

Direct and indirect exposure to pets – risk of sensitization and asthma at 4 years in a birth cohort

C. Almqvist^{*†‡1}, A.-C. Egmar^{*†1}, G. Hedlin[†], M. Lundqvist^{*}, S. L. Nordvall[§], G. Pershagen[‡], M. Svartengren[¶], M. van Hage-Hamsten^{||} and M. Wickman^{*‡**}

^{*}Occupational and Environmental Health, Karolinska Hospital, Stockholm, Sweden, [†]Department of Woman and Child Health, Karolinska Institutet, Astrid Lindgren Children's Hospital, Stockholm, Sweden, [‡]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [§]Institute of Woman and Child Health, Uppsala University, Uppsala, Sweden, [¶]Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden, ^{||}Department of Medicine, Unit of Clinical Immunology and Allergy, Karolinska Institutet and Hospital, Stockholm, Sweden, and ^{**}Sachs's Children's Hospital, Institute of Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

Summary

Introduction There are conflicting data on the association between early exposure to pets and allergic diseases. Bias related to retrospective information on pet ownership has been addressed as a reason for distorted study results.

Objective To elucidate how early exposure to cat and dog relates to IgE-sensitization and asthma in children at 2 and 4 years of age, in a prospective birth-cohort study.

Methods Four thousand and eighty-nine families with children born 1994–1996 in predefined areas of Stockholm answered questionnaires on environmental factors and symptoms of allergic disease at birth, one, two and four years of age. Dust samples collected from the mothers' beds at birth were analysed for Fel d 1 and Can f 1 in a subgroup of the cohort. Blood samples taken at four years from 2614 children were analysed for allergen-specific IgE to common airborne allergens. Risk associations were calculated with a multiple logistic regression model, with adjustment for potential confounders.

Results A correlation was seen between allergen levels and reported exposure to cat and dog. Exposure to cat seemed to increase the risk of cat sensitization, OR (odds ratio) 1.44 (95% confidence interval 1.03–2.01), whereas dog exposure did not have any effect on dog sensitization, OR 1.16 (0.79–1.72). Dog ownership was related to a reduced risk of sensitization to other airborne allergens, OR 0.36 (0.15–0.83), and a similar tendency was seen for cat ownership OR 0.63 (0.37–1.07). Early dog ownership seemed to be associated with a lower risk of asthma, OR 0.50 (0.24–1.03), with no corresponding effect after cat ownership, OR 0.88 (0.56–1.38).

Conclusion Early exposure to cat seems to increase the risk of sensitization to cat but not of asthma at 4 years of age. Dog ownership, on the other hand, appears to be associated with lowered risk of sensitization to airborne allergens and asthma. Both aetiological relationships and selection effects have to be considered in the interpretation of these findings.

Keywords allergens, allergy and immunology, animals, asthma, cats, child, dogs, domestic, endotoxins, prevention, primary

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Introduction

The theoretical paradigm that allergen exposure induces sensitization, and that continued exposure leads to clinical asthma, has recently been questioned [1]. Pets in the household, particularly cats, have been extensively studied and found – variously – to both decrease and increase the risk of sensitisation and allergic diseases in childhood [2–6]. In the German Multicenter Allergy Study (MAS) study, a dose–response relationship was reported between levels of both cat

and dust mite allergen and subsequent sensitization at 3 years of age, whereas some years later no relation between early exposure to indoor allergens and wheezing was seen [7, 8]. This indicates separate mechanisms for development of childhood asthma and sensitization. Immunologic models have been put forward to explain modified immune responses in atopic and non-atopic individuals [9, 10]. Concurrently, indirect exposure to cat has been shown to worsen asthma in children already sensitized to cat, which implies a need for secondary intervention [11].

Most previous studies have focused on effects of early exposure to cat and house dust mites, whereas exposure to dog has been somewhat overlooked. A few studies have implied that early exposure to dog reduces the risks of wheezing and sensitization [12, 13], and a recent study showed

¹Authors contributed equally to the manuscript.

Correspondence: Catarina Almqvist, MD, PhD, Occupational and Environmental Health, Karolinska Hospital, Norrbacka 3rd floor, S-171 76 Stockholm, Sweden. E-mail: catarina.almqvist@kbh.ki.se

two or more dogs or cats in childhood to reduce sensitization [14]. To our knowledge, no study with prospective design has examined whether early direct and indirect exposure to cat and dog contributes to different risks for sensitization and allergic disease. The aim of this study was to elucidate the pattern of allergen-specific IgE sensitization and asthma after early exposure to cat or dog in a large prospective birth cohort (BAMSE).

Methods

Study population and questionnaire data

From February 1994 until November 1996, 4089 new-born infants (2065 boys and 2024 girls) were included in a prospective study. This study base comprised 75% of all eligible children born in predefined areas of Stockholm who fulfilled the inclusion criteria. Study design, enrolment, criteria for inclusion and the data collection procedure are described in detail elsewhere [15]. Data on allergic heredity, pet exposure, detailed residential characteristics and socio-economic factors were requested in questionnaires filled out by the parents when the child was 2 months old (median age). 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, and information on exposure factors.

The response rates for the questionnaires at 1, 2 and 4 years of age were 96%, 94% and 91%, respectively. Heredity for allergic disease was defined as doctor-diagnosed asthma and/or hayfever in combination with allergy to furred pets or pollens in one (single heredity) or both parents (double heredity). Early exposure to pets was reported in the first questionnaire either as keeping of cat or dog at home (direct exposure), or regular contact with relatives with a cat or dog at home (indirect exposure). Asthma at two years of age was defined as >3 episodes of wheezing between 3 months and 2 years of age combined either with inhaled steroids or signs of hyper-reactivity (wheezing or severe coughing at exaltation and cold weather, or disturbed coughing at night) without ongoing cold. Asthma at 4 years of age was defined as >3 episodes of wheezing over the last year, or ≥ 1 episode if the child had been given inhaled steroids. These definitions of asthma are slightly modified from the International Study of Asthma and Allergic disease in Childhood (ISAAC) questionnaires in combination with 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 [16, 17]. Socio-economic index was measured by the Nordic standard occupational classification and Swedish socio-economic classification [18].

Dust samples

In order to evaluate questionnaire data on exposure to pets, 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 for cat (Fel d 1) and dog (Can f 1) allergen content. The dust samples had been collected at the time of the first

questionnaire when the children were about two months of age. The parents were asked to vacuum the mattress of the mother's bed with their own vacuum cleaner for 2.5 min in a standardized way. They were requested not to change sheets for 14 days before collection. A small disposable filter bag (Allergy Control Products Inc., Ridgefield CT, USA) was inserted at the front hose of the vacuum cleaner, before attachment of a nozzle for vacuuming textiles. After collection, the filter bags were sealed in plastic bags and stored at -20°C until extracted, and Fel d 1 and Can f 1 levels were measured as described earlier [19]. Allergen concentrations were expressed as $\mu\text{g/g}$ dust. Dust samples with Fel d 1 levels below the detection limit ($0.055 \mu\text{g/g}$) were assigned a value of $0.054 \mu\text{g/g}$, and Can f 1 levels below detection limit ($0.200 \mu\text{g/g}$) were assigned $0.199 \mu\text{g/g}$ for statistical analysis.

Clinical examination and allergen-specific IgE

At 4 years of age, the children were invited to a clinical examination for blood sampling and lung function test. 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 $\geq 0.35 \text{ kU/L}$ and sensitization as at least one positive CAP.

Statistical analyses

To identify potential confounders we ran several models with a number of covariates, and our final model was based on a combination of the strength of association with the outcome, clinical relevance and confounding of the association between exposure to furred pets and the outcome. Early exposure 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'. In addition, 'no exposure' was compared to 'any exposure', including indirect exposure and ownership. The relationship between the health outcomes and exposure to cat or dog was analysed with multivariate logistic regression and the results are presented as adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). Heredity, gender, maternal smoking, mother's age and socio-economic index were identified as confounders. 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 3729 children for analyses at 2 years and 3596 (88% of the original study base) for analyses at 4 years of age. A total of 2614 children agreed to let blood samples be drawn at the examination, of whom 2573 (63% of the study base) had complete data on the questionnaires.

Median levels and inter-quartile range (IQR) are presented for cat Fel d 1 and dog Can f 1 allergen. Due to the skewed distribution of allergen levels with many samples below detection limit, a non-parametric test (Mann-Whitney) was performed to compare the groups with and without reported cat or dog ownership in the questionnaires. The association

between levels of allergen-specific IgE to cat or dog and levels of cat or dog allergen in dust samples from the home was estimated with linear regression.

All analyses were performed with the statistical software program Stata 7.0 (Stata, College Station, TX, USA).

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

Results

Pet ownership and allergen levels

Cat ownership at the median age of two months was reported by 10.0% of the families, dog ownership by 5.2%, and <1% (34 families) kept both a cat and a dog. Among those without a cat or a dog at home, approximately one in three reported cat or dog at relatives that the child regularly met (indirect exposure).

Questionnaire data on exposure to cat and dog were consistent with the allergen levels in the dust samples. The median levels of Fel d 1 in homes with a cat were significantly higher than in homes with indirect exposure to cat, where the levels were significantly higher than in homes without any reported contact with cats (Fig. 1). Corresponding result was obtained for exposure to dog and levels of Can f 1.

Sensitization and wheezing

Fifteen percent (392) of the children were positive in Phadiatop[®] at 4 years of age. Eleven percent had IgE antibodies to birch or timothy, 5.9% to cat and 4.5% to dog. Background variables in the whole group and among those who did or did not consent to blood samples being drawn are illustrated in Table 1, along with those who had asthma and were positive in Phadiatop[®] at 4 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. An increased prevalence of asthma was seen among children with

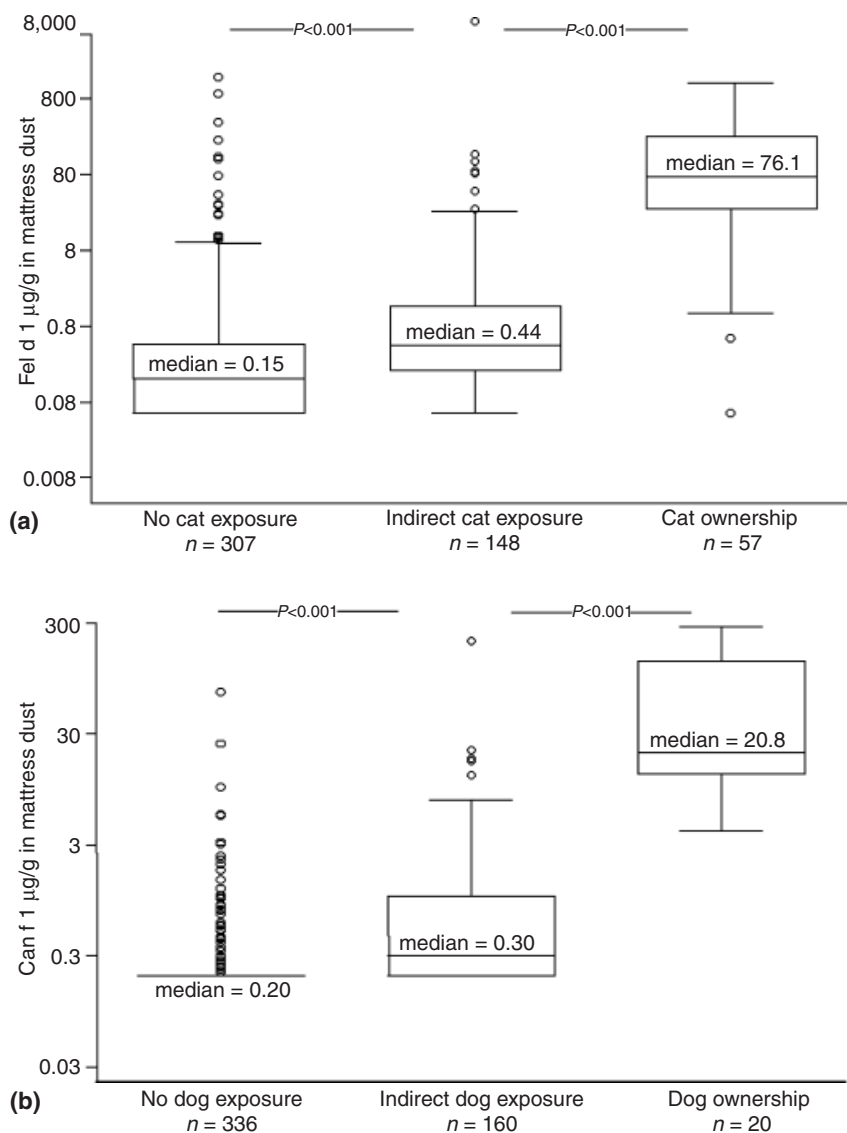


Fig. 1. (a) Questionnaire data on cat exposure and levels of cat allergen Fel d 1 in dust samples in the BAMSE cohort study. (b) Questionnaire data on dog exposure and levels of dog allergen Can f 1 in dust samples in the BAMSE cohort study.

Table 1. Distribution of background factors among children 4 years of age in the BAMSE cohort; the whole study group (3596) was subdivided into those with asthma, the group who consented to giving blood samples (2573) subdivided into those with positive Phadiatop[®], and the group who did not give consent to blood samples (1023)

	Total		Asthma at 4 years		Total blood samples		Positive Phadiatop [®]		No blood samples	
	N	N %	n	n %	N	N %	n	n %	N	N %
Gender										
Boy	1821	50.6	155	8.5	1313	51.0	240	18.3	508	49.7
Girl	1775	49.4	95	5.4	1260	49.0	152	12.1	515	50.3
Heredity*										
None	2526	70.2	135	5.4	1786	69.4	226	12.7	740	72.3
Single	958	26.7	96	10.0	709	27.6	135	19.0	249	24.3
Double	112	3.1	19	17.0	78	3.0	31	39.7	34	3.3
Mothers age >25										
No	262	7.3	41	15.7	191	7.4	37	19.4	71	6.9
Yes	3334	92.7	209	6.3	2382	92.6	355	14.9	952	93.1
Maternal smoking										
No	3121	86.8	202	6.5	2237	86.9	336	15.0	884	86.4
Yes	475	13.2	48	10.1	336	13.1	56	16.7	139	13.6
SEI†										
Blue collar	622	17.3	64	10.3	433	16.8	73	16.9	189	18.5
White collar	1550	43.1	115	7.4	1144	44.5	179	15.7	406	36.7
Management/self-employed	1424	39.6	71	5.0	996	38.7	140	14.1	428	41.8
Cat‡										
No exposure	2122	59.0	150	7.1	1517	58.9	234	15.4	605	59.1
Indirect exposure	1114	31.0	75	6.7	797	31.0	123	15.4	317	31.0
Ownership	360	10.0	25	6.9	259	10.1	35	13.5	101	9.9
Dog‡										
No exposure	2321	64.5	158	6.8	1663	64.6	261	15.7	658	64.3
Indirect exposure	1088	30.3	84	7.7	782	30.4	121	15.5	306	29.9
Ownership	187	5.2	8	4.3	128	5.0	10	7.8	59	5.8

*Heredity for allergic disease defined as doctor-diagnosed asthma and/or hay fever in combination with allergy to pets or pollens in one (single) or both (double heredity) parents. †SEI = socio-economic index. ‡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.

heredity for allergic diseases and those with young or smoking mothers. There was a clear association between sensitization and asthma at 4 years of age; 67 of the 197 children with asthma at 4 years of age were sensitized to at least one of the inhalant allergens tested, OR 3.2 (95% CI 2.3–4.4), $P < 0.001$. On the other hand, 82% of the sensitized children did not report any asthma. Sufficient statistical power was not achieved to permit analysis of associations between levels of allergen-specific IgE to cat or dog and the levels of cat or dog allergen at home. Only for 21 individuals with allergen-specific IgE to cat did we also have analysed allergen levels.

Early exposure to cat and outcome

Early indirect exposure to cat gave increased odds of sensitization specifically to cat, whereas the risk of sensitization to airborne allergens other than cat was reduced. The same trend, albeit not significant, was seen among children with cat at home (Table 2). When groups with direct and indirect exposure to cat were combined, an increased risk of sensitization to cat was seen. Reported direct or indirect cat

exposure at 2 months of age did not significantly influence the prevalence of asthma at 2 or 4 years of age (Table 3).

Early exposure to dog and outcome

Among those reporting dog ownership at the median age of two months, only 10 children out of 128 were sensitized to any of the airborne allergens tested at the age of four, OR adj. 0.43 (95% CI 0.22–0.84). This pattern did not change when a cut-off point for sensitization of 0.7 kU/L was applied. Table 2 illustrates how early dog ownership did not significantly affect sensitization to dog, whereas the risk of sensitization to airborne allergens other than dog was clearly reduced. This reduced risk of sensitization to other airborne allergens after exposure to cat or dog was shown for birch, OR adj. 0.62 (95% CI 0.40–0.98) and timothy, OR adj. 0.56 (95% CI 0.31–1.00). Keeping of dog at two months of age tended to reduce the prevalence of asthma, particularly at 4 years of age (Table 3).

Heredity

Sensitization was reduced in children without heredity for allergic diseases, whose families owned a dog when the child was born (Table 4). For cat the results appeared less

Table 2. Early exposure* to cat and dog in relation to sensitization to cat or dog at 4 years of age in a cohort study, BAMSE

	Sensitization to cat				Sensitization to airborne allergens other than cat		
	<i>N</i>	<i>n</i>	OR‡	(95% CI)	<i>n</i>	OR‡	(95% CI)
Cat							
No exposure†	1517	74	1		160	1	
Any exposure	1056	77	1.44	(1.03–2.01)	81	0.71	(0.53–0.94)
Indirect exposure	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)
Dog							
No exposure†	1663	92	1		–		
Any exposure	910	59	1.08	(0.76–1.53)			
Indirect exposure	782	55	1.20	(0.84–1.71)			
Ownership	128	4	0.45	(0.16–1.27)			

	Sensitization to dog				Sensitization to airborne allergens other than dog		
	<i>N</i>	<i>n</i>	OR‡	(95% CI)	<i>n</i>	OR‡	(95% CI)
Cat							
No exposure†	1517	65	1		–		
Any exposure	1056	51	1.07	(0.73–1.58)			
Indirect exposure	797	40	1.09	(0.72–1.65)			
Ownership	259	11	1.00	(0.51–1.97)			
Dog							
No exposure†	1663	69	1		192	1	
Any exposure	910	47	1.16	(0.79–1.72)	84	0.76	(0.58–1.01)
Indirect exposure	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)

*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, socio-economic index.

Table 3. Early exposure* to cat and dog in relation to asthma at 2 and 4 years of age in a cohort study, BAMSE

	Asthma at 2 years				Asthma at 4 years			
	<i>N</i>	<i>n</i>	OR‡	(95% CI)	<i>N</i>	<i>n</i>	OR‡	(95% CI)
Cat								
No exposure†	2207	188	1		2122	150	1	
Any exposure	1522	129	0.92	(0.72–1.17)	1474	100	0.86	(0.66–1.13)
Indirect exposure	1146	98	0.93	(0.72–1.21)	1114	75	0.86	(0.64–1.15)
Ownership	376	31	0.87	(0.58–1.30)	360	25	0.88	(0.56–1.38)
Dog								
No exposure†	2423	195	1		2321	158	1	
Any exposure	1306	122	1.09	(0.85–1.39)	1275	92	0.95	(0.72–1.25)
Indirect exposure	1113	106	1.13	(0.88–1.46)	1088	84	1.03	(0.78–1.37)
Ownership	193	16	0.87	(0.51–1.49)	187	8	0.50	(0.24–1.03)

*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, socio-economic index.

consistent, with no clear influence of exposure on sensitization in those with and without allergic heredity.

Discussion

Our main finding in this prospective birth cohort is that there seems to be a difference in the pattern of IgE-sensitization after early exposure to cat and dog. Early cat exposure

appears to increase the risk of sensitization to cat, whereas exposure to dog has no such effect. Dog ownership early in life, on the other hand, seems to lower the risk of sensitization to pollen allergens at 4 years of age. This has been implied in previous studies and may be explained either by a co-variation between dog ownership and lower risks of sensitization due to selection, or an immune response evoked by dog ownership with an effect on sensitisation [14, 20, 21]. Clinically, cat exposure seems to elicit more severe symptoms

Table 4. Early exposure* to cat and dog in relation to sensitization stratified for heredity, at 4 years of age in a cohort study, BAMSE

		No heredity			Single/Double heredity		
	<i>N</i>	<i>n</i>	OR‡	(95% CI)	<i>n</i>	OR‡	(95% CI)
Cat							
No exposure‡	1519	136	1		99	1	
Indirect exposure	800	67	0.95	(0.70–1.31)	56	0.95	(0.66–1.38)
Ownership	259	23	0.75	(0.47–1.20)	12	1.33	(0.65–2.71)
Dog							
No exposure‡	1667	153	1		109	1	
Indirect exposure	783	67	0.98	(0.72–1.34)	54	0.90	(0.62–1.30)
Ownership	128	6	0.43	(0.18–1.00)	4	0.40	(0.14–1.15)
Cat or dog							
No exposure‡	1055	103	1		68	1	
Indirect exposure	1158	94	0.87	(0.64–1.17)	83	0.88	(0.61–1.27)
Ownership	365	29	0.64	(0.41–0.99)	16	0.84	(0.45–1.57)

*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, maternal smoking, maternal age, socio-economic index.

than dog, but we have not found any previous report on differences in sensitization [22]. A selection of pet ownership based on family history of allergic disease, maternal smoking and socio-economic factors has been shown in this population-based birth cohort [23], and it is possible that parts of our results should be interpreted as selective effects. However, a selection for direct and indirect exposure was particularly strong only for cats, whereas dogs were only avoided in families with parental dermatitis.

The number of cat and dog owners in our study (10% and 5%, respectively) is fairly low, from an international perspective. Despite this, the levels of allergen in homes without cat and dog are in keeping with what has been found in earlier studies from Scandinavia, the UK and the US [24–26], though significantly higher than those reported from Germany [7, 8]. Cat allergen has been shown to be transferred in clothes from homes with cats to homes without cats, which is also illustrated by the intermediate levels of allergen in the group with indirect exposure [27].

The contradictory results of other studies regarding the relationship between exposure and subsequent sensitization have been difficult to interpret. A bell-shaped dose-response curve between cat allergen levels and sensitization, different from the linear association [28], has been implied, with increased risk of sensitization at moderate allergen levels and decreased risk at high allergen levels [10]. The children in our study who were exposed to cats indirectly had allergen levels at home fairly similar to those classed as moderate in a cross-sectional study by Custovic et al. [29], and both studies showed similarly increased risk of sensitization. Nonetheless, our children with cat at home and higher allergen levels still had increased risk of sensitization, which rather implies an absence of dose-response [30]. However, since children in the Stockholm area are not primarily exposed and sensitized to house dust mites (only four children out of 512 had levels of Der p 1 or Der f 1 > 1 µg/g), the pattern of sensitization to cat may be different from that in other parts of the world. Another reason our results differ from those of others [4, 6, 14] might be that because we could identify non-pet-owning

children who reported close contacts with cat or dog outside the home, we were able to distinguish between 'no' and 'any' exposure. Thus we could avoid including exposed children in the reference category, who may otherwise dilute any associations between allergen exposure and health effects. The risk of sensitization to dog allergen appeared slightly increased if a child was indirectly exposed to dog, and decreased if the child had a dog at home. This raises the question whether a dog at home contributes to reduce the risk of allergic disease, an effect that might be owing to exposure to endotoxins or a different life-style possibly combined with more outdoor activities. Endotoxin, an intrinsic part of the outer membrane of gram negative bacteria, may be abundant in house dust particularly in houses with furred pets, and protect against allergen sensitization by enhancing Th1 immunity [31]. In line with this, several studies from rural areas have suggested that endotoxin protects against development of asthma and atopic sensitization [32, 33]. However, why dog ownership should be more protective than keeping of cat remains to be clarified.

Another finding of the study was a trend towards reduced risk of asthma at four years of age following early exposure to dogs. Dog exposure in infancy has previously been shown to reduce wheezing, but without effect on atopy measured as total serum IgE [12]. In our study, however, we have too few individuals in the groups, to be able to evaluate the risk association between exposure to dog and asthma in combination with sensitization. Early cat exposure showed no significant association with asthma at 2 or 4 years of age, despite the increased risk of sensitization to cat.

We have focused on pet exposure at a median age of two months and not made any attempts to adjust for later exposure, because of risks of disease-related misclassification of exposure. This of course gives an uncertainty to the results, as does the relatively few individuals in some groups, particularly those combining pet ownership and heredity for allergy.

It has been implied that the 'protective' effects and the risks of pet ownership can only be studied among individuals

without allergic heredity, since those with heredity will develop allergic disease anyway [13]. Those with heredity for allergic diseases who avoid direct pet exposure may nonetheless be exposed to allergen levels sufficiently high to induce sensitization. Thus, a possible explanation of the reduced risk of pollen sensitization if exposed to cat or dog, is selection mechanisms with parental awareness of their child's predisposition to develop atopic disease and consequent avoidance of exposure to pets, both direct and indirect. To better study the association between early pet exposure and disease, a larger study with randomization of cat and dog owners including families with allergic heredity would have to be performed, but this is difficult to justify ethically.

Thus, we conclude that even if early exposure to cat increases the risk of sensitization to cat in this birth cohort, early exposure to cat or dog is not related to an increased risk of asthma at four years. Furthermore, it seems that dog ownership is associated with a decreased risk of pollen sensitization. Whether this is an effect of immune modulation or of selection for pet ownership only, cannot be resolved in our study, which illustrates the complexity of this issue.

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