

G. LICCARDI^{1,2}, A. SALZILLO¹, L. CALZETTA³, A. PICCOLO¹, G. MENNA⁴, P. ROGLIANI³

Can the presence of cat/dog at home be considered the only criterion of exposure to cat/dog allergens? A likely underestimated bias in clinical practice and in large epidemiological studies

¹Department of Chest Diseases, Division of Pneumology and Allergology. High Speciality "A. Cardarelli" Hospital, Naples, Italy

²Postgraduate School of Respiratory Medicine, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

³Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

⁴Veterinary

KEY WORDS

Allergen exposure; allergic rhinitis; allergic sensitization; bronchial asthma; cat, dog, cat/dog allergy, hypersensitivity; pet

Corresponding author

Gennaro Liccardi
Department of Chest Diseases
Division of Pneumology and Allergology
High Speciality "A. Cardarelli" Hospital
Piazzetta Arenella 7, 80128 Naples, Italy
Phone: +39 081 747 3335-4-3
Fax: +39 081 747 3331
E-mail: gennaro.liccardi@tin.it

Summary

An important aspect of allergic sensitization to furry animals is the association of dog and cat exposure in early childhood with the incidence of respective allergies later in life. This topic is very controversial, because some authors have found a "facilitating" effect, while others have noticed a "protective" or even no significant effect in individuals living in urban areas. It is likely that some biases could be responsible of these contradictory findings. Cat/dog ownership or their presence in indoor environments are considered usually the main criteria to assess the exposure to these pets in studies' questionnaires. Even in clinical practice "are there animals at home?" is the common query usually done when collecting anamnestic data.

In our opinion, these commonly used questions should not be considered the main index of exposure to pet allergens, because they can lead to erroneous interpretation of the clinical significance of positive skin prick tests for pet allergens as well as of the real risk of exposure to allergens of dog/cat in epidemiological studies. Consequently, we suggest a new, more realistic, classification of modalities of exposure to pet allergens in "real life" based on five possible conditions.

Although domestic animals have been kept in our homes for thousands of years, the last one hundred years have seen two major developments: firstly, the combination of clean water, shoes, separation from animals, and helminth eradication that we refer to as hygiene, and secondly, the lifestyle changes associated with overheated, airtight homes and indoor sedentary entertainment. The result has been a dramatic increase in immediate hypersensitivity to indoor allergens including those of common pets (1).

Exposure to animal allergens constitutes a relevant risk factor for the development of allergic sensitization and respiratory allergic diseases, such as asthma and rhino-conjunctivitis in susceptible individuals (2,3). Cats and dogs are the most common

pets living indoor environments and the frequency of their ownership is highly variable in Europe ranging from 7.2 to 35% for the cats and from 5.4 to 35% for the dogs (4). The prevalence of allergic sensitization to cats/dogs varies in different countries according to cultural differences, environmental factors and rate of pet ownership.

An important aspect of allergic sensitization to furry animals is the association of dog and cat exposure in early childhood with the incidence of respective allergies later in life. This topic is very controversial because some authors have found a "facilitating" while others have noticed a "protective" or even no significant effect in individuals living in urban areas (5-16). On the contrary, it is widely recognized that early exposure to animals,

especially cattle, in the farms may induce a “protective” effect on development of respiratory allergy later in life (17,18). It is likely that some biases could be responsible of these contradictory findings. Recent studies suggested that the seemingly protective effect of pet exposure might be a result of a “healthy pet keeping effect” or a “selective avoidance” because parents with asthmatic diseases tend to keep their child from being exposed to cats/dogs to avoid a possible allergic sensitization (19,20).

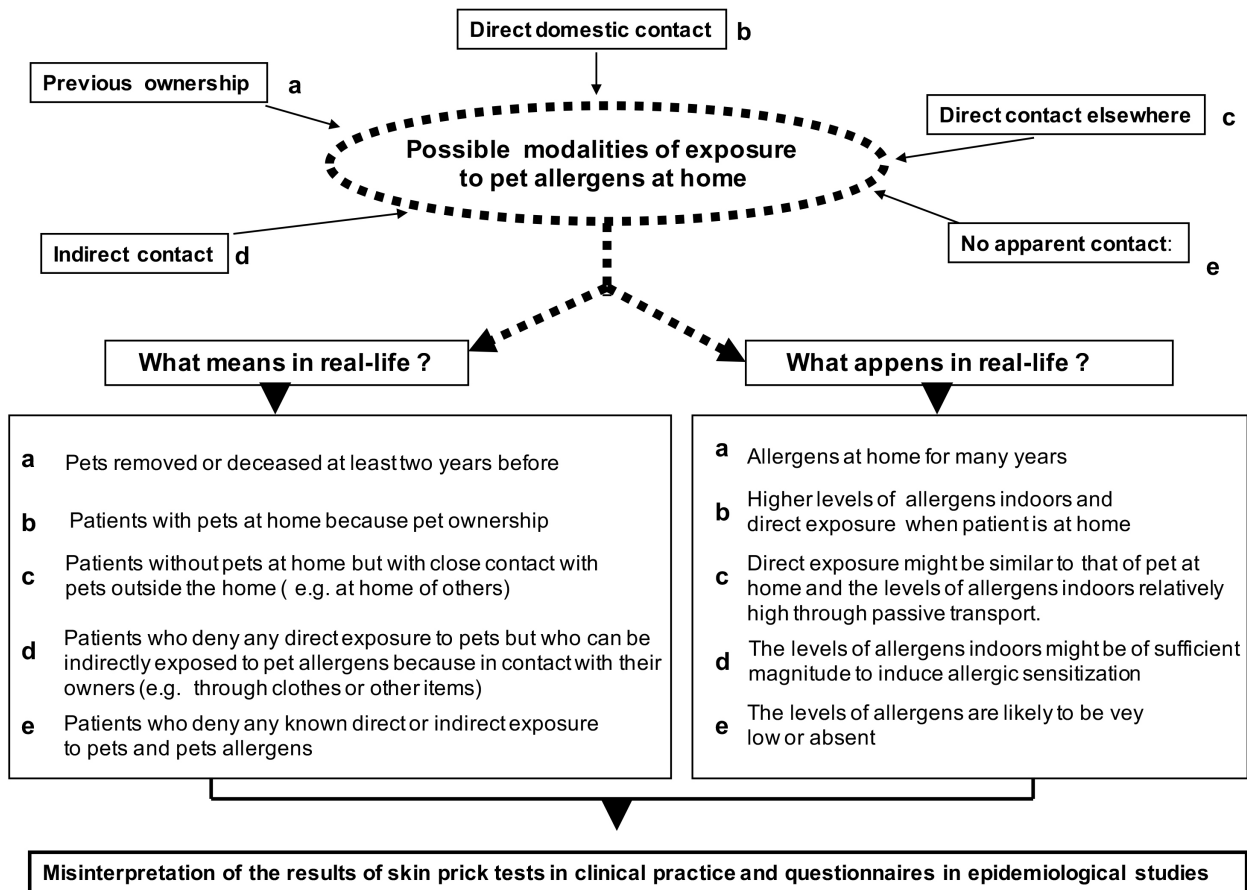
In our opinion, a serious and underestimated limitation to the conclusions of these particular studies should be acknowledged. Cat/dog ownership or their presence in indoor environments is usually considered the main criteria to assess the exposure to these pets in study questionnaires. Even in clinical practice, “are there animals at home?” is the common query usually done when collecting anamnestic data.

These commonly used questions should not be considered the main index of exposure to pet allergens and, consequently, the

main risk factor for allergic sensitization either in clinical practice or in large epidemiological studies.

Dynamic distribution of the main pet allergens indoors is complex, depending on production, aero-dispersion, sedimentation and passive transport through clothes and other items. These variables determine a diffuse presence of pet allergens (indirect exposure) also in indoor environments without pets and in those where pets are no longer present for a long time (e.g. voluntary removal or re-location, natural death etc.) (21). The higher is the frequency of pet ownership in a given community the higher will be the degree of pet allergen contamination of pet-free private homes (22). In this context, also in some public places (schools, day care centres, means of transport etc.), passive transfer constitutes the exclusive modality of common pet or other animal allergens contamination (23-25). Finally, several studies have shown that amounts of pet allergens passively transferred in pet-free environments are of sufficient magnitude to induce

Figure 1 - Suggested modalities of exposure to pet allergens and possible consequences in “real-life”.



allergic sensitization in susceptible, atopic individuals, and to trigger respiratory symptoms in already and highly pet-sensitized subjects (26,27). In developed countries, the consequence of pet allergen ubiquity is a persistent stimulation of airways similar to that induced by dust mite, that would increase the risk of allergic sensitization either directly or by a cross-reaction mechanism involving albumins and lipocalins (28-30).

On the base of this background, we suggest a new, more realistic classification of possible modalities of exposure to pet allergens (figure 1).

Figure 1 clearly shows that only the condition “b” is reported usually in collecting anamnestic data during clinical consultations, and in the questionnaires utilized for large epidemiological studies on the relationship between early exposure to pet allergens and subsequent enhancing or protective effect on allergic sensitization to these allergens. In the conditions “a, c and d”, the presence of pets at home is considered “formally negative” in patients’ responses and in the questionnaires but the level of exposure (direct / indirect) to pet allergens could be outstanding. Only the condition “e” should be considered at the lower risk of pet allergen exposure after having certainly excluded any direct as well as “indirect contact”. It is evident that these biases can lead to erroneous interpretation of the clinical significance of positive skin prick tests for pet allergens as well as of the real risk of exposure to allergens of dog / cat in epidemiological studies.

We have used this classification of exposure either for common / less common pets, pests or for a bigger animal such as horse, in this last case with some modifications. In these studies we have shown the role of these different modalities of exposure on the prevalence of allergic sensitization to several furry animals (31-38).

We think that our classification could be of particular importance to evaluate the modality of pet exposure at home in all countries characterized by a high frequency of pet ownership. It is likely that, in these countries, the “average amount” of pet allergens indoors could be high (or very high in some particular conditions) also in the absence of a pet at home. In conclusion, the magnitude of exposure to pet allergens at home is not related exclusively to pet ownership / presence of a pet indoors but it can be also relevant without a pet living with the inhabitants. These considerations should be taken into account during the planning of epidemiological studies on the relationship between exposure to pet and development of allergic sensitization to pet allergens. In clinical practice, a real assessment of the risk and clinical significance of allergic sensitization to pet allergens is crucial for the management of patients (pet-avoidance measures, allergen immunotherapy, pharmacological treatment of respiratory symptoms etc.).

We believe that the topic of animal allergy is very important not only for clinical but also for emotional implications in all

pet-owner patients and especially in children. The love for animals in general and for pets in particular is increasing worldwide, so we wish to underline the necessity for an adequate assessment of risk factors for allergic sensitization and possible prevention strategies by using a more realistic evaluation of possible modalities of exposure.

References

1. Kelly LA, Erwin EA, Platts-Mills TAE. The indoor air and asthma: the role of cat allergens. *Curr Opin Pulm Med.* 2012;18:29-34
2. Liccardi G, D’Amato G, D’Amato L, Salzillo A, Piccolo A, De Napoli I, Dente B, Cazzola M. The effect of pet ownership on the risk of allergic sensitization and bronchial asthma. *Respir Med.* 2005;99:227-33.
3. Hentges F, Leonard C, Arumugan K, Hilger C. Immune response to mammalian allergens. *Front Immunol.* 2014;21;5:234. doi: 10.3389/fimmu.2014.00234. eCollection 2014.
4. Eller E, Roll S, Chen CM, Herbarth O, Wichman HE, Berg A et al. Meta-analysis of determinants for pet ownership in 12 European birth cohort on asthma and allergies: a GA2LEN initiative. *Allergy.* 2008;63:1491-8.
5. Pyrhonen K, Nayha S, Laara E. Dog and cat exposure and respective pet allergy in early childhood. *Pediatr Allergy Immunol.* 2015;26:267-55.
6. Lodge C, Allen K, Lowe A, et al. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. *Clin Dev Immunol.* 2012;2012:176484.
7. Chen C, Tischer C, Schnappinger M, Heinrich J. The role of cats and dogs in asthma and allergy - a systematic review. *Int J Hyg Environ Health.* 2010;213:1-31.
8. Lødrup Carlsen K, Roll S, Carlsen K, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One.* 2012;7:e43214.
9. Chen C, Morgenstern V, Bischof W, et al. Dog ownership and contact during childhood and later allergy development. *Eur Respir J.* 2008;31:963-973.
10. Smallwood J, Ownby D. Exposure to dog allergens and subsequent allergic sensitization: an updated review. *Curr Allergy Asthma Rep.* 2012;12:424-428.
11. Dharmage S, Lodge C, Matheson M, Campbell B, Lowe A. Exposure to cats: update on risks for sensitization and allergic diseases. *Curr Allergy Asthma Rep.* 2012;12:413-23.
12. Dong GH, Wang J, Liu MM, Wang D, Lee YL, Zhao YD. Allergic predisposition modifies the effects of pet exposure on respiratory disease in boys and girls: the seven northeast of China (snec) study. *Environmental Health.* 2012;11:50.
13. Brunekreef B, Von Mutius E, Wong G, Odhiambo J, Garcia-Marcos L, Foliaki S. ISAAC Phase Three Study Group. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis, and eczema. *Epidemiology.* 2012;23:11-50.
14. Almqvist C, Gargen F, Kemp AS, Li Q, Crisafulli D, Tovey ER, Xuan W, Marks GB, CCAPS Investigators. Effects of early cat or dog ownership on sensitization and asthma in high-risk cohort without disease-related modification of exposure. *Pediatr Perinatal Epidemiol.* 2010;24:171-78.

15. Mandahane PJ, Sears MR, Poulton R, Greene JM, Lou WY, Taylor DR, Hancox RJ. Cats and dogs and the risk of atopy in childhood and adults. *J Allergy Clin Immunol.* 2009;124:745-50.
16. Fasce L, Tosca MA, Silvestri M, Olcese R, Pistorio A, Rossi GA. "Early" cat ownership and the risk of sensitization and allergic rhinitis in Ligurian children with respiratory symptoms. *Ann Allergy Asthma Immunol.* 2005;94:561-5.
17. Wlasiuk G, Vercelli D. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. *Curr Opin Allergy Clin Immunol.* 2012;12:461-6.
18. Campbell BE, Lodge CJ, Lowe AJ, Burgess JA, Matheson MC, Dharmage SC. Exposure to "farming" and objective markers of atopy: a systematic review and meta-analysis. *Clin Exp Allergy.* 2015;45:744-57.
19. Bertelsen RJ, Carlsen KC, Granum B, Carlsen KH, Haaland G, Devupalli CS, Mun the-Kaas MC, Lovi K M. Do allergic families avoid keeping furry pets? *Indoor Air.* 2010;20:187-95.
20. Baxi SN, Phipatanakul W. The role of allergen exposure and avoidance in asthma. *Adolescent Med State Art Rev.* 2010;21:57-71.
21. Liccardi G, D'Amato G, Russo M, Canonica GW, D'Amato L, M, Passalacqua G. Focus on cat allergen (Fel d 1): immunological and aerodynamic characteristics, modality of airway sensitization and avoidance strategies. *Int Arch Allergy Immunol.* 2003;132:1-12.
22. Heinrich J, Bedana GB, Zock JP et al. For The Indoor Working Group of The European Community Health Survey II. Cat allergen level: its determinants and relationship to specific IgE to cat across European centers. *J Allergy Clin Immunol.* 2006;118:674-81.
23. Berge M, Munir AK, Dreborg S. Concentrations of cat (Fel d 1), dog (Can f 1) and mite (Der f 1 and Der p 1) allergens in the clothing and school environment of Swedish schoolchildren with and without pets at home. *Pediatr Allergy Immunol.* 1998;9:25-30.
24. D'Amato G, Liccardi G, Russo M, Barber D, D'Amato M, Carreira J. Clothing is a carrier of cat allergens. *J Allergy Clin Immunol.* 1997;99:577-8.
25. Liccardi G, Barber D, Russo M, D'Amato M, D'Amato G. Human hair: an unexpected source of cat allergen exposure. *Int Arch Allergy Immunol.* 2005;137:141-4.
26. Bollinger ME, Eggleston PA, Flanagan E, Wood RA. Cat antigen in homes with and without cats may induce allergic symptoms. *J Allergy Clin Immunol.* 1996;97:907-14.
27. Munir AKM, Einarsson R, Schou C, Dreborg SKG. Allergens in school dust. I. The amount of the major cat (Fel d 1) and dog (Can f 1) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. *J Allergy Clin Immunol.* 1993;91:1067-74.
28. Liccardi G, Asero R, D'Amato M, D'Amato G. Role of sensitization to mammalian serum albumin in allergic disease. *Curr Allergy Asthma Rep.* 2011;11:421-6.
29. Nordlund B, Konradsen JR, Kull I, Borres MP, Onell A, Hedlin G, Gronlund H. IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobulin are markers of bronchial inflammation in severe childhood asthma. *Allergy.* 2012;67:661-9.
30. Liccardi G, Dente B, Restani P, Senna GE, Falagiani P, Ballabio C, D'Amato G. Respiratory allergy induced by exclusive poly-sensitization to serum albumins of furry animals. *Eur Ann Allergy Clin Immunol.* 2010;42:127-30.
31. Liccardi G, Salzillo A, Piccolo A, Russo M, D'Amato G. Sensitization to furry animals in an urban atopic population living in Naples, Italy. *Allergy.* 2011;66:1500-1.
32. Liccardi G, D'Amato G, Antonicelli L, Berra A, Billeri L, Canonica GW et al. Sensitization to horse allergens in Italy: A multicentre study in urban atopic subjects without occupational exposure. *Int Arch Allergy Immunol.* 2011;155:1103-14.
33. Liccardi G, Salzillo A, Cecchi L, D'Amato M, D'Amato G. Is cat-keeping the main determinant of new-onset adulthood cat sensitization? *J Allergy Clin Immunol.* 2012;129:1689-90.
34. Liccardi G, D'Amato G, Canonica GW, Dente B, Passalacqua G. Severe respiratory allergy induced by indirect exposure to rabbit dander: a case report. *Allergy.* 2004; 59:1237-8.
35. Liccardi G, Piccolo A, Dente B, Salzillo A, Gilder JA, Russo M, D'Amato G. Rabbit allergens: a significant risk for allergic sensitization in subjects without occupational exposure. *Respir Med.* 2007;101:333-9.
36. Liccardi G, Passalacqua G on behalf of the Allergy Study Group of the Italian Society of Respiratory Medicine (SIMEr). Sensitization to rabbit allergens in Italy - A multicentre study in atopic subjects without occupational exposure. *Int Arch Allergy Immunol.* 2006;141:295-9.
37. Liccardi G, Salzillo A, Dente B, Piccolo A, Lobefalo G, Russo M, Gilder JA, D'Amato G. Horse allergens: an underestimated risk for allergic sensitization in an urban atopic population without occupational exposure. *Respir Med.* 2009;103:414-20.
38. Liccardi G, Salzillo A, Sofia M, Piccolo A, Dente B, Russo M, D'Amato M, Stanziola A, D'Amato G. Sensitization to rodents (mouse/rat) in an urban atopic population without occupational exposure living in Naples, Italy. *Eur Ann Allergy Clin Immunol.* 2012;44:200-4.