

# Development of atopy and wheezing symptoms in relation to heredity and early pet keeping in a Swedish birth cohort

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The role of pet keeping during infancy for the development of allergy and asthma is still controversial. The objective of this population-based birth cohort study was to assess the development of atopy and different wheezing phenotypes during the first 4 yr of life in relation to heredity and early pet keeping. The cohort comprised all 1228 infants living in a Swedish county who were born over a 1-yr period. The parents replied to repeated questionnaires and 817 of the children were skin prick tested both at 1 and 4 yr. Cat keeping during the first year of life was associated with an increased risk of a positive skin prick test to cat at 1 yr of age [odds ratio (OR) 2.2, 95% confidence interval (CI) 0.9–5.6], but neither with sensitivity nor clinical symptoms of allergy at 4 yr. Dog keeping during the first year of life was associated with an increased risk of early-onset transient wheezing, but only in children with parental asthma (adjusted OR 4.3, 95% CI 1.5–12.1). In contrast, early dog keeping had an inverse association with sensitivity to pollen allergen at 4 yr (adjusted OR 0.3, 95% CI 0.1–0.9) and late-onset wheezing (adjusted OR 0.4, 95% CI 0.2–1.0). Thus, pet keeping during the first year of life was not associated with an increased risk of atopy at 4 yr, although a positive SPT to cat was more common at 1 yr. Our findings may even suggest that dog keeping during the first year of life might provide some protection from pollen allergy and late-onset wheezing and increase the risk of early-onset transient wheezing in children with heredity for asthma.

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The evidence for pet avoidance as a strategy for primary prevention of atopic diseases has been increasingly questioned because the suggestion that early exposure to furry animals at home would lead to tolerance and less asthma at school age (1). A number of subsequent studies have shown an inverse relationship between pet ownership and atopy both in children (2–6) and in adults (7, 8). Furthermore, children living on animal farms have fewer allergic diseases compared with children living in non-farming families or in cities (9). Life style patterns related to socio-economic status may, however, confound the analyses of the association between pet keeping and asthma or atopy (10). However,

atopic disease is the result of an interaction between genes and environment (11). Furthermore, family history of asthma and allergies may also affect the behaviour and exposure to allergens. An inverse relationship between pet ownership and atopy could partly be explained by the avoidance of pets in families with an atopic disposition (2, 12).

In cross-sectional studies, it is difficult to distinguish between causes and consequences. Prospective birth cohort studies facilitate an evaluation of the association between pets and atopy. We have in this birth cohort study collected information whether the families actively avoided pet keeping because of asthma or

allergies in the family. Our aim was to assess the relationship between a family history of asthma and atopy, early pet keeping and the development of positive skin prick tests and different wheezing phenotypes during the first 4 yr of life after adjustment for avoidance measures and potential confounders.

## Material and methods

### Study area

Jämtland is a county in northern Sweden where half the area is forest, 25% is mountains and only 2% is left for farming areas and villages. Fifty per cent of the children live in Östersund, which is the largest town in the area, with 43,500 inhabitants, few industrial plants and low levels of outdoor air pollutants. The other half of the population is distributed over the county, living in small towns with 1000–4000 inhabitants or in rural areas over an area of 49,400 sq.km. The mean annual temperature in Östersund (latitude 61°) is 2.5°C and the annual precipitation is 484 mm. We have previously demonstrated that sensitivity to house dust mite is rare in this area (2).

### Study design

The study was designed to investigate prospectively the development of allergy in a birth cohort of 1231 children. The cohort included all the children living in Jämtland and born during the period February 1996 to January 1997 at Östersund Hospital. The families were enrolled either at the first visit to the antenatal clinic or at the birth of the child. Three babies died during the first year of life, leaving 1228 infants.

At enrolment, the parents of 857 children (70%) replied to the first questionnaire about living conditions, smoking habits, the keeping of pets and symptoms of asthma and allergy in the family. The parents were also asked whether they had avoided pet keeping and, if so, for what reason.

When the children were 1-yr old, the study nurse interviewed the parents of 1043 children (85%) about breast-feeding, infectious diseases, antibiotic courses, changes in home environment and allergic symptoms during the first year of life.

At 4 yr, a questionnaire concerning home environment, symptoms of allergic diseases and pet ownership was mailed to the parents, and 801 (65%) responded. The parents of 736 children

replied to questionnaires on symptoms at both 1 and 4 yr of age.

The questions related to symptoms were based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (13).

### Definitions

Heredity for asthma or allergic rhinoconjunctivitis was defined as an affirmative answer to the question: 'Has the child's mother or father ever had asthma' or 'allergic symptoms from the eye or the nose?'

Twelve-month prevalence of wheezing was defined as an affirmative answer to the question: 'Has your child experienced any wheezing from the chest during the last 12 months?' Early-onset transient wheezing was defined as reported wheezing only during the first year of life. Early-onset persistent wheezing was defined as wheezing both at 1 and 4 yr of age. Late-onset wheezing was defined as wheezing between 3 and 4 yr of age but no wheezing during the first year of life.

Pet keeping was defined as either cat or dog ownership. Avoidance of pet keeping was defined as an affirmative answer to the question: 'Have you actively avoided pet keeping (already at the birth of the index child) because of allergies or asthma in other family members?'

### Skin prick tests

Skin prick tests were performed at 1 yr of age in 1040 children (85%) and at 4 yr of age in 879 children (72%). In all, 817 of the 1228 children (67%) participated at both 1 and 4 yr. The tests were performed on the volar side of the lower arm and standardized extracts of five allergens, i.e. egg, milk, birch, timothy and cat (Solu-Prick SQ, ALK-Abeló, Hørsholm, Denmark) were applied with lancets from ALK. The potency of the inhalant allergens was 10 histamine equivalent prick units (HEP). Histamine dihydrochloride, 10 mg/ml, was used as a positive control. The test was considered positive for a particular allergen if the mean wheal diameter was at least 3 mm in diameter after 15 min. The mean diameter of the histamine wheal was 4.4 mm (s.d. 0.6) at 1 yr and 4.0 mm (s.d. 0.7) at 4 yr. Children were instructed to avoid antihistamines for 72 h before the test. The same study nurse carried out all the tests. The reproducibility of the skin prick test technique was checked repeatedly according to recommendations in the ISAAC phase II manual (14).

## Statistics

All the data were coded and entered into the database module of the SPSS statistics software (SPSS Inc., Chicago, IL, USA). All the subsequent analyses were performed using this package (version 10.0). The chi-square test or, when appropriate, Fisher's exact test, was used to compare rates between groups. Statistical significance was set at the 5% level. Multivariate logistic regression analyses were used to obtain estimates of odds ratios for sensitization and reported symptoms, with adjustments for significant co-variables. The association between pet keeping and sensitization and symptoms was assessed after exclusion of children, whose parents had avoided pet keeping already at the birth of the index child because of asthma and allergies in other family members.

## Ethical aspects

The Ethics Committee at the University of Umeå approved the study. Informed consent was obtained from the parents when skin prick tests were performed.

## Results

The number of children with at least one positive skin prick test was doubled between 1 and 4 yr. As summarized in Table 1, 7% (56 of 817) of those children who participated in the skin prick test at both 1 and 4 yr of age had at least one positive skin prick test at 1 yr, when compared with 13% (110 of 817) at 4 yr. In all, 4.5% (37 of 817) were skin test positive at both ages. In children only tested on one occasion, a positive SPT was recorded in 7% (15 of 223) at 1 yr and 8% (five of 62) at 4 yr. Egg was the dominating allergen at 1 yr, while at 4 yr cat and birch were the major sensitizing allergens. There were no significant differences in atopic heredity, gender, birth weight, breast-feeding and pet ownership between those who did and did not participate in the skin prick tests. Five of 21 children with a positive skin test to cat allergen at 1 yr had a negative test to cat allergen at 4 yr.

Table 1. Positive skin prick tests in 817 children tested at both 1 and 4 yr of age

| Allergens | 1 yr     | 4 yr    | 1 and 4 yr |
|-----------|----------|---------|------------|
| Egg       | 36 (4%)  | 11 (1%) | 8 (1%)     |
| Milk      | 13 (2%)  | 6 (1%)  | 6 (1%)     |
| Timothy   | 1        | 17 (2%) | 0          |
| Birch     | 2 (0.2%) | 49 (6%) | 2 (0.2%)   |
| Cat       | 21 (3%)  | 72 (9%) | 16 (2%)    |

The 12-month prevalence of wheezing was 24% (174 of 736) at 1 yr and 17% (124 of 736) at 4 yr among those participating in the study at both ages. The corresponding prevalence rates were 20% (61 of 304) at 1 yr and 13% (nine of 68) at 4 yr among children participating at only one occasion. Among the children participating at both 1 and 4 yr, the prevalence of wheezing only at 1 yr (early-onset transient wheezing), both at 1 and 4 yr (early-onset persistent wheezing) and only at 4 yr (late-onset wheezing) were 16% (119 of 736), 7.5% (55 of 736) and 9.4% (69 of 736), respectively. Early-onset transient wheezing showed a linear association with number of older siblings ( $p = 0.02$ ). The prevalence of recurrent wheezing (at least three episodes of wheezing) during first year of life was 5.3% (39 of 736) and almost half of them were wheezing also at 4 yr of age (16 of 39). Children with early-onset, persistent wheezing and late-onset wheezing were more likely to have positive skin prick tests both at 1 and 4 yr of age (Table 2). In all, 7% (50 of 736) had asthma diagnosed by a doctor at 4 yr of age.

Sensitivity to cat allergen at 1 yr was not associated with wheezing at that age but was associated with an increased risk at 4 yr (odds ratio, OR, 5.3, 95% confidence interval, CI, 2.0–13.5). The positive predictive value of a positive test to cat allergen for wheezing at 4 yr of age was 41% in non-wheezing 1-yr-old-children. However, only seven of the 69 children with wheezing at four, but not at 1 yr had a positive test to cat allergen at 1 yr.

Parental hay fever and asthma were independent determinants of sensitization and symptoms in the child (Tables 3 and 4). Paternal and maternal hay fever had a direct association with sensitization to inhalant allergens at 4 yr of age. Maternal asthma had a strong relationship with early onset persistent wheezing and was also a risk factor for late-onset wheezing.

In all, 205 children kept dogs at home during their first year of life. The corresponding number during the second year of life was 173 and 90% of those (155 of 173) kept dogs already during their first year of life. The number of children

Table 2. Crude odds ratios (95% CI) for skin test positivity at 1 and 4 yr of age in children with different types of wheezing

|                           | At least one positive skin prick test |               |
|---------------------------|---------------------------------------|---------------|
|                           | 1 yr                                  | 4 yr          |
| Early transient wheezing  | 0.4 (0.1–1.1)                         | 0.5 (0.3–1.1) |
| Early persistent wheezing | 3.2 (1.5–6.8)                         | 2.8 (1.5–5.4) |
| Late-onset wheezing       | 5.0 (2.6–9.5)                         | 3.1 (1.7–5.7) |

Table 3. Sensitization to inhalant allergens at 1 and 4 yr of age in relation to pet ownership and a family history of asthma and hay fever

|                             | Pos SPT to cat at 1 yr |                      |                      | Pos SPT to cat at 4 yr |                      |                      | Pos SPT to pollen at 4 yr |                      |                      |
|-----------------------------|------------------------|----------------------|----------------------|------------------------|----------------------|----------------------|---------------------------|----------------------|----------------------|
|                             | %                      | Crude OR<br>(95% CI) | Adj. OR*<br>(95% CI) | %                      | Crude OR<br>(95% CI) | Adj. OR*<br>(95% CI) | %                         | Crude OR<br>(95% CI) | Adj. OR*<br>(95% CI) |
|                             | n = 835                |                      |                      | n = 820                |                      |                      | n = 820                   |                      |                      |
| Paternal hay fever (yes/no) | 5.1/2.7                | 2.0 (0.9–4.4)        | 2.5 (1.1–6.0)        | 14.9/6.7               | 2.4 (1.5–4.0)        | 2.8 (1.6–4.9)        | 14.4/5.1                  | 3.1 (1.8–5.2)        | 2.5 (1.4–4.6)        |
| Paternal asthma (yes/no)    | 2.6/3.3                | 0.8 (0.2–2.7)        | 0.5 (0.1–1.9)        | 11.0/8.2               | 1.4 (0.7–2.6)        | 0.7 (0.3–1.4)        | 11.9/6.6                  | 1.9 (1.0–3.6)        | 1.1 (0.5–2.2)        |
| Maternal hay fever (yes/no) | 4.3/2.9                | 1.5 (0.7–3.4)        | 1.8 (0.7–4.4)        | 13.6/6.9               | 2.1 (1.3–3.4)        | 2.0 (1.1–3.5)        | 12.1/5.6                  | 2.4 (1.4–4.0)        | 2.0 (1.1–3.7)        |
| Maternal asthma (yes/no)    | 2.9/3.3                | 0.9 (0.3–2.6)        | 0.7 (0.2–2.3)        | 13.9/7.5               | 2.0 (1.1–3.4)        | 1.7 (0.9–3.2)        | 9.7/6.8                   | 1.5 (0.8–2.7)        | 1.1 (0.5–2.2)        |
|                             | n = 683                |                      |                      | n = 647                |                      |                      | n = 647                   |                      |                      |
| Dog keeping†                |                        |                      |                      |                        |                      |                      |                           |                      |                      |
| Never                       | 3.2                    | 1.0                  | 1.0                  | 7.4                    | 1.0                  | 1.0                  | 7.9                       | 1.0                  | 1.0                  |
| First year of life          | 3.9                    | 1.2 (0.5–3.0)        | 1.2 (0.5–2.9)        | 7.1                    | 1.0 (0.5–1.8)        | 0.9 (0.4–1.8)        | 2.5                       | 0.3 (0.1–0.8)        | 0.3 (0.1–0.9)        |
| After first year of life‡   |                        |                      |                      | 2.1                    | 0.3 (0.0–2.0)        | 0.3 (0.0–2.4)        | 4.3                       | 0.5 (0.1–2.2)        | 0.7 (0.2–3.1)        |
| Cat keeping†                |                        |                      |                      |                        |                      |                      |                           |                      |                      |
| Never                       | 2.8                    | 1.0                  | 1.0                  | 7.0                    | 1.0                  | 1.0                  | 6.6                       | 1.0                  | 1.0                  |
| First year of life          | 5.6                    | 2.1 (0.9–4.9)        | 2.2 (0.9–5.6)        | 9.0                    | 1.3 (0.7–2.6)        | 1.6 (0.8–3.5)        | 5.5                       | 0.8 (0.4–1.9)        | 1.2 (0.5–2.9)        |
| After first year of life‡   |                        |                      |                      | 1.7                    | 0.2 (0.0–1.7)        | 0.3 (0.0–2.1)        | 3.3                       | 0.5 (0.1–2.1)        | 0.6 (0.1–2.6)        |

\*After multiple logistic regression adjusting for paternal hay fever, paternal asthma, maternal hay fever, maternal asthma, maternal smoking, older siblings, gender and dog and cat keeping.

†After exclusion of all children, who had reported avoidance of pet keeping during the first year of life because of asthma or allergies in other family members.

‡Pet keeping not until after first year of life.

Table 4. Wheezing at 1 and 4 yr of age in relation to pet ownership and a family history of asthma and hay fever

|                                                 | Transient wheezing<br>(at 1 yr but not at 4 yr of age) |                      |                      | Persistent wheezing<br>(at 1 and 4 yr of age) |                      |                      | Late onset wheezing<br>(at 4 yr but not at 1 yr of age) |                      |                      |
|-------------------------------------------------|--------------------------------------------------------|----------------------|----------------------|-----------------------------------------------|----------------------|----------------------|---------------------------------------------------------|----------------------|----------------------|
|                                                 | %                                                      | Crude OR<br>(95% CI) | Adj. OR*<br>(95% CI) | %                                             | Crude OR<br>(95% CI) | Adj. OR*<br>(95% CI) | %                                                       | Crude OR<br>(95% CI) | Adj. OR*<br>(95% CI) |
| n = 719                                         |                                                        |                      |                      |                                               |                      |                      |                                                         |                      |                      |
| Paternal hay fever (yes/no)                     | 18.8/14.8                                              | 1.3 (0.8–2.1)        | 1.3 (0.8–2.2)        | 8.5/6.7                                       | 1.3 (0.7–2.5)        | 1.1 (0.7–2.2)        | 10.3/9.0                                                | 1.2 (0.6–2.1)        | 1.2 (0.6–2.2)        |
| Paternal asthma (yes/no)                        | 18.6/15.3                                              | 1.3 (0.7–2.2)        | 1.1 (0.6–2.1)        | 11.3/6.5                                      | 1.9 (0.9–3.8)        | 1.6 (0.8–3.7)        | 9.3/9.4                                                 | 0.8 (0.4–1.8)        | 0.7 (0.3–1.8)        |
| Maternal hay fever (yes/no)                     | 17.4/15.4                                              | 1.2 (0.7–1.8)        | 1.0 (0.6–1.7)        | 9.4/6.3                                       | 1.6 (0.9–2.9)        | 0.7 (0.3–1.4)        | 13.5/8.0                                                | 1.8 (1.1–3.1)        | 1.4 (0.7–2.5)        |
| Maternal asthma (yes/no)                        | 17.5/15.4                                              | 1.2 (0.7–2.0)        | 1.2 (0.7–2.1)        | 20.0/4.5                                      | 5.3 (2.9–9.6)        | 5.9 (2.9–11.7)       | 15.8/8.0                                                | 2.2 (1.2–3.8)        | 1.9 (1.0–3.5)        |
| n = 594                                         |                                                        |                      |                      |                                               |                      |                      |                                                         |                      |                      |
| Dog keeping during first year of life† (yes/no) | 19.2/13.4                                              | 1.5 (1.0–2.4)        | 1.5 (0.9–2.6)        | 7.3/6.0                                       | 1.2 (0.6–2.5)        | 1.5 (0.7–3.2)        | 5.1/10.8                                                | 0.4 (0.2–0.9)        | 0.5 (0.2–1.0)        |
| Cat keeping during first year of life† (yes/no) | 16.0/14.9                                              | 1.1 (0.6–1.9)        | 1.1 (0.6–1.9)        | 3.8/7.1                                       | 0.5 (0.2–1.3)        | 0.4 (0.1–1.3)        | 6.9/9.7                                                 | 0.7 (0.3–1.4)        | 0.7 (0.3–1.6)        |

\*After multiple logistic regression adjusting for paternal hay fever, paternal asthma, maternal hay fever, maternal asthma, maternal smoking, older siblings and dog and cat keeping.

†After exclusion of all children, where pet keeping had been avoided during the first year of life because of asthma or allergies in other family members.

with cat keeping during the first year of life was 153. Of 121 children with cat keeping during second year of life, 96 children (79%) were exposed already during their first year of life.

Avoidance of cat or dog keeping at the birth of the child was common in families with a history of asthma or atopy, but it did not protect the child from sensitization. In all, 15% (27 of 176) were sensitized to cat allergen at 4 yr of age in children whose families had avoided pet keeping because of asthma or allergies in other family members. The corresponding rate of sensitization in the remaining children was 7% (48 of 703) ( $p = 0.001$ ). Furthermore, pet owners got rid of their pets if the

children got sensitized. Of the 21 children with a positive test to cat allergen at 1 yr, 14 were exposed to either a cat or a dog at home (eight cat owners and eight dog owners), and 13 of 14 families removed the pet after 1 yr of age. In addition, 48 children became pet owners after infancy, none of whom had a positive test to cat allergen at 1 yr. As a consequence, at 4 yr, a positive test to cat allergen was inversely related to current pet ownership (OR 0.4, 95% CI 0.1–1.0 and OR 0.4, 95% CI 0.1–0.8, respectively).

Infants who were exposed to cats at home during their first year of life had an increased likelihood of positive skin test to cat at 1 yr

(Table 3). Sensitivity to cat (Table 3) and wheezing at 4 yr of age (Table 4) were not associated with cat exposure at home during the first year of life.

Dog keeping during the first year of life was associated with a decreased risk of sensitization to pollen allergen at 4 yr (Table 3). The lower risk of sensitization to pollen persisted after adjustments for older siblings, maternal smoking, parental hay fever and asthma and the avoidance of pet keeping because of allergies in other family members. Dog keeping during the first year of life was also associated with a decreased risk of late-onset wheezing, but tended to be associated with an increased risk of early-onset transient wheezing during the first year of life (Table 4). The positive association between dog keeping and early-onset, transient wheezing was only observed in children with parental asthma (OR 2.8, 95% CI 1.3–6.4) and not in children without parental asthma (OR 1.0, 95% CI 0.6–1.7). The association between dog keeping and transient wheezing in children with parental asthma was even stronger after exclusion of families who had avoided pet keeping because of allergies or asthma in other family members (OR 3.9, 95% CI 1.5–10.4). The adjusted OR was 4.3 (95% CI 1.5–12.1) after multivariate analyses.

## Discussion

The strength of this study, focusing on potential effects of pet keeping at birth and during infancy, is its longitudinal design and that the children were enrolled already at birth. Cat keeping during infancy was related to sensitivity to cat allergen at 1 yr but not at 4 yr. Dog keeping during infancy was associated with an increased risk of wheezing at 1 yr, but a reduced risk of sensitivity to pollen and late-onset wheezing at 4 yr. These associations persisted after adjustment for sibship size, maternal smoking, atopic heredity and avoidance of pet keeping because of allergies in other family members. As expected, family history was the major determinant of sensitization and symptoms during the first 4 yr of life. Avoidance measures were also more likely in families with a history of asthma and hay fever.

Several studies indicate that maternal heredity is more important than a paternal history of either asthma (5, 15–17), hay fever (16) and atopic sensitization (18). The strong association with the mother may be due to the fact that she also influences her offspring during foetal life and through the breast milk. Thus, persistent and late onset wheezing were closely related only to

maternal asthma. Such findings could also be related to misclassification if e.g. the mothers underreport symptoms in the fathers. However, most questionnaires were completed by both parents and the prevalence of asthma and hay fever were similar in mothers and fathers. Moreover, both maternal and paternal hay fever contributed to an increased risk of sensitization to inhalant allergens at the age of four.

A history of asthma and atopy may also affect the behaviour in the family. Avoidance of pet keeping was often undertaken because of allergies in other family members. When the index child was born, 20% of our families had actively avoided pets because of allergies in other family members. We have no information related to possible pet exposure outside home. However, the infants spent most of their time at home and did not attend day care. The avoidance of pet keeping did not prevent sensitization, apparently because allergens are ubiquitous in the community (19). Children are exposed to pet allergens also without direct contacts with the pets (20). Avoidance measures bias the association between pet keeping and atopy or asthma. We have therefore either stratified or adjusted for atopic heredity as well as reported avoidance measures in our analyses.

Allergic symptoms in the child and a positive skin prick test at 1 yr of age influenced the family awareness of allergies and their attitude to pet keeping. Thus, pets were introduced after the first year of life only in families of skin prick test negative children. Furthermore, 13 of 14 families with a pet and a child with a positive test to cat allergen at 1 yr, subsequently got rid of the cat. We cannot entirely exclude that some parents waited for the outcome of the skin prick test until they decided about pet keeping. However, most children with pet keeping, particularly dog keeping, during their second year of life had been exposed to pets at home already before the skin prick test at 1 yr of age.

Although exposure to pet allergen at home was based on parental reports obtained repeatedly over a 4-yr period some misclassification could not be excluded. As children with pets at home are exposed to much higher levels of pet allergens than children without pets (19, 21) and objective measurements also have limitations (22), such measurements would probably not have affected our conclusions. Cat ownership during the first year of life was associated with a positive skin prick test to cat allergen at 1 yr. However, early pet keeping did not affect either sensitization or symptoms at 4 yr of age, supporting the results of a recent cohort study from Germany (23).

Several studies suggest that exposure to high levels of pet allergens in infancy might in fact facilitate the induction of tolerance (1–8, 24). Our study may indicate that both cat and dog keeping could provide some protection from late-onset wheezing, although the association was only significant for dog keeping.

Dog ownership during the first year of life was also associated with a decreased risk of sensitization to pollen at 4 yr, even after adjustment for avoidance measures. These findings are consistent with a number of recent studies. A cohort study from Germany demonstrated an inverse relationship between early dog keeping and atopic dermatitis at 2 yr of age (6), and in another study hay fever and sensitivity to pollen was inversely related to regular contacts with dogs during the first year of life (4). Data from a birth cohort in Detroit indicated that pet exposure during infancy protected against sensitivity to both indoor and outdoor allergens at 7 yr of age (25). Furthermore, a lower prevalence of sensitivity to pollen was observed in Dutch school children, who had been exposed to pets at home during the first 2 yr of life (26). Our findings are also consistent with another Swedish birth cohort study showing a lower risk of asthma and sensitivity to pollen at 4 yr in children with dog keeping during first year of life (21). Furthermore, living on a farm during childhood has been associated with a reduced risk of sensitivity to grass pollen (27). Exposure to high levels of endotoxin and other microbial compounds have been suggested as an explanation for the lower prevalence of atopy in children living on a farm with live-stock or poultry (28). We did not analyse the content of allergen and endotoxin in house dust, but the presence of pets in the home has been linked to increased levels of endotoxin in house dust in other studies (29, 30). Thus, higher levels of endotoxin and other micro-organisms may possibly contribute to the lower risk of pollen allergy and late-onset wheezing in children with families keeping a dog, but a protective effect from pet keeping on wheezing could also be mediated by mechanisms independent from exposure to endotoxin (31).

Early-onset transient wheezing was more likely in children with pet keeping. We used a wide definition of early-onset wheezing and included all children with at least one wheezing episode during the first year of life. The association with number of older siblings suggests that wheezing was induced by respiratory infections, particularly as parental asthma was not a risk factor for early-onset transient wheezing. However, our

study indicated an interaction between a family history of asthma and pet keeping. Thus, dog keeping was a risk factor for early-onset transient wheezing only in children with a family history of asthma. Our findings could be consistent with two other studies, suggesting that recurrent wheezing during infancy was more likely in children with greater exposure to house dust endotoxin (30, 32). One of these studies was based on a cohort where all children had heredity for asthma or allergies (30). The other cohort demonstrated an increased risk of wheezing in children exposed to high concentrations of endotoxin only in children with a family history of atopy (32).

Atopic status was based on skin prick tests. One may argue that it is not appropriate to use the same definition of a positive skin test in a 1-yr-old infant and a 4-yr-old child. However, the histamine wheals were of similar sizes (4 mm) at 1 and 4 yr. Some previous studies have considered the test as positive when the wheal had half that size of the histamine wheal (33). We preferred to have a high specificity rather than a high sensitivity and we therefore used 3 mm as a cut-off point. The same investigator performed all the tests at both ages and the skin prick test technique was checked several times during the study. Thus, it is less likely that measurement error would explain changes in atopic status from age one to four.

To summarize, pet keeping during first year of life was not associated with an increased risk of atopy at 4 yr of age. Our study may even suggest that dog keeping during the first year of life could provide some protection from pollen allergy and late-onset wheezing. Moreover, dog keeping contributed to an increased risk of early-onset transient wheezing, but only so in children with parental asthma.

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