

# Influence of interaction of environmental risk factors and sensitization in young asthmatic children

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**Background:** The increasing prevalence of asthma and allergy in many countries demands evaluation of potential risk factors to improve the possibility of prevention.

**Objective:** We studied the association between exposure to cat and dog allergen and allergic sensitization in young children with asthma and interactions with potential environmental risk factors.

**Methods:** One hundred eighty-nine young children with asthma were evaluated. IgE antibodies to cat and dog were analyzed. Questionnaires were filled in focusing on exposure to cats and dogs, environmental tobacco smoke (ETS), and signs of home dampness as indicated by window pane condensation (WPC) during the first years of life. House dust was analyzed for content of cat (Fel d 1) and dog (Can f 1) allergen.

**Results:** There was a strong association between the degree of reported exposure to cat and dog and the concentration of the respective allergens in floor dust. A dose-response relationship was found between cat exposure, measured as either reported degree of cat exposure or cat allergen levels in dust, and sensitization both to cat and dog. No such relationship was found between exposure and sensitization to dog. WPC increased the risk for sensitization to cat (odds ratio = 2.6, 95% confidence interval 1.2-5.8), whereas ETS strongly tended to do so both to cat and dog. Interaction was found between exposure to ETS, WPC, and high levels of cat allergen (>8 µg/g dust). The presence of all 3 risk factors revealed a multiplicative interaction with a high risk of sensitization to cat (odds ratio = 42.0, 95% confidence interval 3.7-472.8).

**Conclusions:** Keeping cats indoors may be a health hazard for infants and young children at risk for development of asthma, particularly when they live in a damp house and their parents smoke. (*J Allergy Clin Immunol* 1999;104:755-62.)

**Key words:** Asthma, children, cat, dog, allergen, Fel d 1, Can f 1, sensitization

## Abbreviations used

|       |                             |
|-------|-----------------------------|
| BHR:  | Bronchial hyperreactivity   |
| CI:   | Confidence interval         |
| ETS:  | Environmental tobacco smoke |
| OR:   | Odds ratio                  |
| RAST: | Radioimmunosorbent assay    |
| WPC:  | Window pane condensation    |

Allergy to furred pets such as cat and dog is of great importance in childhood asthma. This is particularly true for the Scandinavian countries where the keeping of pets indoors is common. Between 25% and 30%<sup>1,2</sup> of families with infants and young children and 40% to 50%<sup>3-5</sup> of those with children of school age keep pets in Swedish urban areas, a habit that also appears to be increasing in the United States.<sup>6</sup> As a consequence, direct exposure to pets is widespread, and indirect exposure to allergens from furred pets is almost unavoidable, especially in day-care centers, schools, and wherever children gather.<sup>7,8</sup>

It is well known that exposure to pet allergens may trigger asthma in the sensitized child. The risk of allergic sensitization appears in general to increase with exposure early in life, particularly during the first few years or possibly even the first few months.<sup>9-14</sup> Because children at that age spend a lot of time indoors, the exposure in the home is probably important for sensitization. Some studies report a lack of an association between pet exposure and sensitization to such pets.<sup>15,16</sup> Few studies have focused on the topic of exposure and sensitization to pets in young asthmatics.<sup>9,14,16,17</sup> The possible risks associated with exposure to animal pets in early life deserve further examination, particularly when the focus is on indoor adjuvant factors for sensitization.<sup>4,18</sup>

Because allergy to furred animals is important for the development of asthma<sup>19</sup> and cat is the major indoor inducer of allergic sensitization in Sweden, the search for explanations for the increasing prevalence of asthma<sup>20,21</sup> should take into account exposure to pet allergens. We have previously reported, in a case-control study of children less than 4 years old, that exposure to pets—particularly cats—increases the risk of asthma with sensitization to cat or dog.<sup>2</sup> The risk of sensitization in asthmatic children increased further with the presence of exposure to environmental tobacco smoke (ETS) and poor ventilation, as indicated by window pane condensation (WPC).<sup>2</sup>

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In this study we assessed the relationships between sensitization, as indicated by serum IgE antibodies to cat and dog in young children with asthma, and exposure to these pets as indicated by the floor dust content of allergen and questionnaire reports.

## MATERIAL AND METHODS

### Cases and study design

One hundred ninety-three consecutive asthmatic children, aged 1 to 4 years, were included in the study. They had been referred to the pediatric allergy clinics at the Danderyd, Huddinge, and St Görän/Karolinska Hospitals in Stockholm between May 1990 and May 1992 for evaluation of asthma. These children constituted the case group in an earlier published case-control study.<sup>2</sup>

The children were referred either after a hospital admission, as a consequence of repeated visits to the emergency department, or from general pediatricians. Asthma was defined as  $\geq 3$  episodes of wheezing regardless of etiology. No siblings were included in the study, nor were any children with lung disease from prematurity included. A letter of information and a questionnaire were mailed to the parents with an appointment for an initial visit to a pediatric allergy nurse. At that visit informed consent for participation in the study was obtained and the questionnaire was collected. A capillary blood sample was drawn from the child, and serum was frozen ( $-20^{\circ}\text{C}$ ). The parents were given instructions for dust sampling. A later visit to a pediatric allergologist included a structured clinical examination. The numbers of obstructive periods, emergency visits, and hospital admissions were registered, as well as a history of clinical sensitivity to airborne allergens. Further, bronchial hyperreactivity (BHR) as indicated by reactivity to ETS, cold air, and exercise was recorded, as well as severity of asthma symptoms and pharmacologic treatment level. The treatment of the patients was reviewed, and standardized written instructions about measures for allergen avoidance were given. In 4 cases neither serum nor home dust samples were obtained, and these patients were excluded. Nineteen serum samples and 26 dust samples were missing because of losses during transportation. In another 6 serum samples and 4 dust samples, the amount of material was only sufficient for analyses of IgE antibodies to cat and content of cat allergen, respectively. In all these cases the available data from analysis of either serum or dust samples were included.

The final results are thus based on data from 189 children and 189 homes, terms that are used interchangeably in the article.

### Questionnaire

The questionnaire focused on family history, atopic symptoms, and various indoor environmental conditions in the patients' homes. Family history for atopic disease was defined as parental history of atopic disease.

Infant feeding patterns during the first year of life were elicited, as were dietary manipulations during pregnancy aimed at reducing the risk of allergy in the child. Information was also obtained about parental tobacco smoking after the birth of their children. Exposure to ETS was defined as in the previous study,<sup>2</sup> regular parental smoking in the home during the child's first 2 years of life. More than 2 cm of condensed water on the bottom inside of double-glazed windows (WPC) in the bedroom or living room in the winter was used as an indication of poor ventilation.<sup>22</sup> Special emphasis was put on direct and indirect exposure to furred animals, particularly cat and dog. In the evaluation of the data, such reported exposure during the first 2 years of life was graded into 3 different categories: no exposure (ie, no obvious direct or regular indirect contacts for any family member with cat or dog), low exposure (ie, direct contact less than 4 days a month or indirect exposure of the child to cat or dog

in the homes of friends, neighbors, summer house, or other locations regularly visited by family members), and high exposure (ie, cat or dog in the current or previous home or nursery day-care center of the child or in any other home where the child had lived more than 3 days a month). The high-exposure group was in some analyses subdivided into "no cat/dog at home," when there was no cat or dog in the present home, and "cat/dog at home."

### Determination of IgE antibodies

Specific IgE measurements were performed for cat (e1) and dog (e5) (Pharmacia CAP System RAST FEIA, Pharmacia and Upjohn Diagnostics, Uppsala, Sweden), as recommended by the manufacturer. A positive radioallergosorbent test (RAST) result was defined as a value  $\geq 0.35$  kU/L (RAST class 1 = 0.35-0.69 kU/L, RAST class  $\geq 2$  =  $\geq 0.70$  kU/L).

### Sampling, processing, and analysis of dust

Dust samples in the children's homes were collected by the parents from a living room carpet, or if there was none, from the floor, as described in a written protocol. A nozzle containing a filter paper and attached to the family's own vacuum cleaner was used. Six square meters were vacuumed for 4 to 5 minutes.<sup>23</sup> The dust samples were sieved through a 300- $\mu\text{m}$  mesh screen and extracted in PBS at pH 7.4 (1:40 wt/vol) overnight at  $4^{\circ}\text{C}$  under constant rotation. After centrifugation the extracts were stored at  $-20^{\circ}\text{C}$  until analyzed.

### Quantification of Fel d 1 and Can f 1

A 2-site monoclonal ELISA was used for determination of Fel d 1 (Chapman MD, Indoor Biotechnologies).<sup>24</sup> The detection limit of the assay was 0.05  $\mu\text{g}$  per gram of dust, with a coefficient of variation  $<4\%$ .

Cell culture supernatants with antibody reactivity against Can f 1 (kindly provided by Albersee R) were purified with use of protein G Sepharose 4 Fast Flow according to the manufacturer's instructions (Pharmacia Biotechnology, Uppsala, Sweden). One microgram per disc of purified anti-Can f 1 mAb was coupled to cyanogen bromide-activated discs (Pharmacia Diagnostics),<sup>25</sup> which were incubated either with dust sample (diluted 1:100-1:500) or dog standard (International Dog Standard, *Canis domesticus* hair/dander extracts 84/685, National Institute for Biological Standard and Control). After washes, a patient serum (1:20) with IgE to dog (RAST class 5, 90 kU/L to dog) was added for incubation at room temperature. After repeated washing procedures, iodine 125-labeled rabbit antihuman IgE (Phadebas RAST anti-IgE Tracer, Pharmacia Diagnostics) was incubated overnight. After the final wash the count rate was measured in a multigamma counter (LKB). One International Unit of the International Dog Standard has been estimated (personal communication, Albersee R) to 1 ng of Can f 1. The detection limit of the assay was 0.06  $\mu\text{g/g}$ , with a coefficient of variation  $<8\%$ . All the samples were tested in duplicate.

### Statistics

Crude odds ratios (OR) with 95% confidence intervals (CI) for various exposures (ie, suspected risk factors for allergic sensitization) were calculated with use of the SPSS 8.0 package (SPSS, Chicago, Ill). Logistic regression analyses were performed and expressed as adjusted ORs with 95% CI, with the same package. The Mann-Whitney signed-rank test was used for analysis of continuous data. Tests for trends were performed according to the method proposed by Mantel,<sup>26</sup> with use of 2-tailed *P* values, when the relationships between different degrees of sensitization and different levels of cat or dog exposure were studied.

The study was approved by the Ethics Committee of the Karolinska Institute. Informed written parental consent was obtained.

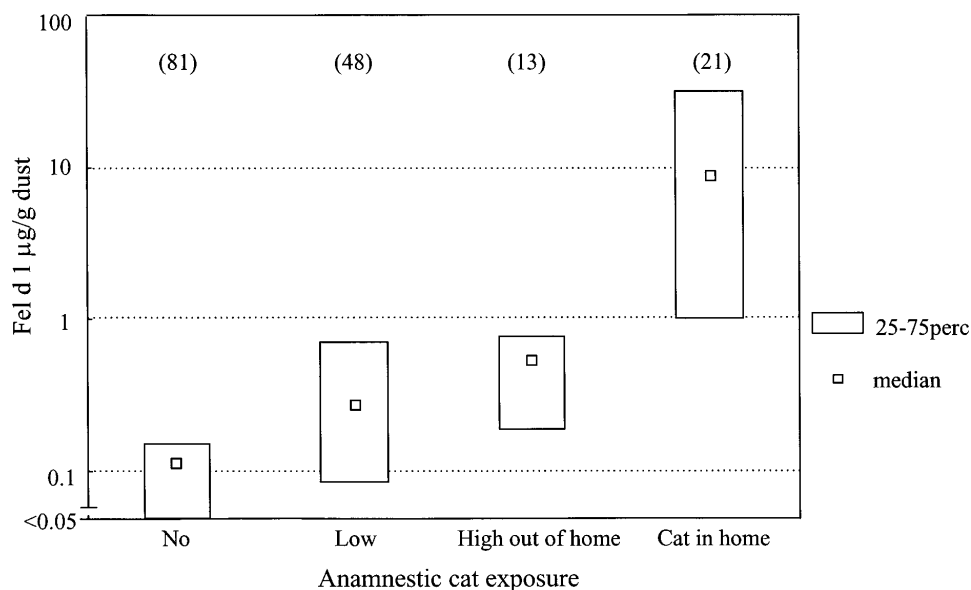


**FIG 1.** Level of cat allergen (Fel d 1) in floor dust in relation to reported exposure to cat. Total number in each group within brackets.

## RESULTS

### Serum IgE antibodies

Thirty-nine of 170 analyzed sera were RAST positive to cat, and 33 of these were also RAST positive to dog. Thirty-seven of 164 children's sera were RAST positive to dog and 32 of the 37 also to cat.

### Cat and dog exposure and relationship to allergen content in dust

Cats had been kept during some period of the first 2 years of the children's life in 26 homes (14%). Another 15 children (8%) had high exposure to cat outside the home, 60 (32%) had low exposure, and 88 (46%) had no obvious previous exposure to cat. The level of Fel d 1 in 163 analyzed dust samples exceeded 8 µg/g of floor dust in 18 homes, ranged from 2 to 8 µg/g of dust in samples from 13 homes, and from 0.2 to 2 µg/g in samples from 55 homes. In 38 homes Fel d 1 was barely detectable (<0.2 µg/g of dust), and in another 39 homes cat allergen was not detectable. There was an obvious correlation between reported exposure to cat and dust content of Fel d 1 in the homes (Fig 1). Samples from homes with low reported exposure to cat and from homes with high exposure outside the home both had significantly higher levels of Fel d 1 in dust than those in the group with no exposure to cat ( $P < .01$  in both instances).

During some period in the first 2 years of life of 14 children, a dog had been kept in the home. Another 11 children had high exposure to dog outside the home, whereas 75 reported low and 90 no obvious current or previous exposure to dog. One hundred fifty-nine dust samples were analyzed for content of Can f 1, which was detectable in 94 of these. The levels of Can f 1 exceeded 8 µg per gram of dust in 9 homes, were in the range of 2

to 8 µg/g in 11 homes and 0.2 to 2 µg/g in 45 homes, and below 0.2 µg/g, albeit detectable, in 29 homes. A high degree of correlation was found between the reported exposure to dog and the dust content of Can f 1 (Fig 2). Low exposure and high exposure to dog outside the home were reflected in a significantly higher concentration of Can f 1 in dust compared with that in dust from homes without reported exposure ( $P < .05$  and  $P < .01$ , respectively).

### Sensitization to allergens and the influence of exposure to cat and dog

Reported exposure to cat, adjusted for age, and the presence of ETS and WPC were related to sensitization to cat as indicated by the occurrence of serum IgE antibodies. Thus 14 of 38 children with high exposure had serum IgE antibodies  $\geq 0.35$  kU/L to cat (adjusted OR = 2.5) and 10 of 49 with low exposure (adjusted OR = 1.1) compared with 15 of 83 without reported cat exposure,  $P$  trend = .03 (Table I). The degree of exposure was also associated with the level of IgE antibodies. Thus 12 of the 38 with reported high exposure to cat exhibited serum IgE antibodies  $\geq 0.70$  kU/L (adjusted OR = 10.4) and 9 of 49 (adjusted OR = 5.6) with low exposure compared with 3 of 83 in the group with no reported exposure,  $P$  trend < .01 (Table I). There was also a dose-response association between cat allergen levels in house dust and degree of sensitization to cat, adjusted for age and presence of ETS and WPC (Table I). Six of 16 children exposed to concentrations of Fel d 1 in house dust more than 8 µg/g exhibited serum IgE antibodies  $\geq 0.70$  kU/L (adjusted OR = 7.1) and 7 of 56 (adjusted OR = 1.6) when the dust content of Fel d 1 ranged from 0.2 to 8 µg/g compared with 5 of 75 when the dust content of Fel d 1 was less than 0.2 µg/g,  $P$  trend < .01 (Table I). Thus, when trying to deter-

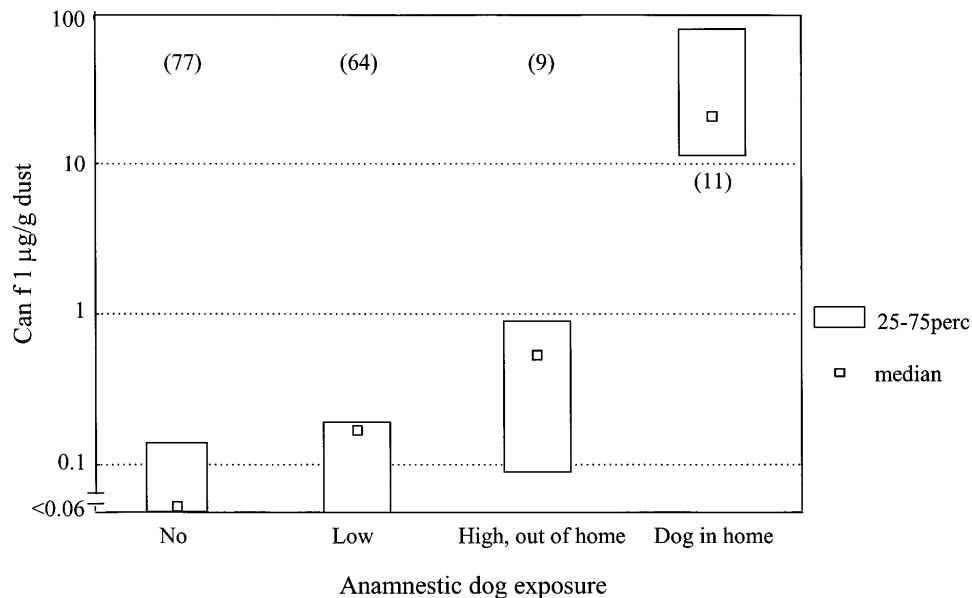


**FIG 2.** Level of dog allergen (Can f 1) in floor dust in relation to reported exposure to dog. Total number in each group within brackets.

**TABLE I.** Risk for being sensitized to cat as indicated by a RAST level  $\geq 0.35$  kU/L or  $\geq 0.70$  kU/L to Fel d 1 in relation to exposure to risk factors: anamnestic cat exposure, cat allergen (Fel d 1) levels in home dust, parental smoking (ETS), and signs of home dampness (WPC)

| Risk factor                     | RAST e1 cat $\geq 0.35$ kU/L |                      | RAST e1 cat $\geq 0.70$ kU/L |                      |
|---------------------------------|------------------------------|----------------------|------------------------------|----------------------|
|                                 | Crude OR (95% CI)            | Adjusted OR (95% CI) | Crude OR (95% CI)            | Adjusted OR (95% CI) |
| Anamnestic exposure to cat      |                              |                      |                              |                      |
| Low (n = 49) vs none (n = 83)   | 1.2 (0.5-2.8)                | 1.1 (0.4-2.9)*       | 5.2 (1.3-20.5)               | 5.6 (1.4-22.5)*      |
| High (n = 38) vs none (n = 83)  | 2.6 (1.1-6.3)                | 2.5 (1.0-6.3)*       | 11.3 (2.9-43.7)              | 10.4 (2.5-43.2)*     |
| Fel d 1 µg/g dust               |                              |                      |                              |                      |
| 0.2-8 (n = 56) vs <0.2 (n = 74) | 1.0 (0.4-2.5)                | 0.7 (0.3-2.1)†       | 2.3 (0.6-8.3)                | 1.6 (0.4-6.3)†       |
| >8 (n = 16) vs <0.2 (n = 74)    | 5.2 (1.6-16.5)               | 4.0 (1.2-13.8)†      | 11.6 (2.7-50.2)              | 7.1 (1.5-34.2)†      |
| ETS                             |                              |                      |                              |                      |
| Yes (n = 94) vs no (n = 76)     | 2.5 (1.2-5.5)                | 2.2 (0.9-4.9)‡       | 3.0 (1.1-7.9)                | 2.1 (0.7-6.5)‡       |
| WPC                             |                              |                      |                              |                      |
| Yes (n = 47) vs no (n = 120)    | 2.2 (1.0-4.6)                | 2.6 (1.2-5.8)§       | 2.2 (0.9-5.5)                | 2.9 (1.1-8.0)§       |

Risks are given either as crude ORs with 95% CIs or as ORs adjusted for risk factors calculated through logistic regression. Number of children in each exposure group is given in parentheses.

\*Adjusted for age, ETS, WPC, and anamnestic dog exposure with use of logistic regression.

†Adjusted for age, ETS, WPC, and high Can f 1 exposure with use of logistic regression.

‡Adjusted for age, WPC, and anamnestic cat and dog exposure with use of logistic regression.

§Adjusted for age, ETS, and anamnestic cat and dog exposure with use of logistic regression.

mine the threshold level for sensitization to cat (RAST  $\geq 0.35$  kU/L or RAST  $\geq 0.70$  kU/L), we found the most obvious threshold effect at an allergen level of 8 µg per gram of dust, adjusted OR = 4.0 (Table I).

No corresponding relationship was found between exposure and sensitization to dog at any threshold level. This was true both for reported exposure and for exposure indicated by dog allergen levels in house dust (Table II). The degree of cat exposure assessed by either questionnaire or measurement of Fel d 1 in house dust was associated with serum IgE levels to dog. Thirty-four per-

cent of the children who were highly exposed to cat exhibited IgE antibodies to dog compared with 25% of the children reporting low cat exposure and 14% of the unexposed children, *P* trend <.01 (Table II).

### Association of WPC and ETS with allergen content in dust

WPC in winter was reported in 50 of the 189 homes. No association was found between reported WPC and the median dust contents of Fel d 1 or Can f 1, but a higher proportion of homes, 14 of 46 (30%), with reported WPC

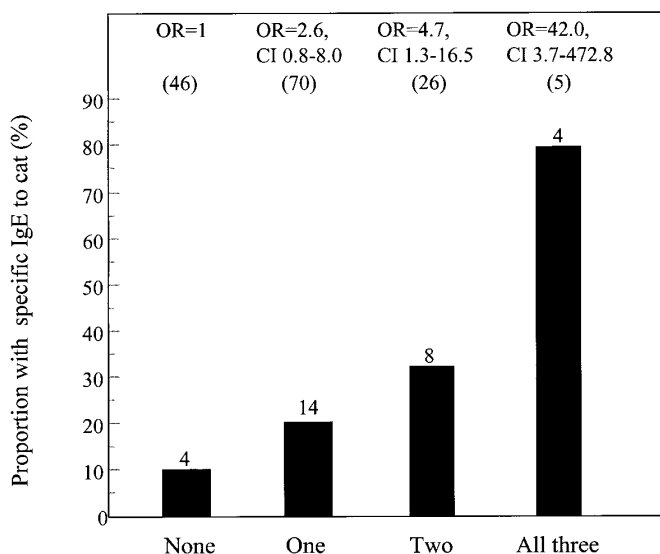


**FIG 3.** Relationship between number of risk factors (exposure to Fel d 1 >8 µg/g dust, ETS, WPC) and specific IgE to cat among 146 asthmatic children less than 5 years old. Total number in each group in parentheses. Number of sensitized children in bold. ORs are given with 95% CI.

**TABLE II.** Risk for being sensitized to dog as indicated by RAST level ≥0.35 kU/L to Can f 1, in relation to exposure to risk factors: anamnestic dog and cat exposure, dog and cat allergen (Can f 1 and Fel d 1) levels in home dust, parental smoking (ETS), and signs of home dampness (WPC)

| Risk factor                     | RAST e5 dog ≥0.35 kU/L |                      |
|---------------------------------|------------------------|----------------------|
|                                 | Crude OR (95% CI)      | Adjusted OR (95% CI) |
| Anamnestic exposure to dog      |                        |                      |
| Low (n = 67) vs none (n = 74)   | 1.0 (0.5-2.3)          | 1.1 (0.5-2.6)*       |
| High (n = 23) vs none (n = 74)  | 1.3 (0.4-4.0)          | 1.3 (0.4-4.0)*       |
| Anamnestic exposure to cat      |                        |                      |
| Low (n = 47) vs none (n = 81)   | 2.0 (0.8-4.8)          | 2.0 (0.8-5.1)†       |
| High (n = 36) vs none (n = 81)  | 3.2 (1.3-8.1)          | 3.0 (1.1-7.8)†       |
| Can f 1 µg/g dust               |                        |                      |
| 0.2-8 (n = 50) vs <0.2 (n = 80) | 0.8 (0.3-1.8)          | 0.8 (0.3-1.9)‡       |
| >8 (n = 8)                      | No case                | No case              |
| Fel d 1 µg/g dust               |                        |                      |
| 0.2-8 (n = 53) vs <0.2 (n = 73) | 1.2 (0.5-3.0)          | 1.1 (0.4-2.9)§       |
| >8 (n = 16) vs <0.2 (n = 73)    | 3.0 (0.9-10.0)         | 2.6 (0.7-8.6)§       |
| ETS                             |                        |                      |
| Yes (n = 90) vs no (n = 74)     | 2.0 (0.9-4.3)          | 2.0 (0.9-4.5)        |
| WPC                             |                        |                      |
| Yes (n = 46) vs no (n = 115)    | 1.8 (0.8-3.8)          | 1.9 (0.8-4.2)        |

Risks are given either as crude ORs with 95% CI or as ORs adjusted for risk factors calculated through logistic regression. Number of children in each exposure group is given in parentheses.

\*Adjusted for age, ETS, WPC, and anamnestic cat exposure with use of logistic regression.

†Adjusted for age, ETS, WPC, and anamnestic dog exposure with use of logistic regression.

‡Adjusted for age, ETS, WPC, and high Fel d 1 exposure with use of logistic regression.

§Adjusted for age, ETS, WPC, and high Can f 1 exposure with use of logistic regression.

||Adjusted for age, ETS, WPC, and anamnestic dog and cat exposure with use of logistic regression.

exhibited Fel d 1 concentrations more than 2 µg per gram of dust than homes without WPC, 17 of 117 (15%). After adjustment for the presence of cat in the home, the association between reported WPC and Fel d 1 concentrations more than 2 µg per gram of dust did not reach statistical significance (adjusted OR = 2.7, 95% CI 0.9-7.7).

No corresponding associations were found between WPC and the level of Can f 1 allergen in dust.

ETS was reported from 106 of 189 homes. Dogs tended to be more prevalent in the homes of smokers than those of nonsmokers, 11 of 106 versus 3 of 83 ( $P = .08$ ), as was the keeping of cats, 18 of 106 versus 8 of 83 ( $P =$

.15). The respective levels of Fel d 1 and Can f 1 were not associated with ETS after adjustment for presence of cat and dog.

### ETS and WPC exposure, relationship to sensitization and interactions with allergen exposure

The presence of WPC in the homes significantly (adjusted for age, presence of ETS, and anamnestic cat and dog exposure) influenced sensitization (RAST  $\geq 0.35$  kU/L) to cat (adjusted OR = 2.6) (Table I) and strongly tended to do so for dog (adjusted OR = 1.9) (Table II), whereas exposure to ETS (adjusted for age, presence of WPC, and anamnestic cat and dog exposure) among the children had a strong tendency to influence sensitization to cat (adjusted OR = 2.2) (Table I) and dog (adjusted OR = 2.0) (Table II).

WPC, ETS, and exposure to cat allergen independently increased or tended to increase the risk of sensitization to cat, but there was also an interaction between these 3 risk factors, and the highest risk was observed when all 3 were present. Thus 80% of the children exhibited IgE antibodies to cat when exposed to all 3 risk factors versus 9% when none of the 3 was present (OR = 42.0, 95% CI 3.7-472.8) (Fig 3). With 2 risk factors (ie, 2 of ETS, WPC, and high levels of cat allergen), an additive effect on the risk for sensitization was found, whereas there was a synergistic effect when all 3 factors were present (Fig 3).

### Association between sensitization to cat-dog and asthma severity

No correlation was found between sensitization (RAST  $\geq 0.35$  kU/L) to cat or dog and severity of asthma as indicated by severity of symptoms, pharmacologic treatment level, frequency of recurrent wheezing (more than 5), number of hospital admissions (more than 1), or reports of increased signs of BHR (data not shown). In all children but one respiratory infections sometimes triggered asthma symptoms. Forty-six percent of those with IgE antibodies to cat and dog were reported to show symptoms of asthma after exposure to pets.

## DISCUSSION

In this case study we report an association between previous and current exposure to cat and sensitization to cat in young asthmatic children and that the degree of sensitization reflects the degree of exposure. We also report that other potential risk factors (ie, ETS and signs of home dampness [WPC]) synergistically increased the risk for such sensitization, in particular in connection with simultaneous exposure to both these factors.

In clinical practice it is customary to advise parents of children with asthma not to keep furred pets in their homes. This is simple and in most cases necessary advice for children who are already sensitized (eg, to cat). That such measures would prevent allergic sensitization rests on weaker scientific grounds. Thus, although direct

exposure to animal allergens is presumed to be a prerequisite for sensitization, only a few epidemiologic studies have confirmed the relationship.<sup>4,14,18,28</sup> Except for one recent study,<sup>27</sup> these studies, however, are long-time retrospective studies in the sense that data were collected after classification of allergic disease. Others have failed to demonstrate a relationship between keeping pets and sensitization to such animals.<sup>15,16</sup> A failure to demonstrate an association may, at least in part, be explained by a disinclination of parents in families with a known hereditary risk for atopic disease to keep pets and by recall bias.<sup>29</sup> In epidemiologic studies this may lead to underestimation of the risk for sensitization related to exposure to pets. Furthermore, exposure to animal pet allergens occurs not only in the homes but also in day-care centers, schools, etc. In contrast with other studies, a much more detailed analysis of exposure, such as exposure out of home and irregular indirect contact, is included in this study. When atopic disease develops in children with a strong genetic predisposition despite execution of allergen avoidance measures in the home environment, it may even lead to the misinterpretation that early exposure to furred pets may induce tolerance.

Because the cat appears to produce a more "aggressive" allergen than the dog,<sup>30</sup> it was not unexpected that exposure to cat would involve the highest risk of sensitization of the two. Sensitization to dog may take longer time to develop when there is no concomitant exposure to cat. It was also noteworthy that animal allergen content in floor dust was raised as a consequence of family members' contacts with cats or dogs outside the home (eg, allergen is brought to the homes on clothes). Although we found an increased risk of sensitization particularly associated with direct exposure and with Fel d 1 levels above 8  $\mu\text{g}$  per gram of dust, a level that has been suggested to be a threshold for induction of sensitization,<sup>31</sup> it cannot be excluded that exposure at lower levels may be associated with an increased risk of sensitization in the long run. A relationship between exposure and sensitization to cat is strongly suggested by the finding of a dose-response relationship between degree of early exposure to cat and degree of sensitization, as indicated by the levels of specific IgE antibodies. This was also found in a recent epidemiologic study of sensitization to cat.<sup>27</sup> It is notable that the latter study also deals with young children, who are more likely to spend most of their time in the home. In older children the relationship might be obscured by the effect of exposure elsewhere.

Relationships between allergen dose and sensitization has earlier been reported for house dust mite<sup>12</sup> and for cat.<sup>27</sup> We found that sensitization to cat occurring at low and intermediate degrees of allergen exposure in the homes was most evident when the children were also exposed to ETS or WPC. Ambient tobacco smoke is an important factor in childhood "wheezy bronchitis."<sup>1,32</sup> It is a well-known trigger of asthma in children.<sup>33</sup> The finding that exposure to ETS promotes atopic sensitization to cat in young asthmatic children is supported by previous studies reporting an increased risk for atopic sensitiza-

tion in children exposed to ETS.<sup>4,18,34</sup> This indicates a particularly hazardous effect of tobacco smoke because it has been reported that the most severe and persistent asthmatics are recruited from this group.<sup>19,35</sup> In this study the risk of recall bias is probably diminished by the limited time period to recall, in average just more than 2 years. Thus misclassification of exposure must be expected to be evenly distributed among the subgroups (ie, those with and without IgE antibodies to furred pets) that were only identified after exposure data were collected, before information of specific sensitization was accessible to the parents. Hence misclassification of exposure is likely to diminish the observed associations. This is also true for collection of dust samples by parents instead of investigators, especially because the parents had detailed written instructions on how to perform the collection in a standardized manner.<sup>36</sup> Consequently, the detected associations are not likely to have been caused by bias.

Cat allergen is made up of very fine particles, which may be airborne for long periods.<sup>37</sup> This may be one explanation for the sensitizing capacity of cat allergen. Few corresponding data are available concerning dog allergen. It is possible that reduced air exchange is an important factor for the trapping of allergens as finely dispersed and volatile as cat allergen. Higher levels of cat allergen in homes with signs of poor ventilation (ie, occurrence of WPC) might indicate accumulation of allergens in such dwellings. It is notable that questionnaire data, such as reported WPC and other signs of dampness in the homes, have been found to be associated with the development of atopic disease.<sup>4,38-40</sup>

This association may indicate that poorly ventilated homes and public buildings, because of their indoor dampness, may have contributed to the increasing prevalence of atopic disease in regions with a cold climate.<sup>3,39,40</sup>

The observed additive, but in particular also the multiplicative, interaction between allergen from furred pets, ETS, or WPC stresses the importance, but also the possibilities, of preventive measures in allergic asthma by eliminating any one of these 3 factors. The dose-dependent influence of exposure to cat allergen indicates that even a limited reduction of allergen levels in the home of children may have some allergy-preventing effect. The impact of sensitization to airborne allergens and asthma symptoms in early childhood on the long-term prognosis of asthma<sup>41-43</sup> clearly points out the possible value of primary prevention.

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