



Cutaneous and serological responses to cat allergen in adults exposed or not to cats

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KEYWORDS

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Summary *Background:* The relationship between pet ownership and the risk of developing respiratory allergic sensitization to pet allergens is still controversial.

Objective: To determine the degree of cutaneous immediate hypersensitivity and the levels of specific IgE and IgG4 antibodies to cat allergen in cat sensitized patients directly or indirectly exposed to this animal.

Methods: We studied 112 adolescents and adults sensitized to cat allergens (43 with and 69 without a cat at home). There were also 52 control subjects, 27 atopic non-sensitized to cat and 25 non-atopic. The degree of immediate hypersensitivity was assessed by using, in duplicate, skin prick test with four five-fold dilutions of cat hair allergen extract with the content of its major allergen Fel d 1 quantified in micrograms plus positive (10 mg/ml histamine chlorhydrate) and negative (saline solution) controls. The resulting wheal areas were analysed by means of Parallel Line Assay. A blood sample was collected from every patient and control subjects for the evaluation of serological cat specific IgE and IgG4 antibodies.

Results: Patients with cat at home had a lower cutaneous response than patients without this pet. The difference in the skin sensitivity was estimated in 3.4 times ($P < 0.01$). There was no statistical difference between the levels of cat specific IgE antibodies in the two groups of patients ($P = 0.065$). The levels of Fel d 1 specific IgG4 antibodies showed a statistically significant association with the presence of cat at home, with higher levels in patients owing cat at home than in patients without this pet ($P < 0.001$).

Conclusion: The results of this study demonstrate that direct cat exposure in adolescents and adults with respiratory allergy is associated with a lower cutaneous response to cat allergenic extract, assessed by SPT and compared with indirect exposure. In patients with cat at home mean levels of specific IgE are statistically comparable whereas the levels of IgG4 are higher in comparison with subjects not

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exposed to cats. The role of indirect exposure to cat allergens in airways sensitization also in adults is emphasized. Moreover, patients with cat at home show a cutaneous and serological sensitization to cat allergen not higher in comparison with subjects not exposed to cats.

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Introduction

Recent studies have clearly demonstrated a concentration-response relationship between exposure to the allergens of house dust mites and development of allergic sensitization in susceptible individuals.^{1,2} Some studies reported also that inner city children are more likely to become allergic to other indoor allergens such as those produced by cockroach and mouse when they are exposed to increasing amounts of cockroach³ or mouse allergenic materials.^{4,5}

By contrast several studies carried out in rural communities have indicated a lack of association between early contact of children with farm animals and development of respiratory allergy.^{6,7} Although some previous studies have suggested an increased prevalence of specific sensitization in patients exposed to high amounts of cat or dog allergen,^{8–11} there is now consistent evidence that the relationship between exposure to cat/dog allergens in domestic environments and the risk of allergic sensitization to these materials is not linear.^{12–15} Custovic et al.¹⁶ have consistently shown that in adults, the prevalence of sensitization to cat is decreased when patients were exposed to the lowest and highest amounts of cat allergen. In another study the same authors have demonstrated that, in adults, cat ownership was associated with a reduced prevalence of sensitization to cat and dog allergens.¹⁷

This issue is, in general, complex probably because available studies show substantial differences in study design, definition of exposure and outcome, selection mechanisms for pet contact, family history of allergic diseases, socioeconomic factors, etc.^{18–23} Allergen skin sensitization is widely used as a marker of allergy in clinical practice and epidemiological studies. However, the assessment of specific sensitization to pet allergens in exposed/not-exposed patients of available epidemiological studies is usually performed with standard skin prick tests (SPTs), a wheal diameter ≥ 3 mm being considered "positive"^{24,25} and/or by evaluating specific serological IgE antibodies.^{14,26–28} To our knowledge no study has previously investigated the degree of cutaneous response to different dilutions of cat allergenic extract (as assessed by measuring wheal dia-

eters). In theory, it should be expected that patients directly exposed to cat should exhibit stronger cutaneous responses to cat allergen. On the basis of this background the aim of our study was to determine, using an efficient and sensitive SPT method other than the evaluation of IgE and IgG4 antibodies, the degree of immediate hypersensitivity to cat allergens in a selected group of cat sensitized adolescents and adults who had owned the animal for at least 10 years (current and direct exposure) compared with sensitized subjects who had never owned a cat and not were frequently in contact with cats elsewhere (indirect exposure).

Material and methods

Patients

From a population of 1251 subjects living in Naples area who were consecutively evaluated in our Allergy Service from May 1, 2001 to April 30, 2002 for respiratory symptoms of a suspected IgE-mediated aetiology we selected all patients with immediate positive skin reaction to cat allergens. Twenty-seven subjects sensitized to other allergens but not to cat and 25 non-atopic individuals served, respectively, as atopic and negative controls. Among 112 men and women sensitized to cat (and other allergens), 43 owned a cat for an arbitrary period of time (at least 10 years) and 69 had never owned this animal (Fig. 1). An internal questionnaire specifically designed for the study was completed by the same allergists during the screening consultation: the results of SPTs, personal and clinical data, periods of symptoms and characteristics of cat ownership were carefully recorded. All patients gave their informed consent before being submitted to SPTs with cat allergenic extract. Table 1 shows the clinical characteristics of recruited patients. The classification of nasal and bronchial symptoms has been performed according to International Guidelines.^{29,30}

To avoid a possible bias in selection procedure for cat ownership, we excluded 55 cat sensitized patients who declared to refuse cat ownership for personal and/or family history of allergy (Fig. 1).

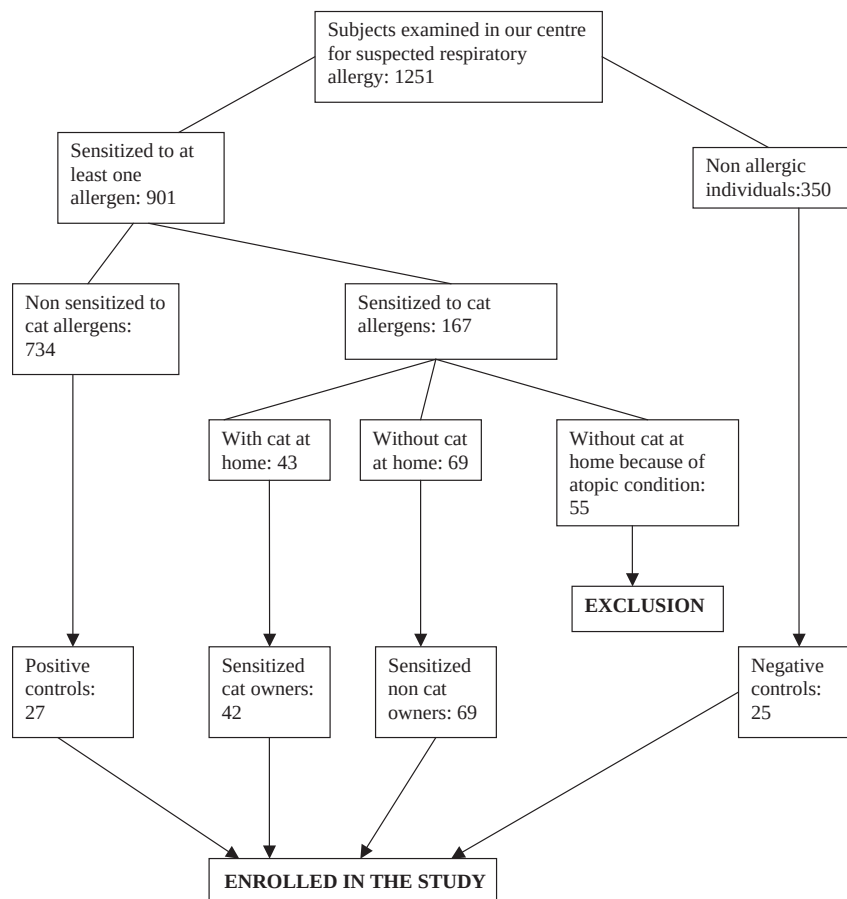


Figure 1 Flow-chart describing modality of patients enrollment.

Patients with a personal exposure to cat allergens (cat at home) from the first months of life were also excluded from the study. In Table 2 inclusion and exclusion criteria are shown.

Allergen extracts

The commercial allergen extracts used for screening SPTs were provided by ALK Abelló Group Milan, Italy. The routine panel of allergens included *Dermatophagoides pteronyssinus* and *D. farinae*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog hair, *Parietaria*, Grass mix, *Artemisia vulgaris*, *Olea europea*, *Betula pendula*, *Cupressus sempervirens* and *Corylus avellana*. These allergens were considered the most frequent causative agents of respiratory allergy in our geographical area. The allergen extracts used for assessing cat sensitization were produced by ALK-Abelló from cat hair. The content of the *Fel d 1* major allergen was assessed by monoclonal antibody (mAb) based RIA.³¹

Skin-prick-tests (SPTs)

SPTs for assessing the degree of immediate hypersensitivity to cat allergen were carried out in duplicate for each of the four five-fold dilutions of a glycerinated *Felis domesticus* allergen extract of with a know content of Fel d 1 at the following concentrations: 70, 14, 2.8 and 0.56 µg/ml. Positive (10mg/ml histamine HCl) and negative (saline solution in glycerin-phenol solution) controls were used in order to demonstrate a normal cutaneous response. The puncture technique was performed by the same operator using metallic disposable sterile lancets ("ALK Lancets") with an 1 mm-long tip. The wheal areas were registered 15 min after the test. The contour of wheals were outlined with a fine-tip rolling black pen and transferred by means of adhesive tape to Case Record Forms (CRF) which contained also all personal and clinical characteristics of enrolled patients. Wheal areas were read by means of a scanner connected to a software for image analysis (Image Master Software, Pharmacia Biotech AB). Double data entry and checking of discrepancies was performed for all

Table 1 Demographic and clinical data of included patients.

	Cat-sensitized			P-value	Controls		P-value*
	Cat at home (n = 43)	Not at home (n = 69)	All (n = 112)		Atopic (n = 27)	Non-atopic (n = 25)	
Age (yr) [†]	30.2 (10.3)	26.7 (12.1)	28.0 (11.5)	0.114 [‡]	38.4 (12.9)	45.0 (15.0)	<0.001 [§]
Duration (yr) [†]	20.5 (11.4)	16.0 (9.3)	17.7 (10.4)	0.023 [‡]	—	—	—
Sex				0.004 [¶]			0.196 [¶]
Male	10 (23.3%)	35 (50.7%)	45 (40.2%)		12 (44.4%)	15 (60.0%)	
Female	33 (76.7%)	34 (49.3%)	67 (59.8%)		15 (55.6%)	10 (40.0%)	
Rhinitis				0.138 [¶]			<0.001 [¶]
Absent	0 (0%)	0 (0%)	0 (0%)		0 (0%)	25 (100%)	
Mild-Interm	0 (0%)	4 (5.8%)	4 (3.6%)		9 (33.3%)	0 (0%)	
Mild-Pers	4 (9.3%)	4 (5.8%)	8 (7.1%)		4 (14.8%)	0 (0%)	
Mod-Sev Int	29 (67.4%)	53 (76.8%)	82 (73.2%)		8 (29.6%)	0 (0%)	
Mod-Sev Pers	10 (23.3%)	8 (11.6%)	18 (16.1%)		6 (22.2%)	0 (0%)	
Asthma				0.401 [¶]			<0.001 [¶]
Absent	14 (32.6%)	33 (47.8%)	47 (42.0%)		11 (40.7%)	24 (96.0%)	
Mild-Interm	9 (20.9%)	14 (20.3%)	23 (20.5%)		5 (18.5%)	0 (0%)	
Mild-Pers	5 (11.6%)	6 (8.7%)	11 (9.8%)		3 (11.1%)	0 (0%)	
Mod-Pers	15 (34.9%)	15 (21.7%)	30 (26.8%)		6 (22.2%)	1 (4.0%)	
Sev Pers	0 (0%)	1 (1.4%)	1 (0.9%)		2 (7.4%)	0 (0%)	
Conjunctivitis				0.770 [¶]			<0.001 [¶]
Absent	4 (9.3%)	9 (13.0%)	13 (11.6%)		7 (26.9%)	25 (100%)	
Mild	28 (65.1%)	38 (55.1%)	66 (58.9%)		13 (50.0%)	0 (0%)	
Moderate	10 (23.3%)	20 (29.0%)	30 (26.8%)		6 (23.1%)	0 (0%)	
Severe	1 (2.3%)	2 (2.9%)	3 (2.7%)		0 (0.0%)	0 (0%)	
IgE (KU/l)**	3.2 (1.1–29.5)	2.7 (1.0–6.9)	2.7 (1.0–9.6)	0.065 ^{††}	0 (0–0)	0 (0–0)	—
IgG4 (AU/l)**	160 (58–665)	22 (1–44)	36 (13–120)	0.000 ^{††}	0 (0–0)	0 (0–0)	—

*Between cat-sensitized, atopic and non-atopic controls.

[†]Mean (sd).[‡]Student *t*-test.[§]ANOVA.[¶]Chi-square test.^{**}Median (interquartile range).^{††}Mann-Whitney test.

clinical data and wheal areas. Descriptive statistics were calculated by means of SPSS Statistical Software after a logarithmic transformation.

Routine SPTs for patient screening were similarly performed. The diameters of the induced wheals were also calculated being considered as positive wheals larger than 3 mm in diameter.³²

Prevalence of cat ownership in Naples area

The prevalence of cat ownership in Naples area was calculated by telephone interviews on a random

sample of 1601 families by simply asking whether they had or not a cat at home. The geographical area where the prevalence of cat ownership has been calculated and where the enrolled patients usually live is the same.

Collection of serum samples

Approximately 4 ml of serum was collected from every patient and atopic/negative control subject and stored at –20 °C.

Table 2 Inclusion and exclusion criteria.

Inclusion criteria

- Aged 14 or older
- A positive SPT (≥ 4 mm wheal diameter) to a commercial available extract of cat.
- Adequate "wash out" from antiallergic medications
- Patients with current and direct cat contact (keeping a cat at home for at least 10 years)
- Only occasional contact with cats (never cat at home and no frequent contact elsewhere)

Exclusion criteria

- Less than 14 years of age
- Pregnant women and patients with infections, neoplastic diseases, metabolic disorders or severe skin diseases
- Patients under psychotropic or other drugs that might interfere with the cutaneous response
- Patients under or who have been under immunotherapy for cat allergens
- Cutaneous hyperreactivity (negative control more than 3 mm diameter) or hyporeactivity (negative skin reaction to histamine)
- Patients keeping a cat at home for less than 10 years.
- Patients not keeping a cat at home but frequently in contact with cats elsewhere
- Patients keeping a dog indoors.
- Patients who refused cat ownership for personal and/or family history of allergy.
- Patients exposed to cat allergens (cat at home) from the first months of life.

Evaluation of cat specific IgE and IgG4 antibodies

Specific IgE to cat extract was determined by the Pharmacia CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden).

Specific IgG₄ to *Fel d 1* was determined by ELISA. Polystyrene 96-well plates (Costar 3590, Corning, NY, USA) were coated for 90 min. at 37 °C with 50 µl of purified *Fel d 1*³³ at 2.5 µg/ml in PBS buffer. The coated wells were blocked with 1% bovine serum albumin (BSA) in PBS, and then incubated for 1 h at room temperature with 50 µl of patient's serum (1/5 dilution). After washing with 0.1% Tween-20 in PBS, wells were incubated for 1 h at room temperature with a 1/1000 dilution of the peroxidase-labelled mAb antihuman IgG₄ HG4T9.³⁴ Plates were washed again, and then developed by incubating with 50 µl of peroxidase substrate buffer (0.012% H₂O₂, 0.66 mg/ml *o*-phenylenediamine, OPD; Dako, code S 2045). The reaction was stopped after 30 min with 50 µl of 2 M H₂SO₄, and the optical density (OD) was measured at 492 nm. Assays were performed in duplicate. As negative control it was used blocking buffer, showing an OD less than 0.05 units in all cases.

Results were expressed in arbitrary units (AU)/L by interpolating in a control curve obtained with a *Lolium perenne* pollen extract on solid phase and a pool of sera from grass-allergic patients with an adjusted specific IgG₄ concentration of 29 kAU/L.

Statistical analysis

All the statistical analysis except the analysis of skin response was performed with SPSS. The comparison of frequencies was performed by the Chi-square test. Non-parametric test were used for the analysis of IgE and IgG₄ results. Otherwise, Student *t*-tests or ANOVA were applied. The differences in cutaneous reactivity was analysed by means of Parallel Line Assay (AIASA CRS PLA, ALK-Abelló, S.A.).

Results

All cat sensitized patients were polysensitized, with high rates of sensitization to other epithelia (83% to dog), pollens (83% to *Parietaria*, 59% to grasses) and mites (67% *D. pteronyssinus*) (Table 3). There were no differences in terms of severity of the disease between owning or not a cat at home. However, in the group with cat at home the frequency of females was significantly higher and the time of evolution longer. More than 50% of cat sensitized patients had asthma and the severity of rhinitis was moderate to severe in almost 90% of them. Atopic controls were similar to cat sensitized patients in terms of severity (Table 1). Cat specific tests (SPT, IgE and IgG₄) were negative in controls.

Table 4 lists the results of SPTs with cat allergen extracts. These specific SPTs confirmed, in all cat

allergic individuals, skin sensitization to cat allergens assessed by standard (screening) SPTs. The geometric mean of wheal areas for patients with cats at home was significantly lower than for patients without them at the four five-fold dilutions tested. By means of PLA the difference in skin sensitivity can be estimated in 3.4 times, meaning that, in order to obtain the same skin response in both groups it is necessary to multiply by 3.4 the extract concentration in patients with cat (Fig. 2). The 95% confidence interval for the difference is 2.6–4.6.

Although some patients with cat at home showed very high levels of cat specific IgE, the median value did not differ significantly between the two groups ($P = 0.065$, Fig. 3). On the contrary, the levels of cat specific IgG4 antibodies were significantly associated with the presence of the cat at

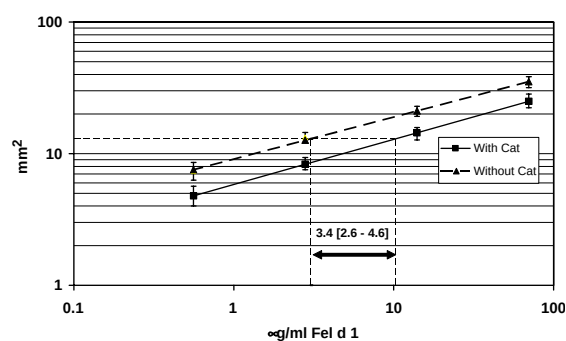


Figure 2 Comparison of the skin response by PLA to cat allergen extracts for patients with and without cat at their homes.

Table 3 Sensitization to common allergens.

Allergen extract	Atopic controls (n=27) (%)	Cat sensitized (n=112) (%)
Grasses	11.1	58.9
<i>Parietaria</i>	44.4	83.0
<i>Olea</i>	14.8	25.7
<i>Dermatophagoides</i>	63.0	67.3
Cat	0.0	100
Dog	0.0	83.0
<i>Alternaria</i>	0.0	7.7
<i>Artemisia</i>	18.5	23.3
<i>Cupressus</i>	0.0	0.0
<i>Betula</i>	0.0	0.0
<i>Cladosporium</i>	0.0	0.0
<i>Corylus</i>	0.0	0.0

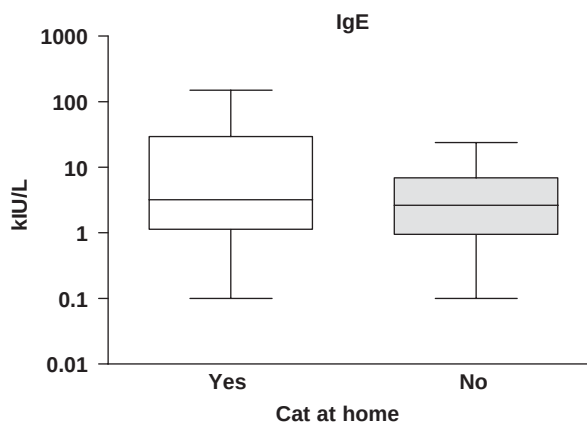


Figure 3 Comparison of the cat specific IgE levels for patients with and without cat at their homes. Negative values are assigned an arbitrary value of 0.1 kIU/L for illustration purposes in a logarithmic scale. Mann-Whitney P -value for group comparison of 0.065.

Table 4 Skin tests for cat allergen extracts.

Fel d 1 (µg/mL)*	Cats at home (n = 42)			No cats at home (n = 69)			P-value†
	95% CI limits			95% CI limits			
	G. Mean	Lower	Upper	G. Mean	Lower	Upper	
70	25.1	22.1	28.4	34.8	31.6	38.4	<0.001
14	14.1	12.6	15.7	20.9	19.1	22.9	<0.001
2.8	8.3	7.4	9.3	13.2	12	14.4	<0.001
0.56	4.6	3.9	5.6	7.7	7	8.5	<0.001
Histamine	24.1	21.9	26.6	24.1	22.5	25.7	0.968
Neg control	0	0	0	0	0	0	

Wheal areas in mm^2 .

G. Mean, geometric mean. CI, confidence interval.

^{*}Fel d 1 concentration in the allergen extract.

[†]Student t -test.

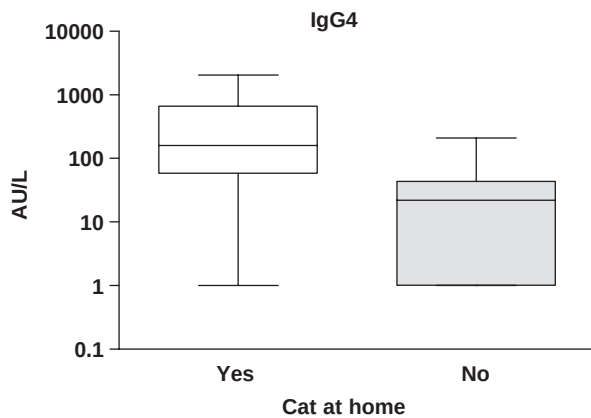


Figure 4 Comparison of the Fel d 1 specific IgG4 levels for patients with and without cat at their homes. Negative values are assigned an arbitrary value of 1 AU/L for illustration purposes in a logarithmic scale. Mann-Whitney P -value for group comparison <0.001 .

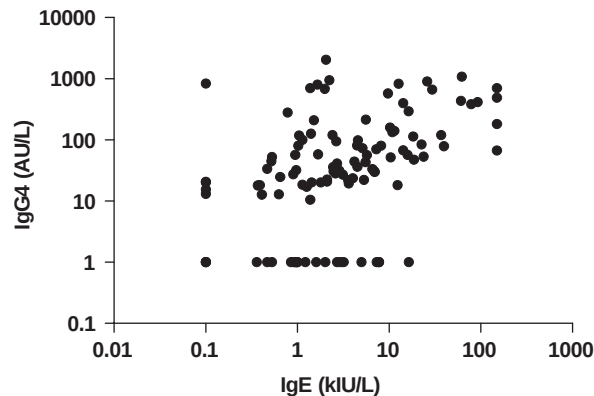


Figure 5 Correlation between cat specific IgE levels and Fel d 1 specific IgG4 levels. Negative IgE and IgG4 values are assigned arbitrary values of 0.1 kIU/L and 1 AU/L, respectively, for illustration purposes in a logarithmic scale. Spearman $r = 0.488$, $P < 0.001$.

home ($P < 0.01$, Fig. 4). IgE levels were positively correlated with IgG4 levels in both groups, with and without cat at home (Spearman $P < 0.001$, Fig. 5). The prevalence of cat ownership in the Naples area is 3.1%.

Discussion

Results from recent studies on the relationship between exposure to pet or pet allergens and allergic sensitization were conflicting.^{35,36} Available studies have evaluated the presence or not of allergic sensitization to cat/dog allergens using

standard SPTs and/or specific serological IgE determinations in large populations exposed or not exposed to these animals.

SPTs to natural allergen extracts represent the hallmark of immediate hypersensitivity and play a key role in allergy diagnosis. However standard SPTs performed by a single commercially available allergenic extract, in some circumstances may produce false positive or negative responses depending from different factors influencing skin test reactivity or from the technique used to skin test such as vertical pressure for 1 s or the angle of pricker during the entry to skin.³⁷ The use, in duplicate, of different dilutions of an allergenic extract, as performed in allergen standardization procedures, represents a more reliable method to assess the biological cutaneous events associated with allergic sensitization because it greatly reduces the risk of false positive or negative responses.^{38,39}

The results of this study suggest that cat ownership (characterized by a direct exposure to cat allergens) is not associated, as it could be expected, with a higher degree of immediate hypersensitivity to cat allergenic extract. Our data emphasize that even the low amounts of cat allergen inhaled as a consequence of indirect exposure are of sufficient magnitude to determine a higher cutaneous immediate hypersensitivity response in comparison to that induced by direct exposure to cat. Previous studies have indicated that even the low amounts of cat allergens found in homes without cats may induce allergic sensitization and/or trigger respiratory symptoms in highly susceptible individuals.^{40–42} In these studies, no direct comparison between exposed and not exposed individuals has been carried out. Moreover our findings were emphasized by the fact that in Naples area, the amounts of cat allergens are likely to be low in environments without cats because the prevalence of cat ownership is rather low (3.1%). In fact it has been suggested that in communities with a significant number of pets, passive exposure may be the primary cause of allergic diseases related to animals.⁴³ This is an important topic because pet allergens must be now considered as “ubiquitous” being found in many different environments where pets have never been kept.^{44–46} Clothing of pet owners have been indicated as carriers of allergens in pet-free environments.^{47–49}

The optimum measure or gold standard of exposure to pet is not established,^{18,50} in some studies exposure has been measured by means of questionnaire⁵¹ and in others by measuring pet allergen levels in collected dust.²⁷ However, categorizing the degree of exposure by using

questionnaires is difficult to perform¹⁸ and controversies still exist on the modality of collecting dust (from the carpet or from the air using an air sampler/personal sampler).⁵⁰ This is the reason why we have chosen to consider the presence or not of a cat at home as an index of intensive exposure to cat allergens even in the absence of evaluation of these materials in the domestic environments of our patients. Other studies have adopted the same criteria. For example Oberle et al.⁵² have demonstrated that allowing cats to be in the child's bedroom from the first year of life onwards may be an indicator of intensive exposure to cats even without monitoring the levels of *Fel d* 1. Moreover, de Meer et al.⁵³ studied the presence and timing of cat ownership by age 18 and the effect on atopy and asthma at age 28 in the absence of evaluation of environmental levels of cat allergens. Finally, it is important to outline that well-conducted studies have demonstrated higher levels of allergens in houses containing domestic animals versus houses without pets^{54,55} and that the aim of our study was not to evaluate a dose-response relationship between the level of exposure to cat allergen and the degree of allergic sensitization.

A further reason for considering the presence of cat at home as an index of intensive exposure to cat allergens derives from our exclusion criteria. As indicated in Table 2 we excluded from the study all patients with an "intermediate" condition of cat ownership such as those without a cat at home but frequently exposed to cats elsewhere for different reasons. Consequently, our patients without cat at home were, with rare exceptions, never in contact with cats and can be considered as indirectly exposed to cat allergens. On the contrary, in the cat-owner group, patients usually live in direct contact with their cats for many hours every day and consequently they can be considered as directly exposed to cat allergens. The significance of this distinction has been outlined also in the article of Almqvist et al.²²

Since all our cat sensitized subjects showed SPTs that were positive to other important allergens such as those derived from *Parietaria*, grasses, dust mites, dogs, etc., we cannot quantify the role of cat sensitization on patients' symptoms. Very few studies have evaluated the levels of cat specific IgG4 and IgE antibodies in sera of children and adults with current or indirect exposure to cat.^{12,56,57} In a proportion of these subjects (approximately 15%) higher levels of serological IgG4 are associated with lower or absent amounts of IgE. The high level of IgG4 associated with not IgE formation^{58,59} or less IgE production without

any effects mediated by IgG4,⁶⁰ other than a possible immunological effect of endotoxins' production⁶¹ is now considered the main mechanisms of the so-called "protective effect" of pet ownership on development of allergic sensitization and bronchial asthma. By contrast, a positive correlation between serum levels of IgE and IgG4 has been demonstrated in our patients. A possible explanation of this difference is that our patients (adolescent and adults) were directly exposed to cats for at least 10 years but not from the first months of life. In these conditions it is likely that these susceptible individuals developed an IgE antibody response after the previous indirect exposure to cat allergens and then an IgG4 antibody response as a consequence of cat ownership.

In conclusion, our study suggests that in susceptible individuals, allergic sensitization to cat can also be strongly determined by the low amounts of these allergens inhaled as a consequence of indirect exposure to cat. The degree of immediate hypersensitivity to cat, as determined by SPTs performed with different dilutions of cat allergens, in non exposed patients is higher in comparison with subjects with cat at home. Moreover, the degree of serological sensitization to cat allergens, as determined by evaluation of specific IgE antibodies, is not statistically different in the two groups of patients. It could be expected an higher level of specific IgE antibodies in patients directly exposed to cats. A possible explanation of our finding is that current exposure to cats may induce a "protective effect" also in adults, other than in children. In other words, cat ownership could "modulate", in already sensitized adults, the increasing degree of allergic sensitization to cat allergens as a consequence of intensive exposure to cats, by a modified immunological response involving IgG4 and IgE antibodies.

It is our opinion that a higher attention should be attributed to the problem of the ubiquity of cat allergens and to the necessity of developing new strategies for controlling the dispersal of these allergenic materials through the clothes of cat owners.⁶²⁻⁶⁴ In fact, the wide distribution of even low amounts of cat allergens in the most of cat-free indoor private/public environments may determine a high degree of allergic sensitization in susceptible individuals. Consequently, patients sensitized to cat allergens and not owning a cat should be alerted that allergy to cat may develop also without the contact with the animal, and that an indirectly induced sensitization can be sometimes higher in comparison with that determined by cat at home. These indirectly sensitized subjects should be alerted to avoid massive inhalations of

cat allergens such as those determined by entering into indoor environments containing several animals (for example, pet shops, cat shows),⁶⁵ to prevent the possibility of exacerbations of respiratory symptoms. Moreover, Henriksen et al.¹⁴ showed in non-smoking, steroid-naïve asthmatics a tendency towards increased levels of exhaled nitric oxide (eNO) among those both sensitized and exposed to the actual pet.

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