

Original article

Allergic sensitization to cat in childhood as major predictor of incident respiratory allergy in young adults

Background: Little is known on the predictive value of sensitization to specific aeroallergens in children with respect to asthma and hay fever incidence in young adulthood. We followed the incidence of asthma and hay fever in children (mean age 11 years) over 9 years, and analyzed the predictive value of sensitization to five common aeroallergens.

Methods: Three consecutive surveys were conducted in East German school children. Specific IgE antibodies to birch and timothy grass pollen, house dust mite, cat, and cladosporium were measured. In 1207 out of the 2453 children, the 9-year incidence of asthma and hay fever was assessed by reported doctors' diagnoses. For sensitization, diagnostic parameters were determined and logistic regression analyses controlled for relevant confounders.

Results: A total of 176/78 incident hay fever/asthma cases occurred equaling a cumulative incidence of 1.93/0.86% per year. Incident asthma was associated with previous sensitization to cat [risk ratio (RR) 3.49, 1.57–7.74] and grass pollen (RR 1.79, 1.01–3.19), whereas incident hay fever was associated with each allergen, with grass pollen (RR 6.00, 4.04–8.90) and cat (RR 5.36, 2.87–9.99) exhibiting the strongest associations. When mutually adjusting for all allergens, sensitization to cat remained significantly associated with asthma and hay fever. The latter was also associated with sensitization to grass pollen. The highest positive predictive values for asthma and hay fever were obtained for cat sensitization (10/49 = 20.4% and 23/49 = 46.9%).

Conclusions: Childhood sensitization to cat and grass pollen predicts the incidence of asthma and hay fever in young adulthood. The predictive capacity differs by allergen and manifestation of atopy.

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Respiratory allergies are a major public health problem, especially in children and young adults (1, 2). A strong association between allergic sensitization to common aeroallergens and respiratory allergies has been well established (3–9). In fact, sensitization to an aeroallergen is a pathogenetic prerequisite for allergic rhinitis (hay fever) and the extrinsic type of asthma and therefore mandatory to make a diagnosis. Subjects who are sensitized, but not affected with respiratory allergies, have a higher risk for developing asthma or hay fever in the future. This has been investigated in a few studies in young children, including birth cohorts and adults using follow-up times of mainly 3–4 years (10–12), whereas only one Swedish study investigated the predictive values

of childhood sensitization for asthma and hay fever in young adulthood (13).

The purpose of this study was to investigate the risks which are associated with sensitization to common aeroallergens in childhood for asthma and hay fever incidence in adulthood. We thereby intended to observe a cohort for a longer time period and to give specific results for five common aeroallergens. In addition to testing for associations, we were also interested in the predictive diagnostic capability of allergic sensitization and therefore calculated different diagnostic parameters. A large population-based sample of East German school children was recruited and followed-up to answer these questions.

Methods

Study design and population

The baseline of this prospective study constitutes three repeated cross-sectional studies, which were performed in three regions of

Abbreviations: CI, confidence interval (95%); *Der p*, *Dermatophagoides pteronyssinus*; HDM, house dust mite; LR⁺, likelihood ratio (positive); OR, odds ratio; NPV, negative predictive value; PPV, positive predictive value; RAST, radio allerge sorbens test; RR, risk ratio; SPT, skin prick test.

Saxony-Anhalt (East Germany) between September and July of 1992/1993, 1995/1996, and 1998/1999 to assess various allergy-related health outcomes (14). The study design and results regarding health effects and the body burden of pollutants have been published elsewhere in more detail (15–17).

Briefly, two of the study regions ('Bitterfeld' and 'Hettstedt') were heavily polluted in the past by emissions from large power plants burning brown coal with a high sulfur content (up to 5%), chemical plants, and smelters. The third area ('Zerbst') served as a control area with background pollution. Children of three age groups (5–7, 8–10, and 11–14 years) from all schools in Zerbst and Hettstedt were invited to participate. In the larger area of Bitterfeld, schools were chosen to represent each regional district. Parents gave written consent after they had received an information letter. The clinical examinations took place at schools and kindergartens. The study protocol was approved by the University of Rostock Ethics Committee.

Follow-up

A questionnaire-based follow-up study was performed in all participants of the previous surveys between October 2003 and March 2004. The target population comprised 2453 participants of the earlier three surveys for whom measurements of allergen-specific IgE antibodies were available at any time and who were born before September 15, 1986 (to assure a minimum age of 18 years at follow-up, range 18–26 years). The target population represents 46% (2453/5360) of the total survey population of the three cross-sectional surveys. After excluding those who had moved out of the area or died, 2394 persons remained in the sample. A reminder and a second copy of the questionnaire were sent out when the initial follow-up questionnaire was not returned. In case the questionnaire returned with unknown address, the subjects were telephoned. When the persons were reached by phone and were willing to participate, a questionnaire was either sent to the new address or the answers were obtained by telephonic interview.

Outcome assessment

Allergen specific IgE antibodies. Venous blood samples were drawn at the time of the initial surveys (September–July of 1992/1993, 1995/1996, and 1998/1999) and allergen specific IgE antibodies to five common aeroallergens [*Dermatophagoides pteronyssinus* (*Der p*), timothy grass pollen, birch pollen, cat, and *Cladosporium herbarum*] were determined by standard laboratory procedures (RAST-CAP-FEIA, Pharmacia, Uppsala, Sweden). All analyses were carried out by Pharmacia (Freiburg, Germany). The detection limit for RAST reactivity was set at 0.35 kU/l.

Questionnaire

Standardized instruments (questionnaire of the initial surveys) were mailed to the parents together with the invitation letter and checked for completeness at the time of examination. The questionnaire covered basic demographic characteristics, the parental school education (six categories: no formal graduation, graduation after 8, 10, or 12 years of school, graduation from technical college, and graduation from university) as a proxy parameter for the socioeconomic status as well as the parental history of atopic diseases (asthma, hay fever, or atopic eczema).

Identical questions regarding an ever doctor's diagnosed hay fever or asthma were used in all three surveys.

In the follow-up questionnaire, subjects were asked, with respect to hay fever and asthma, whether they ever suffered from these diseases and, if so, whether a doctor had diagnosed hay fever or asthma. Only cases with doctors having diagnosed the disease were included in the analysis. Cases were regarded as incidental when the corresponding questions in the previous surveys had been denied. Similarly, the cases where a positive answer in the previous surveys had not been confirmed in the follow-up study were regarded as remissions.

Statistical analyses

Based on the diagnostic 2×2 tables for asthma or hay fever incidence and sensitization to different allergens, we calculated sensitivity and specificity as well as predictive values and positive likelihood ratios (LR^+).

Risk ratios (RR) were estimated by odds ratios (OR) as measures of association in multiple logistic regression analyses. Ninety-five percent confidence interval (CI) were given as measures of stability. Regression models investigated the association between asthma or hay fever incidence as dependent variable and the sensitization to different allergens as independent variable. Age, sex, parental history of atopic diseases, study region, and parental school education were included as further independent variables. In addition, these models were extended by including all tested allergens in parallel.

All statistical analyses were carried out using the software packages SPSS (SPSS Inc., Chicago, IL, USA) for Windows 13.0.

Results

A total of 1207 follow-up questionnaires were obtained. In detail, 542, 494, and 171 subjects of the first, second, and third baseline surveys responded to the follow-up. This equals a response of 50.4%. Of the remaining 1187 subjects, most of them were not accessible by phone (78) or had no identifiable telephone number (892). Only a few (67) persons actively refused participation or other reasons were given (50).

Responders had a higher social status than nonresponders, as expressed by the parental school education. For all other relevant parameters given in Table 1, no significant differences were obtained.

Of the 1207 participating subjects 22 (1.8%), 72 (6.0%), and 121 (10.0%) had a history of a doctor's diagnosed asthma, hay fever, and atopic eczema, respectively, at the time of the initial survey. Overall, 187 persons were affected at baseline and therefore excluded from the follow-up analysis on incidental asthma and hay fever. A further nine subjects with incomplete data were excluded, leaving 1011 persons in the final sample. The mean age in this group at the time of the initial surveys was 11.3 years (SD 1.46) and 53.2% were boys. In 16.2%, a positive parental history of atopic diseases was given.

The prevalence of allergic sensitization at the time of the initial surveys (September–July of 1992/1993, 1995/1996, and 1998/1999) for these 1011 subjects is given in Table 2. Baseline radio allerge sorbens test (RAST) results were available for 1002 of the 1011 children, but the number of assessments may vary for single allergens when not enough

Table 1. Baseline characteristics of responder and nonresponder

Variable (%)	Responder (n = 1207)	Nonresponder (n = 1187)
Age (mean)	11.53	11.59
Sex (male)	54.0	51.4
RAST grass pollen	22.9	21.5
RAST birch pollen	13.0	12.2
RAST <i>Der p</i>	16.6	17.5
RAST cat	7.9	6.4
RAST cladosporium	4.9	4.0
History of atopic eczema	10.0	8.4
History of hay fever	6.1	5.2
History of asthma	2.1	1.5
Parental history of atopic diseases	27.2	27.5
Parental school education		
No formal graduation	0.8	1.2
Graduation after		
8 years of school	4.8	9.6
10 years of school	48.1	52.8
12 years of school	3.2	2.4
Graduation from technical college	28.6	22.6
Graduation from university	14.6	11.4*

RAST, radio allerge sorbens test; *Der p*, *Dermatophagoides pteronyssinus*.

* $P < 0.05$.

serum was available. Twenty-nine percent of the children exhibited specific IgE antibodies to at least one allergen. Most children were sensitized to grass pollen and house dust mite (*Der p*). Roughly half of the children (51.1%) were sensitized to a single allergen only.

The mean follow-up time was 9 years (4–12 years). Within this period 176 incident cases of hay fever were observed, resulting in an average cumulative incidence of 1.93% per year. During the same time, 78 new asthma cases occurred which can be expressed as average cumulative incidence of 0.86% per year. In 9 and 6 out of 72 and 22 cases, respectively, an earlier positive history of hay fever and asthma was not confirmed by the follow-up. We investigated the associations between a baseline sensitization to different aeroallergens and the later development of asthma or hay fever.

RAST reactivity and incident asthma

As shown in Table 2, only sensitization to cat and grass pollen was significantly associated with the later development of asthma, whereby the effect is more pronounced for sensitization to cat. Table 3 gives the corresponding diagnostic values for the single allergens. Again, sensitization to cat has the most important prognostic value for asthma. According to these data, 20.4% of the children sensitized to cat will develop asthma within the next 9 years (positive predictive value). Given a positive test, the chance of developing asthma is three times higher than that of not developing asthma (LR^+).

RAST reactivity and incident hay fever

Sensitization to each of the tested allergens is significantly associated with an increased risk of a future development of hay fever (Table 2). Thereby, sensitization to grass pollen and cat exhibited the strongest associations. As in asthma, the best predictive value was obtained for sensitization to cat. Almost every second child (46.9%) sensitized to cat developed hay fever within the following 9 years (Table 4). Expressed as LR^+ , it is four times more likely to develop hay fever than not, given the test was positive.

Mutual adjustment for all allergens

As many children were sensitized to at least two allergens, it is not clear whether the associations as described above are the results of a sensitization to the particular allergen or due to co-sensitization. Therefore, we have tested the same regression models and included all other allergen-specific measurements in parallel. For asthma incidence only sensitization to cat remained an important predictor (RR 3.23, CI 1.23–8.43), whereas sensitization to grass pollen did not reach statistical significance (RR 2.07, CI 0.98–4.36). For hay fever incidence, however, grass pollen sensitization remained the strongest predictor (RR 4.91, CI 2.90–8.30) with sensitization to cat being the only

Table 2. Prevalence of RAST reactivity at school age and association with incident asthma and hay fever during a 9-year follow-up

	n/N	%	Incident asthma		Incident hay fever	
			RR*	95% CI	RR*	95% CI
Grass	172/991	17.4	1.79	1.01–3.19	6.00	4.04–8.90
Birch	78/924	8.4	1.08	0.45–2.60	3.85	2.31–6.40
<i>Der p</i>	138/1002	13.8	1.32	0.68–2.56	2.51	1.63–3.87
Cat	49/994	4.9	3.49	1.57–7.74	5.36	2.87–9.99
Cladosporium	28/924	3.0	1.70	0.49–5.84	3.97	1.77–8.91
Any	272/931	29.2	1.44	0.85–2.44	4.78	3.29–6.95

RAST was performed at age 5–14 years.

RAST, radio allerge sorbens test; *Der p*, *Dermatophagoides pteronyssinus*; RR, risk ratio; CI, confidence interval.

*Adjusted for sex, age, parental school education, parental atopic diseases, and study region.

Table 3. Predictive diagnostic capacity of RAST reactivity at school age on incident asthma during a 9-year follow-up

	Incident cases by previous sensitization status		Sensitivity	Specificity	PPV	NPV	LR ⁺
	RAST positive	RAST negative					
Grass	18/171	57/816	24.0	83.2	10.5	93.0	1.4
Birch	6/77	66/843	8.3	91.6	7.8	92.2	1.0
<i>Der p</i>	13/138	64/860	16.9	86.4	9.4	92.6	1.2
Cat	10/49	66/941	13.2	95.7	20.4	93.0	3.1
Cladosporium	3/28	68/892	4.2	97.1	10.7	92.4	1.4
Any	26/271	47/656	35.6	71.3	9.6	92.8	1.2

RAST was performed at age 5–14 years.

RAST, radio allerge sorbens test; *Der p*, *Dermatophagoides pteronyssinus*; LR⁺, likelihood ratio (positive); NPV, negative predictive value; PPV, positive predictive value.

Table 4. Predictive diagnostic capacity of RAST reactivity at school age on incident hay fever during a 9-year follow-up

	Incident cases by previous sensitization status		Sensitivity	Specificity	PPV	NPV	LR ⁺
	RAST positive	RAST negative					
Grass	72/172	100/815	41.9	87.7	41.9	87.7	3.4
Birch	30/78	130/842	18.8	93.7	38.5	84.6	3.0
<i>Der p</i>	41/138	134/860	23.4	88.2	29.7	84.4	2.0
Cat	23/49	151/941	13.2	96.8	46.9	84.0	4.2
Cladosporium	12/28	150/892	7.4	97.9	42.9	83.2	3.5
Any	94/272	74/655	56.0	76.6	34.6	88.7	2.4

RAST was performed at age 5–14 years.

RAST, radio allerge sorbens test; *Der p*, *Dermatophagoides pteronyssinus*; LR⁺, likelihood ratio (positive); NPV, negative predictive value; PPV, positive predictive value.

other allergen which was significantly associated (RR 3.00, CI 1.41–6.37).

Discussion

In this large population-based follow-up study of children, we demonstrated that within a panel of five common aeroallergens, only sensitization to cat is associated with a significantly increased risk of developing doctor's diagnosed asthma within the next 9 years. Twenty percent of the children who were positive to cat allergen at age 11 years developed asthma within the next 9 years. In contrast, sensitization to each aeroallergen was significantly associated with hay fever incidence. This association was especially prominent for sensitization to grass pollen and cat, which remained as the only allergens being significantly associated with incident hay fever when taking sensitization to all allergens into account. Forty-seven percent of the children who were positive to cat allergen at age 11 years developed hay fever within the next 9 years.

There are a few cohort and follow-up studies to which the results of this study can be compared with. Sensitization to food allergens might be more important in birth cohorts than in the age groups we have investigated. The German MAS cohort study could show that children being sensitized to food allergens (hen's egg,

cow's milk, soy, or wheat) for more than 1 year have significantly elevated risks of developing allergic rhinitis (OR 3.4) and asthma (OR 5.5) within the first 5 years of life (10). Similarly, it was shown that these children have a significantly increased risk (OR 3.3) of developing seasonal allergic rhinitis up to 7 years when being sensitized to food allergens within the first 2 years of life (18). Furthermore, it was shown for this group, that sensitization to hen's egg at 1 year increases the risk of allergic sensitization to aeroallergens at the age of 3 years significantly (19).

A study, which is quite comparable with ours, was conducted in Sweden in the late 1980s (13). A total of 1112 teenagers with a mean age of 14 years were prick-tested and reinvestigated assessing the incidence of asthma and rhinoconjunctivitis 4 years later ($n = 990$). The incidence rates of 1.1 and 1.0% per year for asthma and rhinoconjunctivitis were obtained, and atopy [at least one positive skin prick test (SPT) to 10 common aeroallergens] was revealed to be a significant predictor of incident asthma cases. In contrast to our findings, atopy did not predict rhinoconjunctivitis.

With respect to sensitization to aeroallergens and the development of asthma in children, Swedish cohort study provides detailed data (20). More than 2000 first and second grade school children were prick-tested and followed-up for 3 years. The incidence of physician diagnosed asthma was associated with sensitization to

cat (OR 7.4), dog (OR 4.0) and birch pollen (OR 3.1). We also could identify sensitization to cat as a significant predictor of asthma incidence. Sensitization to birch pollen, however, was not relevant to our group, which might be in part explained by geographical variations of allergen exposure. Dog allergens were not included in our test panel. In another Swedish study, a sample of 1370 young adults (20–44 years) was investigated and SPT was carried out, following the ECRHS protocol and re-examined after 3 years (11). The onset of asthma was significantly associated only with sensitization to pets (OR 2.4), not differentiating between cats and dogs. These findings accord well with our results. With respect to the onset of allergic rhinitis, sensitization to pets, birch pollen, and parietaria was identified as positive factors. In contrast, we found significant associations between the onset of hay fever and all tested aeroallergens.

In a cohort study from Tucson, Arizona, 6-year-old patients received cold air challenge and SPT (21). After a mean follow-up of 4.4 years, sensitization to at least one allergen was associated with a significantly increased risk of developing new asthma (OR 3.6). A long-term (23 years) follow-up of university students revealed that sensitization to pollen leads to an increased risk in developing asthma (22).

With respect to the persistence of asthma symptoms, it was shown in a 17-year follow-up of 9-year-old children that sensitization to HDM and cat was associated with persistent or relapsing wheezing (23). In addition, it was demonstrated that sensitization to pets is associated with the incidence of occupational asthma (24).

This study has methodological strengths and limitations. Although prospective studies like this are less prone to systematic errors, selection bias cannot be ruled out completely. There is a chance that parents whose children had a positive allergy test are more aware of allergic symptoms and tend to see a doctor more often than those whose children were tested negative. We have no data, however, to test the presence or the magnitude of this potential bias. We chose doctors' diagnosed diseases as a more specific endpoint. There is a chance that we would have achieved a higher incidence with symptom-oriented questionnaires. However, this might have also increased the number of false-positive cases. The findings and the interpretation of these findings are therefore restricted to doctors' diagnosed cases.

Similarly, the results refer to sensitization as measured by RAST. It is unclear how far these findings would be applicable to SPT results. We performed SPT in the first and second initial survey only, with allergens from different manufactures. Therefore, we decided not to analyze the predictive capacity of SPT sensitization to incident respiratory allergy.

We achieved a response of 50.4% which seems acceptable when considering the average follow-up time of 9 years and the life period from children to young adults with major changes in life circumstances. However, concerns about the quantitative and qualitative implications might be raised. The remaining sample size of 1011 subjects was still large enough to detect clinically relevant and significant differences. With respect to a potential systematic qualitative error (selection bias), we were able to compare responders and nonresponders for relevant parameters. Subjects with a higher social status participated more frequently, but there was no indication for a differential participation of subjects with an atopic background (sensitization, personal or parental history of atopic diseases).

We would consider the population-based setting, the sample size, and the long follow-up time in the period from childhood to young adulthood as well as the measurement of several specific IgE antibodies, which also allowed for analyses under mutual adjustment, as strengths of this study.

We conclude that childhood sensitization to cat and grass pollen predicts the incidence of asthma and hay fever in young adulthood. The predictive capacity differs by allergen and with respect to different manifestations of atopy.

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