

Original article

Allergy markers in adults in relation to the timing of pet exposure: the EGEA* study

Background: Studies suggest that early childhood exposure to pets may protect from the development of atopy, but limited information is available on adults. The association of allergy markers in adulthood with current and childhood exposure to pets was studied considering retrospectively the window of exposure.

Methods: Immunoglobulin E (IgE), skin prick tests (SPT), eosinophils were related to exposure to pets in 187 adult asthmatic cases and 243 controls from the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) study. Analyses were redone after exclusion of subjects who removed pets or experienced symptoms to animals to take into account selection in that retrospective study.

Results: In asthmatic cases, current exposure to pets was unrelated to SPT positivity (+), whereas childhood exposure was significantly related to less SPT+ to any allergen, and to cat in particular, with an association restricted to those exposed before 2 years of age [OR = 0.30 (CI 0.12–0.76)]. Considering the relative timing of exposure in relation to asthma onset showed that the protective effect of exposure to pets occurs for pet exposure starting before asthma onset [OR for SPT+ = 0.19 (CI 0.08–0.48)].

Conclusion: Results support the hypothesis that exposure to pets in early life, and in particular before asthma onset, may protect against allergen sensitization in adulthood.

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Changes in environmental factors have been proposed to explain the increase in the prevalence of asthma and allergy observed in the last decades in developed countries (1). Among them are the changes in lifestyle, such as increase in indoor exposure to allergens, which is a known risk factor for the development of allergic diseases. Furred pets, cats in particular, are an important source of allergens aggravating asthmatic symptoms (2), and are responsible for acute asthma attacks (3) and asthma severity in those with established disease (4). However, pets may have either a deleterious or a protective role on allergy in relation to the timing of exposure. Recent prospective studies conducted in children have provided strong evidence that exposure to cats and dogs in infancy has a protective role on allergic symptoms or sensitization till late childhood (5–9). Two hypotheses have been proposed to explain that protective effect on allergy. First, exposure to pets, like exposure to farm animals, through exposure to endotoxin (10) may favour the maturation of the immunological system towards the Th1 pathway, protecting from the Th2 pro allergic profile (11–12). More recently, another hypothesis

has been proposed, according to which high exposure to an allergen might protect from sensitization to that allergen through a modified Th2 response (13). An animal model further suggested that the relative window of exposure towards specific events, such as sensitization, may be crucial (14). In that model, exposure to endotoxin before or simultaneously to allergen exposure favours a Th1 pattern (14).

Limited information is available on adults, with the notable exception of the European Community Respiratory Health Survey (ECRHS) conducted in young adults in which an inverse relation between childhood exposure to cat and sensitization to cat in later life was evidenced (15). Negative associations may be related to selection bias, i.e. those allergic to cat remove cats, which leads to a negative association. Nevertheless, the protective effect of childhood cat remained after stratification on respiratory symptoms in the presence of animals, in individuals from family history of allergy (15). A similar pattern was observed for dog (16) independent of parental history of allergy.

The aims of the study were to investigate the associations of current and past exposure to cat and dog with allergy phenotypes [skin prick test (SPT) response, total Immunoglobulin E (IgE), specific IgE and eosinophilia] in adult asthmatic cases recruited in chest clinics and

*See Appendix for the EGEA Cooperative group.

nonasthmatic controls from the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) and to examine whether the occurrence of pet exposure before or after asthma onset influences allergy phenotypes in adulthood.

Material and methods

Subjects

The EGEA study combines a case-control study and a family study. The detailed protocol has been described elsewhere (17). Briefly, asthmatic probands were recruited in chest clinics from six clinical centres. Inclusion criteria were place of birth, area of residence, age, familial structure and a positive answer to four standardized questions based on international questionnaires (*Have you ever had attacks of breathlessness at rest with wheezing? Have you ever had asthma attacks? Was this diagnosis confirmed by a physician? Have you ever had an asthma attack in the last 12 months?*). Adult controls were recruited through electoral rolls ($n = 208$), surgery departments ($n = 26$) and social security check-up centre ($n = 76$). Comparability of cases and controls and descriptive results have been previously reported. Most of the present analysis concerns the 187 adult ($=18$ years of age) asthmatic cases with data on IgE and Phadiatop. Some results are also presented for the 243 nonasthmatic controls.

Methods

Subjects answered a detailed questionnaire on indoor characteristics of households with questions relating to current or past exposure to domestic animals (type of animals, if it was allowed into the bedroom, number of years of exposure, age at start of exposure). Exposure to cat or dog in childhood was classified into three groups according to the window of exposure to cat or dog in childhood: (i) individuals who did not keep a cat or a dog before 16 years of age, (ii) those who owned a cat or a dog before 2 years of age, (iii) the remainders who started owning a cat at or after 2 years and before 16 years of age. Current exposure was defined as owning a cat or a dog at the time of the survey. In this paper the word pet means cat and/or dog. Triggers of asthma attacks, in particular to animals and, more generally, questions regarding symptoms (in the last year) occurring in the presence of animals (cough, sneezes, runny nose, wheeze, shortness of breath, watering or itchy eyes) were recorded.

Total IgE were measured by radioimmunoassay (Pharmacia diagnostics, AB, Guyancourt, France). Samples were tested for circulating specific IgE to common aeroallergens (pollens, house dust mites, moulds, animal epithelia) using the Phadiatop® (Pharmacia diagnostics, AB). SPT to cat, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, *Alternaria tenuis*, timothy grass, olive, birch, *Parietaria judaica*, ragweed, *Aspergillus* and *Blattella germanica* were performed. Atopy was defined as having a positive skin test (≥ 3 mm than the control) to any of the 11 allergens. Eosinophilia was determined as both a percentage greater than 5% and a number greater than 300/mm³.

Statistical analysis

Due to the retrospective nature of the study, special attention was given to the analysis of correlates of potential selection bias, according to methods well established for the healthy worker effect (18), reflecting here animal avoidance among the available data. A short total duration of exposure (<5 years), and reported symptoms in presence of animals were considered. To assess the

consistency of various answers, the Kappa coefficient was used for studying the agreement between symptoms in presence of animals and asthma triggers.

Then the analysis of the associations of pets' exposure to allergy markers was conducted in several steps. First, the analysis of current exposure and past exposure to pets in relation to SPT response to any allergen, and specifically to cat allergen, Phadiatop and eosinophilia was conducted through logistic regression models including age and sex. Similar analyses on total IgE were performed by linear regression of log 10 (IgE) using IgE score corrected for age, sex and smoking (17) based on the regression in the EGEA control group. In asthmatics, analyses were then performed to refine the information on the window of childhood exposure considering first the windows defined in absolute terms (early = starting before or at 2 years of age, late = starting after 2 years of age). Finally, the relative window of exposure was studied by considering those for whom exposure to pet started before or after the age of asthma onset. Taking into account correlates of potential animal avoidance was performed for the analysis based on windows of childhood exposure. Results were unchanged after removal of nearly half of the subjects (see below). That part of the analysis could not be performed when considering the relative window of exposure because of small numbers.

Results

Characteristics of the study sample

As expected, asthmatic cases had significantly higher IgE levels, and more often atopy, positive Phadiatop, and

Table 1. Description of the study sample

	Asthmatic cases ($n = 187$)	Nonasthmatic controls ($n = 243$)	<i>P</i>
Men (%)	51.3	49.0	
Age, mean $\pm$ SD	39.8 $\pm$ 13.4	42.1 $\pm$ 12.7	
Allergy markers			
SPT+, any of 11 allergens, %	68.7	30.9	**
Cat +, %	26.3	6.4	**
Phadiatop, %	70.1	21.0	**
IgE, GM, IU/ml (95% CI)	179 (10–3172)	32 (2–580)	**
Eosinophilia (%eos $>5\%$), %	29.9	7.2	**
Pet (dog or cat) exposure			
Current exposure, %	54.6	39.0	*
Childhood exposure			
No, %	34.8	48.6	
Yes, only after 2 years of age, %	25.5	16.7	
Yes, at or before 2 years of age, %	39.7	34.7	*
Symptoms in the presence of animals			
Cough, %	8.3	0.8	**
Sneezes, %	23.3	3.8	**
Runny nose, %	18.3	2.1	**
Wheeze, %	18.3	0.4	**
Shortness of breath, %	20.0	0.0	**
Watering or itchy eyes, %	20.6	3.4	**
Any symptom, %	40.0	5.0	**
Asthma attacks triggered by animals, %	42.2	—	

* $P \leq 0.01$, ** $P \leq 0.001$.

eosinophilia than nonasthmatic controls (Table 1). Exposure to pets was more frequent in cases than in controls, both for childhood and current exposure, and these associations were unchanged when excluding subjects who lived in the countryside. Among those who had a cat exposure in their life, only 21% of the cases and 25% of the controls had a cat both in their childhood and currently. A similar pattern occurred for dog exposure with figures of 34 and 28%, respectively. Upper, lower or ocular symptoms in the presence of pets were more often reported in cases than in controls (Table 1) and in women than in men [OR = 1.8, CI (0.98–3.26)]. Among cases, 42% reported attacks triggered by animals. These subjects were roughly the same as those who reported any symptom to animals ($\kappa = 0.86$).

Potential selection towards pet ownership

Associations of atopy with pet exposure may be related to selection bias. Atopic subjects might choose not to have a pet or to part with pets, thus modifying the statistical association. Table 2 shows that indeed asthmatic cases with a pet in childhood, but for less than 5 years in their life, had more often positive SPT response, in particular to cat, than subjects with no pets in childhood and even more than subjects who kept pets for more than 5 years. Furthermore, symptoms in the presence of animals were markedly more often reported in those who have had a pet for less than 5 years than in others.

Current exposure to pets

Overall, current exposure was unrelated to IgE, SPT and Phadiatop. No association was observed with any allergy marker except eosinophilia, which was significantly increased in the exposed, with prevalences of

Table 2. Relationship of atopy and symptoms in the presence of animals according to the duration of exposure to pets in asthmatic cases

	No pets (<i>n</i> = 64)	Yes, duration ≤5 years (<i>n</i> = 13)	Yes, duration >5 years (<i>n</i> = 107)	<i>P</i> overall
Allergy markers				
SPT+, any of 11 allergens, %	83.9	76.9	57.4	0.002
Phadiatop+, %	79.7	92.3	61.7	0.009
Cat SPT+, %	30.7	53.9	18.8	0.01
Cat wheal size, mm (all subjects)	1.82	4.08	1.05	0.003
Cat wheal size, mm (Cat+)	5.58	6.79	4.95	0.21
Symptoms in the presence of animals				
Cough, %	3.2	30.8	8.9	0.005
Sneezes, %	22.2	53.9	19.8	0.02
Runny nose, %	15.9	53.9	15.8	0.003
Wheeze, %	20.6	46.2	13.9	0.04
Shortness of breath, %	20.6	38.5	16.8	
Watering or itchy eyes, %	25.4	38.5	15.8	0.09
Any symptoms, %	39.7	76.9	35.6	0.02
Asthma attacks triggered by animals, %	40.3	71.4	38.3	0.06

22.5% vs 36.2% in cases and of 4.2% vs 12.1% in controls for unexposed and exposed, respectively. The pattern was similar when considering separately subjects exposed to cat or to dog, except for eosinophilia, where the association was restricted to those with a dog [OR = 2.13 (CI 1.10–4.13) for cases and 3.01 (CI 1.10–8.22) for controls]. Considering eosinophilia based on the count showed that the relation was no longer observed for the cases whereas it persisted for the controls but weaker. Cases with a cat had more often SPT+ to cat, but the difference did not reach statistical significance. Adjustment for age, gender and smoking did not modify the previous associations (Table 3). For controls, current

Table 3. Relationship between current and childhood exposure to pets and allergy markers in asthmatic cases

	SPT+, cat, OR (95% CI)	SPT+, any OR (95% CI)	Phadiatop OR (95% CI)	IgE, GM (IU/ml)	Eos >5% OR (95% CI)
All (<i>n</i> = 187)					
Current exposure					
No	1.00	1.00	1.00	211	1.00
Yes	1.23 (0.61–2.49)	0.89 (0.44–1.82)	1.06 (0.54–2.10)	165	2.14 (1.08–4.28)
Childhood exposure					
No	1.00	1.00	1.00	220	1.00
Yes, only after 2 years of age	1.08 (0.46–2.57)	0.40 (0.14–1.13)	0.93 (0.35–2.51)	185	0.39 (0.14–1.07)
Yes, at or before 2 years of age	0.30 (0.12–0.76)	0.16 (0.06–0.40)	0.33 (0.14–0.74)	165	1.50 (0.70–3.22)
Excluding those with symptoms in presence of animals or short duration of pet ownership† (<i>n</i> = 102)					
No	–‡	1.00	1.00	157	1.00
Yes, pet exposure starting after 2 years of age	–	0.27 (0.07–0.96)	0.38 (0.11–1.27)	134	1.27 (0.33–4.97)
Yes, pet exposure starting before or at 2 years of age	–	0.20 (0.07–0.58)	0.25 (0.09–0.69)	197	2.45 (0.86–6.98)

† <5 years of pet ownership in life among those with a pet in childhood.

‡ Odds ratios (ORs) were not computed as no subject was SPT+ to cat in one cell (see Fig. 1).

Figures are age and gender adjusted ORs for SPT, Phadiatop and eosinophilia and age, gender and smoking adjusted for IgE (see Material and methods).

exposure was not statistically related to allergy markers, but some trend was observed however in the direction of a negative association for SPT+ to cat and Phadiatop [OR = 0.51 (CI 0.16–1.69); OR = 0.60 (CI 0.30–1.20), respectively]. Results were unchanged after taking into account age, gender, smoking, country living and social characteristics such as education level.

Childhood exposure to pets

Childhood exposure to pets before 16 years of age was significantly related to less SPT positivity to any allergen, and Phadiatop positivity. The association with SPT+ to cat exhibited a similar pattern, but the difference was not statistically significant. No difference was observed for total IgE and for eosinophils.

Refining the window of exposure, according to the age at which home exposure to pet started, showed that the difference regarding those without and with childhood exposure was nearly restricted to the group with early (before 2 years of age) exposure (Fig. 1). The pattern was particularly clear for cases, with similar prevalences for those without a pet in childhood and those with a pet between 2 and 16 years of age, whereas those with a pet between birth and 2 years of age had markedly less atopy. A similar trend was observed for total IgE, for which the difference was statistically significant in controls only. In cases, the number of positive SPT responses among those without pet in childhood, those who had a pet after and before 2 years of age were in mean 2.0, 2.3 and 1.2, respectively ($P < 0.01$). Among cases who were SPT positive to cat, cat wheal size means were 4.9, 5.3 and 3.2 mm, respectively ($P = 0.04$). In cases, those with pets before 2 years of age had significantly more eosinophilia,

but this related to dog exposure only. No difference was observed for controls, but there were too few subjects sensitized to cat to be analysed. For positive SPT to any allergen and for positive Phadiatop, odds ratios (ORs) were 0.73 (CI 0.39–1.37) and 0.51 (CI 0.23–1.12), respectively.

Taking into account age, gender, smoking, country living and social characteristics such as education level did not change the previous results and adjusted ORs and means are presented on Table 3. Positive SPT response was markedly decreased in those with a pet before 2 years of age with an OR of 0.16 taking those without pet in childhood as reference. Models with all potential confounders are not given in the tables as they were not convergent, but stratified analyses show that ORs were unchanged. After adjustment, the relationships for eosinophilia remained for current exposure to pets, restricted to dog exposure, an association that disappeared after excluding those who were currently exposed to dog.

Excluding those with short exposure (7.5% of cases and 3.5% of controls), those with any perceived hyper-responsiveness symptom (40% and 5%, respectively) or both (42% and 9%, respectively) confirmed previous findings and showed that the negative associations with SPT response or positive Phadiatop in cases and with IgE in controls remained related to childhood pet ownership, in particular for early exposure (Table 3). The ORs for atopy were unchanged after exclusion of subjects with potential selective removal of animals. The analysis was not performed for cat SPT+ as there remained too few positive subjects. Finally, analyses were performed after exclusion of those with parental history of asthma and results were similar.

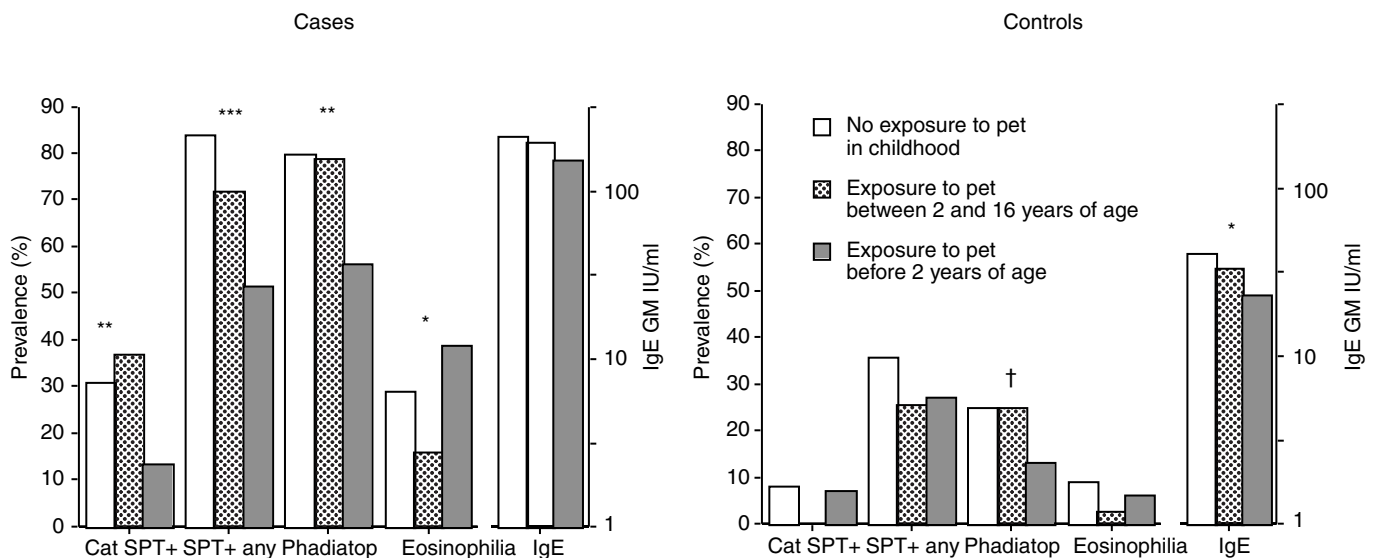


Figure 1. Prevalence of allergy markers according to the timing of exposure to cat or dog. † $P \leq 0.10$, * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, global comparison of exposure in childhood.

Table 4. Relationship between allergy markers and the arrival of pets in childhood before or after the onset of asthma in cases

	<i>n</i>	Cat wheal size mm	SPT+ (any), %	Phadiatop+, %	IgE GM, IU/ml
Asthma without pet (1)	64	1.82	83.9	79.7	220
Pet after asthma onset (2)	23	3.39	86.4	91.3	229
Pet before asthma onset (3)	94	0.99	55.1	58.5	152
Adjusted odds ratio (95% CI)					
(3) vs (2)			0.22 (0.06–0.84)	0.15 (0.03–0.70)	
(3) vs (1)			0.19 (0.08–0.48)	0.36 (0.17–0.80)	
(2) vs (1)			0.82 (0.16–4.34)	2.33 (0.43–12.77)	

Values are age, gender smoking adjusted IgE and age and gender adjusted odds ratios (five individuals excluded due to missing data on asthma age of onset).

Pet exposure before and after asthma onset

The effect of early exposure to pets may relate to the timing of exposure during the lifespan in absolute terms and/or to specific events, such as pre- or post-sensitization or asthma. As shown in Table 4, the prevalence of SPT+ was high and similar in asthmatics without pet and in those whose pet arrived after their asthma onset (83 and 86%, respectively). By contrast, asthmatics who had a pet before their asthma onset had markedly lower positive SPT response (55%). The ORs adjusted for age and gender confirm these findings. The pattern was similar when considering *Dermatophagoides pteronyssinus* positivity instead of positivity to any allergen (percentages were 47, 68 and 32% for those with asthma without pet, pet after and before asthma, respectively). Further stratification according to both age at the arrival of the pet and relative timing towards asthma onset was limited by small numbers. However, there was a consistent pattern showing that it is the relative timing towards asthma onset which plays the major role. In those with a pet at or before 2 years of age, prevalences of SPT+ were 50% vs 80% for those with pets before (*n* = 65) and after (*n* = 5) asthma respectively. In those with pet exposure after 2 years of age, figures were 66 and 87% in those with pet exposure before (*n* = 29) and after (*n* = 16) asthma, respectively. Analyses based on Phadiatop+ gave similar results to those obtained for SPT+. For total IgE and cat wheal size, nonsignificant similar patterns were observed.

Discussion

In this cross-sectional study, a lower prevalence of positive allergy markers was evidenced in adults who were exposed to pets during childhood, and particularly during the first 2 years of life, than in those without such an exposure. Results were unchanged after excluding from the analysis subjects who kept pets for few years or reported symptoms in presence of animals in order to minimize a potential selection bias. Considering then the timing of exposure towards asthma onset, results showed that asthmatics exposed to pets before the onset of their

asthma had less atopy than those exposed after it. When considering both the window of exposure (before 2 years of age) and the relative timing towards asthma onset, the latter seems to play the major role. No relation was observed between allergy markers and current pets' ownership.

The protective effect found in our investigation could be the reflection of the selection bias inherent to cross-sectional studies. To remove such a bias, it would have been necessary to realize a cohort study till adulthood including regular objective measurements of exposure since birth and information about the arrival, the avoidance and removal of pets. So far, the subjects from birth cohorts that have been undertaken were at most adolescents (5, 9, 19). Avoidance of pets by parents from atopic families has been reported (2), but this pattern varies according to various countries. Whereas it has been observed in Sweden (20) and in Finland (21), a Canadian study in postpartum women with or without asthma did not confirm such avoidance (22) and no difference in exposure to the cat or to the dog between the children whose mothers had or did not have history of asthma was observed in United States (19). A strong selection of that type is unlikely in our population, as more asthmatic cases owned a cat or a dog in childhood than controls.

Avoidance of pets for health reasons may represent a bias similar to that occurring in hiring unhealthy subjects at exposed work places. Removal of pets for health reasons may represent a bias similar to that related to changes from exposed work places. Extensive literature has addressed issues related to the healthy worker effect and methods to take such biases into account have been described (18). When longitudinal information is not available, detailed study of correlates of changes of exposure due to health is warranted. Consideration of external reference of exposure is also useful. Short stay at exposed workplaces/life with pets and reported symptoms at work/in presence of pets are useful items to consider. Indeed, the subjects who removed very quickly their animals were more often atopic than those who kept their cat longer. In our study, information about the reason for not having or removing pets was not available, but it has been previously shown that respiratory symptoms in presence of animals is a major reason for removal of pets

(23) and information about symptoms in the presence of animals was available.

In the present study, the negative association between early-life exposure and atopy in adulthood remained after exclusion of both a short duration of exposure and/or with perceived symptoms to pets, which represents half of asthmatic cases. Among cases, the strength of the relation of atopy to pet exposure before asthma onset makes unlikely that such association could be explained by a potential recall bias. In controls, results were unchanged when excluding those with parental history of allergy. Similarly, in the ECRHS survey, it was shown that the negative effect of childhood exposure to pet on specific IgE to cat held after stratification on respiratory symptoms to pet or house dust (which includes cat allergens) (15). Furthermore, the ECRHS study provides external reference of exposure to pets in a representative sample of the general population. In that study, 50% of the subjects from the French centres reported to have an animal in childhood, a figure very similar to the 55% of the asthmatic cases in the EGEA study.

No association between current exposure to pets and atopy, Phadiatop and total IgE was observed. Current exposure to cat was unrelated to cat sensitization, whereas a positive association was observed in the population-based ECRHS study (15), but the selection of subjects in the two surveys was different. The association of eosinophilia with current exposure to dog observed in the present study may be related to parasites in dogs (24).

In children, a protective effect on atopy of owning a pet in early childhood has been reported (5, 6), but longitudinal information is available only till adolescence (8, 9). Results from a follow-up study in the general population have shown that children exposed to cat, but not to dog, had less atopy to cat till 12–13 years (5). Recent observations showed that children exposed to dog, but not to cat, had less asthma-like symptoms till 12 years, but no association was observed for atopy (7). Even in a sample of high-risk children a negative association was indicated between pets in infancy and Phadiatop but not with skin sensitivity at 7 years (25). However, other studies conducted in the general population (26) or in asthmatics (27) did not confirm these associations.

In adults, few reports have addressed the association of childhood exposure to adult allergy. A clinical study on 200 asthmatics showed no association of exposure to cat or dog and skin reactivity to animals, but there was no distinction between current and childhood exposure (27). Analyses conducted in 13 000 adults 20–44 years from the ECRHS showed that atopy (defined by specific IgE to grass, house dust mite or cat) was negatively related to dog ownership in childhood [OR = 0.85 (CI 0.78–0.92)] and in a lesser extent to cat ownership in childhood (association of borderline significance) (16). Parental allergy did not modify the relation, which suggests that selection bias unlikely explains the association, as such families were more likely to remove pets for health

reasons. A separate analysis on specific IgE to cat showed a significant protective effect of cat ownership in childhood in families with a history of atopy [OR = 0.77 (CI 0.63–0.94)] (15). Our observations of a clear pattern in asthmatic cases and a weak signal in controls fit with findings of the ECRHS study. The strength of the associations in the ECRHS survey was markedly lower than in the present study but there was no distinction between early and late childhood exposure. Designs such as the ECRHS survey in the general population and such as ours with a substantial number of clinically based asthmatics provide complementary information.

The association of a long duration of exposure to pets since early childhood with less atopy may be explain by tolerant immune response. Recently, Platts-Mills et al. showed that children exposed to a high dose of cat allergen presented an increase production of specific IgG to cat including IgG4 rather than IgE (13). In agreement with the hypothesis that high exposure to animals may be beneficial is the report of a decrease in the severity of skin test reactivity to animals in relation to the intensity of exposure (9, 27). Our results are consistent with the hypothesis that early and prolonged exposure to specific allergens may induce the production of specific IgG4 to these allergens and to develop a tolerant immune response. It would have been of interest to have information on the level of bacterial antigens, endotoxin or pet allergen exposure, which could have allowed to quantify the various exposures.

The lowest rate of SPT positivity to any allergen was observed in asthmatics who were exposed to pets before the onset of their asthma fits with the hypothesis of the importance of relative timing. In the present study, the onset of sensitization was unknown, which precludes testing in humans the hypothesis originating from the animal model described by Tulic et al. (14). However, an analysis according to the onset of asthma in childhood was performed, which often is concomitant or posterior to sensitization. An animal model has already suggested that the relative timing of exposure to endotoxins and to allergens may be of particular importance for the determination of a protective or deleterious effect (14). Exposure to bacterial LPS before or few days after sensitization blocked in rats the production of specific IgE and increased the level of specific IgG. Conversely, exposure to LPS a long time after sensitization decreased specific-IgG level and increased specific IgE (14). These findings are supported by the observations of Gereda et al. who followed infants at high risk of asthma from 9 to 24 months of age. They showed that chronic exposure to house dust endotoxin induced a Th1 response (assessed by the production of IFN- γ) associated with a decrease in sensitization to various house dust allergens (28). Exposure to LPS and house dust allergens were concomitant in that study.

In conclusion, our observations are consistent with a protective role of early and prolonged exposure to pet on

atopy in adulthood. Mechanisms involved in the interplay of pets with allergy are not clearly known and may involve an influence upon the immunological maturation in early life, and later a tolerant immune response. Before taking any public health recommendation, specific studies regarding intervention (beneficial or deleterious effect of removing pets from nonsensitized asthmatic families) need to be undertaken (29). Further long-term longitudinal surveys with repeated evaluation of exposure to pets and atopic status over the lifespan could clarify the relative timing of events.

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Appendix

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References

- PATINO CM, MARTINEZ FD. Interaction between genes and environment in the development of asthma. *Allergy* 2001;**56**:279–286.
- APELBERG BJ, AOKI Y, JAAKKOLA JJ. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol* 2001;**107**:455–460.
- INGRAM JM, SPORIK R, ROSE G, HON-SINGER R, CHAPMAN MD, PLATTS-MILLS TAE. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens to sensitization and asthma among children living in Los Alamos, New Mexico. *J Allergy Clin Immunol* 1995;**96**:449–456.
- POLLART SM, CHAPMAN MD, FIOCCO GP, ROSE G, PLATTS-MILLS TA. Epidemiology of acute asthma, IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. *J Allergy Clin Immunol* 1989;**83**:875–882.
- HESSELMAR B, ÅBERG N, ÅBERG B, ERIKSSON B, BJÖRKSTÉN B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999;**29**:611–17.
- WIJGA A, SMIT HA, BRUNEKREEF B, GERRITSEN J, KERKHOF M, KOOPMAN LP et al. Are children at high familial risk of developing allergy born into a low risk environment? The PIAMA Birth Cohort Study. *Clin Exp Allergy* 2001;**31**:576–581.
- REMES ST, CASTRO-RODRIGUEZ JA, HOLBERG CJ, MARTINEZ FD, WRIGHT AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;**108**:509–515.
- PERZANOWSKI MS, RONMARK E, PLATTS-MILLS TA, LUNDBACK B. Effect of cat and dog ownership on sensitization and development of asthma among preteen-age children. *Am J Respir Crit Care Med* 2002;**166**:696–702.
- OWNBY DR, JOHNSON CC, PETERSON EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002;**288**:963–972.
- ENRIQUEZ C, NWACHUKU N, GERBA CP. Direct exposure to animal enteric pathogens. *Reviews on Environmental Health* 2001;**16**:117–131.
- LIU AH. Endotoxin exposure in allergy and asthma: reconciling a paradox. *J Allergy Clin Immunol* 2002;**109**:379–392.
- KAUFFMANN F, ORYSZCZYN MP, MACCARIO J. Protective role of country living on SPT, IgE and asthma in adults from the EGEA study. *Clin Exp Allergy* 2001;**32**:379–386.
- PLATTS-MILLS T, VAUGHAN J, SQUILLACE S, WOODFOLK J, SPORIK R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross sectional study. *Lancet* 2001;**357**:752–756.
- TULIC MK, WALE JL, HOLT PG, SLY PD. Modification of the inflammatory response to allergen challenge after exposure to bacterial lipopolysaccharide. *Am J Respir Cell Mol Biol* 2000;**22**:604–612.
- ROOST HP, KUNZLI N, SCHINDLER C, JARVIS D, CHINN S, PERRUCHOU AP. Role of current and childhood exposure to cat and atopic sensitization. *European Community Respiratory Health Survey*. *J Allergy Clin Immunol* 1999;**104**:941–947.
- SVANES C, JARVIS D, CHINN S, BURNEY P. Childhood environment and adult atopy: results from the European Community respiratory health survey. *J Allergy Clin Immunol* 1999;**103**:415–420.
- ORYSZCZYN MP, ANNESI-MAESANO I, CHARPIN D, PATY E, MACCARIO J, KAUFFMANN F. Relationships of active and passive smoking to total IgE in adults of EGEA-(Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy). *Am J Respir Crit Care Med* 2000;**161**:1241–6.
- EISEN EA. Healthy worker effect in morbidity studies. *Med Lav* 1995;**86**:125–138.
- CELEDON JC, LITONJUA AA, RYAN L, PLATTS-MILLS T, WEISS ST, GOLD DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. *Lancet* 2002;**360**:781–782.

20. ALMQVIST C, EGMAR AC, VAN HAGE-HAMSTEN M, BERGLIND N, PERSHAGEN G, NORDVALL SL et al. Heredity, pet ownership, and confounding control in a population-based birth cohort. *J Allergy Clin Immunol* 2003;**111**:800–806.
21. JAAKKOLA JJ, JAAKKOLA N, PIIPARI R, JAAKKOLA MS. Pets, parental atopy, and asthma in adults. *J Allergy Clin Immunol* 2002;**109**:784–788.
22. JOYCE DP, CHAPMAN KR, BALTER M, KESTEN S. Asthma and allergy avoidance knowledge and behavior in post-partum women. *Ann Allergy Asthma Immunol* 1997;**79**:35–42.
23. BRUNEKREEF B, GROOT B, HOEK G. Pets, allergy and respiratory symptoms in children. *Int J Epidemiol* 1992;**21**:338–342.
24. JUCKETT G. Pets and Parasites. *Am Fam Physician* 1997;**56**:1763–1774.
25. BURR ML, MERRETT TG, DUNSTAN FDJ, MAGUIRE MJ. The development of allergy in high-risk children. *Clin Exp Allergy* 1997;**27**:1247–1253.
26. WARNER JA, LITTLE SA, POLLOCK I, LONGBOTTOM JL, WARNER JO. The influence of exposure to house dust mite, cat, pollen and allergens in the homes on primary sensitisation in asthma. *Pediatr Allergy Immunol* 1991;**1**:79–86.
27. DESJARDINS A, BENOIT C, GHEZZO H, L'ARCHEVEQUE J, LEBLANC C, CARTIER A. Exposure to domestic animals and risk of immunologic sensitisation in subjects with asthma. *J Allergy Clin Immunol* 1993;**91**:979–986.
28. GEREDA JE, LEUNG DYM, THAT-AYATIKOM et al. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet* 2000;**355**:1681–1683.
29. MARKS GB. What should we tell allergic families about pets? *J Allergy Clin Immunol* 2001;**103**:500–502.