

Does early exposure or sensitization to inhalant allergens predict asthma in wheezing infants? A 20-year follow-up

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ABSTRACT

Early sensitization to inhaled allergens predicts later asthma and allergy until school age, but studies on early exposure have given conflicting results. The purpose of this study was to evaluate the association between early wheezing, early exposure, or sensitization to pets and pollens and later asthma or allergy until adulthood. We have prospectively followed-up a cohort of 83 infants hospitalized for bronchiolitis in 1981–1982. Cat and dog ownership (early exposure) and inhalant allergen-specific IgE measurements (early sensitization) were registered at <3 years of age. Later, asthma and allergy were evaluated repeatedly between 3 and 20 years of age. Twenty-eight children were exposed to pets in early life, and 8 children were sensitized to pets and 10 children were sensitized to pollens. Birth season and early exposure or sensitization to pets were not significantly associated with later asthma and allergy. Wheezing was present at 3–6 years of age in 8 of 10 children sensitized to pollens (OR, 5.07; 95% CI, 1.48–17.31 versus nonsensitized), and asthma was present in 4 of 9 children at 8.5–10 years of age (OR, 9.53; 95% CI, 2.01–45.54). In multivariate analyses, early sensitization predicted asthma until 13.5–16 years of age. Seasonal rhinoconjunctivitis was not significantly associated with early exposure or sensitization to pets or pollens. In wheezing infants, early sensitization to seasonal pollens predicts subsequent wheezing and asthma until adolescence. No association was found between early exposure and sensitization to pets and later outcome.

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Early exposure to inhalant allergens may lead to sensitization^{1–3} with increased risk for later allergy and even asthma^{1,2,4} or to tolerance with opposite outcomes.^{4–7} Therefore, the studies on early exposure to, e.g., furred pets, have given varying results. Some have found no association with allergy^{7,8} or asthma,^{9,10} whereas others have found that the effect is dependent on inherited factors. Early exposure to dog dander has decreased asthma risk in children from nonasthmatic families^{4,7,11} but increased asthma risk in children with asthma in parents.^{1,4,11} In addition, the influence seems to depend on the different phenotypes of wheezing. Continuous exposure to dogs during the 1st year of life may increase the risk for early, transient wheezing but decrease the risk for later persistent wheezing.¹¹

In birth cohort studies, early sensitization to inhalant allergens has predicted subsequent asthma until 5–7 years of age^{12–14} and lung function impairment until 13 years of age.¹⁴ In postbronchiolitis studies, sensitiza-

tion to inhalant allergens has been associated with increased asthma risk until school age.^{15–17} Thus far, the association between sensitization in early life and asthma in adulthood has been documented for food allergens only.¹⁸ However, inhalant allergens, particularly indoor allergens, have been more predictive in population-based follow-ups until puberty.¹⁴

We have prospectively followed-up, for 18–20 years, a group of children hospitalized for bronchiolitis in infancy. Data on pet contacts at home and day care were registered until 3 years of age, and serum inhalant allergen-specific IgE was studied at the ages of 1.5–2 years and 2.5–3 years. The subjects have attended clinical follow-up visits at the ages of 2–3 years, 4.5–6 years, 8.5–10 years, and 18–20 years,^{19–22} and a questionnaire study at 13.5–16 years of age.²³ The aim of this study was to evaluate the association between early exposure and sensitization to pets and pollens and later wheezing, asthma, and allergy in children hospitalized for bronchiolitis in infancy.

PATIENTS AND METHODS

Basic Data on Admission

All 83 children <2 years of age who were hospitalized for bronchiolitis in Kuopio (Finland) University Hospital in 1981–1982 were recruited in this study.¹⁹ Bronchiolitis was defined as expiratory wheezing

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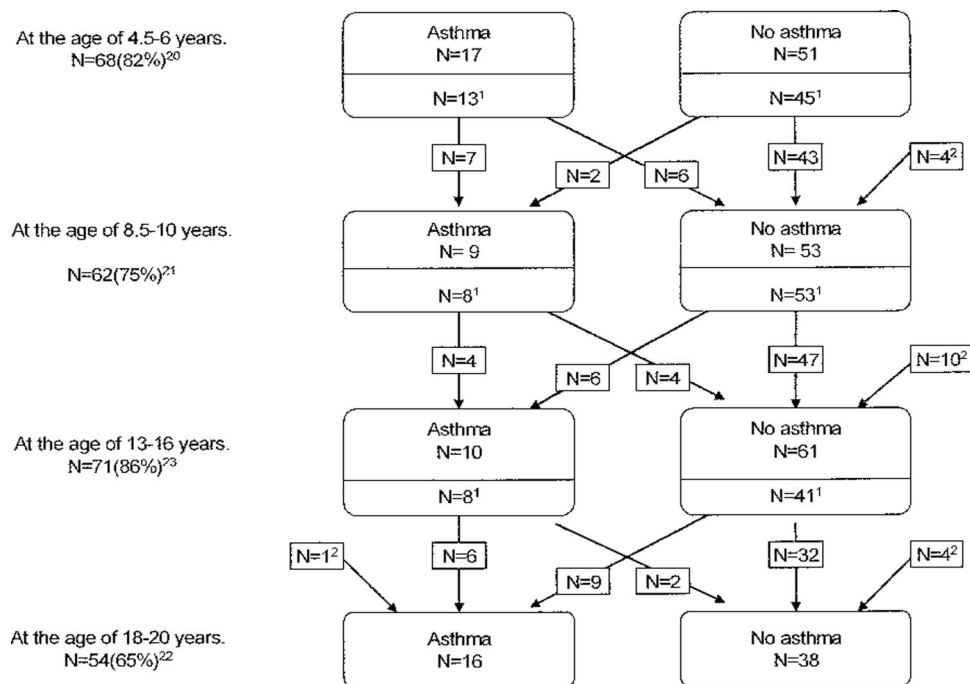


Figure 1. The patient flow and numbers of asthma cases from 4.5–6 years to 18–20 years of age. ¹Number of subjects attending both of the two consecutive follow-up visits. ²Number of subjects attending the follow-up only at the later of the two consecutive visits.

and/or prolonged expirium during respiratory infection.²⁴ The wheezing episode was the first one in 61 (73%) cases, 56 (67%) were male patients and 45 (54%) were <12 months age.¹⁹ The etiology of infection was studied by antigen and antibody assays. Respiratory syncytial virus (RSV) was detected in 33/83 (40%) cases.²⁴

Exposure and Sensitization Data

The children were divided into three groups based on birth season; those born in January to April (winter to spring), in May to August (summer), and in September to December (autumn). The seasons represent different patterns of early exposure to pollens, viral infections, and cold weather. The pollen seasons in our area are May (birch pollen), June to July (timothy and other grass pollens), and August (mugwort pollen).²⁵ Most outbreaks of respiratory viral infections take place from October to December,²⁶ as did the RSV epidemic in 1981.²⁷ The autumn and winter months, from September to April, are cold in our area, with a need for artificial heating of houses and much time spent inside. Artificial heating, with insufficient ventilation of the houses to save energy, increases the exposure to indoor allergens.²⁸ On the other hand, indoor environment is dry and the amounts of house-dust mites (HDMs) are low.²⁹ Data on cat or dog exposure at home or at day care were collected prospectively on admission and at all visits until 3 years of age. The data were registered by 6-month age periods.

Serum allergen-specific immunoglobulin (Ig) E (RAST; Pharmacia Diagnostica, Uppsala, Sweden) was measured in 81 children before the age of 3 years, in 67 children at 1.5–2 years, and in 76 children at 2.5–3 years of age. The studied allergens were birch, timothy grass, and mugwort pollens; dander of cats and dogs; HDM *Dermatophagoides pteronyssinus*; and mold *Cladosporium herbarum*. The presence of IgE to any allergen at the detection level (>0.35 kU/L) at either measurement was regarded to show sensitization to that allergen.³⁰

Follow-Up Data

The prospective follow-up was continued by clinical studies at the ages of 4.5–6 years, 8.5–10 years, and 18–20 years^{22–24} and by a questionnaire study on asthma status at the age of 13.5–16 years.²³ Data on doctor-diagnosed wheezing episodes were collected prospectively at the control visits until 6 years of age, and recurrent wheezing, registered separately for each age period, was present in 44/76 (58%) children at 2–3 years,¹⁹ in 25/67 (37%) children at 3–4 years,²⁰ and in 17/68 (25%) children at 4.5–6 years of age.²⁰

The subsequent asthma status was screened on control visits at 8.5–10 years, 13.5–16 years, and 18–20 years of age. In addition, the presence of allergic rhinoconjunctivitis was defined at all control visits. The patient flow and numbers of asthma cases through follow-up are presented in Fig. 1. The definitions of asthma and allergic rhinoconjunctivitis were age dependent and are described in Table 1.

Table 1 The definitions of bronchiolitis, asthma, and allergic rhinoconjunctivitis at the different ages of the follow-up

Recurrent wheezing	One or more physician-diagnosed wheezing episodes during the preceding year
Asthma	Ongoing maintenance medication for asthma or:
At the age of 8.5–10 yr	The history of ≥ 3 wheezing episodes ever in life ²¹
At the age of 13.5–15 yr	Physician-treated wheezing episode during the preceding year ²³
At the age of 18–20 yr	A pathological home PEF monitoring in the subjects with wheezing or prolonged cough (≥ 1 mon) during the preceding year ²²
Allergic rhinoconjunctivitis	
At the ages of 4.5–6 yr and 8.5–10 yr	Physician-diagnosed allergic rhinitis or conjunctivitis with symptoms during the preceding 12 mon
At the ages of 13.5–15 yr	Symptoms of rhinitis or conjunctivitis during the pollen season of the preceding 2 yr

PEF = peak expiratory flow.

Statistics

Chi-square and Fisher's exact tests were used in univariate analyses, and logistic regression in multivariate analyses, adjusted first for RSV etiology of bronchiolitis (leading to recruitment into the study) and then further adjusted for parental asthma and, finally, adjusted for sex, age on admission, and parent-reported wheezing before bronchiolitis.

Ethics

The joint Ethics Committee for Human Research of Kuopio University and Kuopio University Hospital approved this study, and an informed consent was obtained from all study subjects and at least from one parent.

RESULTS

Season of Birth and Early Exposure to Furred Pets

Twenty-six (31%) children were born in winter/spring, 29 (35%) children were born in summer, and

28 (34%) children were born in autumn. Thirty-three (40%) children were hospitalized for RSV bronchiolitis, 75% of them during an epidemic from October to December 1981. Thirty children (38%) were exposed to furred pets at home or at day care, 21 to cats and 20 to dogs. The exposure had taken place before 6 months in 21 (70%) cases. Among the 33 RSV patients, 6 (18%), 16 (49%), and 11 (33%) patients were born during the three seasons ($p = 0.052$), respectively, and 11 (33%) patients were exposed to furred pets ($p = 0.467$).

Early Sensitization

As seen in Table 2, 17 (21%) children were sensitized to inhalant allergens: 9 to furred pets and 10 to seasonal pollens. Six (23%) children born in winter/spring, compared with 4–7% of those born in other times, were sensitized to pets ($p = 0.018$). In contrast, there was no significant association between the season of birth and sensitization to seasonal pollens

Table 2 Early sensitization to inhalant allergens, defined by the presence of allergen-specific IgE in serum

Allergen	Specific IgE >0.35 kU/L		
	1–2 yr ($n = 67$)	2–3 yr ($n = 76$)	1–3 yr ($n = 81$)
Dander of furred pets	8 (12%)	5 (7%)	9 (11%)
Cat	5	5	6
Dog	3	2	5
Seasonal pollens	5 (7%)	7 (9%)	10 (12%)
Birch	4	4	5
Timothy grass	4	5	7
Mugwort	1	1	1
<i>D. pteronyssinus</i>	2 (3%)	2 (3%)	3 (4%)
<i>C. herbarum</i>	1 (1%)	1 (1%)	2 (2%)
At least one positive	12 (18%)	10 (13%)	17 (21%)

Data on specific IgE were available from 81/83 children: from 67 children at 1–2 yr and from 76 children at 2–3 yr of age.

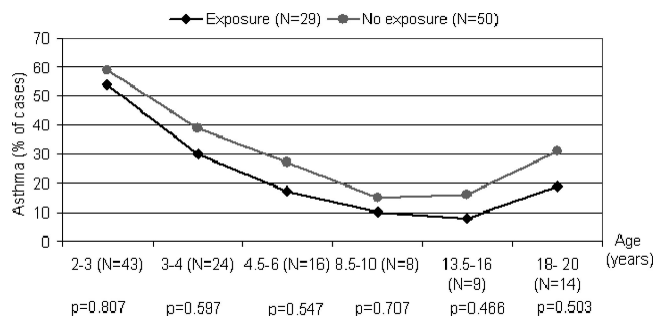


Figure 2. Exposure to furred pets in early childhood, presented in relation to later wheezing and asthma up to 18–20 years of age. For the definition of exposure and sensitization, see the text and for the definition of wheezing and asthma at different ages, see Table 1. Both exposure and sensitization to pets were present in only one child and the RAST tests were not done to one exposed child. These children were excluded from the present analyses. Repeating the analyses by including these two children into the exposed and sensitized groups, respectively, did not change the results. The p values are calculated versus nonexposed and nonsensitized children. Percentages are calculated from the children with exposure, sensitization, and follow-up data available.

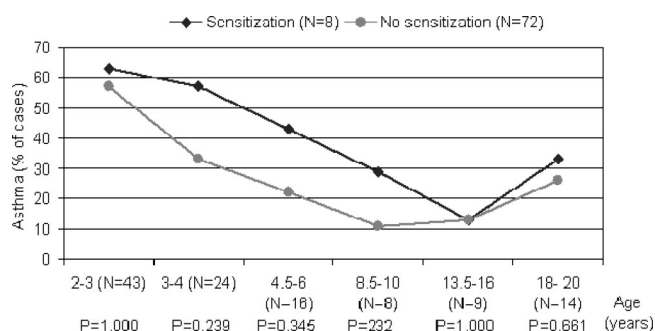


Figure 3. Sensitization to furred pets in early childhood, presented in relation to later wheezing and asthma up to 18–20 years of age. For the definition of exposure and sensitization, see the text, and for the definition of wheezing and asthma at different ages, see Table 1. Both exposure and sensitization to pets were present in only one child and the RAST tests were not done to one exposed child. These children were excluded from the present analyses. Repeating the analyses by including these two children into the exposed and sensitized groups, respectively, did not change the results. The p values are calculated versus nonexposure and nonsensitization cases. Percentages are calculated from the children with exposure, sensitization data, and follow-up data available.

(data not shown). Among the 33 RSV patients, only 2 (6%) were sensitized to pets/pollens ($p = 0.012$ versus 15 [30%] in non-RSV cases). Doctor-diagnosed asthma in a parent was present in 8/79 (10%) families, and 5/8 (63%) children were sensitized to inhalant allergens (versus 12/71 [17%] in nonasthma families). Only 2 of these 8 children were exposed and 1 was sensitized to pets.

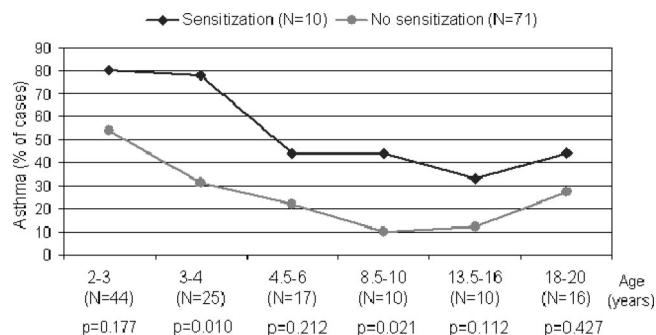


Figure 4. Sensitization to seasonal pollens in early childhood, presented in relation to later wheezing and asthma up to 18–20 years of age. For the definition of exposure and sensitization, as well as of wheezing and asthma at different ages, see text. The p values versus nonsensitized children. For percentage calculations, see Fig. 2.

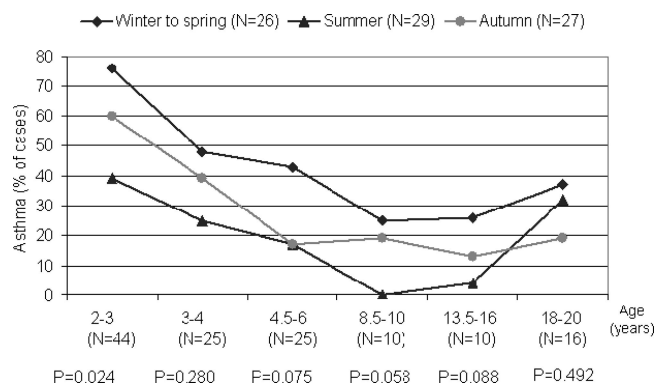


Figure 5. The season of birth, presented in relation to later wheezing and asthma up to 18–20 years of age. For the definition of exposure and sensitization, as well as of wheezing and asthma at different ages, see text. The p values versus nonsensitized children. For percentage calculations, see Fig. 2.

Early Exposure and Sensitization versus Later Outcome: Univariate Analyses

Neither early exposure nor sensitization to furred pets had any significant association with later wheezing or asthma (Figs. 2 and 3). Instead, early sensitization to seasonal pollens increased the risk of wheezing and asthma, but significantly at the ages of 3–4 years and 8.5–10 years only (Fig. 4). The children born in winter/spring carried the greatest risk for later wheezing, but the difference versus other birth seasons was significant at 2–3 years of age only (Fig. 5). Neither early exposure to furred pets nor early sensitization to pets or pollens had any association with later allergic rhinitis or conjunctivitis (Table 3). Likewise, the season of birth had no such association (data not shown).

When sensitizations to furred pets and seasonal pollens were combined, early sensitization increased the risk of wheezing at 3–4 years and asthma increased the risk at 8.5–10 years of age; no association was found with later atopy (data not shown). When the data

Table 3 Early exposure to furred pets and early sensitization to furred pets or seasonal pollens, presented in relation to later allergic rhinitis or conjunctivitis

Allergic Rhinoconjunctivitis	Exposure to Pets* (<i>n</i> = 28)	<i>p</i>	Sensitization to Pets* (<i>n</i> = 8)	<i>p</i> #	Sensitization to Pollens (<i>n</i> = 10)	<i>p</i>
Aged 4.5–6 yr						
Present (<i>n</i> = 11)	3 (18%)§	0.736	2 (25%)§	0.607	2 (22%)*	0.631
Absent (<i>n</i> = 57)	20		6		7	
Aged 8–10 yr						
Present (<i>n</i> = 12)	3 (15%)	0.734	2 (25%)	0.650	1 (11%)	0.673
Absent (<i>n</i> = 50)	17		7		8	
Aged 13.5–16 yr						
Present (<i>n</i> = 27)¶	8 (31%)	0.311	2 (22%)	0.466	4 (44%)	0.726
Absent (<i>n</i> = 43)	18		7		5	
Aged 18–20 yr						
Present (<i>n</i> = 15)	3 (17%)	0.215	2 (29%)	1.000	2 (22%)	1.000
Absent (<i>n</i> = 39)	15		5		7	

For the definition of exposure and sensitization, see the text. For definitions of allergic rhinoconjunctivitis, see Table 1.

*Both exposure and sensitization to pets were present in only one child and the RAST tests were not done to one exposed child. These children were excluded from the present analyses. Repeating the analyses by including these two children into the exposed and sensitized groups, respectively, did not change the results.

#The p values are calculated vs nonexposure and nonsensitization cases.

§For percentage calculations, see Table 1.

¶Data on allergic symptoms was available in one participant with no information on asthma status at the age of 13.5–16 yr.

on asthma and atopy were combined, the diagnosis was atopic asthma in four to eight cases at the childhood visits and only in two adults at the 18- to 20-year visit. These numbers are too small for any stratified analyses.

Early Exposure and Sensitization versus Later Asthma: Multivariate Analyses

The main negative result of the univariate analyses that early exposure and sensitization to furred pets did not influence on the risk of later wheezing and asthma was confirmed also by the multivariate model (Table 4). Logistic regression adjusted for RSV etiology of bronchiolitis and further for parental asthma gave rather similar results as crude analyses. The significant association of early sensitization to seasonal pollens with wheezing and/or asthma until 8.5–10 years of age was confirmed by a similar logistic regression. In further analyses with adjustments for sex, age, and wheezing history on admission, only one result changed. The association between early sensitization to seasonal pollens and asthma at the age of 13.5–16 years became statistically significant (OR, 7.99; 95% CI, 1.09–58.52). The results did not change when one child with both exposure and sensitization to pets and another exposed child with no data on sensitization were included in the analyses.

DISCUSSION

Increasing evidence suggests, that early life exposure to furred pets decreases^{4,5,7} but early sensitization increases^{12–15} the risk of later wheezing and asthma. In this study, we were not able to confirm either observation. Instead, early sensitization to seasonal pollens increased asthma risk until the age of 13.5–16 years, but the effect was not any more significant in adults. The result is in line with the other postbronchiolitis study of our group with follow-up done until 13–15 years of age.^{15–17}

The association between early exposure to furred pets and later diminished tendency for wheezing has been well established among children with low asthma risk.^{4,7,11} In a retrospective study from Sweden, daily exposure to cats during the 1st year of life protected children from asthma and allergic rhinitis at school age.⁵ In the Tucson birth cohort study from Arizona, 1246 children were prospectively followed from birth, and early dog exposure protected from later asthmatic symptoms until 13 years of age.⁷ However, this effect was established only if there was no family history of asthma. In line, Celedon *et al.* found that cat exposure at the age of 2–3 months decreased the risk for wheezing in 1- to 5-year old children if the mothers had no asthma, but increased the asthma risk in 3- to 5-year old children if the mothers had asthma.⁴ The result was opposite in a recent Dutch study,¹ where dog allergen

Table 4 Multivariate analysis: Logistic regression adjusted for RSV etiology of bronchiolitis

Outcome	Exposure to Pets*	Sensitization to Pets*	Sensitization to Pollens	Sensitization to Any Allergen
Wheezing at 3–6 yr of age# (<i>n</i> = 25)§	7	4	7	10
Crude	0.70 (0.24–2.04)¶	2.67 (0.54–13.08)	7.97 (1.51–42.19)	5.07 (1.48–17.31)
Adjusted	0.81 (0.26–2.49)	3.72 (1.08–12.85)	6.45 (1.17–35.47)	4.07 (1.15–14.42)
Asthma at 8.5–10 yr of age (<i>n</i> = 9)	2	2	4	6
Crude	0.63 (0.12–3.44)	3.13 (0.49–19.87)	7.52 (1.51–37.46)	9.56 (2.01–45.54)
Adjusted	0.61 (0.11–3.38)	2.66 (0.41–17.34)	6.31 (1.23–32.40)	8.15 (1.67–39.94)
Asthma at 13.5–16 yr of age (<i>n</i> = 10)				
Crude	0.43 (0.08–2.24)	0.95 (0.10–8.74)	3.86 (0.78–9.30)	2.67 (0.65–10.97)
Adjusted	0.45 (0.09–2.39)	0.79 (0.08–7.48)	3.27 (0.64–16.72)	2.23 (0.52–9.65)
Asthma at 18–20 yr of age (<i>n</i> = 16)	3	2	4	6/14
Crude	0.50 (0.12–2.13)	1.38 (0.22–8.50)	2.13 (0.49–9.30)	2.18 (0.61–7.82)
Adjusted	0.54 (0.13–2.34)	1.14 (0.18–7.33)	1.65 (0.36–7.64)	1.71 (0.45–6.55)

Logistic regression with no adjustment and adjusted for RSV etiology of bronchiolitis: ¶OR (95% CI).

*Both exposure and sensitization to pets were present in only one child and the RAST tests were not done to one exposed child. These children were excluded from the present analyses. Repeating the analyses by including these two children into the exposed and sensitized groups, respectively, did not change the results.

#Wheezing at either 3–4 yr or 4.5–6 yr of age.

§Data available in 50 children.

exposure at 3 months of age predicted persistent wheezing until 4 years of age in children with non-atopic mothers, but not in the whole study population of 1127 children. Likewise, in two large population-based cohort studies from Germany and South England the results were negative, as were our results.^{9,10} The children were not analyzed in relation to inheritance, and no significant association was found between early pet exposure and asthma at 5–7 years of age.

The outcome after early exposure to furred pets has varied in postbronchiolitis studies. In a Swedish study, 47 children hospitalized for RSV bronchiolitis were prospectively followed-up until 13 years of age,³¹ and no association was found between daily pet exposure at ≤1 year of age and later asthma. These findings are in accordance with our present results. However, in our later study on 92 infants hospitalized for bronchiolitis, a furred pet at home in early childhood protected them from asthma, evaluated 3 years after bronchiolitis, at the mean age of 4 years,¹⁵ but no more at 7 years and 11–13 years of age.^{16,17} The influence of early pet exposure may be related to the age at the onset of wheezing. In a recent Swedish birth cohort study, 1228 children were followed for 4 years,¹¹ and keeping a dog at home during the 1st year of life increased the risk for early onset transient wheezing but decreased the risk of late-onset wheezing, regardless of family asthma or atopy.

There is only one previous prospective study concerning sensitization in early life and asthma in adulthood. A British birth cohort included 100 children with atopy in parents, and skin test reactivity to food allergens during the 1st year of life predicted asthma at 22 years of age.¹⁸ A similar result was found also for inhalant allergens, but in adjusted analyses, only sensitization to food allergens was an independent risk factor. In a German cohort study, 1314 children were followed from birth to 13 years of age and, and specific IgE to food and inhalant allergens were measured yearly until the age of 7 years and at the age of 10 years.^{13,14} A positive result in infancy predicted asthma at school age, but only if the child still reacted to inhalant allergens.^{13,14} Instead, transient sensitization before 2 years of age had no association with later asthma.¹³ Early sensitization to indoor allergens of cats, dogs, and mites, but not to seasonal outdoor allergens or food allergens, predicted bronchial hyper-reactivity at the age of 7 years and lung function abnormalities at the age of 7–13 years.¹⁴ In a recent study in 521 children from Manchester, U.K., specific IgE to cat, dog, and mite allergens at 3 years of age predicted the continuation of wheezing at least until 5 years of age.¹² In the present study, early sensitization to seasonal pollens predicted subsequent wheezing and increased asthma risk until the age of 13.5–16 years, as was also seen in our other postbronchiolitis follow-up

at the ages of 4, 7, and 11–13 years.^{15–17} In adulthood, this association was no more significant, probably because of many other risk factors, which the subjects at risk for asthma meet during childhood and adolescence.

Season of birth may influence the pattern of early allergic sensitization and further to the risk of later asthma³² allergic disease.³³ Birth just before or during a pollen season is assumed to increase the risk of both early sensitization and later allergy.^{2,3} However, in a Swedish study, children born during tree pollen season were less likely to develop allergic rhinoconjunctivitis and specific IgE antibodies to pollens by the age of 12–15 years.⁶ The development of tolerance might be an explanation for this unexpected result. In our study, children who were born in winter or spring (before pollen season) or in summer (during pollen season) were no more often sensitized to pollens than other children. In addition, season of birth and early sensitization had no association with later allergy. The result is partly in disagreement with the other finding of this study that later asthma was connected with early sensitization to seasonal pollens. Skin testing was not done systemically during the follow-up, and the definition of allergy was based on symptoms alone. This shortcoming in the study design may have influenced the results. Skin-prick tests were done at 18–20 years of age,²² and reactivity was not associated with early life sensitization.

The different results concerning the role of indoor allergens in early life and later asthma, observed in the present and other studies, may reflect different climates and housing conditions.²⁹ In Finland, as in other northern countries, artificial heating and restriction of ventilation of the houses is needed for 6–9 months yearly. Particularly in winter, the indoor air is dry. Consequently, the amounts of HDMs are low²⁹ and sensitization to them is rare, as seen in this study and in many earlier studies from northern countries.^{34,35}

The strengths of the present study are the long follow-up times from infancy to adulthood, a careful prospective registration of wheezing until 6 years of age, and clinical asthma diagnoses at prospective follow-up visits from 8.5–10 years to 18–20 years of age. Data on pet contacts at home and day care were registered at all visits until 3 years of age, and serum allergen-specific IgE was measured twice before 3 years of age. The data allowed versatile analyses of the association between early pet exposure and early sensitization to pets and pollens and subsequent wheezing and asthma. Because there is increasing evidence that infants with RSV bronchiolitis have less asthma and allergy and infants with asthma in parents have more asthma and allergy, compared with other bronchiolitis patients,^{31,36} multivariate

analyses were done adjusted, *e.g.*, for RSV etiology of early wheezing and parental asthma.

The main limitation of this study is the lack of a control group with no wheezing in infancy. However, our main interest was to assess whether exposure or sensitization data can be used to screen those wheezing infants who are at a particular risk for asthma in later life. For this purpose, nonwheezing controls are not necessary. The other limitation is the large number of dropouts, although a 66% participation rate is acceptable for a clinical 20-year follow-up study. However, the numbers of cases was small in subgroup analyses, *e.g.*, not allowing stratified analyses for atopic asthma.

In conclusion, our study showed that wheezing infants with early allergic sensitization to inhalant allergens, especially to pollens, are at particular risk for subsequent wheezing and asthma. Our findings did not give support to the idea that early exposure to furred pets may protect children from later allergy or asthma.

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