

Exposure to birch pollen in infancy and development of atopic disease in childhood

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Background: The relationship between early allergen exposure, sensitization, and development of atopic disease remains controversial. In 1993, extremely high levels of birch pollen were recorded in Stockholm, Sweden, creating the unique opportunity to study children with different exposures during infancy.

Objective: We sought to assess the influence of early high-dose exposure to an inhalant allergen (birch pollen) on sensitization and development of atopic disease in children.

Methods: A total of 583 children with atopic heredity born in Stockholm in February through April 1992, 1993, or 1994 were investigated at age 4.5 to 5 years. The children were examined and underwent skin prick testing with inhalant and food allergens. IgE antibodies (RAST) against birch pollen and recombinant birch pollen allergen (rBet v 1) were analyzed in serum.

Results: The children born in 1993 (high-dose exposure at 0-3 months) were more often sensitized (ie, positive skin prick test response) to birch pollen than the children born in 1994 (low-dose exposure; 17.8% and 8.8%, respectively; odds ratio [OR], 2.4; 95% CI, 1.2-4.6). A tendency in the same direction was seen for children born in 1992 (high-dose exposure at 12-15 months; OR, 1.7; 95% CI, 0.9-3.2). The results were supported by the RAST analyses. The prevalence of bronchial asthma, allergic rhinoconjunctivitis, and atopic dermatitis did not differ between the birth-year groups. However, the prevalence of pollen- and animal dander-induced allergic asthma was increased in the children born in 1993 (OR, 2.6; 95% CI, 1.2-5.6). An interaction between early high-dose exposure to birch pollen and cat in the household was suggested for sensitization to cat ($P = .06$).

Conclusion: Exposure to high levels of birch pollen in infancy increases the risk of sensitization to the same allergen, as well as the risk of allergic asthma. (*J Allergy Clin Immunol* 2002;110:78-84.)

Key words: Aeroallergens, atopy, infancy, sensitization, tolerance

Abbreviations used

OR: Odds ratio

rBet v 1: Recombinant birch pollen allergen

SPT: Skin prick test

The prevalence of allergic diseases in childhood has increased over the past decades, especially in many western industrialized countries. Every third child has an atopic disorder.^{1,2} The prevalence of atopic disease is lower in Eastern Europe than in Sweden and the former West Germany.^{3,4} Early infections, change in vaccination programs, and lifestyle factors have been proposed to play a role in the development of atopic diseases.⁵⁻⁷ Interestingly, children in families with an anthroposophic lifestyle and children living on farms are less atopic than other children.^{8,9} However, possible protective factors have not yet been elucidated in detail.

Several studies have tried to clarify whether there is an association between early exposure to inhalant allergens, sensitization, and development of atopic disease. Exposure to furred pets or mites during infancy has been proposed as a risk factor by some,^{10,11} whereas others have found the opposite.¹² Some studies indicate that pollen allergy is more common in children born just before the pollen season, but the evidence is not consistent.¹³⁻¹⁷ Thus the role of early exposure to inhalant allergens for development of sensitization and atopic disease remains controversial.

In the spring of 1993, the birch pollen levels in Stockholm were more than 10 times higher than those in 1992 and 50 times higher than those in 1994. This phenomenon provided a unique opportunity to investigate the effect of high-dose allergen exposure during the first months of life in children born during the same season but in different years. The aim of this study was to evaluate whether high-dose exposure to birch pollen correlated with sensitization and atopic disease.

METHODS

Study population

Children living in southwestern Stockholm (Brännkyrka, Skärholmen, Hägersten, Huddinge, and Botkyrka municipalities) and born in Stockholm County between February and April 1992, 1993, or 1994 were investigated (Table I). All children were 0 to 3 months old during their first birch pollen season. A total of 2237 children were identified from birth records. When the children were 4 years old, the families were approached with a questionnaire concerning allergic symptoms in the children and their parents.

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TABLE I. Selection of children for the study

	High-dose exposure to birch at 1 y of age in children born in 1992	High-dose exposure to birch at 0-3 mo in children born in 1993	Low-dose exposure to birch at 0-3 mo in children born in 1994
Screening stage			
Selected for screening	735	781	721
Responded to screening questionnaire	619 (84.2%)	666 (85.3%)	598 (82.9%)
Atopic heredity by history	305	367	351
Clinical assessment			
Invited*	254	254	250
Declined participation	33	40	27
Did not come to examination	30	17	28
Final study groups	191	197	195

*Randomly selected among those with atopic heredity who answered the screening questionnaire.

Answers were obtained for 1883 (84.2%) children, and 1023 of these reported a family history (one or both parents) of atopic disease, including asthma, allergic rhinoconjunctivitis, atopic dermatitis, or food allergy. Among those with a family history of atopic disease, 758 children were randomly selected and invited to participate in the study. From this group, a total of 175 declined to participate or did not come to the clinical examination, which left 583 children for clinical assessment (191, 197, and 195 children in the respective birth-year groups). The self-reported atopic symptoms in the children who declined participation or did not come to examination were equally distributed within the 3 groups.

The local ethics committee at Huddinge University Hospital approved the study. Informed consent was obtained from parents and children.

Medical examination

All children were examined at the age of 4.5 to 5 years in the pediatric allergy clinic at Huddinge University Hospital by the same pediatrician (A.K.). The parents were asked to complete a questionnaire about atopic symptoms in the child, as well as social and environmental factors. Each child was clinically classified with respect to asthma, allergic rhinoconjunctivitis, atopic dermatitis, and food allergy. Bronchial asthma was defined as 3 or more episodes of wheezing or any episode of wheezing if related to exposure to pollen, furred pets, or both. Among the children with bronchial asthma, allergic asthma was diagnosed if the children reacted with wheezing when exposed to pollen, furred pets, or both during a period free of airway infection. Allergic rhinoconjunctivitis was diagnosed if rhinitis, conjunctivitis, or both appeared at least twice after exposure to a particular allergen, seasonal exposure, or both and was unrelated to an infection. Atopic dermatitis was defined according to the method of Hanifin and Rajka.¹⁸ Food allergy was diagnosed as acute onset of symptoms, such as skin reactions, wheezing, vomiting, or diarrhea, on more than one occasion after ingestion or contact with a particular food.

Skin prick tests (SPTs) were performed against inhalant and food allergens. All SPTs were performed by the same nurse on the volar side of the lower arm, according to the manufacturer's instructions (ALK, Copenhagen, Denmark). The SPTs included allergens from birch, timothy grass, cat, dog, horse, *Dermatophagoides pteronyssinus*, *Cladosporium* species (Soluprick, 10 histamine-equivalent potency, ALK), egg white (Soluprick; wt/vol ratio, 1:100), codfish (Soluprick, 1:20), peanut (Soluprick, 1:20), hazelnut (Soluprick, 1:20), cows' milk (3% fat, standard milk), and soy bean protein (Soluprick, 1:20). Histamine chloride, 10 mg/mL, was used as a pos-

itive control, and the allergen diluent was used as the negative control. A wheal diameter of 3 mm or larger recorded after 15 minutes was considered positive. In accordance with Pepys' definition,¹⁹ a child with at least one positive SPT response was classified as atopic.

A blood sample was obtained from the arm vein after local anesthesia (EMLA). The blood was centrifuged at 1200g, and serum was separated and stored at -18°C. Circulating IgE antibodies (RAST) against birch pollen and recombinant birch pollen allergen (rBet v 1) were determined with the Pharmacia CAP system (Pharmacia Upjohn, Uppsala, Sweden). An IgE antibody level of 0.35 kU/L or greater was considered significant. However, for some analyses, we also used a cut-off level of 3.5 kU/L.

Pollen measurements

Pollen counts have been continuously monitored at the Swedish Museum of Natural History in Stockholm since 1973. Pollen is collected in a Burkard trap. Into this suction trap, pollen enters a narrow orifice directed into the wind and adheres to a Vaseline- and glycerine-coated celluloid tape on a slowly rotating drum. Once daily, the tape is moved to microscope slides and analyzed for estimation of the pollen content of the air.^{20,21}

Statistical analysis

Data were analyzed by using Stata 7.0 software (Stata Corporation, College Station, Tex). Odds ratios (ORs) and 95% CIs were calculated for signs and symptoms of atopy in children born before the pollen season in 1992 and 1993 in relation to children born in 1994 and adjusted for differences in background variables by using multiple logistic regression analysis. The variables chosen reflected the situation after birth of the respective child: breast-feeding exclusively during the first 4 months of life, maternal smoking, and presence of furred pets (cats, dogs, and rodents) in the household. The interaction between exposure to cat in the household and exposure to birch pollen was analyzed by adding an interaction term between variables for pollen and cat exposures to the model. A likelihood test was performed, comparing this model with a simpler model.

RESULTS

The total pollen counts for the 3 spring seasons reported in Stockholm were as follows: 1992, 2194; 1993, 26,805; and 1994, 435 counts/m³ air (Fig 1).

The 583 children participating in the study included 283 boys and 300 girls. The mean age at examination was 4.9 years (range, 4.7-5.2 years). Demographic data are present-

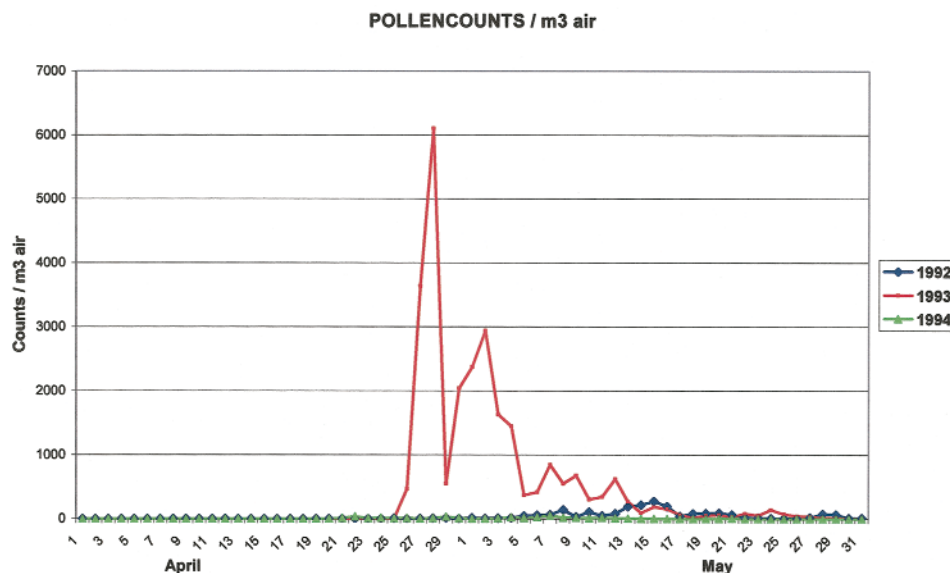


FIG 1. Total pollen counts for the 3 spring seasons: 1992, 2194; 1993, 26,805; and 1994, 435 counts/m³ air.

TABLE II. Demographic data and risk factors for atopic disease in children from Stockholm, Sweden, born before the pollen season in 1992, 1993, or 1994

Characteristics	High-dose exposure to birch at 1 y of age in children born in 1992 (n = 191)	High-dose exposure to birch at 0-3 mo in children born in 1993 (n = 197)	Low-dose exposure to birch at 0-3 mo in children born in 1994 (n = 195)
Demographics			
Mean age (y)	4.9	4.8	4.9
Age range (y)	4.8-4.9	4.8-4.9	4.9-4.9
Male/female sex	103/88	92/105	88/107
Risk factors			
Breast-feeding exclusively ≤4 mo	53 (27.8%)	51 (26.0%)	38 (19.8%)
Household pets (cat, dog, rodent)			
Ever (after birth of child)	59 (31.1%)	70 (36.8%)	61 (32.1%)
0-3 mo of age	45 (33.6%)	43 (32.1%)	46 (34.3%)
Cat in the household			
Ever (after birth of child)	41 (21.5%)	37 (18.8%)	35 (17.9%)
0-3 mo of age	30 (15.7%)	26 (13.2%)	28 (14.4%)
Maternal smoking			
Ever (after birth of child)	54 (28.3%)	57 (28.9%)	45 (23.1%)
Present	40 (20.9%)	43 (21.8%)	32 (16.4%)
0-3 mo of age	41 (21.5%)	47 (23.9%)	26 (13.3%)
During pregnancy	42 (21.0%)	47 (23.9%)	27 (13.9%)
Paternal smoking			
Ever (after birth of child)	46 (24.1%)	47 (23.9%)	38 (19.5%)
Present	41 (21.5%)	34 (17.3%)	28 (14.4%)
Parental atopy: heredity by history			
Mother	138 (72.3%)	134 (68.0%)	139 (71.3%)
Father	116 (60.7%)	130 (66.0%)	117 (60.0%)
Both	65 (34.0%)	65 (33.0%)	61 (31.3%)

ed in Table II. The groups were generally comparable regarding breast-feeding, maternal smoking, and exposure to pets. However, the mothers of the children born in 1994 smoked less during pregnancy and the first 3 months of the baby's life than the mothers of the children born in 1992 or 1993. Clinical data, as well as SPT and RAST results, are presented in Table III. Two children refused SPTs, and 48

declined intravenous blood tests. The children born in 1993 (high-dose exposure at 0-3 months) had an increased occurrence of positive SPT responses (≥ 3 mm) to birch pollen compared with that of the children born in 1994 (low-dose exposure at 0-3 months), with prevalence rates of 17.8% and 8.8%, respectively. The children born in 1992 (low-dose exposure at 0-3 months, high-dose exposure at 1

TABLE III. Signs and symptoms of atopy in children aged 4 to 5 years in Stockholm, Sweden, and born before the pollen season in 1992, 1993, and 1994

	High-dose exposure to birch at 1 y of age in children born in 1992 (n = 191)	High-dose exposure to birch at 0-3 mo in children born in 1993 (n = 197)	Low-dose exposure to birch at 0-3 mo in children born in 1994 (n = 195)
Clinical symptoms or history of atopic disease			
Total	108 (56.8%)	103 (52.3%)	92 (47.2%)
Bronchial asthma	53 (27.8%)	45 (22.8%)	43 (22.1%)
Previous	17 (8.9%)	14 (7.1%)	16 (8.2%)
Current	36 (18.9%)	31 (15.7%)	27 (13.9%)
Allergic asthma	16 (8.4%)	24 (12.2%)	10 (5.1%)
Atopic dermatitis	100 (52.4%)	80 (40.6%)	91 (46.7%)
Previous	22 (11.5%)	16 (8.1%)	15 (7.7%)
Current	78 (40.5%)	64 (32.5%)	74 (38.5%)
Allergic rhinoconjunctivitis	41 (21.5%)	33 (16.8%)	32 (16.4%)
Food allergy	21 (11.1%)	31 (15.8%)	24 (12.3%)
SPT			
Test done	190 (99.5%)	197 (100.0%)	194 (99.5%)
Any positive result	48 (25.3%)	56 (28.4%)	38 (19.6%)
Birch	27 (14.2%)	35 (17.8%)	17 (8.8%)
Timothy grass	14 (7.4%)	16 (8.1%)	10 (5.2%)
Cat	18 (9.5%)	22 (11.2%)	20 (10.3%)
Dog	11 (5.8%)	18 (9.1%)	17 (8.8%)
Horse	8 (4.2%)	7 (3.6%)	5 (2.6%)
<i>D pteronyssinus</i>	1 (0.5%)	2 (1.0%)	2 (1.0%)
<i>Cladosporium</i> species	1 (0.5%)	1 (0.5%)	1 (0.5%)
Hen's egg	4 (2.1%)	6 (3.1%)	3 (1.6%)
Hazelnut	16 (8.4%)	21 (10.7%)	13 (6.7%)
Peanut	9 (4.8%)	14 (7.1%)	10 (5.2%)
Codfish	0 (0.0%)	3 (1.5%)	3 (1.6%)
Milk	0 (0.0%)	0 (0.0%)	3 (1.6%)
Soy	3 (1.6%)	0 (0.0%)	0 (0.0%)
RAST, birch			
Test done	169 (88.5%)	182 (92.4%)	179 (91.8%)
Positive test result	25 (14.8%)	29 (15.9%)	19 (10.6%)
RAST rBet v 1			
Test done	170 (89.0%)	185 (93.9%)	180 (92.3%)
Positive test result	25 (14.7%)	29 (16.8%)	19 (10.0%)

Asthma, rhinitis,
other respiratory
diseases

year of age) also tended to have more positive SPT responses to birch pollen (14.2%) than the children born in 1994. SPT responses for perennial allergens were comparable in the 3 groups (eg, positive SPT responses to cat were found in 9.5% [1992], 11.2% [1993], and 10.3% [1994]). Results of RAST analysis (with a cut-off level of 0.35 kU/L) against birch more often appeared positive in children born in 1992 (14.8%) and 1993 (15.9%) compared with children born in 1994 (10.6%), although the differences between the 3 years were less pronounced than for the SPTs. The RAST analysis against rBet v 1 followed the same pattern: 14.7%, 16.8%, and 10.0%, respectively. When 3.5 kU/L was used as a cut-off level for RAST analysis against birch and Bet v 1, these results were confirmed.

The cumulative incidence of bronchial asthma, allergic rhinoconjunctivitis, and atopic dermatitis was not significantly different between the groups. However, the cumulative incidence of pollen-induced asthma, animal dander-induced asthma, or both was increased in the high-dose exposure group born in 1993 (12.2%) compared with the low-dose exposure group born in 1994 (5.1%).

Comparisons between exposure groups adjusted for potential confounding factors (sex, maternal smoking, breast-feeding, and domestic pets) are presented in Table IV. The occurrence of allergic asthma in children born in 1993 was significantly higher compared with that of the group born in 1994 (OR, 2.6; 95% CI, 1.2-5.6), as was SPT positivity to birch (OR, 2.4; 95% CI, 1.2-4.6). Results in the same direction were seen for RAST positivity to birch (OR, 1.6; 95% CI, 0.9-3.1) and rBet v 1 (OR, 1.9; 95% CI, 1.0-3.6). No significant differences were seen when comparing children born in 1992 with those born in 1994, but the corresponding ORs were consistently higher in the former group.

Data for sensitization to cat allergen (SPT) in relation to birch pollen exposure and the presence of a cat in the household are shown in Table V. Overall, the presence of a cat in the household during the first 3 months of life was associated with an increased risk of sensitization to cat (OR, 2.1; 95% CI, 1.1-4.0). An interaction was suggested between high-dose exposure to birch pollen and cat in the household in relation to sensitization to cat (*P*

TABLE IV. OR for signs and symptoms of atopy in children aged 4 to 5 years in Stockholm, Sweden, born before the pollen seasons in 1992 and 1993 in relation to children born before the pollen season in 1994

	High-dose exposure to birch pollen at 1 y in children born in 1992, n = 191, OR (95% CI)*	High-dose exposure to birch pollen at 0-3 mo in children born in 1993, n = 197, OR (95% CI)*
Atopy†	1.4 (0.9-2.1)	1.2 (0.8-1.8)
Bronchial asthma	1.3 (0.8-2.0)	1.0 (0.6-1.7)
Allergic asthma	1.6 (0.7-3.6)	2.6 (1.2-5.6)
Allergic rhinoconjunctivitis	1.3 (0.8-2.2)	1.0 (0.6-1.8)
Atopic dermatitis	1.3 (0.8-1.9)	0.8 (0.5-1.2)
Any positive SPT response	1.3 (0.8-2.1)	1.7 (1.0-2.7)
Positive SPT response to birch	1.7 (0.9-3.2)	2.4 (1.2-4.6)
Positive RAST result to birch	1.4 (0.7-2.7)	1.6 (0.9-3.1)
Positive RAST rBet v 1 result	1.5 (0.8-2.9)	1.9 (1.0-3.6)
Positive SPT response to timothy grass response	1.4 (0.6-3.3)	1.6 (0.7-3.7)
Positive SPT response to cat	0.9 (0.4-1.7)	1.1 (0.6-2.1)

*ORs and 95% CIs were adjusted for sex, maternal smoking, breast-feeding, and pets in the household. If the CI did not include 1.0, the result is statistically significant at a *P* value of less than .05.

†Clinical symptoms or history of atopic disease.

TABLE V. ORs (95% CIs) for sensitization to cat related to different cat and birch pollen exposures in children aged 4 to 5 years in Stockholm, Sweden, born before the pollen seasons in 1992 and 1993 in relation to children born in 1994

	Birch pollen exposure					
	Low-dose birch pollen exposure at the first 0-3 mo of life in children born in 1994 (n = 195)		High-dose birch pollen exposure at the first 0-3 mo of life in children born in 1993 (n = 197)		High-dose birch pollen exposure at 1 y in children born in 1992 (n = 191)	
	No. sens/exp	OR (95% CI)	No. sens/exp	OR (95% CI)	No. sens/exp	OR (95% CI)
Cat in the household at the first 0-3 mo of life						
No	18/167	1.00	15/171	0.8 (0.4-1.6)	13/161	0.7 (0.3-1.5)
Yes	2/28	0.7 (0.1-3.1)	7/26	3.1 (1.1-8.6)	5/30	1.7 (0.6-4.9)

ORs and 95% CIs were adjusted for sex, maternal smoking, and breast-feeding. If the CI did not include 1.0, the result is statistically significant at a *P* value of less than .05.

No. sens/exp, Number sensitized to cat/number exposed.

= .06). No such interaction was indicated for sensitization to birch (data not shown).

DISCUSSION

This study demonstrated a dose-dependent relationship between exposure to airborne birch pollen during infancy and sensitization to the same allergen in children, assessed by the prevalence of positive SPT responses. The RAST analysis against birch pollen and rBet v 1 supported these results. The cumulative incidence of allergic asthma (ie, asthma caused by exposure to pollen, animal dander, or both) was increased in high-dose compared with low-dose exposed children. Thus in this specific group of patients with asthma, sensitization and symptoms of atopic disease correlated.

Our data are supported by earlier observations concerning exposure to cat.²² The clinical outcome of exposure to airborne allergens during the early postnatal period has been a topic of great interest for several decades. Thus Businco et al¹⁵ found an increased sensitization

against mite allergen in children born in June through September, when the environmental mite allergen levels were high. Björkstén and Suoniemi¹³ reported that more children among those born just before the pollen season were sensitized to birch pollen than among those born after the season. On the other hand, Nilsson et al¹⁷ found that children born during the spring were less likely to have sensitization to pollen and symptoms of allergic rhinoconjunctivitis. If they were born in September through February, they had an increased incidence of sensitization to food allergens (ie, egg, milk, and wheat) and of atopic disease in general. However, Schäfer et al¹⁶ could not find any correlation among month of birth, early exposure to inhalant allergens (birch pollen, grass pollen, house dust mites, or cat epithelia), and later development of atopic disease in an unselected cohort of children followed to 5 to 6 years of age.

The diverging results in these studies might be explained by methodological problems caused by confounding factors, such as seasonal effects, exposure to other allergens, climate conditions, and year-to-year vari-

ation in pollen levels. In the present study only children with atopic heredity were included, and they were thoroughly characterized with regard to potential confounding factors for development of atopy. Furthermore, the families lived in the same area of Stockholm and had not moved from this area during the first 5 years of their children's lives. The exposure to birch pollen was documented by daily pollen counts. Thus disease-related misclassification of exposure was unlikely.

In our study high-dose exposure to birch pollen was related to an increased risk for IgE sensitization to birch pollen. However, sensitization to cat was primarily seen in those with combined exposure to cat in the household and to high doses of birch pollen during the first 3 months of life. On the other hand, Hesselmar et al¹² demonstrated a protective effect of early cat ownership on asthma and sensitization to cats. In a prospective birth cohort in Germany, Lau et al²³ found a dose-response relationship between exposure to Der p 1 and Fel d 1 and development of specific sensitization but no relationship between exposure and prevalence of asthma, wheeze, or bronchial hyperreactivity at 7 years of age.

Taken together, these observations might indicate that differences in dosage and duration of allergen exposure during early life might play a role for the outcome. Short high-dose exposure, as during a pollen season, and long-term exposure to furred pets or mites at home or in day-care might result in different risks of sensitization or development of tolerance. Furthermore, a combination of high-dose exposure to several inhalant allergens during the postnatal period of life could be particularly important for both sensitization and later development of clinical atopic disease. In our study the pollen levels in 1993 were unusually high, which must be taken into consideration. Exposure to these allergen levels at 1 year of age (children born in 1992) might also have added some risk for sensitization.

It has recently been shown that all newborn babies have a T_H2-like (atopic) response to allergens, possibly because of transplacental leakage of small allergens or peptides from mother to fetus.^{24,25} Most babies can later switch to a T_H1-like (nonatopic) response with induction of tolerance.²⁴⁻²⁶ This change in the T_H1/T_H2 paradigm during the postnatal period can probably explain a transient increase in specific IgE antibodies, without subsequent development of specific allergy, which has been observed in most healthy nonatopic infants.²⁷ It has been postulated that maternal blocking IgG antibodies could pass the placenta and contribute to tolerance by protecting the baby from IgE sensitization.^{28,29} This was hypothesized by Jarrett as early as the 1970s on the basis of results from animal studies.³⁰⁻³² The maternal pollen antigen-specific IgG levels have been shown to be low during the months before the pollen season. During high allergen exposure (eg, during the pollen season of 1993), the levels of protective IgG antibody might have been insufficient. However, the protective IgG antibody hypothesis has to be proved by means of further prospective studies.

In our study the cumulative incidence of asthma in the 3 birth-year groups was 27.8% (1992), 22.8% (1993), and 22.1% (1994). This is higher than that reported from the same area in previous studies.^{3,11,14,33} However, the cumulative incidence of allergic asthma, when children reacted to pollen, furred pets, or both, was only 8.4% (1992), 12.2% (1993), and 5.2% (1994). The comparatively high occurrence of bronchial asthma is explained by the selection, in our study, of children with atopic heredity. At least 20% of the children had 1 or 2 parents with asthma, which increases the risk of asthma, especially if combined with other environmental risk factors. In addition, all our families lived in an urban area, which has been shown to increase the risk for development of asthma and atopy.³³ The definition for asthma could also differ between studies.

Cross-sectional studies are susceptible to certain types of bias, such as recall bias. The children in our study were investigated at the age of 5 years, and parents probably remember quite well. However, there is a risk of disease-related misclassification of exposure for certain factors, such as parental smoking and household pets,³⁴ that might bias the results. Cohort effects and selection bias (parents of a child with asthmatic symptoms, atopic symptoms, or both might be more interested in participating in the study) could also have an influence. Nevertheless, this should not differ between the 3 birth-year groups of children. Furthermore, our data were adjusted for potential confounding factors, such as heredity, sex, parental smoking, breast-feeding, and domestic pets.

In conclusion, exposure to high levels of birch pollen in early infancy (0-3 months) increases the risk of sensitization (measured by means of SPTs) to the same allergen in children with atopic heredity, and some susceptibility could last during the first year of life. Combined high-dose exposure to birch pollen and other inhalant allergens might increase the risk of sensitization to other inhalant allergens. The cumulative incidence of bronchial asthma in general, allergic rhinoconjunctivitis, and atopic dermatitis at 5 years of age did not appear elevated in the high-dose exposure group, but assessment of the long-term effect requires further follow-up. On the other hand, early high-dose exposure to birch pollen seemed to increase the occurrence of allergic asthma.

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