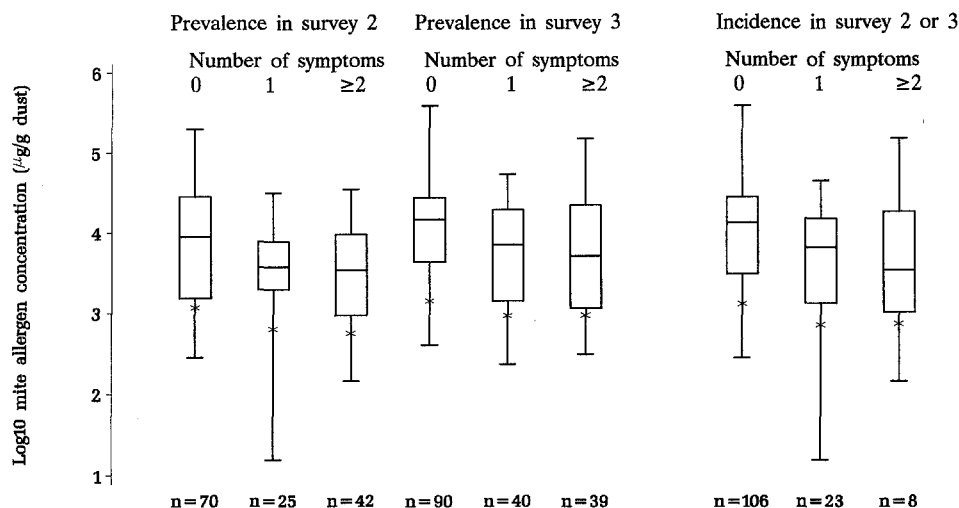


FIG. 2. Distribution of mite allergen concentration stratified for prevalences and incidence of asthma-like symptoms in children sensitized to mite allergens. Lower, middle, and upper lines of the boxes represent 25th, 50th, and 75th percentiles, respectively; lower and upper limits of the bars are minimum and maximum percentiles; crosses indicate the mean values.

started at early school age are not available in the literature. However, in a Swedish study comprising more than 1600 children, a cumulative prevalence of asthma of 3.8% was found between birth and the age of 7 years,¹² whereas at the age of 11 years, the cumulative prevalence had increased to 5.3%.¹³ Even in adults, new onset of wheezing has been demonstrated by a recent study.⁶ Thus our observation on new onset of asthma-like symptoms between the ages of 7 and 10 years is in accordance with earlier reports.

Statistical importance of those factors associated with more than one asthma-like symptom in the initial cross section (sensitization to mite allergens and animal danders, history of hay fever and eczema, LGA, male gender, parental atopy) was consistently present during the course of the study. This is suggested by comparable ORs seen for all four cross-sectional analyses (Table II). The longitudinal model allows more precise estimation of the average risk levels of the variables. Most of these factors have been identified earlier as representing independent risks of bronchial asthma or other atopic manifestations in childhood.^{4, 14} Parental history of atopy was found to be associated with allergic sensitization, as well as with clinical manifestations in the offspring.^{13, 15} Allergic sensitization to common inhalant allergens, particularly to dust mite allergens and pet danders, is more prevalent in patients with asthma compared with the nonatopic population,^{1, 16} and allergic sensitization predisposes subjects to react with airway obstruction in the case of allergen exposure.¹⁷ Of

the atopic manifestations, eczema usually occurs earliest and can therefore be used as an indicator of increased susceptibility to development of inhalant allergy later in life.¹⁸ Children born prematurely are in part affected by restrictive or obstructive lung function.¹⁹ Therefore it is not surprising that LGA turns out to be an independent risk factor for asthma-like symptoms even at school age. Finally, an unknown biologic cause of relatively increased occurrence of asthmatic symptoms might exist in boys; however, the effect seems to diminish with increasing age.^{20, 21} Hence, the results of our analysis of prevalences of asthma-like symptoms are compatible with those of earlier studies.

Recurrence of symptoms in identical individuals in consecutive cross sections appears to reflect prognostic importance of several risk factors mentioned above for the persistence of asthmatic symptoms (Table II). In contrast to the results regarding prevalence and persistence, the analysis of incidence of more than one asthma-like symptom identifies only two risks as being statistically important for such a new onset. These are sensitization to mite allergens (OR = 2.3) and parental atopy (OR = 2.1). Regarding the latter, we cannot exclude the possibility that atopic parents had been more sensitive to clinical signs in their children than healthy parents. However, overreporting in the case of sensitization to mite allergens is not plausible, because then a parallel tendency should also occur for pollens. Two other longitudinal studies addressed the risk of IgE-mediated reactiv-

ity to common inhalant allergens for developing respiratory symptoms.^{5,6} In young adults sensitization to pollens was identified as a risk factor for developing hay fever later on.⁵ Also in adults it was shown that the presence of IgE antibodies binding to mite antigen antedated the onset of wheezing.⁶ The results of the latter study are not only in accordance with our finding of sensitization to mite allergen as a risk factor for new onset of asthmatic manifestation but also suggest that this sequence must also be expected in adolescence and adulthood. However, neither for this study nor for the cited studies can it be excluded that clinical signs were present some years before the study and have not been realized or remembered or had diminished for a longer time. Nevertheless, even if the latter should be true in a lot of our cases, sensitization to mite allergen is linked significantly at least to recurrence of asthma-like symptoms.

The development of asthmatic signs in mite-sensitized children does not seem to depend on mite allergen exposure (Fig. 2), although an association of exposure to dust mite allergens and development of asthma was reported.²² With regard to this, there can be a number of reasons for our negative findings. First, the sort of exposure assessment we used could have been inappropriate. However, it is highly comparable to the procedure used by other investigators who had positive results. Moreover, mite allergen exposure measured in our study shows significant association with the incidence of specific sensitization.⁹ Second, allergen exposure could cause sensitization, and after this has happened a dose-response relationship between exposure and onset of clinical symptoms is only weak. Third, exposure to other indoor and outdoor allergens, which was not assessed in our study, could have been of importance. Furthermore, the relationship between allergen exposure and asthmatic complaints could be confounded by individual nonspecific airway responsiveness. Finally, because of the relatively small number of incidence cases with sensitization to mite allergen and exposure assessment (Fig. 2; $n = 23$, $n = 8$), the statistical power to find or exclude significant differences in exposure might be low. On the other hand, even no weak trend for increased mite antigen concentrations in the incidence cases can be seen. A recent study found no correlation of mite density in mattresses and increased symptoms in asthmatic children exposed to high concentrations of mite allergen; the authors speculated that other factors could explain this manifestation.²³

Because mite allergen concentrations found in our region are comparably high, a questionable diminution of clinical responsiveness could not be excluded. Nevertheless, IgE-mediated hypersensitivity to mite allergens is clearly associated with bronchial asthma in childhood. Therefore allergen avoidance appears to be of crucial relevance for preventing asthma in children. However, although dust mite allergy is a worldwide problem, in many locales with low mite infestation factors other than mite allergy might be decisive for the development of clinical disease. Our data suggest that restriction of asthma might be more likely if sensitization to mite allergens could be prevented. Strategies to achieve this aim in the population at risk must be drawn up.

In conclusion, our study shows an onset of asthmatic symptoms of 2.4% per year in children unaffected at the beginning of school age. Of the factors identified earlier as representing a risk for bronchial asthma in children, sensitization to mite allergens and parental atopy remain significant also for the new onset of asthmatic symptoms. Because the level of mite allergen exposure cannot explain the clinical development, the way to reduce asthma onset in children of school age should be early measures to prevent sensitization to mite allergens.

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