

From the DEPARTMENT of WOMAN and CHILD HEALTH and the  
INSTITUTE of ENVIRONMENTAL MEDICINE,  
KAROLINSKA INSTITUTET

# CAT AND DOG ALLERGENS

## DISPERSAL, EXPOSURE AND HEALTH EFFECTS IN CHILDHOOD

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STOCKHOLM 2002

CAT AND DOG ALLERGENS – DISPERSAL, EXPOSURE AND HEALTH EFFECTS IN CHILDHOOD

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THE EYES OF A CHILD  
I SEE IT IN THE EYES OF A CHILD  
NO LAZY LITTLE LIES OR DECEITFUL GUISE  
JUST WHAT'S TRUE  
IN THE EYES OF A CHILD

KATARINA STENSTRÖM, THE REAL GROUP

I SUSPECT THAT A LARGE PART OF THE FORMAL SCIENTIFIC LITERATURE IS  
HARDLY EVER READ AT ALL

MADDOX, LANCET 1968;2:1071<sup>1</sup>

## ABSTRACT

The association between pet ownership in childhood and subsequent asthma and sensitisation is very controversial. Intriguing but contradictory reports have caused considerable uncertainty in families who wish to avoid asthma and allergic disease in their children. At the same time, many children with asthma experience a worsening of their disease when they come in contact with furred pets. The aim of this thesis is to elucidate how allergen exposure affects development and worsening of asthma and sensitisation in childhood.

The first study examined dispersal of cat allergen borne on clothing from homes with cats to schools and further to homes without cats. Airborne cat allergen was collected with personal pumps in six classes with many (>25%) and six classes with few (<10%) cat owners, and in homes of children with and without cats. Dust samples were collected from clothes and mattresses. Airborne cat allergen levels in classrooms were higher than in homes of non-cat-owners, but lower than in homes with cats. There was a five-fold difference in the levels of airborne cat allergen between classes with many and few cat owners. Allergen levels in non-cat-owners' clothes increased after a school day. Non-cat-owners in classes with many cat owners had higher levels of cat allergen at home. This indicates that allergen is spread via clothing from homes with cats to classrooms, and further to homes without cats.

The second study was designed and performed in order to evaluate how this indirect cat exposure at school affects asthmatic children with cat allergy. 410 children, 6-12 years of age, who were being treated for asthma, were allergic to cats and had no cat at home were identified. Peak expiratory flow (PEF), asthma symptoms, medication and contact with pets were recorded twice daily during the last week of summer holiday and the second and third weeks of school. Children in classes with many (>18%) cat owners reported significantly decreased PEF, more days with asthma symptoms, and increased use of medication after school started. Those in classes with few cat owners did not report any change. This suggests a worsening of asthma in children allergic to cats, after indirect exposure to cat at school.

The third and fourth studies are based on a large prospective birth-cohort study, BAMSE. Parents of 4,089 children born 1994-96 answered a questionnaire at birth on allergic heredity and exposure to cat or dog. Symptoms of allergic disease were reported at one, two and four years of age. At four years, 2,614 children agreed to blood samples for allergen-specific IgE to common inhalant allergens. Early cat exposure increased the risk of cat sensitisation, OR 1.44 (95% CI 1.03-2.01), without any effect on asthma. Early dog ownership was associated with a reduced risk of sensitisation to airborne allergens other than dog, OR 0.36 (0.15-0.83) and a trend towards lower risk of asthma, OR 0.50 (0.24-1.03). However, there was a selection of pet ownership into the study. Cats were less frequently kept in families with parental asthma, rhinoconjunctivitis, pet or pollen allergy (3.5-5.8%) than in families without any parental allergic disease (10.8-11.8%). Dogs were less common in families with (3.3%) than without (5.9%) parental atopic eczema. What effect this selection may have on the associations between pet exposure and allergic disease is discussed in the thesis.

Thus, cat and dog allergens are ubiquitous and difficult to avoid. This, in combination with selection mechanisms makes it very difficult to study associations between early pet exposure and subsequent allergic disease. At the same time, indirect cat exposure at school worsens asthma in already sensitised children, which has clear implications for secondary prevention.

**Key words:** *child, asthma, allergy and immunology, cats, dogs, allergens, IgE, schools, clothing, PEF, heredity, prospective studies, confounding factors, primary prevention, environment and public health*

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## LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

- I. **Almqvist C**, Larsson PH, Egmar A-C, Hedrén M, Malmberg P, Wickman M. School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. *J Allergy Clin Immunology* 1999; 103:1012-1017
- II. **Almqvist C**, Wickman M, Perfetti L, Berglind N, Renström A, Hedrén M, Larsson K, Hedlin G, Malmberg P. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med* 2001; 163:694-698
- III. **Almqvist C**, Egmar A-C, Hedlin G, Lundqvist M, Nordvall SL, Pershagen G, Svartengren M, van Hage-Hamsten M, Wickman M. Direct and indirect exposure to pets – risk of sensitisation and asthma at four years in a birth cohort. Submitted.
- IV. **Almqvist C**, Egmar A-C, van Hage-Hamsten M, Berglind N, Pershagen G, Nordvall SL, Svartengren M, Hedlin G, Wickman M. Heredity, pet ownership and confounding control in a population-based birth cohort. Submitted.

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## **ABBREVIATIONS AND DEFINITIONS**

AEDS	Atopic eczema/dermatitis syndrome
Allergy / Allergic disease	Asthma, rhinoconjunctivitis or AEDS elicited by exposure to certain stimuli
Atopy	Predisposition to produce IgE antibodies in response to allergens, and to develop typical symptoms such as asthma, rhinoconjunctivitis or AEDS
BAMSE	Barn Allergi Miljö i Stockholm – en Epidemiologisk undersökning (Children Allergy Environment in Stockholm – an Epidemiological survey)
BHR	Bronchial hyperreactivity
Can f 1	Canis familiaris 1; dog allergen
CI	Confidence Interval
DRH	Decreased Respiratory Health
ECRHS	European Community Respiratory Health Survey
ELISA	Enzyme-linked immunosorbent assay
Fel d 1	Felis domesticus 1; major cat allergen
IgG, G4	Immunoglobulin G and G4
IgE	Immunoglobulin E
ISAAC	International Study of Asthma and Allergy in Childhood
OR	Odds Ratio
PEF	Peak Expiratory Flow
Sensitisation	IgE sensitisation: process in which an individual produces IgE antibodies in response to allergen exposure; not necessarily combined with symptoms
SPT	Skin Prick Test
Sp-IgE	Allergen-specific IgE
Th	T helper lymphocyte

## INTRODUCTION

### Asthma

#### *History*

The word asthma (ασθμα), meaning “exhale with open mouth”, was first used by the ancient Greeks. It appears in print for the first time in the Iliad (241, 0 10) with the meaning of a short-drawn breath, a hard breath or panting. Homer speaks about a warrior who died at the end of a furious battle with “asthma and perspiration”. The earliest texts where “ασθμα” is found as a medical term are those of Hippocrates (460-360 BC). He recognised the paroxysmal nature of the asthmatic attacks, noticed the foamy expectoration and suggested as a prognostic sign the formation of a humpback before puberty.<sup>2</sup> Hippocrates also had an aetiological proposal; “sometimes a foreign body enters into /the trachea/ ... and occupies the pathways impeding both inhalation and exhalation and producing tachypnoea”.<sup>3</sup>

#### *Definition*

There is currently no gold standard for defining asthma in childhood. This difficulty reflects not only the lack of a single biological marker or clinical test for asthma but also the varying expressions of symptoms, multiple aetiological factors, heterogeneous responses to treatments, and differing outcomes.<sup>4</sup> Current definitions are in fact descriptions of the characteristics of the disease, as set forth in the *Guidelines for the Diagnosis and Management of Asthma*, which state that asthma is a “chronic inflammatory disorder of the airways” characterised by “recurrent episodes of wheezing, breathlessness, chest tightness, and coughing”. Furthermore, “these episodes are usually associated with widespread, but variable, airflow obstruction”.<sup>5</sup>

Epidemiological studies are rather limited as to how to diagnose respiratory disease. Wheezing is the most common symptom asked for in questionnaires, though the frequency and duration of wheezing episodes used to define asthma varies between different research groups.<sup>6</sup> Other symptoms asked for include shortness of breath and recurrent cough. Questionnaires can be supplemented with measurement of bronchial hyperresponsiveness (BHR) and other testing in subsamples of the subjects. However, symptoms and BHR should usually be analysed separately rather than combined because the agreement between BHR and clinical asthma is poor.<sup>7</sup>

Several epidemiological studies have suggested that there are different phenotypes of asthma. Early wheezing is often correlated with viral infections and not associated with family history of asthma. These children may have reduced airway calibre early in life, but the majority have no signs of reduced lung function at age 11.<sup>8,9</sup> Late onset non-atopic wheezing, starting around age 2-3, may be triggered by viral infections or exercise, and often improves during the first school years. In contrast, children whose wheezing begins before age 3 and persists to age 6 (persistent wheezers) characteristically have clinical features of atopy, high IgE levels, positive skin tests and a strong family history of asthma.<sup>10</sup> In addition, these children often



become sensitised early in life.<sup>11</sup> Persistent wheezers also seem to develop chronic airway inflammation, reduced pulmonary function, increased asthma symptomatology and need of more medication.<sup>12</sup> Pinpointing risk factors and identifying children who will be affected by this form of asthma may allow us to alleviate their disease.

### **Prevalence**

A number of epidemiological studies indicate that the prevalence of allergic airway diseases has been increasing in the recent decades, for reasons that are not yet completely understood.<sup>13-15</sup> Systematic international comparison by the International Study of Asthma and Allergy in Childhood (ISAAC) has revealed a large difference in prevalence of asthma and allergic diseases in school-age children over the world. The highest 12-month prevalence for asthma has been seen in the UK, Australia, New Zealand and the Republic of Ireland (>20%), followed by centres in North, Central and South America. The lowest occurrence is in some Eastern European countries, China, and India (<5%).<sup>16</sup> There is no consistent evidence for a change in severity of the disease, nor is there any firm data on what proportion of the increase is due to a heightened awareness of respiratory symptoms, a change in diagnostic labelling, or a real increase in morbidity.<sup>17</sup> Only a few studies have shown a parallel increase in objective measures of asthma such as skin prick test (SPT), IgE-sensitisation or BHR.<sup>18</sup>

### **Treatment**

Treatment of asthma in children is primarily based on  $\beta_2$ -agonists and inhalation corticosteroids, with addition of leucotriene antagonists or long-acting  $\beta_2$ -agonist if needed. The dose of inhalation steroid recommended is individual, from 100-200  $\mu\text{g}$  budesonide /day (or equivalent doses of other corticosteroids) up to > 800  $\mu\text{g}/\text{day}$  if the asthma exacerbation is combined with a viral infection.<sup>19</sup>

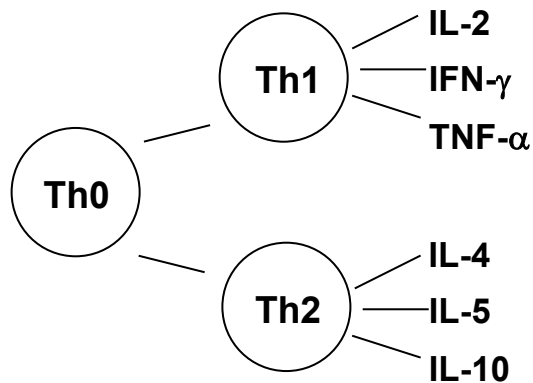
## **Immunology**

### **Atopy and IgE-sensitisation**

According to the revised nomenclature for allergy, “atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or atopic eczema/dermatitis (AEDS)”.<sup>20</sup> However, it has been claimed that the increasing prevalence of asthma is not with certainty associated with a parallel increase in atopy, and that the proportion of asthma cases attributable to atopy varies from 25 to 63% with a weighted mean of 37%.<sup>21</sup> At the same time, early allergic sensitisation has been shown to be an important risk factor for persistent asthma, especially in children with family history of allergic diseases.<sup>22,23</sup> Consequently, allergen exposure during the early years of life and its role in the course of the disease has come forward as an important issue and is continually being discussed.

## Th1 / Th2

T cell immune and inflammatory pathways are thought to play an important role in allergy and asthma symptomatology. T cells regulate or organise most types of immune responses to foreign proteins by secreting cytokines such as interleukins (IL) or interferons (IFN) and can be categorised into phenotypes (Th0, Th1, Th2) on the basis of their products (Figure 1).



**Figure 1.** T-cell regulation and allergic inflammation.

Th2 cells initiate the immediate allergic response by releasing proinflammatory cytokines such as IL-4, IL-5 and IL-10. In turn, these cytokines stimulate IgE production, induce tissue eosinophilia and promote the growth of mucosal-type mast cells. By contrast, Th1 cells are primarily involved in classic delayed hypersensitivity and have been proposed to inhibit Th2-driven processes.<sup>24</sup> Placenta-derived Th2-type cytokines are required for successful gestation and are present in utero. Non-atopic children have a more rapid transition from the predominantly Th2-type responses at birth than do atopic children, where this transition is delayed and Th2-type responses allowed to persist.<sup>25</sup>

## Environmental determinants of asthma and atopy

Although genetic predisposition to asthma is well recognised, genetic factors alone cannot explain the increase in the prevalence of asthma during the past 20 years. The role of environmental factors in asthma and sensitisation is further supported by the large differences in the prevalence of allergic diseases in different countries, and between groups with similar ethnic background living in the same country.<sup>16,26,27</sup> Possible environmental determinants include changes in life style or altered indoor climate, which in turn may increase the exposure to indoor allergens.

It has also been suggested that a reduced microbial pressure during infancy and early childhood could result in a slower maturation of the immune system. In line with this, children with older siblings and children who start early in day care seem to show lower prevalence of allergic disease.<sup>28</sup> Use of antibiotics early in life might increase the risk of allergic disease, though these data are inconsistent.<sup>29,30</sup> An anthroposophic life style appears

to reduce the prevalence of atopy,<sup>31</sup> and the intestinal microflora may affect development of allergic diseases.<sup>32</sup> There is also coherent evidence that exposure to a farming environment confers some protection against atopy and allergic diseases. The protection is not limited to a specific allergen, but is rather a down-regulation of immune responses in individuals exposed to endotoxin.<sup>33,34</sup>

Male sex, prematurity, low socio-economic status, low physical fitness and young mother are other suggested risk factors for asthma.<sup>35-39</sup> Maternal smoking during pregnancy and postnatal exposure to tobacco smoke seems to be related to the risk of early-onset asthma, with more than additive effects if combined with parental history of atopy.<sup>8,40</sup> Tobacco smoke in conjunction with allergen exposure and damp housing has been suggested to be a risk factor for sensitisation in children with asthma.<sup>41</sup> The role of indoor allergen exposure in causing sensitisation and asthma has emerged as an important research focus.

## **Allergens**

In Sweden, the most common indoor allergens are those from cat and dog, in contrast to many other parts of the world, where allergens from house dust mites and cockroaches are widespread. Mite allergens Der f 1 and Der p 1 are carried on large particles, and only a small proportion is considered directly respirable. Outdoor pollen allergens, predominantly those from birch and timothy, are also common in Sweden during a limited time of the year.

### ***Cat allergen Fel d 1***

The major cat allergen Fel d 1 is a 38-kDa glycoprotein homodimer composed of two 17-kDa subunits, each comprised of two disulfide-linked peptide chains of 70 and 92 amino acids.<sup>42-44</sup> It was first identified from cat pelt extracts in the 1970s, and initially called Cat allergen 1.<sup>45</sup> Fel d 1 is produced by sebaceous glands and squamous epithelial cells in the dermis, and, after secretion, spreads from the root to the tip of the hair strand and over the epidermis, the spreading enhanced by licking and grooming.<sup>46-48</sup> Fel d 1 has also been found in the cat's salivary, lacrimal and perianal glands.<sup>49,50</sup> The production of Fel d 1 is under hormonal control; more is produced in male than in female cats.<sup>51</sup> Castration of male cats reduces Fel d 1 production, and injection of testosterone into castrated cats permit Fel d 1 production to recover.<sup>52,53</sup>

Fel d 1 is excreted in large amounts, and the daily production has been reported to be somewhere between 3 and 7 µg per day.<sup>47</sup> Significant amounts (approximately 25%) of cat allergen Fel d 1 are associated with small particles (<5 µm), which remain airborne for long periods, and – once deposited – can be thrown back into the air by minimal disturbance in the room.<sup>54,55</sup>

Fel d 1 elicits IgE responses in 90-95% of patients with cat allergy and accounts for 60-90% of the total allergenic activity of cat extracts.<sup>56-58</sup> The minor allergen cat serum albumin has been cloned and shown to induce IgE responses in about 20% of patients with cat allergy.<sup>57,59</sup> In addition, cystatin Fel d 3 was recently cloned from cat skin and found to elicit IgE responses in 10% of cat allergic persons.<sup>60</sup>

## **Dog allergen Can f 1**

Can f 1 and Can f 2 are the two major allergens present in dog dander extracts, with molecular weights of 19 and 23 kD, respectively.<sup>61</sup> Can f 1 is produced by tongue epithelial tissue and has homology with the von Ebner's gland, whereas Can f 2 is produced by the tongue and parotid gland.<sup>62</sup> Approximately 20% of airborne Can f 1 is associated with small particles (<5 µm diameter).<sup>63</sup> In terms of allergenic importance, Can f 1 and Can f 2 cause IgE responses in 70% and 23%, respectively, of patients with dog allergy, and dog albumin represents an important allergen for up to 35% of patients who are allergic to dogs.<sup>61,64</sup>

## **Allergen exposure**

Cat and dog allergens can be collected in dust samples by vacuuming dust reservoirs, and can be measured accurately with commercially available sensitive immunoassays.<sup>42,56,65</sup> Fel d 1 and Can f 1 have been found in dust samples from many different environments apart from homes with cats: schools, day care centres, hotels, cinemas, pubs, buses, trains, hospitals, department stores and homes without cats.<sup>66-71</sup> Upholstered seats contain higher levels of allergen than carpeted floors,<sup>68</sup> which in turn contain higher levels than smooth floors.<sup>72</sup> In schools, it has been suggested that chairs have higher levels of allergen than desks and floors, and in day care centres higher amounts were found on mattresses, sofas, soft toys and curtains than on tables, chairs and floors.<sup>67,69</sup> This indicates that textiles and clothes contain higher levels of allergen than other materials. Accumulation of cat allergen in environments without cats has also been shown to correlate with the number of visitors who either have a cat at home or are in regular contact with a cat.<sup>69,71</sup>

However, cat and dog allergens are to a large extent airborne and the allergen levels in air do not always correlate with those in dust.<sup>73-75</sup> Airborne levels of cat allergen Fel d 1 have been reported to vary greatly between homes with and without cat and dog.<sup>54,63,74,76</sup> Reliable methods for collecting allergen, and sensitive assays for measuring low levels of allergen are essential to estimate dispersal of allergens, and to correctly assess personal exposure to airborne cat allergen in cat-free areas.

## **Allergen avoidance**

Several studies have shown that Fel d 1 is still present in homes where a cat has lived previously, and even in houses where no cat had ever lived.<sup>77,78</sup> It is not clear whether repeated washing of cats removes allergen from the cat and leads to progressive reductions in the quantity of allergen in the home, but it seems as if cats and dogs have to be washed at least once a week to reduce airborne levels of Fel d 1 and Can f 1.<sup>79-82</sup> Vacuum cleaning seems to provoke increases in airborne Fel d 1, primarily that carried by large particles, though there is less leakage from vacuum cleaners with HEPA- or microfilters.<sup>83,84</sup> The use of tannic acid or Allerpet/c to reduce allergen levels also has limited effect on cat allergen.<sup>80,85,86</sup> De Blay et al managed to reduce cat allergen levels without getting rid of the cat by washing the cat, reducing the amount of furniture, vacuuming, and filtering the air.<sup>79</sup> This is a very time-consuming way to reduce allergen levels, and may be motivated only in subjects

sensitised to cats who really want to keep their cat at home. It is not feasible to suggest that families without a cat at home, who suffer from indirect cat exposure, undertake these avoidance measures.

## Epidemiology

Epidemiological (*epi*=among, *demos*=people, *logos*=doctrine) studies can assess relations between exposure and disease in human populations. In order to calculate risk associations, it is of great importance that exposure and outcomes are clear and specific.<sup>87</sup> Pet exposure for example can be estimated through reported pet ownership, pet contact or by measuring pet allergen at home. Outcomes can be assessed through reported symptoms, diagnoses or medication. Measures of association, such as odds ratio (OR), are the preferred way of expressing results of dichotomous outcomes – eg, sick versus healthy. Confidence intervals (CI) around these measures indicate the precision of these results. OR and CI reveal the strength, direction, and a plausible range of an effect as well as the likelihood of chance to occur.<sup>88</sup> Attributable or aetiologic fraction denotes the proportion of a disease that is attributable to a certain risk factor in a population.

Data on exposure and outcome can be collected prospectively or retrospectively.

*Cross-sectional studies* can examine the presence or absence of exposure and disease at a certain time. Since both exposure and outcome are ascertained at the same time, the temporal relation between the two might be unclear. Data on exposure may also be collected in retrospect, but the data may then be subject to recall bias.

*Cohort studies* proceed in a logical sequence, from exposure to outcome. An exposed and an unexposed group are followed prospectively in time to determine outcomes. If the exposed group develops a higher prevalence or incidence of the outcome than the unexposed group, then the exposure is associated with an increased risk.

*Case-control studies* start with an outcome and look for exposure retrospectively. Nested case-control studies are performed within a cohort study.

*Randomised controlled trials* are the gold standard of epidemiological research. Participants are assigned exposures purely by chance. They are then followed prospectively, as in cohort studies. This reduces the likelihood of bias in determination of outcomes.

In order to be able to evaluate whether a study measures what it set out to measure (internal validity), potential bias has to be taken into consideration. Bias in epidemiological research denotes deviation from the truth.<sup>89</sup> There are three general categories of bias.

*Selection bias*: the exposed and unexposed groups differ in some important respect aside from the exposure. Participation bias is one type of selection bias.

*Information bias*: information about outcome is obtained in different ways for exposed and unexposed: *differential* such as recall bias in cross-sectional studies may increase or decrease the risk, depending on direction of the bias; *non-differential* tends to obscure real difference.

*Confounding*: the results can be accounted for by the presence of a factor associated with both exposure and outcome but not directly involved in the causal pathways. Confounding can be controlled for through restriction, matching, stratification or with multivariate techniques.

Finally, *chance* is another source of bias, which is measured by the p value.

Different types of bias or misclassification of exposure or disease may distort or obscure true risk associations. For example, families who have a pet and want to keep it might report wheezing less often than those without a pet, and families with an atopic constitution might choose not to report on pet ownership if the primary prevention program advises them not to keep pets. Thus, critical interpretation epidemiological studies is essential in order to make proper prevention programs.

### **Allergen exposure, sensitisation and asthma**

The case for a causal relationship between allergen levels, sensitisation and asthma would best be supported by evidence for a dose-response relationship between exposure and symptoms (Figure 2). A close relationship between asthma and sensitisation (Figure 2,b) to indoor allergens has been confirmed in many studies, but the causal relation between allergen exposure and subsequent sensitisation or asthma is rather controversial. A review of the literature in 1998 suggested increased risk for sensitisation in childhood after early exposure to pets,<sup>90</sup> whereas another review found little consistent association between allergen exposure and asthma prevalence.<sup>91</sup> A recent meta-analysis concluded that pet exposure increased the risk of wheezing in older children,<sup>92</sup> and more recent studies have added conflicting data on the relationship between pet exposure and sensitisation or asthma in children, adolescents and adults. In an attempt to summarise the literature on associations between allergen exposure and subsequent sensitisation or asthma, the most often cited works have been arranged in Table 1. Only associations between pet exposure and disease are shown, so it should be stressed that the table is not complete in any way. For example, potential confounders and other identified risk factors for asthma or sensitisation have not been included in the table.

**Table 1.** Studies on early exposure to cat or dog and subsequent IgE-sensitisation or asthma.

Author	Study design	Age; no	Exposure	Outcome	Result	Comment
Wahn <sup>93</sup> (MAS, Germany) 1997	Prospective cohort	0-3y; 1,314 (67%) (499 high-risk)	allergens cat, mite 6, 18m questionnaire 1,3,6m; 1,2,3y	Sp-IgE mite, cat 1, 2, 3 y	Dose-response allergen exposure – sensitisation	Atopic family history enhances dose-response
Lau <sup>94</sup> (MAS, Germany) 2000	Prospective cohort	0-7; 1,314 (71%) (49%)	allergens cat, mite 6, 18m, 5y questionnaire 1,3,6m; 1,2,3,7y	doctor-diagnosed asthma; BHR Sp-IgE mite, cat	No association allergen exposure – asthma, BHR Positive association atopy – asthma, BHR	Low levels of cat allergen
Tariq, <sup>95</sup> UK 1998	Prospective cohort	0-4; 1,456 (84%) (67%)	cat or dog ownership	SPT	No association pet ownership – atopy	<50% of asthma cases attributed to atopy
Nafstad, <sup>96</sup> Norway 2001	Prospective cohort	0-4; 3,754 (67%)	cat and dog ownership at birth	atopic eczema, rhinitis, asthma	Neg association pet ownership – atopic eczema 0-6m Neg association pet ownership – rhinitis 4y, weak – asthma 4y	Selection bias?
Remes, <sup>97</sup> USA 2001	Prospective cohort	0-13y; 1,246 (86%), (~50%)	cat and dog ownership at birth	wheezing total S-IgE or SPT 9m, 6, 11y	Negative association early dog exposure – asthma No association dog exp – atopy	<i>Parental asthma</i> : no association early dog exposure – asthma
Ownby, <sup>98</sup> USA 2002	Prospective cohort	0-6; 835 (57%)	number of cats or dogs at home in the 1 <sup>st</sup> year	SPT, Sp-IgE cat, dog, mite, pollen	Negative association ≥two dogs or cats in childhood – atopy	Association more obvious in boys than girls
Celedon, <sup>99</sup> USA 2002	Prospective cohort	0-5; 498 (90%)	cat allergen Fel d 1 >8 µg/g dust at 2m of age wheezing (by telephone questionnaires twice a year)	wheezing total S-IgE	Neg association cat exp– wheeze <i>if no maternal asthma</i> : Pos association cat exp – wheezing increasing with age <i>if maternal asthma</i> : p	87.4% of those exposed to a cat in early life still exposed to a cat Baseline IgE-value differs. See also <sup>100</sup>
Perzanowski, <sup>100</sup> Sweden 2002	Prospective cohort from 7y	7-8, 10-11; 3,431 (63%)	cat or dog ever in the house; data on exposure before 1996 collected retrospectively	doctor-diagnosed asthma SPT	Neg assoc ever cat – atopy <i>if parental allergy</i> Neg assoc ever cat – asthma prevalence <i>if parental asthma</i>	Inverse associations only in children <i>with family history</i> – distorted See also <sup>99</sup>
McConnell, <sup>101</sup> USA 2002	Prospective cohort from 9y	9-16; 3,535	cat and dog ownership	wheezing, asthma	Positive association dog ownership – wheeze	32% of new asthma cases attributable to pets
Gehring, <sup>102</sup> ECRHS 2001	Nested case-control	25-50; 405	cat allergen Fel d 1 in mattress	wheeze, Sp-IgE	Pos association Fel d 1 – wheeze, irrespective of atopy	
Hesselmar, <sup>103</sup> Sweden 1999	Case-control	7-9, 12-13; 412	cat or dog ownership	SPT, asthma, allergic rhinitis,	Neg association pet ownership – rhinitis 7-9y, - asthma 12-13y neg association cat ownership – SPT 12-13 y	Similar results without children whose parents had decided against pet keeping

Author	Study design	Age; no	Exposure	Outcome	Result	Comment
Jaakkola, <sup>104</sup> Finland 2002	Case-control	21-63; 521 cases, 932 controls	furred pets currently and in the past	incident asthma	Pos association pet in the past and asthma, neg association pet currently and asthma	Explained by selective avoidance
Roost, <sup>105</sup> ECRHS 1999	Cross-sectional	20-44; 18,097 (75%)	cat exposure in childhood	Sp-IgE cat	Negative association early cat exposure – atopy Positive correlation community prevalence of cat – atopy	Neg association seen in particular among those <i>with</i> family history of atopy – distorted study result?
Svanes, <sup>106</sup> ECRHS 1999	Cross-sectional	20-44; 18,530 (75%)	dog ownership in childhood	Sp-IgE grass, mite, cat, <i>Cladosporium</i>	Negative association early dog exposure – adult atopy	Adjusted for atopic family history
Bråbäck, <sup>107</sup> Sweden 2001	Cross-sectional	10-11; 2,108 (84%) (74%)	current or former pet ownership	SPT, wheeze, rhinitis	Neg association cat ownership – atopy (if no family history) and rhinitis No assoc dog exp–	Higher prevalence of sensitisation in northern vs southern Sweden, related to number of pets
Burr, <sup>108</sup> UK 1999	Cross-sectional	12-14y; 25,393 (79%)	pet at present	wheeze	Positive association pet at present – wheeze	
Brunekreef, <sup>109</sup> Holland 1992	Cross-sectional	6-12; 3,344 (73%)	pet ownership current and past reasons to remove pets	respiratory symptoms	Severity of resp symptom (spt): pets currently, 0 past: <i>no spt</i> pets currently and past: <i>mild spt</i> never had pets <i>moderate spt</i> past pets, no currently: <i>sev spt</i>	Explained by selection; pet avoidance in allergic individuals
Anyo, <sup>110</sup> Holland 2002	Cross-sectional	7-12y; 2,729 (65%) (48%)	cat and dog ownership never, in the past and currently	SPT, S-IgE, hayfever, asthma	Neg association current pet ownership – atopy and hayfever Pos association past pet ownership – asthma	Explained by selection and pet avoidance Inverse relation early pet exposure – pollen sens-
Lanphear, <sup>111</sup> USA 2001	Cross-sectional	<6y; 8,257	dog ownership	doctor-diagnosed asthma	Positive association dog ownership – asthma	Pos assoc pet avoidance – asthma; OR 24
Platts-Mills, <sup>112</sup> USA 2001	Cross-sectional	12-14; 226	cat allergen Fel d 1 at home	SPT, S-IgE, IgG, IgG4; asthma defined as symptomatic BHR	Positive association levels of Fel d 1 – IgG4 Pos association atopy – asthma	Modified Th2 response; high IgG4 in children exp to high levels cat allergen

age of the index children

no; number of children who were involved in the study, (%) = response rate on questionnaires, (%) = response rate on SPT or blood samples

SPT; skin prick test

Sp-IgE; specific serum-IgE antibodies

S-IgE; total S-IgE

atopy= pos SPT, S-IgE or Sp-IgE

BHR – bronchial hyperresponsiveness

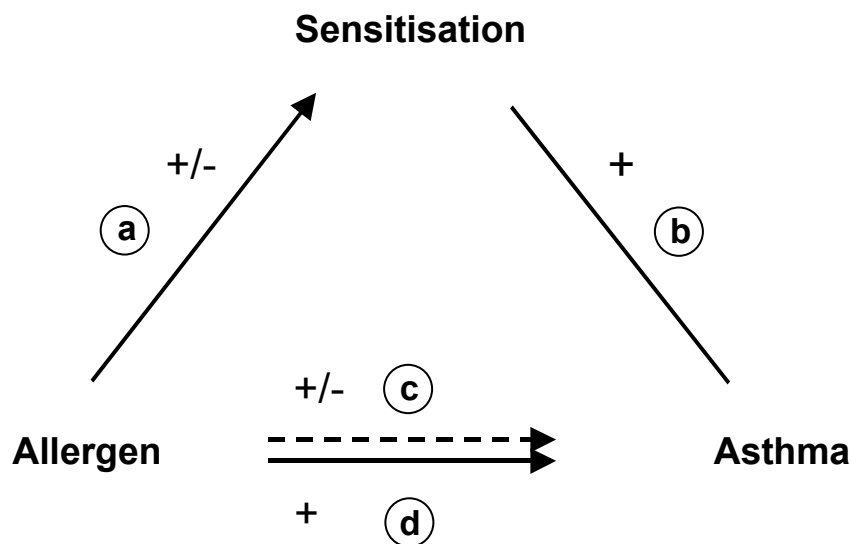
MAS Multicenter Allergy Study

ECRHS; European Community Respiratory Health Survey



**Allergen exposure and subsequent sensitisation – Figure 2,a**

Exposure to an allergen is a prerequisite for sensitisation to that allergen, although there seems to be a genetic propensity for sensitisation. A dose-response relationship between exposure to dust mite allergens at home and sensitisation to mite has been implied in many studies,<sup>113</sup> and has also been seen for cat allergen.<sup>93</sup> Threshold levels for allergen exposure leading to sensitisation and to exacerbations of symptoms have previously been suggested to be 1 and 8 µg, respectively, for cat, and 2 and 10 µg, respectively, for dog.<sup>114,115</sup> However, recent studies have challenged these findings, and suggested that early cat ownership reduces the risk of subsequent cat sensitisation,<sup>103,105</sup> or that children living in a house with “moderate” levels of cat allergen (4 to 20 µg/g dust) are more likely to become allergic to cats than those exposed to >20 µg/g dust.<sup>112</sup> It has also been suggested that early dog ownership reduces the risk of atopy<sup>106</sup> or has no effect<sup>97</sup> on atopy.



**Figure 2.** Relations between **a)** allergen exposure and subsequent sensitisation **b)** established sensitisation and asthma **c)** allergen exposure and subsequent asthma **d)** allergen exposure and asthma in already sensitised. See text.

**Sensitisation and asthma – Figure 2,b**

A strong association between sensitisation and asthma has been shown in many population-based studies.<sup>8,26,112,116,117</sup> The sensitising allergen varies; house dust mite is the major allergen in many parts of the world, whereas cockroaches are common sources of allergen in larger cities in the USA, the mold *Alternaria* in the deserts of Australia and USA, and cats and dogs in Scandinavia.<sup>118-120</sup>

### **Allergen exposure and subsequent asthma – Figure 2,c**

The key study linking allergen exposure in infancy to the subsequent development of asthma is that of Sporik et al, who reported a weak dose-response relationship between early exposure to house dust mite and specific mite sensitisation ( $p=0.06$ ), and associations between early allergen exposure and asthma at 11 years in a small cohort of 67 children.<sup>121</sup> In the large German birth cohort study (MAS), no relation between early indoor allergen exposure and the prevalence of asthma, wheeze, or BHR was seen at seven years of age.<sup>94</sup> A negative association between early dog ownership and asthma was reported from Tucson, Arizona in children without parental asthma.<sup>97</sup>

### **Allergen exposure and asthma in already sensitised children – Figure 2,d**

The debated causal relationship between early exposure and subsequent asthma should not be confused with the association between allergen exposure and worsening of asthma in already sensitised individuals. Cat allergy is common among asthmatic patients in clinical populations and is also a significant risk factor for emergency room visits due to asthma.<sup>114,122</sup> In a case control study on sensitised adults, a higher proportion of those with severe asthma were currently exposed to indoor allergens than those with mild asthma.<sup>123</sup> Likewise, a correlation between allergen levels at home and severity of asthma in sensitised children has been proposed for house dust mite and cockroach exposure.<sup>118,124</sup> In line with this, avoiding the sensitising allergen reduces allergen-induced BHR.<sup>125</sup>

## **Prevention**

There is a very close connection between epidemiology and preventive medicine. Different forms of prevention of allergic diseases in childhood have been defined.

*Primary prevention* addresses healthy children with the aim to prevent development of allergic disease and asthma.

*Secondary prevention* focuses on children who have already developed asthma and allergy, and aims to prevent symptoms, further progression and deterioration of the disease.

The usefulness of primary prevention to reduce asthma and allergic diseases has been much debated.<sup>126-128</sup> For more than a decade, preventive strategies in Sweden have focused on influencing supposed risk factors such as parental smoking, short duration of breast feeding, damp housing and, in high-risk families, keeping of pets. The advice has been given at maternity wards and Child Health Centres, and has thus been available to virtually all families with newborns. However, the relevance of this advice is now being questioned. At the same time, it is clearly important to identify risk factors for symptoms and progression of allergic disease and asthma in already affected subjects, and to apply this knowledge for secondary prevention.

## **AIMS**

The general objective of this work was to study dispersal of cat and dog allergens, and to analyse how allergen exposure affects development or worsening of asthma and IgE-sensitisation in childhood. The specific aims were:

- ✓ to investigate airborne levels of cat allergen (Fel d 1) at schools and in homes with or without cats, and to study clothes as a route for dissemination of allergens between homes and school **(I)**
- ✓ to examine whether exposure to cat allergen at school might induce or increase symptoms in children with asthma and cat allergy **(II)**
- ✓ to elucidate how early exposure to cat and dog relates to allergen-specific IgE sensitisation and asthma in children at two and four years of age, in a prospective birth-cohort study **(III)**
- ✓ to assess selection of pet ownership and the importance of confounding control when evaluating risk associations between exposure and outcome, in a population-based birth cohort study **(IV)**

## MATERIAL AND METHODS

### Study populations

Study **I** is based on questionnaires on pet ownership and symptoms of allergic disease distributed to all 2,042 children and their teachers in 85 school classes grade 4-5 in Järfälla and Upplands-Bro municipalities in Stockholm county. Complete questionnaires were obtained from 1,931 pupils and 83 teachers (response rate, 95%), which constitutes the study population of the first study.

In study **II**, 864 children aged 6-12 years with diagnosed asthma, asthma medication and cat sensitisation (SPT  $\geq 3$  mm or RAST class  $\geq 0.7$  kU/l) were identified from patient charts at five paediatric allergy outpatient clinics in Stockholm (St. Göran, Danderyd, Sachsska, Huddinge and Jakobsberg). A first questionnaire to update information on asthma medication and pet ownership was sent out and answered by 733 families (response rate, 85%). Children receiving continuous asthma medication (inhalation steroids and  $\beta$ -agonists) and without furred pets at home were asked to take part in the study,  $n=521$  (**II**, Figure 1). Four hundred ten children (79%) agreed to participate and were sent diary cards to fill in twice daily for 3 weeks; the last week of the summer holidays and the second and third weeks of school. Three hundred twenty eight (80%) diary forms were returned. Seven forms were blank and 50 forms were regarded as incomplete or were excluded for other reasons, leaving 271 diaries for analysis. In this study population, 179 children reported direct contact with furred pets during the study, and 92 children denied any contact with pets.

The cohort in study **III** and **IV** was recruited at birth, from Child Health Centres in predefined areas of central and north-western Stockholm. Amongst 7,221 children born between February 1994 and November 1996, 477 could never be reached due to incorrect address, and 1,399 never answered or declined participation. Exclusion criteria were planned family move within one year ( $n=699$ ), insufficient knowledge of Swedish ( $n=331$ ), seriously ill child ( $n=57$ ) and an older sibling enrolled in the study ( $n=169$ ), leaving 4,089 children in the study population.

### Study design

Study **I** has a cross-sectional design. The questionnaires were used to identify six school classes with few ( $<10\%$ ) and six classes with many ( $>25\%$ ) cat owners, corresponding to below the 25<sup>th</sup> and above the 75<sup>th</sup> percentiles of cat ownership. Airborne cat allergen levels were measured in these twelve classrooms after collection with personal pumps on two occasions. In addition, 10 children with and 26 children without cat at home were identified and asked to collect airborne allergen at home, and 45 children with and 181 without cat were asked to vacuum their mattresses to collect dust samples. Moreover, allergen content in 31 non-cat-owners' T-shirts was examined after a school day, as well as the content in 15 cat owners' T-shirts worn at home for an afternoon.

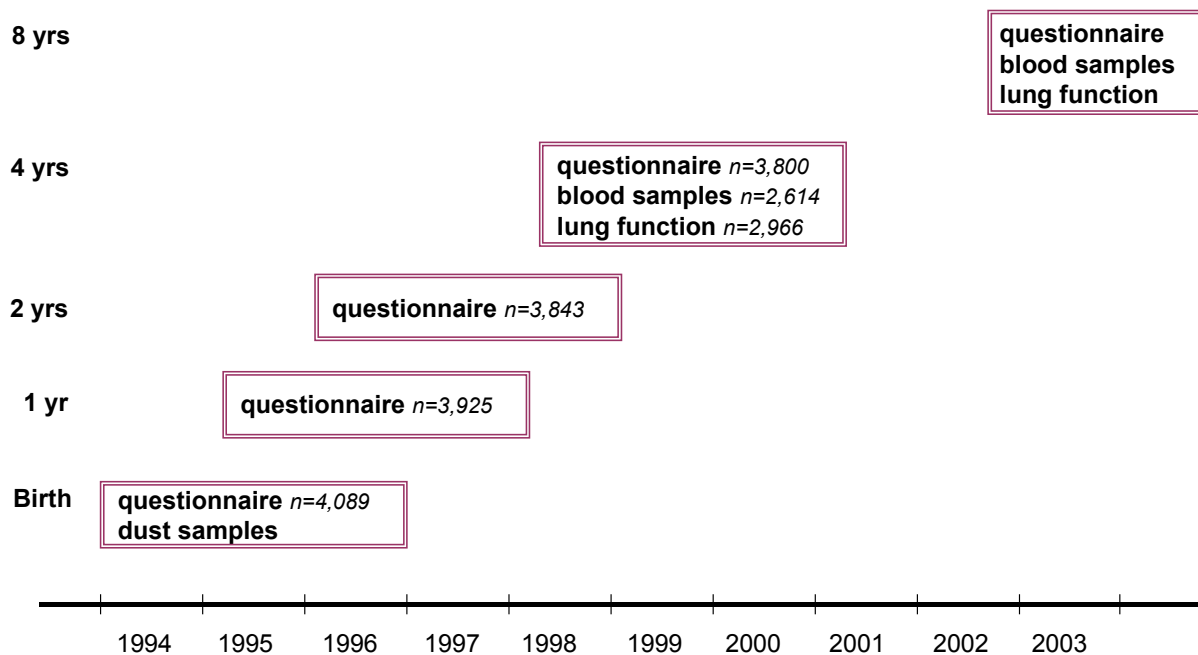
Study **II** is a panel study, i.e. a small cohort that is followed over a short time period. Peak expiratory flow (PEF), asthma symptoms, medication (number of puffs of  $\beta$ -agonists and

steroid dose), fever and/or sore throat, and contact with furred pets were recorded twice daily during the last week of summer holidays and the second and third weeks of school (Figure 3). This method – i.e. use of PEF monitoring and daily diaries – has been recommended in the management of asthma patients.<sup>127</sup> Information on number of children and cat owners in each class was obtained through questionnaires to the teacher, median percentage of cat owners was 18%. The study focused on those who reported no direct contact with furred pets.



**Figure 3.** Study design for the panel cohort (II).

Studies **III** and **IV** derive from a large epidemiological study with prospective design, where a birth cohort is being followed longitudinally over time (Figure 4). The parents answered a first questionnaire with detailed questions on parental history of allergic diseases, pet exposure, residential characteristics, smoking and socio-economic factors when the child was on average two months old. Dust samples for analyses of cat Fel d 1 and dog Can f 1 allergen were collected from the mother’s mattress. When the children were one, two and four years old a similar questionnaire was mailed to all parents, this time with the main focus on symptoms related to wheezing and other allergic diseases in young children. At four years of age, the children were invited to a clinical examination and blood sampling.



**Figure 4.** Flow-chart for the prospective longitudinal birth-cohort BAMSE (**III**, **IV**), including the planned follow-up at 8-9 years

An analysis of non-responders was performed in 1997, and showed more smokers (18% vs 9%) and fewer fathers with asthma (9.4% vs 6.6%) among non-responders than among responders, but no other significant differences in exposure or outcome.

Permission for each study was obtained from the Ethics Committee of Karolinska Institutet. Informed consent was obtained from the parents.

## Allergen levels

At the time of the first study, an amplified ELISA assay had recently been developed, which made it possible to analyse air samples collected with person-carried pumps for cat allergen Fel d 1 in schools and homes without cat (**I**). Not only did this enable us to measure allergen levels in pet-free areas, but it also permitted us to compare the levels of cat allergen in the breathing zones of cat owners and non-cat-owners. This had not been possible with the large high-volume samplers used previously.<sup>75</sup> However, since sampling with person-carried pumps is time-consuming and expensive, other methods to collect airborne allergens have been evaluated. The petri dish sampling method for collection of settling airborne dust correlates well with personal samplers, but the petri dish method does not allow estimation of an individual's exposure.<sup>129</sup> Intra-nasal air samplers have recently been developed, and provide a fairly sensitive method for measurement of personal allergen exposure.<sup>130,131</sup> Nevertheless, there is a limit as to the duration of intranasal sampling and hence low exposure levels may be difficult to detect. Data soon to be published suggest that sampling with person-carried pumps is after all a more sensitive method to assess personal exposure than other methods, and suitable in a low-exposure setting.<sup>132</sup>

The amplified ELISA assay as performed in study **I** detected cat allergen levels down to 42 pg Fel d 1 /m<sup>3</sup> of air at 60 minutes sampling time. Though this method was very sensitive, it was shortly afterwards replaced by a commercially available ELISA assay, using AMPAK signal amplification, that proved to be easier to administer. Values obtained with inter-assay controls between the two methods were very similar,  $r=0.99$ , ( $n=46$ ). Dust samples from mattresses and clothes were analysed essentially as described by the manufacturer, with slight modifications and with in-house extracts to achieve a higher sensitivity (0.025 µg/g dust for mattresses and 50 pg/g garment dust for clothes).

In study **III** and **IV**, dust samples were collected in a standardised way from the mother's mattress at the child's median age of 2 years. A subset of 512 dust samples from the homes of 167 children who had asthma at two years of age and 345 controls was analysed. Cat (Fel d 1) and dog (Can f 1) allergen content was determined by a two-site ELISA using monoclonal and/or polyclonal antibodies. The assays were performed according to the protocols from Indoor Biotechnologies, VA, USA (Professor Martin D. Chapman) except that peroxidase-labelled conjugates were replaced with ALP-labelled streptavidin (DAKO, Denmark). Dust samples with Fel d 1 levels below the detection limit (0.055 µg/g dust) were assigned a value of 0.054 µg/g, and Can f 1 levels below the detection limit (0.200 µg/g) were assigned 0.199 µg/g for statistical analyses.

## Definition of disease

In study **II**, four main indices of respiratory status and medication were calculated for the last week of summer holidays (baseline week, week 0) and for the second and third weeks of school. The indices were: weekly mean morning PEF, days per week with asthma symptoms, weekly average of the number of puffs of  $\beta$ -agonist per day, and weekly average dose of inhaled steroids per day. Since there is an interaction between lung function, symptoms and medication, an outcome variable called “decreased respiratory health” (DRH) was defined as at least three of the following: lower PEF; more days with asthma; increased  $\beta$ -agonist use and increased steroid use, all compared to the baseline week.

For study **III**, asthma at two years of age was defined as >3 episodes of wheezing between three months and two years of age, or >1 episode combined with inhalation steroid treatment. Asthma at four years of age was defined as >3 episodes of wheezing during the last 12 months, or >1 episode of wheezing if the child had been given inhaled steroids. Our definition of asthma is more restrictive than the definition used in the ISAAC studies (>1 episode of wheezing in the last 12 months). We have also taken into consideration the Swedish treatment traditions, which include recommendations that the parents give the wheezy child inhaled steroids as soon as an airway infection starts, and continue for at least a week.<sup>133</sup>

In order to define sensitisation (**III**), all sera were screened with Phadiatop®, a mixture of common inhalant allergens (Pharmacia CAP System™ Uppsala, Sweden). Sera positive in Phadiatop were further analysed for allergen-specific IgE to cat, dog, house dust mite, horse, birch, timothy, rye grass, and *Cladosporium herbarum* (Pharmacia CAP System™, specific IgE FEIA). A positive CAP was defined as  $\geq 0.35$  kU/l and sensitisation as at least one positive CAP. There is an excellent correlation between cat CAP values and IgE levels to Fel d 1.<sup>134</sup>

For study **III** and **IV**, we wanted to define heredity – partly to be able to use it as an adjusting variable in the statistical analyses, but also to use it as an exposure variable on comparing cat and dog ownership. Both parents answered the questionnaires in 86% of the families, which gives us a rather clear picture of their history of allergic diseases. Reported symptoms and doctor’s diagnosis of asthma, rhinoconjunctivitis, AEDS, pollen- and pet allergy in the child’s mother, father and siblings were reported, though not confirmed by SPT or specific IgE. Heredity for allergic disease was defined as doctor-diagnosed asthma and/or hay fever in combination with allergy to furred pets or pollens in one (single heredity) or both parents (double heredity).<sup>135</sup>

## Statistical analyses

Medians and interquartile ranges of allergen levels were calculated. Comparisons between groups (**I**, **III**, **IV**) was performed with non-parametric unpaired tests (Mann-Whitney) and within groups (**I**) with non-parametric paired test (Wilcoxon).

Changes in respiratory status and medication from baseline to each of weeks 2 and 3 were calculated as mean value week 2 or 3 minus mean value week 0 (baseline) and assessed using two-sided paired samples t-test (**II**). In the group of children without pet contact outside

school, an independent t-test was performed to test whether the change from baseline was equal in the groups with many and few cat owners. The results are expressed as the difference in change from baseline with 95% confidence interval and p-value for the t-tests. The chi-square Fisher exact test was used to compare the prevalence of fever and/or sore throat weeks 0 and 2. At the very end, we did a modification of these statistical analyses, as described in the article, with identical results. The relation between DRH and the variable “indirect cat exposure” was examined by logistic regression adjusted for sex, age and fever and/or sore throat.

Early exposure (median age of two months) to cat or dog was analysed with a three-level categorical variable, where “no exposure” was compared to “exposure at relatives” (indirect exposure) and to “ownership” (III). Thus we could avoid including exposed children in the reference category, who may otherwise dilute any associations between allergen exposure and health effects. The relationship between the health outcomes (asthma and sensitisation) and exposure to cat or dog was analysed with multivariate logistic regression. Heredity, gender, maternal smoking, mother’s age and socio-economic index were identified as confounders. In addition, multinomial regression analysis was performed for the outcome “sensitisation” divided into “no sensitisation”, “sensitised to cat (dog)” and “sensitisation to other allergen than cat (dog)”. Data on key variables such as exposure, outcome and potential confounders had to be complete for the individual to be included in the analyses, leaving 3,729 children for analyses at two years and 3,596 (88% of the original study population) for analyses at four years of age. A total of 2,614 children agreed to let blood samples be drawn at the examination, of whom 2,573 had complete data on the questionnaires.

The prevalence of cat or dog ownership by heredity, smoking and socio-economic index was calculated and expressed in percentage along with 95% CI (IV). The outcome cat or dog ownership was adjusted for different hereditary factors, maternal smoking and socio-economic index in a multivariate regression analysis. The results are presented as adjusted ORs and 95% CIs. Four thousand twenty-three children (98%) had complete data on key variables such as reported parental allergy, pet ownership, smoking and socioeconomic factors were included in the analyses.

In multivariate techniques, mathematical modelling examines the potential effect of one variable while simultaneously controlling for the effect of many other factors. A major advantage of these approaches is that they can control for more factors than can stratification.<sup>89</sup> If the odds ratio is interpreted as a relative risk it will always overstate any effect size; the odds ratio is smaller than the relative risk for odds ratios of less than one, and larger than the relative risk for odds ratios of greater than one. However, serious divergence between the odds ratio and the relative risk occurs only with large effects on groups at high initial risk. Therefore qualitative judgments based on interpreting odds ratios as though they were relative risks are unlikely to be seriously in error.<sup>136</sup>

Sample size was calculated based on a given combination of significance level, power, and size of expected effects before the start of the studies. Significance level was set at  $p < 0.05$ .

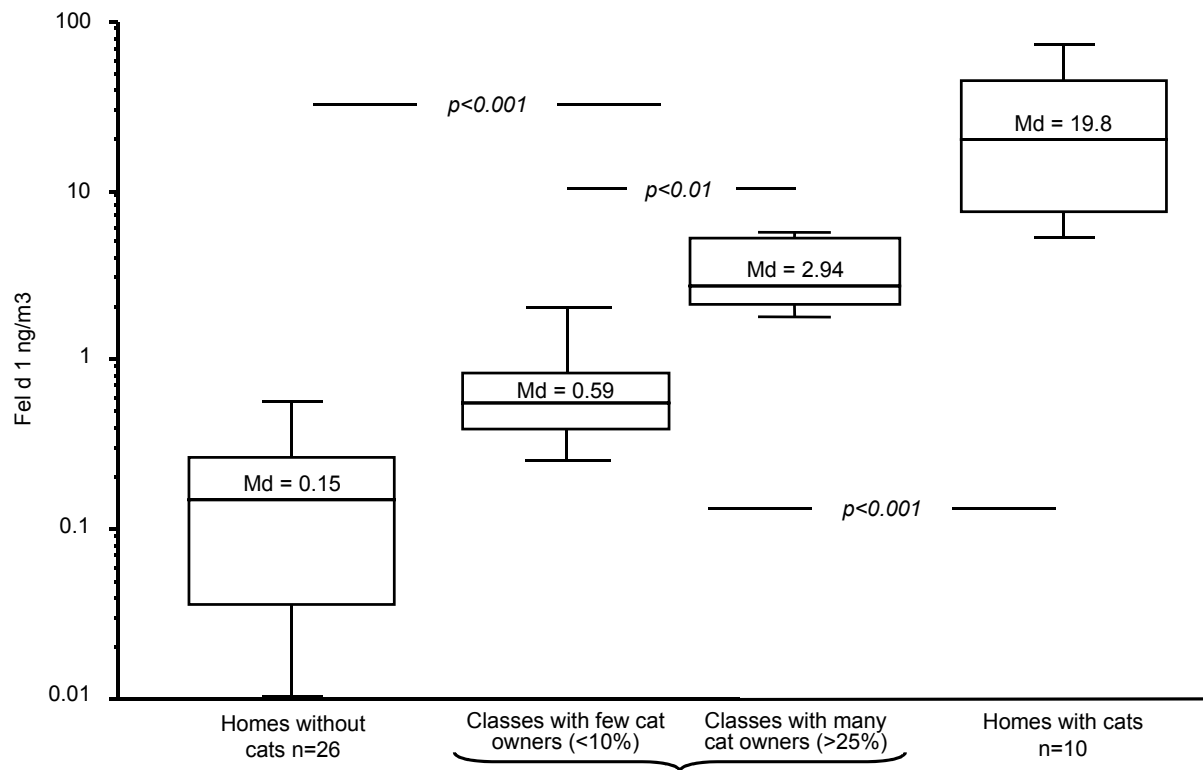
Analyses were performed with Statview 4.0 (I), SPSS 10.0 (II) and STATA 7.0 (III, IV).



## RESULTS AND DISCUSSION

### Dispersal (I, III)

In study **I**, the median airborne cat allergen concentration in classrooms was significantly higher than that found in the homes of non-cat-owners, but lower than that found in homes with cats. There was a 5-fold difference in the median levels of airborne cat allergen between classes with many and few cat owners (Figure 5). Non-cat-owners in classes with many cat owners had higher levels of cat allergen in their mattresses at home than did those in classes with few cat owners. Allergen levels in non-cat-owners' clothes increased after a school day (**I**, Table II). This indicates that allergen is spread through clothing from homes with cats to classrooms, where the allergen is dispersed in air and contaminates the clothes of children without cats. The allergen levels in non-cat-owners' homes correlate with exposure to cat allergen at school.



**Figure 5.** Levels of airborne cat allergen Fel d 1 in the breathing zones of non-cat-owners in classes with many and few cat owners ( $p<0.01$ ) compared with children in homes without cats ( $p<0.001$ ) and children in homes with cats ( $p<0.001$ ). Box plots with medians marked are shown; box corresponds to 25-75 percentiles, and vertical lines correspond to 10% and 90% of the range

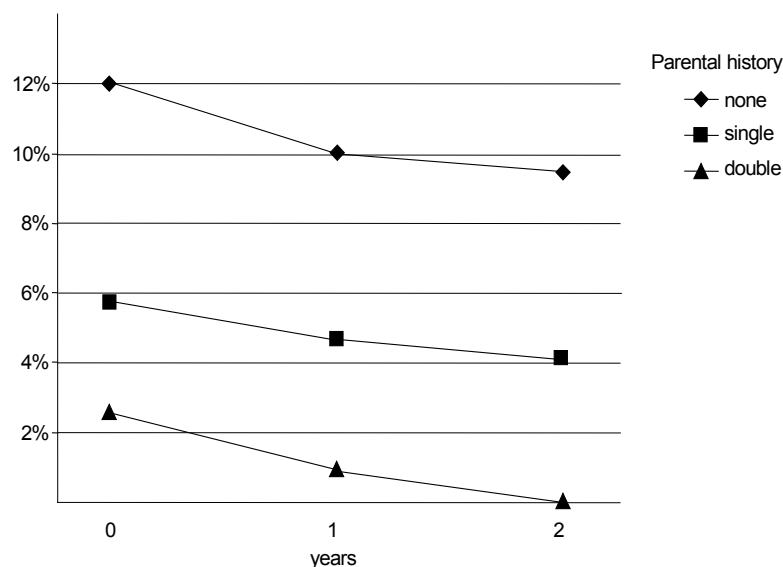
Similarly, study **III** indicates that cat and dog allergen is dispersed from homes with cat or dog (for instance, homes of relatives that the child meets regularly) to homes without such animals. The median levels of Fel d 1 or Can f 1 in pet-free homes where a relative has a cat or dog were significantly higher than those found in pet-free homes without any reported cat or dog contact, but lower than those found in homes with a cat or dog (**III**, Figure 1).

**Comment.** Many studies have previously shown that cat and dog allergens are ubiquitous in environments where these animals are not usually kept.<sup>67, 68,71,137</sup> It has also been shown that allergen is carried in clothing and that pupil cat ownership correlates with allergen levels found on classroom floors.<sup>138-141</sup> However, our study (I) was the first to examine levels of airborne allergen and routes of contamination between homes with cat and school. We could also assess further dissemination of allergens to homes without cats, though our data do not allow us to determine whether the allergen in the mattresses in cat-free homes could be derived from the child's clothes, contaminated at school, or from the clothing of visiting cat owners. The allergen found in cat-free homes where relatives own a cat (III) was equally likely to have come from visiting cat owners' clothes, and from those of the family members. These findings emphasise clothes as an important carrier of allergen: measures to reduce allergen levels in cat-free environments could easily be suggested. Allergen levels in woollen sweaters have been found to increase personal exposure to cat allergen 11 times, and clothing items that are seldom washed contain significantly more cat allergen.<sup>142</sup>

## Exposure (I, III, IV)

### Direct exposure to cat and dog (I, III, IV)

Cat ownership was reported in 18% of the households, and dog ownership in 15% (I). Forty-four percent of the children had some furred pet: cat, dog or rodent. In study III and IV, cat ownership at the median age of two months was reported by 10.0% of the families, dog ownership by 5.2%. Cats were less frequently kept in families with reported parental asthma, rhinoconjunctivitis, pet or pollen allergy (3.5-5.8) than among those without any parental allergic disease (10.8-11.8%). Dog ownership, on the other hand, varied little between the groups with and without parental history of allergic disease, with AEDS as an exception (3.3 vs 5.9%). Furthermore, families with smoking parents and low socio-economic index reported cat and dog at home more often than other families. Cat and dog ownership decreased over time from birth to two years of age, especially in families with allergic heredity (Figure 6).



**Figure 6.** Cat and dog ownership over time from birth to one and two years of age, in families with no, single or double parental history of allergic disease.

Whether this is due to preventive measures or because the index child or a sibling had developed symptoms of allergic disease, we can only speculate.

**Comment.** The number of pet owners is, from an international perspective, fairly low in our cohort. In the UK, pet ownership is more common and about one-third of all homes have a cat, and one-quarter have a dog.<sup>143</sup> Approximately 20% of Swedish households have cats and 16% have dogs.<sup>144</sup> Study **I** and **III** were undertaken at the same time, but far more families had pets in study **I** than in study **III**. This might be because the children in study **I** were older and their families were probably more likely to keep pets than the families with newborn babies in study **III**. It might also be that those in study **I** lived in the suburbs, whereas many of those in study **III** lived closer to the city. We have chosen not to adjust for later pet ownership in the statistical analyses (**III**), since we want to be sure that exposure preceded outcome. It has also been suggested that the window of opportunity for environmental influences to affect the development of childhood asthma is restricted to antenatal or infant exposure.<sup>145-147</sup>

A few of the studies on associations between pet exposure and disease briefly mention whether there is a difference in pet ownership between households with and without family history of allergic disease, but the effect of selection for pet ownership into longitudinal studies has not been examined previously, as far as we know.<sup>98,100</sup> It has been suggested that children with a family history of allergic diseases are born into a low risk environment.<sup>148</sup> It is appealing to ponder on what other factors might influence people in their decision to keep pets, and thereby perhaps confound studies on associations.

### **Indirect exposure to cat and dog – exposure to allergen (I, III, IV)**

Median levels of airborne cat allergen in school classes with many and few cat owners were 2.94 and 0.59 ng/m<sup>3</sup>. These differences in indirect cat exposure between classes with many and few cat owners were applied in study **II**, although there the cut-off was set at  $\leq 18\%$  cat owners. The corresponding levels of Fel d 1 in classroom dust are shown in Table 2, along with levels of mattress-bound cat allergen (**I, III**) and dog allergen (**III**).

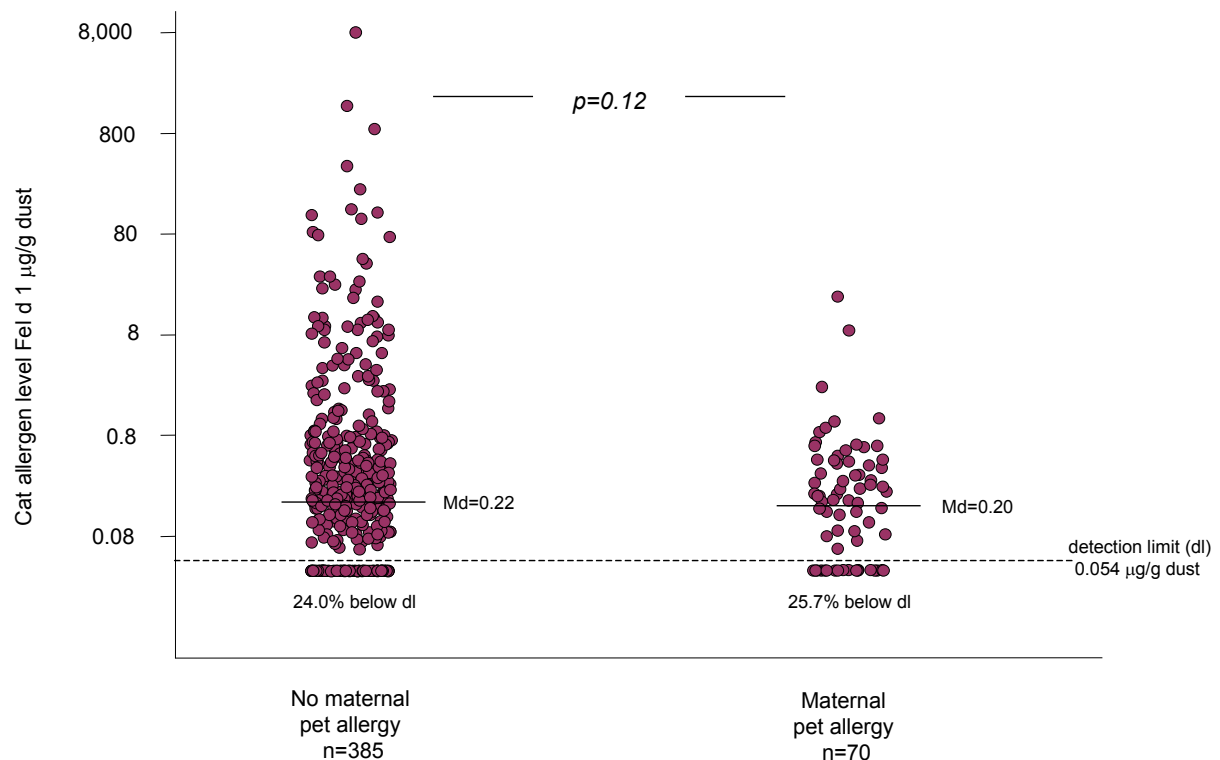
**Table 2.** Median levels of cat and dog allergen with interquartile range (IQR) in dust samples from study **I** and **III**.

Study	Location	Cat allergen Fel d 1			Dog allergen Can f 1		
		(µg/g dust)			(µg/g dust)		
		n	Median	IQR	n	Median	IQR
<b>I</b>	Classroom many cat owners (>25%)	12	2.21	(1.71-2.81)			
<b>I</b>	Classroom few cat owners (<10%)	12	0.77	(0.27-0.96)			
<b>I</b>	Mattress – cat at home	45	87.4	(29.4- 199.4)			
<b>I</b>	Mattress* – class with many cat owners	75	0.85	(0.32-1.64)			
<b>I</b>	Mattress* – class with few cat owners	106	0.38	(0.19-1.21)			
<b>III</b>	Mattress – pet at home	57	71.6	(24.1-269.3)	20	20.8	(12.8-138.2)
<b>III</b>	Mattress – pet at close relative	148	0.44	(0.20-1.40)	160	0.3	(0.20-1.06)
<b>III</b>	Mattress –no direct contact with pet	307	0.15	(0.05-0.44)	336	0.2	(0.20-0.20)

\*among those without cat at home

†pet denotes cat or dog

Families without a cat where the mother reports pet allergy have a tendency towards lower levels of cat allergen at home than families with no maternal pet allergy, which indicates that avoidance measures have been undertaken (Figure 7). That a statistic significance was not reached ( $p=0.12$ ) has been suggested be due to the sample size being too small, but could also be interpreted as an illustration of how difficult it is to avoid indirect exposure to cat. Levels of dog allergen Can f 1 did not differ between families with and without reported maternal history of AEDS (IV, Figure 2). This may either be due to non-detectable dog allergen levels in a large proportion of the dust samples, or to dog allergen not being avoided to the same extent.



**Figure 7.** Cat allergen levels Fel d 1 in 455 families without cat at home, subdivided by maternal pet allergy. Median (Md) concentration of cat allergen and percentage of dust samples below detection limit (dl) marked.

**Comment.** Even if the number of cat and dog owners seems to be fairly low from an international perspective, the allergen levels in homes with cat and dog are in keeping with what has been found in many other parts of the world,<sup>74,76,134,149</sup> though higher than those reported from Germany.<sup>93</sup> In urban Ghana, the proportion of cat and dog owners is comparable to that in the UK, but as the pets are often kept outside, allergen levels in many homes with pets were lower than those in homes without pets in the UK.<sup>150</sup> This indicates that similar proportions of pet ownership in different countries do not equate to similar levels of exposure to allergen, and that actual measurement of Fel d 1 and Can f 1 is essential to estimate individual exposure.

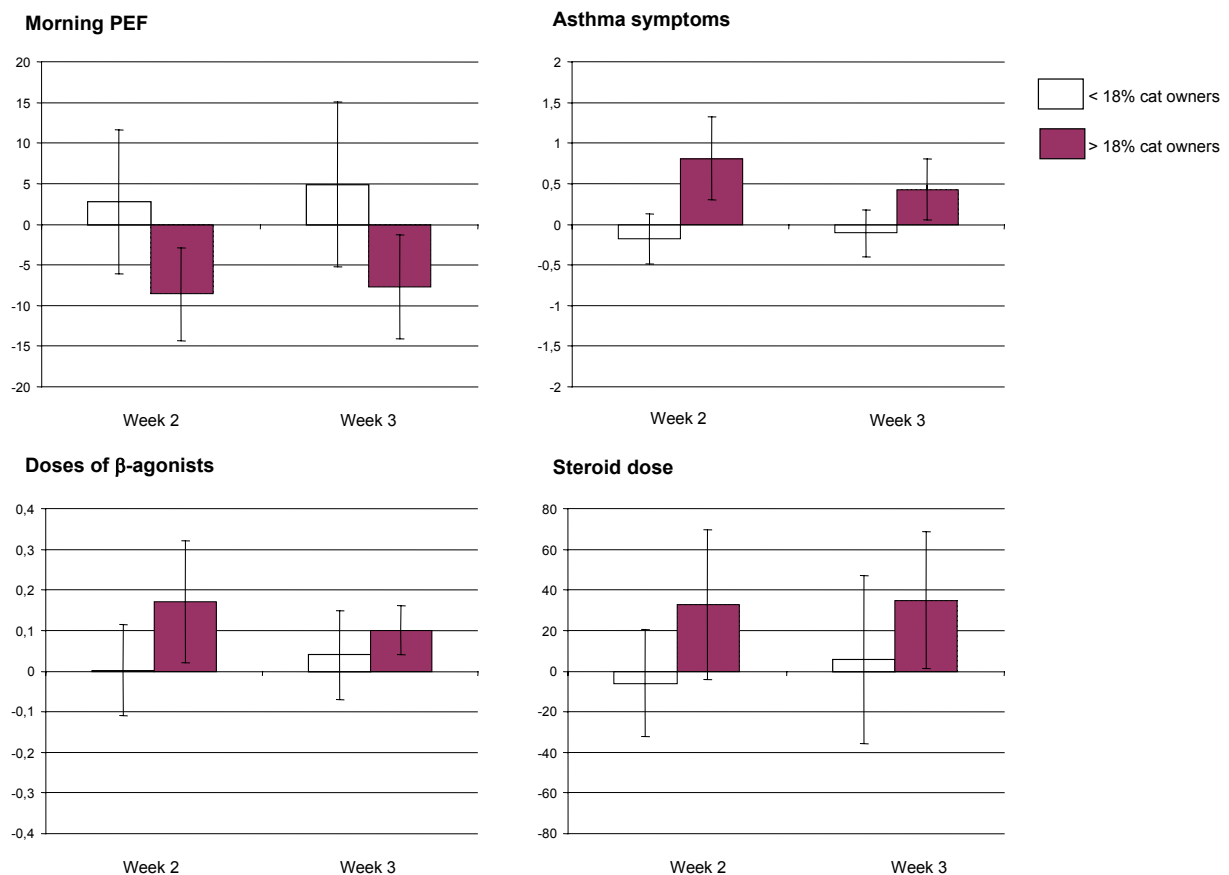
Several studies have clearly shown that it is possible to become sensitised to cat without ever having lived with a cat. The most intriguing evidence comes from the island of Tristan da Cunha where cats were exterminated in 1974 to get rid of toxoplasmosis.<sup>151</sup> Positive skin test reaction to cat was present in six individuals (12.8%) of those born more than one year after

the cats were eliminated. Two of those children had attended school outside the island and might have become sensitised there, but the remaining four children (one of whom was born in 1983) must have become sensitised either from allergen remaining in the homes, or from allergen brought in on visitor's clothes. In an area of Italy where approximately 16% of all households had cats, cat sensitisation was three times more frequent in children who never had a cat at home than in children living with cats.<sup>149</sup> Likewise, a high prevalence of cat sensitisation was seen among asthmatic Japanese children living without cats.<sup>134</sup> A significant correlation between the prevalence of cat ownership in the community and the prevalence of specific sensitisation to cat has been shown in the ECRHS, all those studies indicating that indirect cat exposure probably is an important cause of sensitisation.<sup>105</sup>

## Health effects (II, III, IV)

### *Allergen exposure in children with established asthma and sensitisation (II)*

The main finding of this study is that exposure to cat allergen in a cat-free environment may induce worsening of asthma in cat sensitised children (Figure 8).



**Figure 8.** Changes from baseline to weeks 2 and 3 for weekly average morning PEF (l/min); number of days with asthma symptoms; daily doses of  $\beta$ -agonists; and daily steroid dose ( $\mu$ g) for children in classes with many (>18%) and few ( $\leq$ 18%) cat owners. Columns represent the point estimate and error bars the upper and lower limits of the 95% confidence interval.

Among children in classes with many cat owners (>18%, n=47), lung function expressed as mean morning PEF decreased 3% from baseline week to week 2. Days with asthma symptoms were more than twice as frequent during week 2 than during baseline week, and the children reported a doubling of the average daily use of  $\beta$ -agonists in week 2. Simultaneously, the average daily dose of steroids was 16% higher in week 2 than baseline week. Those in classes with  $\leq$ 18% cat owners (n=45) reported no change.

The risk of decreased respiratory health (DRH) in the group with many cat owners in class was 9-fold increased by week 2 compared with the group in classes with few cat owners, after adjustment for sex, age, and fever and/or sore throat. These data apply to those who denied direct contact with pets during the study period.

For the children who reported direct pet contact during the study (n=179), the morning PEF decreased 1% and the average daily steroid dose increased 6% from week 0 to week 2. No significant change in asthma symptoms or use of  $\beta$ -agonists was reported (II, Table 4). No difference in DRH was seen between classes with many (>20%) and few (<20%) cat owners.

**Comment.** The health effects of indirect allergen exposure have, to our knowledge, not been studied previously. However, several studies have indicated worsening of respiratory symptoms after allergen exposure in sensitised subjects,<sup>74</sup> not the least in occupational settings.<sup>152,153</sup> Repeated low-dose allergen exposure has been shown to increase BHR and induce an inflammatory response in patients with preexisting atopic asthma.<sup>154-157</sup> It was recently suggested that inhaled steroids may prevent airway inflammation after low-dose allergen exposure in mild asthmatics,<sup>158</sup> though the children in our study probably had a more severe asthma and thus deteriorated in their disease despite increased steroid doses. We did not assess inflammatory response in the children, but it has been shown that the short-term risk for deterioration in cases of mild and moderate asthma can be estimated by counting eosinophils or measuring eosinophil proteins.<sup>159</sup>

Thus, studies I and II indicate that allergen avoidance may well be the gold standard for treating cat-allergic children with asthma. However, complete avoidance may be difficult, because of the constant influx of allergen with clothes that have become contaminated at school and other public places. Air cleaners have been shown to reduce levels of airborne allergen, but studies on their clinical usefulness give inconsistent results. In a double-blind placebo controlled trial to evaluate the effect of HEPA air cleaners on cat-allergic subjects with cat at home, there was no effect on disease activity despite decreased levels of cat allergen in the homes of those with active air cleaners.<sup>160</sup> Another research group showed a significant improvement in airway hyperresponsiveness in young asthmatic patients when air cleaners were used in living rooms and bedrooms.<sup>161</sup> Nevertheless, these results apply to homes with cats, and it does not seem feasible to ask families without cat to undertake these environmental control measures in order to clean their air of passively transferred allergen.

It has been suggested that keeping a pet at home will induce tolerance to the pet even in pet-allergic asthmatic subjects. In study I, 170 children reported asthma (N=1,929), and 122 children had asthma along with pet allergy. Among those, 8 children kept a cat or a dog. A recent study in adults indicated reduced late asthmatic response in individuals who had

repeatedly been exposed to low doses of allergen and then undertook a high-dose bronchial allergen challenge.<sup>162</sup> However, the allergen levels administered were very low and did not correspond to those in a house with a cat. On the contrary, it has been shown that asthmatic individuals with pets at home have more symptoms, a higher degree of BHR, more medication and higher inflammatory parameters than asthmatic individuals without pets at home.<sup>163</sup> It was also shown, in a case control study of severe adult asthmatics matched with a mildly asthmatic group, that a higher proportion of the severely asthmatic group were sensitised and exposed to indoor allergens.<sup>123</sup>

### Allergen exposure and subsequent IgE-sensitisation or asthma (III, IV)

The prevalence of asthma at two and four years of age was 8.8% and 7.0%, respectively. Three hundred ninety-two children (15%) were sensitised to at least one inhalant allergen at four years of age. There was no difference in the distribution of background variables in the groups who did or did not agree to give blood samples (III, Table I).

Direct or indirect exposure to cat seemed to increase the risk of cat sensitisation, whereas exposure to dog did not have any effect on dog sensitisation (III). Dog ownership, on the other hand, was related to a reduced risk of sensitisation to other airborne allergens, in particular birch and timothy, with a similar tendency for cat ownership (Table 3).

**Table 3.** Early exposure<sup>†</sup> to cat and dog in relation to sensitisation to cat or dog at 4 years of age in a cohort study, BAMSE.

	N	Sensitisation to cat			Sensitisation to airborne allergens other than cat		
		n	OR**	(95% CI)	n	OR**	(95% CI)
<b>Cat</b>							
No exposure*	1517	74	1		160	1	
Any exposure	1056	77	1.44	(1.03-2.01)	81	0.71	(0.53-0.94)
Exposure at relatives	797	59	1.43	(1.00-2.05)	64	0.73	(0.54-1.00)
Ownership	259	18	1.46	(0.84-2.54)	17	0.63	(0.37-1.07)
<b>Dog</b>							
No exposure*	1663	92	1		-		
Any exposure	910	59	1.08	(0.76-1.53)			
Exposure at relatives	782	55	1.20	(0.84-1.71)			
Ownership	128	4	0.45	(0.16-1.27)			
	N	Sensitisation to dog			Sensitisation to airborne allergens other than dog		
		n	OR**	(95% CI)	n	OR**	(95% CI)
<b>Cat</b>							
No exposure*	1517	65	1		-		
Any exposure	1056	51	1.07	(0.73-1.58)			
Exposure at relatives	797	40	1.09	(0.72-1.65)			
Ownership	259	11	1.00	(0.51-1.97)			
<b>Dog</b>							
No exposure*	1663	69	1		192	1	
Any exposure	910	47	1.16	(0.79-1.72)	84	0.76	(0.58-1.01)
Exposure at relatives	782	43	1.26	(0.85-1.89)	78	0.83	(0.63-1.11)
Ownership	128	4	0.62	(0.22-1.76)	6	0.36	(0.15-0.83)

<sup>†</sup>Contact with cat or dog reported at a median age of 2 months, indirect exposure defined as regular contact with relatives with cat or dog at home

\* Reference category

\*\* Adjusted for gender, heredity for allergic diseases, maternal smoking, maternal age, socioeconomic status of parents

Early dog ownership was weakly associated with a lower risk of asthma, OR 0.50 (0.24-1.03), with no corresponding effect for cats, OR 0.88 (0.56-1.38) (III, Table 4). Maternal pet allergy seems to be the strongest decisive factor for the keeping of a cat or not, whereas dog ownership was less common in families with reported maternal AEDS (IV, Table 2). Whether the selection of pet ownership is due to current or previous symptoms in the family we cannot tell, and neither to what extent primary preventive measures have influenced their choice of not keeping a pet.

**Comment.** It would be presumptuous to claim our results to be more correct than those of others who have tried to calculate the true relationship between pet ownership and ensuing disease. What is so evident here, though, is that any cat contact, be it direct or indirect, is associated with increased risk of cat sensitisation. Our results also suggest a threshold of approximately 0.5 µg Fel d 1/g dust for cat sensitisation early in life in areas free of house dust mites. These children might have been exposed to cat directly or indirectly later in life, but they still had higher risk of sensitisation than those without any exposure to cat at the median age of two months. There was no corresponding increased risk of sensitisation to dog after dog exposure, and the reduced risk of sensitisation to pollen allergens is difficult to explain. It is possible that the results from study III should really be interpreted as an effect of selection of pet ownership. However, study IV indicates that the selection is in fact strong only for cats, whereas dogs were avoided only in families with parental AEDS and reported double pet allergy, besides those with smoking parents and low socio-economic status. When the data are stratified for parental history of allergic disease (III, Table 4), the inverse association between dog exposure and subsequent sensitisation certainly applies to children without allergic heredity. Nevertheless, the point estimate is similar in the group of children with allergic heredity, though the sample size is too small to show a statistically significant effect. The same applies to asthma as an outcome; stratifying the negative association between dog exposure and subsequent asthma, we saw no difference in asthma prevalence between those with and without allergic heredity. It has to be remembered that if the sample of children with allergic heredity exposed to pets early in life had been larger, our results might have been different.

Although dog allergy has been recognised as a clinical problem, cat allergy has received far more scientific interest. The behaviour of domestic cats presumably has an impact also upon the distribution of the allergen. Cats are more likely than dogs to wander all over the house, and sit on furniture such as beds and chairs, in particular to curl up in upholstered ones.<sup>164</sup> Our results imply that there may also be a difference in the pattern of IgE-sensitisation after early exposure to cat and dog. Common epitopes and limited cross-reactivity between cat and dog allergens has been discussed but the data are inconsistent.<sup>134,151,165</sup>

Recently (September 2002), two articles on associations between early exposure to pets and asthma were published. One of them suggested an increased risk of asthma after cat exposure in children with maternal asthma, whereas the other one showed a decreased risk of asthma after cat exposure, especially in children with a family history of asthma.<sup>99,100</sup> The results of the first study can perhaps be attributed to cat exposure in already sensitised children at risk of



asthma, since 88% of the children still held cats. The second study had collected information on cat exposure retrospectively, and this might have resulted in distorted study results and report bias. Anyhow, since both studies were very well conducted and yet show completely disparate results, it is possible that we now are reaching the end of the road and will not be able to come any further on this issue with ordinary epidemiological studies. In order to be able to create proper primary prevention programs, one of the major tasks might be to identify individuals at risk of developing allergic disease. Twin studies have suggested asthma to be inherited in up to 75%<sup>166,167</sup> and whether the maternal influence is stronger than the paternal has been debated.<sup>23,168</sup> In any case, gene-environment interactions are thought to play an important role in the development of allergic disease.<sup>169,170</sup>

In study **IV**, we stress the importance of confounding control and point out that reported maternal pet allergy might be a confounding factor that should be adjusted for in the statistical analyses. At the same time, we adjust for parental history of allergic disease and not for maternal pet allergy or maternal AEDS in study **III**. However, there is no significant difference in the point estimates. No risk association between early cat ownership and asthma at four years was seen after adjusting for maternal pet allergy; 0.91 (0.58-1.43), and if we adjusted the association of dog ownership and asthma for maternal AEDS the negative risk was slightly increased, OR 0.47 (0.23-0.98). It is also worth noting that family pet ownership is affected by history of allergic disease in a sibling, although the number of children with siblings was too low to gain any statistical meaning.

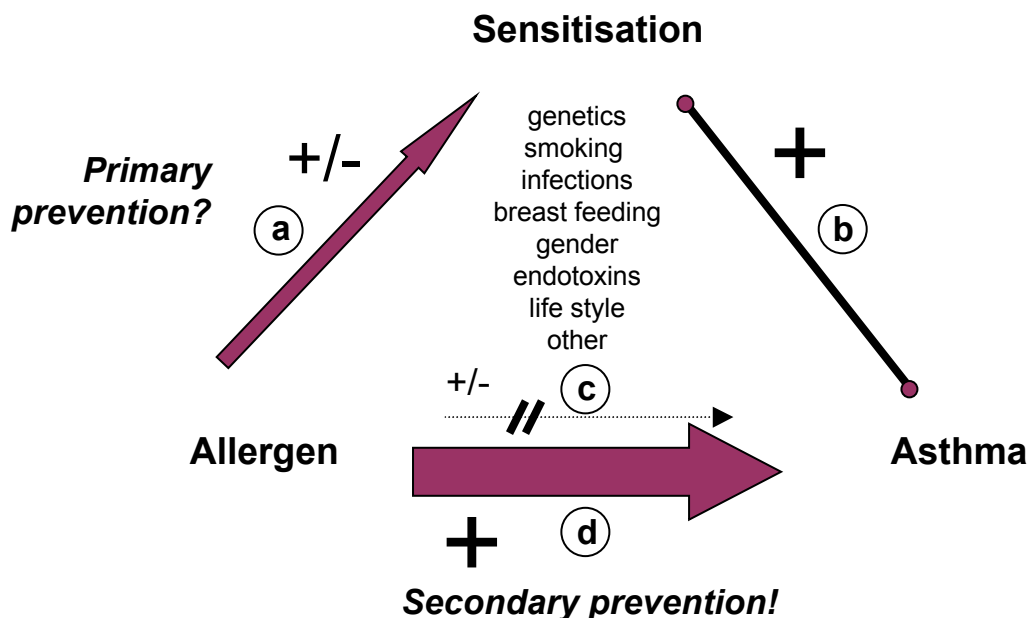
Families with a history of allergic diseases might be less prone to keep pets, and many countries have primary prevention programs where families with heredity for allergic diseases are advised not to keep pets. Meanwhile, cat allergen is ubiquitous in society and may induce sensitisation in predisposed individuals regardless of pet ownership (**I**, **III**). Children with a family history of allergic disease also have a higher risk of becoming allergic themselves. Taken together, this might give distorted study results, especially in studies with a cross-sectional design.<sup>109,110</sup> Figure 6 (page 27) illustrates how cat and dog ownership changes over time from birth to two years of age, depending on family history of allergic disease. The figure suggests how easily a cross-sectional survey on risk associations at two years could be misinterpreted.

## CONCLUSIONS

Based on the presented studies, the following conclusions can be drawn.

- ✓ Cat allergen is transferred from cat owners' homes via school to non-cat-owners' homes in clothing. There is an association between the number of cat owners and the levels of airborne cat allergen in class. Allergen levels in non-cat-owners' homes correlate with exposure to cat allergen at school (I).
- ✓ Asthmatic children allergic to cats suffer a worsening of their disease in conjunction with indirect cat exposure at school start (II). This knowledge can be applied in secondary prevention.
- ✓ Early cat exposure seems to increase the risk of sensitisation to cat but not of asthma at four years of age. Dog ownership appears to be associated with decreased risk of asthma and sensitisation to airborne allergens (III).
- ✓ There appears to be a selection of pet ownership and exposure based on parental history of allergy, maternal smoking and socio-economic factors. This has to be taken into consideration when evaluating risk associations between pet exposure and allergic disease in childhood, even in studies with prospective design (IV).

The causal relationship between allergen exposure and disease has been discussed, and is outlined in Figure 9.



**Figure 9.** Early exposure to cat allergen seems to sensitise (a), but has no correlation with asthma (c). By contrast, early exposure to dog might reduce risks of sensitisation and asthma (a, c), which casts doubt on the value of primary prevention. There is a strong association between sensitisation and asthma (b). Allergen exposure in sensitised children with asthma appears to worsen the disease (d), which supports the use of secondary prevention.

## GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The topic of associations between pet exposure and asthma is very controversial. Many conflicting and intriguing findings have been published in the last couple of years.

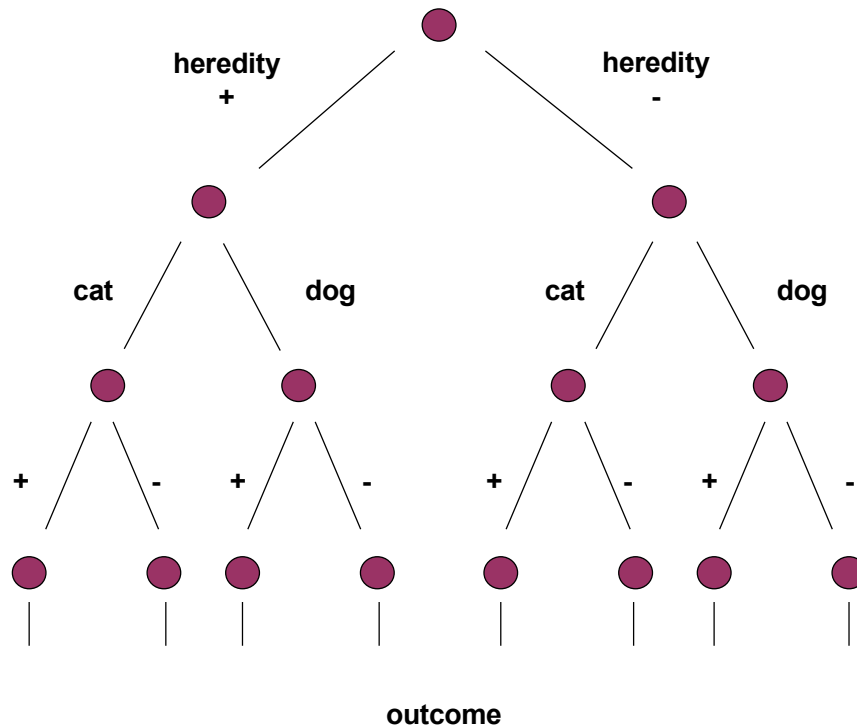
Cat allergen is ubiquitous and difficult to avoid even in allergic families (**I**, **IV**). Sensitisation to cat may even occur at levels below 0.5 µg/g dust, which means that children can become sensitised without ever having met a cat (**III**). However, 70% of our sensitised children did not report any symptoms of asthma at 2 or 4 years, and there was no increased risk of asthma after early cat exposure. Whether those sensitised children are more prone to develop symptoms of allergic disease at a later stage must be further looked into, preferably by following them over time. Cat sensitisation has been suggested to be predictive of new-onset airway hyperresponsiveness in an adult population.<sup>171</sup> It has also been suggested that pure sensitisation is common in the population and does not predict allergic disease.<sup>172</sup> On the other hand, in a group of persistently sensitised 7-year olds, the risk of being asthmatic was confined to those with a parental history of allergic disease.<sup>23</sup>

A linear dose-response between cat allergen levels and sensitisation was seen in the prospective birth cohort in Germany,<sup>93</sup> whereas a bell-shaped dose-response curve with increased IgG4 among children exposed to high levels of cat allergen has been suggested to explain why cats in the house can decrease the risk of sensitisation.<sup>100,112</sup> Our results are not consistent with either of these models, nor do they agree with recent findings that residing in a house with two or more cats or dogs in the first year of life might reduce the subsequent risk of allergic sensitisation to multiple allergens during childhood.<sup>98</sup> However, like Ownby, we did find early exposure to cat or dog to be negatively associated with sensitisation to airborne allergen other than cat or dog. The immunological mechanisms behind this remain to be explained, and selection effects have to be considered (**IV**). One possibility is suggested by the observation that environmental exposure to endotoxins reduces the risk of sensitisation in children.<sup>34</sup>

Although we observed an association between early cat exposure and sensitisation, early cat exposure was not associated with asthma. This is in line with previous studies.<sup>94</sup> More importantly, there was a strong association between sensitisation and asthma,  $p < 0.001$ . This may reflect the susceptibility of an individual with asthma to become sensitised to the perennial allergens that are most prevalent in the environment, rather than an increased risk of asthma when exposed to these allergens. This should be clearly separated from the findings in study **II**, where indirect cat exposure induces respiratory symptoms in already sensitised children.

Given the fact that so many studies present incongruent results – even longitudinal studies in which infants are followed from birth – it is a difficult undertaking to design primary prevention strategies and summarise them in the form of advice. We should not be advising people without heredity for allergic diseases who wish to prevent allergies and asthma in their children to rid their homes of pets. Conversely, we should probably not be recommending pet ownership as prophylaxis against asthma. It is possible that meta-analyses of the effect of selection into studies will be required as well, before we can begin to generalise study results.

A challenging task would be to perform a randomised controlled trial where children are randomised on the basis of heredity for allergic diseases, and then allocated into different arms with and without cat and dog ownership (Figure 10). Only in this way can we ascertain the risk of disease at x years of age, and even then will we have to struggle with the issue of indirect exposure. Such a study would most probably not be approved by the ethical committees, and in the meantime we will have to trust meta-analyses.



**Figure 10.** Randomised controlled trial to examine the association between early pet exposure and subsequent disease (outcome = asthma or sensitisation) depending on heredity.

An ongoing intervention study has shown that living in a low-allergen environment reduces respiratory symptoms in the first year of life in high-risk infants.<sup>173</sup> Data from another British prevention study suggest that even when lower sensitisation rates are achieved, the prevalence of asthma up to age 4 years is not affected.<sup>174</sup> With a better understanding of an individual's genetic background, his or her susceptibility to certain exposures may improve our understanding of the effect of environmental exposure at an individual level. Two general methods have been used to investigate the molecular genetics of asthma: candidate gene approaches and whole-genome screens followed by positional cloning attempts.<sup>175</sup> If genetic studies turn out to be fruitful, they might contribute to the identification of individuals who may respond to certain primary prevention measures or therapeutic intervention strategies.

Even if it turns out that factors other than allergen exposure play a major part in determining which child will develop asthma, so that allergen elimination as a primary prevention measure is proved inefficient, a reduction of allergen exposure will still remain a very important element in secondary prevention. This is illustrated by the results of study II, in which asthmatic children allergic to cat suffer a worsening of their disease in conjunction with

indirect exposure to cat after a period of nonexposure. It is becoming acknowledged that school environments affect children with asthmatic symptoms, and some schools have established allergen avoidance classrooms.<sup>176,177</sup> We saw in an earlier study that levels of cat and dog allergen were significantly correlated to the number of pet owners among children and staff in a day-care centre.<sup>75</sup> It would be of considerable interest to look into possible intervention measures, and ideally take steps to minimise the amount of allergen brought to school in cat owners' clothing (**I**). This could be done either by asking cat owners to wear clean clothes to school and not cuddle with the cat in the morning, or by having children change into school uniform at school. Preliminary data from an ongoing study suggest that levels of cat allergen are lower in classes where the children change into school uniform at school than in control classes.<sup>178</sup> Whether a reduction in allergen levels at school would have an effect on the allergen load in homes without cat remains to be seen, as well as how the health status in sensitised children would be affected.<sup>74</sup> Adequate sampling methods and amplified assays to estimate the level of personal allergen exposure in a low-exposure environment will be essential if such an intervention study is to be performed.

If the reservoirs of allergens in homes and in public places turn out to be difficult to eradicate sufficiently to reduce indirect exposure to indoor allergen, it is important to encourage patients with established asthma and allergy not only to avoid allergens but also to comply with pharmacological therapy. Specific immunotherapy has been shown to reduce sensitivity to allergens such as cat.<sup>179,180</sup> Montelukast, a leukotriene antagonist, seems to efficiently attenuate lower airway responses in cat allergic children with asthma who are exposed to cat.<sup>181</sup> Primary prevention strategies based on the induction of an immune deviation toward a Th1-type immune response to inhalant allergens has been proposed, for example by administering allergen and a suitable adjuvant in a vaccination program.<sup>25,182,183</sup>

Although we can conclude that allergen avoidance will reduce symptoms in sensitised children with asthma, it seems clear that allergen avoidance alone will not reduce the occurrence of asthma and allergic disease. The prevalence of autoimmune diseases such as type I diabetes, multiple sclerosis and Crohn's disease is increasing in parallel with allergic diseases in industrialised countries.<sup>184</sup> An association between allergic and autoimmune diseases in individual patients has also been suggested, even if the data are inconsistent.<sup>185</sup> The frequency of allergic diseases is increased in patients with diabetes and rheumatoid arthritis.<sup>186,187</sup> Decreased incidence of infectious diseases has been suggested to explain these trends, but perhaps one line of research should also focus on whether allergies and autoimmune diseases are caused by infectious agents that have not yet been identified.

Thus, the evidence for a causal relationship between allergens and asthma in a general population hinges on epidemiological findings showing a strong association between specific IgE and asthma in children who already have the disease. Although pet allergens resemble what Hippocrates proposed to be an aetiological mechanism for asthma (and may well be so in already sensitised subjects), it is unlikely that exposure to cats and dogs in early childhood can explain the global increase in the prevalence of asthma.<sup>2</sup>

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From "Sagan om den lilla lilla gumman"

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## POPULÄRVETENSKAPLIG SAMMANFATTNING

Förekomsten av astma och allergier har ökat i västvärlden under de senaste årtiondena. Cirka 7-10% av alla barn i skolåldern har diagnosen astma. Många av dem är dessutom allergiska mot ett eller flera allergen (allergiframkallande ämnen) från t ex katt, hund och björk. Förekomst av antikroppar mot allergen, dvs IgE-sensibilisering, kan mätas i blodet.

Under de senaste åren har det förts en debatt kring hur pälsdjur påverkar utvecklingen av astma och allergier. Vissa studier visar att hund och kattinnehav i barndomen ger ökad risk för allergisjukdom, andra menar att hund och katt skyddar mot allergier. Den här debatten har medfört stor osäkerhet hos familjer som vill undvika astma och allergi hos sina barn. Samtidigt förefaller barn med etablerad astma och IgE-sensibilisering mot ett eller flera pälsdjursallergen försämrats i sin sjukdom när de träffar pälsdjur.

Den här avhandlingen behandlar båda aspekterna på exponering för pälsdjur. Dels hur kattallergen spritt från hem med katt via skola till hem utan katt (studie I) påverkar barn med redan etablerad astma och kattsensibilisering (studie II). Dels om tidig pälsdjursexponering har något samband med astma och IgE-sensibilisering hos barn vid 4 års ålder (studie III) och hur förekomst av allergisk sjukdom i familjen påverkar pälsdjursinnehav (studie IV).

### Studie I

Kattallergen mättes i inandningsluft och i kläder hos elever i årskurs 4 och 5. Eleverna fick bära personburna pumpar under två förmiddagar i klassrummet och en eftermiddag i hemmet. Deras madrasser dammsögs och i tre klasser dammsögs kläder före och efter en skoldag. Analyserna av det uppsugna allergenet utfördes med en metod att upptäcka mycket låga halter kattallergen i damm. I klasser med många kattägare (>25%) var halterna luftburet kattallergen betydligt högre än i klasser med få kattägare (<10%). Elever utan katt i hemmet som gick i klasser med många kattägare samlade på sig stora mängder kattallergen i sina tröjor under en skoldag. Bland elever utan katt i hemmet hade de som gick i klasser med många kattägare betydligt mer kattallergen i sina sängmadrasser än de som gick i klasser med få kattägare. De här resultaten visar att allergen transporteras i kläder från hem med katt till klassrum, där det sprids i luften och överförs till kläder på barn utan katt. Dessa barn är på så vis indirekt exponerade för katt. Även barn som pga pälsdjursallergi eller astma själva undviker att träffa pälsdjur blir på detta vis ändå exponerade för kattallergen.

### Studie II

Alla 6-12 år gamla barn med kattallergi och astma identifierades från fem stora barnallergimottagningar i Stockholm. De barn som medicinerade sin astma med cortisonspray och inte hade några pälsdjur hemma inbjöds att delta i studien. Barnen fick fylla i en dagbokenkät morgon och kväll under tre veckor i samband med skolstart efter sommarlovet. I enkäten rapporterades lungfunktion (PEF), astmasymtom, medicinering och eventuell pälsdjurskontakt. Av de 92 barn som inte hade pälsdjurkontakt under studieveckorna rapporterade de som gick i klasser med många kattägare (>18%) betydligt sämre PEF, mer

astmasymtom och större behov av medicinering än innan skolstart. Barn i klasser med få ( $\leq 18\%$ ) kattägare hade ingen sådan försämring. Detta indikerar att indirekt kattexponering i skola försämrar astmasjukdomen hos barn med redan etablerad astma och allergi.

### Studie III och IV

Studie **III** och **IV** utgår från en stor epidemiologisk studie (BAMSE) där 4,089 barn i delar av Stockholm med nordvästra förorter följts från födelsen. Familjerna besvarade ett frågeformulär om bl a ärftlighet för allergisk sjukdom, rökning och pälsdjursinnehav när barnet var ca 2 månader gammalt. Dammprover för analys av katt- och hundallergen insamlades. Vid 1, 2 och 4 års ålder besvarades enkäter om symtom på allergisk sjukdom. Vid 4 års ålder togs blodprov på 2,614 barn, för analys av IgE-sensibilisering.

Sambandet mellan direkt exponering (katt eller hund hemma) eller indirekt exponering (katt eller hund hos släkting som barnet träffar) vid 2 månaders ålder och risken att ha insjuknat i astma eller IgE-sensibilisering vid 4 års ålder beräknades i studie **III**. Tidig kattexponering visade sig öka risken för sensibilisering mot katt. Däremot sågs ingen relation mellan tidig kattexponering och risken för astma vid 4 års ålder. Tidig hundexponering verkade minska risken för astma men hade inget klart samband med sensibilisering för hund. Exponering för katt eller hund föreföll också minska risken för sensibilisering mot pollenallergien.

I studie **IV** undersöktes urvalet för pälsdjursinnehav vid barnens födelse i BAMSE-studien. Det visade sig att familjer med rapporterad astma, hösnuva, pälsdjur- eller pollenallergi hos föräldrarna hade katt hemma i mycket mindre utsträckning än familjer utan rapporterade allergier (3.5-5.8% jämfört med 10.8-11.8%). Hund undveks bara i familjer med rapporterade eksem hos föräldrarna (3.3% vs 5.9%). Familjer med rökande mammor hade katt (18.8%) och hund (9.2%) i större utsträckning än familjer utan rökande mammor (katt 8.6%, hund 4.6%). Dessutom hade familjer med diagnosticerad pälsdjursallergi hos mamman lägre halter kattallergen i hemmen än andra familjer, vilket kan tyda på att man undviker exponering genom att inte träffa katter, eller att man städar mer utförligt.

Sammanfattningsvis illustrerar studierna (**I**, **III**, **IV**) hur svårt det är att undersöka sambandet mellan tidig pälsdjursexponering och senare sjukdom. Barn till föräldrar med ärftlighet för allergisk sjukdom har större risk att själva utveckla astma och allergier. Dessa familjer undviker pälsdjurskontakt av olika skäl, men exponeras ju ändå för allergen genom passiv överföring från andra djurägare. Om vi kan finna metoder för att identifiera individer med risk att utveckla allergi och astma, skulle förebyggande åtgärder kunna riktas mer specifikt.

Mindre kontroversiellt är att barn som redan har en etablerad astma och IgE-sensibilisering försämras i kontakt med pälsdjursallergen, delstudie **II**. Möjligheter att åtgärda allergenhalterna i skola, förslagsvis genom att minska inflödet av allergen i pälsdjursägares kläder eller skoluniform, återstår att studera.



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## **PAPERS I-IV**