

Original article

Natural history of hay fever and pollen sensitization, and doctors' diagnosis of hay fever and pollen asthma in German schoolchildren

Background: In order to prevent pollen asthma by immunotherapy it is mandatory to know the best time to initiate it. Children with hay fever complaints are at considerable risk of developing pollen asthma. Population-based data on their natural history is urgently needed.

Methods: A longitudinal cohort study was conducted over four years in six rural towns in Baden-Württemberg, Germany. A questionnaire with questions taken from the International Study of Asthma and Allergies in childhood (ISAAC) was filled in every spring and autumn. Hay fever complaints, asthma defining symptoms and new doctors' diagnosis of hay fever and asthma were recorded. Additionally a skin prick test with pollen allergens was performed every autumn.

Results: In 1996, 19.7% of 1101 elementary school children (age: 8.1–9.9 years (5–95%)) were found to be sensitized to pollen and 8.7% had already been diagnosed as having hay fever. In a pooled analysis of 2478 children-summertime, children with positive pollen sensitization had a significantly higher risk of developing hay fever symptoms (2.63; 2.17–3.10 odds ratio (OR); 95% confidence interval (CI)) and of being diagnosed as suffering from hay fever (7.88; 4.70–13.20). Furthermore, although their OR for the development of asthma symptoms during the pollen season was 3.88 (2.48–6.07 CI), it was only 0.69 (0.24–2.01 CI) for doctors' diagnosis of pollen asthma.

Conclusion: Children of elementary school age with pollen sensitization and a history of hay fever are at considerable risk of getting pollen asthma, but they are not quickly diagnosed as such. Specific immunotherapy might be a means of preventing asthma completely in such a situation. Our data helps to estimate the sample size for intervention studies of this kind.

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Key words: allergic sensitization; hay fever; incidence; pollen asthma; school age.

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Accepted for publication 19 December 2001

Prevalence of hay fever and pollen asthma has increased to an unacceptable level over the last decades (1). These chronic diseases, and asthma in particular, are a substantial health problem for children and adults worldwide resulting in high hospital admission rates (2), use of medical services (3) and use of medication (4). Therefore, steps towards reducing the further incidence and prevalence need to be taken urgently. As we do not have sufficient information about the etiology of the increase in prevalence, we cannot act directly to reverse the trend. We see from earlier studies that children with hay fever complaints are at considerable risk of developing asthma symptoms later (5). Thus it is mandatory to find the best time to start early measures against the development of pollen asthma. To achieve this goal more population-based data on the clinical course of hay fever and the incidence of pollen asthma are needed. Such data would allow the timely implementation of successful strategies, such as specific

immunotherapy, to prevent the development of pollen asthma in "high risk" children. The aim of this study is to describe the association between sensitization to pollen allergens, the occurrence of hay fever symptoms and the development of pollen asthma.

Material and methods

Study population and study design

The study was conducted in six rural towns (Freudenstadt, Villingen, Tuttlingen, Ehingen, Welzheim and Aalen) located in and around the Black Forest in the south-west of Germany, with low levels of ambient air pollution from sulfur dioxide or nitrogen dioxide, but with mean-to-high levels of ambient ozone on the German scale, especially in Freudenstadt and Welzheim (Table 1). For later analysis, Freudenstadt and Welzheim were labeled as having ozone values above the mean of all cities, and the other cities were labelled as having ozone values below this mean.

Parents of elementary school children were asked to participate in this study. For each participant, parents or the legal guardian had to

Table 1. Average concentration of important outdoor air pollutants in 1995 (in $\mu\text{g}/\text{m}^3$)

	Aalen	Tuttlingen	Ehingen	Villingen	Welzheim	Freudenstadt
Ozone	35	45	43	52	73	71
NO ₂	26	25	19	19	13	15
PM ₁₀	24	18	25	21	—*	16

*No data available.

sign an informed consent form. The study was approved by the ethics committee of the University Hospital of Freiburg. Every spring and autumn questionnaires were distributed to the pupils at school for their parents and collected a few days later. Additionally, every autumn trained staff members at school performed a skin prick test with grass, birch, and hazel pollen allergens.

Questionnaires

In the distributed questionnaire validated questions from the International Study of Asthma and Allergies in Childhood (ISAAC) were used. We asked the children's parents about hay fever complaints: "Has your child had a problem with sneezing or a runny or blocked nose in the last half year when he/she did not have a cold or the flu?" and "Has your child had itchy-watery eyes in the last half year when he/she did not have a cold or the flu?"; about asthma defining symptoms: "Has your child had wheezing or whistling in the chest in the last half year?". For the investigation of the incidence of pollen asthma, we analyzed in particular the questionnaires from autumn reporting the complaints during the months of March till August.

Furthermore questions were asked about already-existing doctors' diagnosis of hay fever: "Has a doctor diagnosed hay fever for the first time in your child in the last half year?"; and asthma: "Has a doctor diagnosed asthma for the first time in your child in the last half year?". In addition, the questionnaires included many detailed questions on different aspects of the child's present and previous living conditions, and exposure to air pollutants.

Terms describing allergy were used following the position statement of the EAACI nomenclature task force (6).

Skin prick test

Every autumn trained staff members performed a skin prick test at school. Three purified and immunochemically characterized inhalant allergens (grass, birch and hazel pollens; Scherax; Hamburg, Germany) were applied to the forearm in a standardized manner with the aid of a prick lancet (ALK; Hørsholm, Denmark), as described in detail elsewhere (7). Positive reaction to a pollen allergen was defined as a wheal diameter of ≥ 2 mm, and a ratio of allergen wheal size to histamine wheal size of ≥ 0.5 . "Sensitization to pollen" required a reaction to at least one of the three pollen allergens.

Statistical analysis

The effect of sensitization to pollen (confirmed by a positive skin prick test) on the development of symptoms (wheezing; runny nose and/or itchy eyes), or a diagnosis of asthma or hay fever in the consecutive year, was studied. A standard power calculation ($\alpha=0.05$, $\beta=0.2$) was made assuming that 5% of the nonsensitized and 10% of the sensitized population will develop asthma. The required sample size was calculated as twice 474.

While data collection started in spring 1996, our analysis focused on symptoms or diagnoses observed in the years 1997–99. Actual skin prick test data had been obtained in the preceding autumns (1996–98).

Diagnosis of asthma or hay fever was not considered reversible, so analysis of the occurrence of diagnosis was related to survival

analysis. We used the so-called person-year approach described by Cupples et al. (8). This is achieved by dividing the whole observation period into one-year intervals and analyzing the *newly* made diagnoses in each time interval.

For each interval, children with an earlier diagnosis of asthma/hay fever (information obtained in the earlier questionnaires) were excluded, and for those with no earlier diagnosis the incidence of the diagnosis in the respective time interval was analyzed. Since three seasons were under observation, there were up to three contributions to the data-set from each child. A logistic regression model was used to investigate the effect of pollen sensitization on the development of asthma diagnosis or hay fever diagnosis, taking into account further confounders – date of observation/age, gender, atopy (based on parental hay fever and asthma) and mean ozone concentration. The analyzed population for this question consisted of the children with no diagnosis in the first time interval.

Symptoms may be considered to be reversible: this hypothesis was investigated by inspecting the number of children with a positive answer to a symptom question in 1997 and the percentage of them giving a negative answer to the respective question in one of the following years. If hypothesis of reversibility could be maintained, our approach was as follows: for each season, the dependency of symptoms and sensitization to pollen in the preceding autumn was investigated by using Chi-squared tests. A common analysis of the three seasons was performed with a multiple logistic regression model in a similar manner as described above. Again, each child may add up to three observations (one from each season) to the common analysis. The Generalized Estimation Equation (GEE) technique (9) was employed to account for repeated measurements. The analyzed population then consisted of the children who had information about the respective symptom and the preceding skin prick test for at least one season.

Thus the regression models have a similar structure (up to three observations from each child). The difference lies in treating a diagnosis of asthma/hay fever as final (once it has been given, the child is excluded from the further analysis), whereas symptoms may possibly vanish (hence a child showing symptoms in the first season contributes its information to the analysis also from the next two seasons).

Regression models contained the variables "gender" and "date of investigation/age" besides the investigated effect of "pollen sensitization". The effect of further confounders (parental asthma, parental hay fever, German nationality, high ozone area) was evaluated by inspecting possible effect-modification with respect to pollen sensitization. If this was not the case, the confounder was not included in the model. For German nationality, interaction was investigated by testing the significance of the interaction term in the logistic regression model. If $p < 0.15$, the interaction term was included, and separate pollen sensitization effect estimates were given for children with or without German nationality.

Possible drop-out biases were investigated by comparing the analyzed population for each question (as described above) to the initial population of the first season.

For all computations the SAS software package (SAS Institute, Inc., Cary, NC) was used.

Results

Of the 17 elementary schools located in the six study towns, 13 took part. The average levels of outdoor air pollutants in 1995 are shown in Table 1. Initially a total of 1254 questionnaires for parents were distributed to the pupils at school. Completed questionnaires were returned by 1101 children. Demographic characteristics of the population are shown in Table 2. The average age of the children was 8.03 years (range: 7.82–8.39),

Table 2. Study population: demographic characteristics of the participants that could be included in the incidence and risk calculation. Drop out figures in the outcomes "diagnosis" are higher, as children were excluded from the analysis once they got the respective diagnosis

Population	Runny nose		Diagnosis hay fever		Wheezing		Diagnosis asthma		Total n = 1101 initial
	Analysed n (%)	Dropout n (%)	Analysed n (%)	Dropout n (%)	Analysed n (%)	Dropout n (%)	Analysed n (%)	Dropout n (%)	
Characteristics†									
Female gender	467 (50.1)	79 (47.0)	450 (51.6)	96 (41.9)‡	466 (50.1)	80 (47.1)	473 (50.8)	73 (43.2)	546 (49.6)
Parent* with German nationality	627 (70.1)	70 (59.8)‡	587 (70.3)	110 (62.2)‡	625 (70.0)	72 (60.1)‡	622 (69.5)	75 (64.1)	697 (68.9)
Atopy	350 (37.6)	46 (27.7)‡	302 (34.8)	94 (41.4)	352 (37.9)	44 (26.2)‡	339 (36.5)	57 (34.1)	396 (36.1)

* At least one parent.

† Percentage of those in which the information was available.

‡ $P < 0.05$.

49.8% were female (range: 36.1–55.3%), and in 65.3% of the children at least one parent had German citizenship (range: 54.3–76.3%).

Prevalence of pollen sensitization and respiratory disorders in the initial population are shown in Fig. 1. In 1996, 19.7% elementary school children were sensitized to pollen and 8.7% had already been diagnosed as having hay fever, 9.1% reported wheezing in the last 12 months, and 3.8% had been diagnosed as having asthma by a doctor.

The overall drop-out rate after three years of observation was 15.4%. The demographic characteristics of the children included in the final analysis varied slightly depending on the outcome addressed (Table 2). In general there was a tendency for a greater loss of children with nationality other than German and of those without allergic disease in the family reported at the begin of the study.

In Table 3 the incidences of respiratory symptoms and doctors' diagnosis of hay fever and asthma are shown of each year and for the whole observation period.

During the three years (1997–99), an average of 39.2% of the children with a pollen sensitization (PS+) complained about a blocked nose between March and August, but only 12.1% of the children without pollen sensitization (PS–). A higher incidence of newly

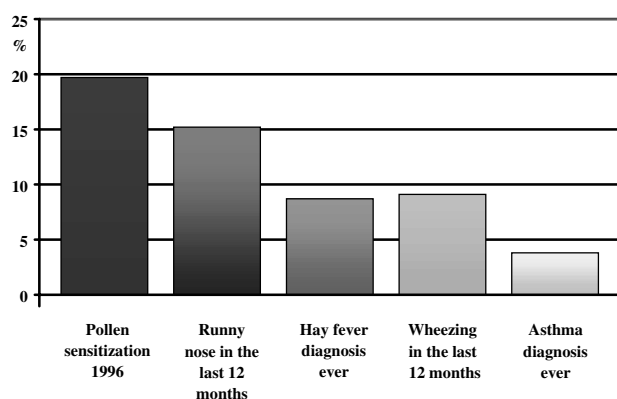


Figure 1. Prevalence of pollen sensitization and 12-months prevalence of respiratory disorders in 1996 (n = 1101).

diagnosed hay fever was also observed 10.0% (PS– = 1.4%). Adjusted incidence of hay fever diagnosis was found to be higher in sensitized children of German nationality (OR = 27; 10–73) than in those of other nationalities (OR = 3.5; 1.5–7), and the respective interaction test found statistical significance ($P = 0.013$).

The incidence of hay fever (doctors' diagnosis) in those children without symptoms of rhinoconjunctivitis in advance, was also higher in the PS+ group (9.2%; PS– = 0.9%). The adjusted OR was 54 (12–237) for children with German nationality and 4.0 (1.3–12.5) for children with other nationalities, respectively, interaction positive ($P = 0.006$).

Wheezing as an asthma defining symptom occurred in 8.0% of the sensitized children (PS– = 2.2%). The adjusted OR was 4.2 (2.2–8.0) for children with German nationality, and 1.4 (0.4–4.8) for children with other nationalities (P for interaction = 0.12). In contrast asthma was diagnosed more often in children without a pollen sensitization (PS– = 1.1%; PS+ = 0.8%). However, the difference was not statistically significant, asthma incidence was equal in both nationality groups.

Air pollutants, especially the peak and mean concentration of ambient ozone, had no influence on the incidence of hay fever symptoms, nor did they influence the number of newly assigned diagnoses. Ozone (high vs mean concentration) exerted a small effect on the incidence of wheeze in the logistic regression (OR 1.9; 95% CI = 1.1–3.5), and was thus taken into account when computing the adjusted ORs.

Discussion

This longitudinal cohort study demonstrates in a population-based sample that sensitization to pollen allergens at school age is strongly associated with subsequent onset of hay fever complaints and a doctors' diagnosis of hay fever.

Because results of the prevalence of sensitization are highly influenced by methodological factors, such as the quality of extracts for skin prick test and the cut-off level for positivity, we used skin prick test criteria that can be regarded as highly reproducible in children over

Table 3. Crude incidence and adjusted odds ratios for hay fever and respiratory symptoms, and doctors' diagnoses of hay fever and asthma in relation to a pollen sensitization in the preceding autumn

	1997*		1998*		1999*		1997–99†		Adjusted OR§	95%CI
	865 observations		751 observations		712 observations		2328 observations			
Sensitized to pollen	yes = 169	no = 696	yes = 185	no = 566	yes = 174	no = 538	yes = 528	no = 1800		
Runny nose, itchy eyes	53 (31.36)	25 (3.59)	42 (22.70)	13 (2.30)	44 (25.29)	12 (2.23)	139 (26.33)	50 (2.78)	2.63	2.17–3.10
	872 observations†		753 observations		659 observations		2284 observations			
Sensitized to pollen	yes = 122	no = 750	yes = 119	no = 634	yes = 108	no = 551	yes = 349	no = 1935		
Diagnosis hay fever	20 (16.39)	11 (1.47)	9 (7.56)	10 (1.58)	6 (5.56)	6 (1.09)	35 (30.10)	27 (1.04)	8.01	4.77–13.47
	856 observations		741 observations		712 observations		2309 observations			
Sensitized to pollen	yes = 169	no = 687	yes = 183	no = 558	yes = 174	no = 538	yes = 526	no = 1783		
Wheezing	16 (9.47)	24 (3.49)	13 (7.10)	11 (1.97)	13 (7.47)	4 (0.74)	42 (7.98)	39 (2.19)	3.28	1.93–5.56
	932 observations†		821 observations		725 observations		2478 observations			
Sensitized to pollen	yes = 169	no = 763	yes = 181	no = 640	yes = 166	no = 559	yes = 516	no = 1962		
Diagnosis asthma	1 (0.59)	11 (1.44)	2 (1.10)	6 (0.94)	1 (0.60)	5 (0.89)	4 (0.78)	22 (1.12)	0.70	0.24–2.02

* Yearly incidence.

† After exclusion of children with already existing doctors' diagnoses of hay fever and asthma.

‡ Pooled data.

§ Adjusted for date of observation/age, gender, atopy (based on familial hay fever and asthma) and ozone in a GEE model.

a long period of time (10). Furthermore, in daily allergy testing, there is good correlation between a “significant” positive skin prick test and high levels of specific IgE (e.g. RAST class 2). The prevalence of pollen sensitization observed compares favourably to recent data obtained in this age group (15). After sensitization to pollen allergens, manifestation of symptoms similar to allergic symptoms, such as itchy eyes or a runny nose, depends on well known risk factors like ambient air pollution or living conditions (11). During our observation period, roughly 40% of children with pollen sensitization reported hay fever symptoms every spring and summer, compared to 12% of children with no pollen sensitization. These findings are in accordance with results from other investigations (12).

The fact that prevalences of atopic and respiratory disorders are increasing in general is indisputable. In population-based studies using identical methods of ascertainment at intervals of 10–15 years, an increase in doctors' diagnosed current asthma from around 4% to 7–10% has been reported (13). In Germany, recent observations have shown comparable prevalences for atopic disorders in this age group (5, 14–18).

The use of the standard ISAAC questionnaire, which has been proven a valid instrument for determination of asthma symptoms (19), permits comparisons with other countries (20) in general. However, the wide range of asthma prevalences from 4.1% to 32.1% reported from the steering committee of the International Study of Asthma and Allergies in Childhood suggests that the use of the term “asthma” and the translation of the word “wheezing” into other languages may produce results which cannot be compared so easily. Such semantic variations may, at least in part, explain the differences in the reported prevalences of asthma (21). Changes in the diagnostic approach and/or parental awareness may also account for differences in reported

incidence. In our study cultural differences and language problems of non-German parents apparently account for a slightly elevated drop-out rate (Table 2).

We were able to demonstrate that children with pollen sensitization have an elevated risk (OR 3.9) of incidence of hay fever symptoms and an OR of about 8 of a later diagnosis of hay fever. No significant correlation was found between pollen sensitization and asthma newly diagnosed by a doctor in the summer. One possible reason for this could be the short observation period and the known fact of decreasing asthma prevalence at the beginning of puberty. However, the diagnostic habits of physicians may also have played a role, as well as reporting bias: people suffering severely from hay fever seldom exercise at the same time, thus avoiding the “chance” of developing severe asthma symptoms leading to doctors' diagnosis. Ozone concentration, alone or when included in the model calculations, had no influence on the rate of doctors' diagnosis of pollen asthma.

It has been shown that immunotherapy is an effective treatment for patients with seasonal allergic rhinoconjunctivitis (22). Its efficacy in allergic asthma has previously been questioned, but recent controlled trials of specific immunotherapy (subcutaneous injection) have documented its effect in allergic asthma (23). Our study was able to define a group of pupils with extraordinarily greater risk for developing definite hay fever diagnosed by a doctor and seasonal wheeze. Observation time was too short to evaluate the risk of transition to doctors' diagnosed seasonal asthma. Earliest prevention of hayfever (and maybe seasonal asthma) might be possible by offering specific immunotherapy to those only sensitized against the respective pollen. Our data will help to estimate the sample size for such interventional studies.

Acknowledgments

We thank Mrs Gurli Bär, Mr Jörg Mattes, Mrs Julia Laule, Mrs Steffi Glaser and Mr Christian Prazak for their excellent assistance in

the field study, in handling the questionnaires and conducting the SPT. This study was funded by the state Baden-Württemberg, project "Umwelt und Gesundheit" (grant no. PUGL 98001).

References

1. BURNEY PGJ, CHINN S, RONA RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973–86. *BMJ* 1990;**300**:1306–1310.
2. HALFON N, NEWACHECK PW. Trends in the hospitalisation for acute childhood asthma, 1970–84. *Am J Public Health* 1986;**76**:1308–1311.
3. ANDERSON HR. Is the prevalence of asthma changing? *Arch Dis Child* 1989;**64**:172–175.
4. KLAUKKA T, PEURA S, MARTIKAINEN J. Why has the utilization of antiasthmatics increased in Finland? *J Clin Epidemiol* 1991;**44**:859–863.
5. KUEHR J, FRISCHER T, KARMAUS W, MEINERT R, BARTH R, URBANEK R. Clinical atopy and associated factors in primary-school pupils. *Allergy* 1992;**47**:650–655.
6. JOHANSSON SGO, O'B HOURIHANE J, BOUSQUET J, et al. A revised nomenclature for allergy. *Allergy* 2001;**56**:813–824.
7. KUEHR J, KARMAUS W, FORSTER J, et al. Sensitization to four common inhalant allergens within 302 nuclear families. *Clin Exp Allergy* 1993;**23**:600–605.
8. CUPPLES LA, D'AGOSTINO RB, ANDERSSON K, KANNEL WB. Comparisons of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med* 1988;**7**:205–218.
9. LIANG KY, ZEGER SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;**73**:13–22.
10. KUEHR J, KARMAUS W, FRISCHER T, et al. Longitudinal variability of skin prick test results. *Clin Exp Allergy* 1992;**22**:839–844.
11. LITONJUA AA, CAREY VJ, WEISS ST, GOLD DR. Race, socioeconomic factors, and area of residence are associated with asthma prevalence. *Pediatr Pulmonol* 1999;**28**:394–401.
12. HIRSCH T, WEILAND SK, VON MUTIUS E, et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999;**14**:669–677.
13. MAGNUS P, JAAKKOLA JKK. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross-sectional surveys. *BMJ* 1997;**314**:1795–1799.
14. FRISCHER T, KUEHR J, MEINERT R, KARMAUS W, URBANEK R. Risk factors for childhood asthma and recurrent wheezy bronchitis. *Eur J Pediatr* 1993;**152**:771–775.
15. NEUPERT T, IHORST G, KARMAUS W, et al. Asthma und asthmatische Beschwerden bei Schulkindern. Vergleich von Gebieten in Deutschland und Österreich. *Z F Gesundheitswesen* 1997;**5**:63–75.
16. WEILAND SK, VON MUTIUS E, HIRSCH T, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999;**14**:862–870.
17. VON MUTIUS E, MARTINEZ FD, FRITZSCH C, NICOLAI T, ROELL G, THIEMANN HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149**:358–364.
18. BRABACK L, BREBOROWICZ A, DREBORG S, KNUTSSON A, PIEKLIK H, BJORKSTEN B. Atopic sensitization and respiratory symptoms among Polish and Swedish school children. *Clin Exp Allergy* 1994;**24**:826–835.
19. JENKINS MA, CLARKE JR, CARLIN JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;**25**:609–616.
20. ASHER MI, KEIL U, ANDERSON HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–491.
21. INTERNATIONAL STUDY OF ASTHMA AND ALLERGIES IN CHILDHOOD (ISAAC) STEERING COMMITTEE. Worldwide variations in the prevalence of asthma symptoms. *ISAAC Eur Respir J* 1998;**12**:315–335.
22. BOUSQUET J, LOCKEY RF, MALLING H-J, (editors). WHO Position Paper. Allergen Immunotherapy: Therapeutic Vaccines for Allergy Diseases. *Allergy*, 1998;**53**:1–42.
23. ABRAHAMSON R, PUY R, WEINER JM. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999;**54**:1022–1041.