A narrative review on allergy and exposure to domestic and non-domestic animals: favorable and unfavorable effects

Gennaro Liccardi[1], Matteo Martini[2,3], Maria Beatrice Bilò[2,3], Lorenzo Cecchi[4], Manlio Milanese[5], Antonino Musarra[6], Ermanno Puxeddu[7], Paola Rogliani[1,7]

[1]Department of Experimental Medicine, Postgraduate School of Respiratory Medicine, University of Rome Tor Vergata, Rome, Italy
[2]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Italy
[3]Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti di Ancona, Ancona, Italy
[4]SOS Allergy and Clinical Immunology, USL Toscana Centro, Prato, Italy
[5]Division of Pulmonology, S. Corona Hospital, Pietra Ligure, Italy
[6]Allergy Unit, Casa della Salute di Scilla, Scilla, Reggio Calabria, Italy
[7]Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome Tor Vergata, Rome, Italy

Summary
The aim of this contribution was to highlight the "favorable" and "unfavorable" roles of domestic and non-domestic animals on airway sensitization processes and on the type/severity of the clinical symptoms induced by their exposure.
We performed a literature research in MEDLINE for allergic manifestations and animals.
Pets can be “allergy friends” through mechanisms related to hygiene hypothesis and translational aspects, the dual role of IgG4 antibodies for pets, and their promising role as healthcare service animals (dogs).
On the contrary, animals can be “allergy enemies” when inducing allergic sensitization and respiratory symptoms (sometimes leading to severe reactions), and also due to cross reactivity with other pets allergens, indirect exposure and ubiquity of their allergens, cross reactivity between Can f 5 and human prostate-specific antigen (PSA). Moreover, in some cases they can trigger anaphylaxis, induce occupational asthma, and act as pests. Finally, we must outline the modest efficacy of allergen immunotherapy (AIT) for their allergens.
From a strictly allergological perspective, it is evident that the "negative" aspects resulting from exposure to domestic / non-domestic animals outweigh the “positive” aspects. As a consequence, it is up to humans to seek new ways to balance the pros and cons by exploring research areas that can allow the best possible coexistence with subjects at risk of allergy with domestic and non-domestic animals.

Key words
Allergic rhinitis; animals; bronchial asthma; cat; dog.

Impact statement
It is evident the need for further studies encompassing prevention aspects, standardization of pet allergens, enhancement of the efficacy of various AIT modalities as well as new immunological approaches.

Introduction

Dogs and cats are the most prevalent pets globally. Recent data indicate that 44.7% of families own a dog, while 35.4% have a cat at home in Italy (1), while allergic sensitization frequency to cats and dogs is reported as 16% and 9%, respectively (2).
Beyond the emotional relationship with humans (including their role in pet therapy), common pets drive relevant economic activities, including breeding, veterinary services, and new pet-related professions (e.g. pet sitters, groomers, pet shop workers, military /police units) and pet product industries (e.g. pet-food, accessories). Furthermore, the increasingly widespread habit of having exotic animals as pets has also increased the frequency of allergic sensitization to these creatures (3, 4). In the strictly allergy context, unlike other allergenic sources, animals can play a dual role in the development of allergic sensitization, either inhibiting or facilitating this process.
The aim of this contribution was to highlight the "favorable" and "unfavorable" roles of domestic and non-domestic animals on airway sensitization processes and on the type/severity of the clinical symptoms induced by their exposure.

Data sources and study selections

We performed a literature research in MEDLINE for randomized and non- randomized trials, systematic reviews and meta-analyses. We selected studies according to the following key words: allergic rhinitis, animals, bronchial asthma, cat, dog, horse, guinea pig, pig, or mouse.

How pets can be “allergy friends”?

The controversial of early exposure to pets on the subsequent development of allergy

Early exposure to animals on the development of allergic sensitization and asthma is a rather controversial topic as it is possible to observe both a "preventive" and a "facilitating" effect on this process. Furthermore, the "protective" effect appears to be more significant in rural environments, compared to urban areas. The rural lifestyle, characterized by contact with farm animals (including cattle), greater presence of microorganisms, less pollution, etc., constitutes a set of factors considered "protective" on the development of allergic pathologies. On the contrary, the urban lifestyle characterized by indoor living, high hygiene standards, and significant pollution, represents several "facilitating" factors. This theory is known as the ‘hygiene hypothesis’ (5).
In a recent review, Indolfi et al. (6) found a relationship between the number of owned pets and a protective effect against allergy and asthma. The likelihood of developing allergy and asthma seems to be influenced by various factors in children, including the genetic background and early exposure to different environmental factors, including allergens that may interact with the gut microbiota and the immune system. In fact, microbiota detected in nasal fluids (7) and indoor dust (8) of individuals with pets at home are likely to be associated to a reduced risk of allergic sensitization. On the contrary, Park et al. (9) have found that early-life exposure to dog reduces atopy but increases the risk of nonatopic bronchial hyper-reactivity (BHR) and nonatopic asthma at 7 years old.
Indolfi et al. (6) and others (10) demonstrated that exposure to pets during early infancy can also reduce the incidence of food allergies.

Dual role of IgG4 antibodies in pet allergy

The clinical significance of IgG4 in allergic diseases is complex and controversial. However, published data indicate that allergen-specific IgG4 plays a multifaceted role in allergic diseases that is protective or pathogenic depending on different allergens or exposure conditions (11). In particular, acute allergen exposure may lead to IgE-mediated histamine-induced hypersensitivity reactions by high-affinity receptor FcϵRI whereas chronic allergen exposure may induce IgG4 formation and allergen binding by

IgG4. The IgG4 binding to the inhibitory receptor FcgRIIb prevents hypersensitivity reactions and induces allergen tolerance (11).

Translational aspects

A better understanding of the pathophysiology of asthma in humans by utilizing animal models of asthma is aimed at improving diagnostics and treatments. Depending on the research question and budget, certain animal models of asthma may be more applicable for use. For this purpose, various animals have been used such as rodents, guinea pigs, rabbit, dogs, sheeps, cats, horses, non-human primates. Naturally occurring animal models of asthma have the benefit of investigating the aspect of chronicity, collecting longitudinal data, and evaluating novel treatments (12).

Role as service animal in healthcare (especially dogs)

Although dogs can induce respiratory allergy, we would like to cite the potential role of service dogs in certain clinical conditions at high risk of anaphylaxis such as surgical interventions in subjects with high allergic risk. Tew and Taicher (13) documented the first report of a service dog used to detect mast cell mediator release in a patient with mastocytosis. This service dog was used not only in a family-centered care model, but also as an additional perioperative monitoring tool to predict the potential occurrence of perioperative mediator release (13). We think that this type of "service" provided by dogs towards subjects at high risk of anaphylaxis should be strongly encouraged.

How pets can be "allergy enemies"?

Induction of allergic sensitization and cross reactivity of pet allergens

At present, eight main allergens characterized by different molecular weights, biochemical properties, and biological functions have been identified both in dogs and cats (14 – 17) (Table 1). Notably, the primary cat allergen (Fel d 1) is responsible for over 90% of allergic sensitizations to cats, while dogs can have various allergens involved, such as Can f 1, Can f 2, and Can f 5 (18,19). In Italy, the frequency of allergic sensitization to cats and dogs were reported to be 16% and 9%, respectively (2). In Northern Europe and the United States, a high frequency of pet ownership leads to a much higher risk of sensitization (up to 50%) (20). Conversely, China exhibits sensitization frequencies similar to those in Italy (14.9% for dogs and 9.3% for cats) (21). As expected, it has been shown that the poly-sensitization to dog and cat allergen components is associated with a high likelihood of allergic symptoms during pet exhibition shows (22).

Allergens from furry animals belong to a restricted number of protein families, mostly lipocalins, albumins, secretoglobins, latherins or cystatin-A (4). Animal dander contains cross-reactive molecules and current efforts aim at defining species-specific allergens with high diagnostic sensitivity (4).

The degree of cross-reactivity between animal allergens varies by species. For example, dog-Can f 1 and cat-Fel d 7 show a moderate risk of cross-reactivity; dog-Can f 3, cat-Fel d 2, horse-Equ c 3 and domestic pig-Sus s 1 have a high risk of cross-reactivity with other serum albumin; dog-Can f 6, cat-Fel d 4, horse-Equ c 1, guinea pig-Cav p 6 and mouse-Mus m 1 demonstrate a moderate cross-reactivity risk with some lipocalins; dog-Can f 8 and cat-Fel d 3 pose a moderate risk; horse-Equ c 6 and horse-Equ a 6 present a high risk (15). The cross-reactivity of animal allergens causes important difficulties both from a diagnostic and therapeutic point of view, for example in the choice of the allergen to treat with AIT. These problems can be mitigated using the Component-Resolved Diagnosis (CRD), which allows to discriminate genuine sensitizations from cross-sensitizations.

A particular condition is the pork-cat syndrome in which patients who are allergic to cat epithelium develop symptoms of allergy after the ingestion of pork meat. Primary sensitization is presumed to be caused by inhaled Fel d 2 (cat serum albumin), with predominantly respiratory symptoms and subsequent reactions to pork due to cross-reactivity between Fel d 2 and pork serum albumin (Sus s 1)

(23). Moreover, it has been shown that some cat immunoglobulins carry alpha-GAL and are believed to play a role in sensitization to this allergen (24, 25)

Mild to severe respiratory symptoms

Studies in cat allergy using controlled methodology of exposure (e.g. natural exposure cat rooms, allergen exposure chambers) have been very useful to demonstrate short- and long-term effects of cat allergen inhalation, thereby providing a more holistic representation of cat allergen-induced respiratory symptoms (26). It is essential to underline that the percentage of pet allergens carried on small particles (about 0.5-2µm) becomes easily airborne, under normal domestic ventilation, and it constitutes the main material able to trigger respiratory symptoms, in sensitized patients (27). In fact, Zeidler et al. (28) demonstrated that common exposure to cat allergens results in significant small airways obstruction and hyperresponsiveness persisting for at least 23 hours. Beyond this timepoint, these changes were no longer detected by conventional physiologic measures.

Sensitization to dog is also an important risk factor for asthma in children. In fact, Kack et al.(29) showed that polysensitization to furry animal allergens and high IgE levels to the dog lipocalins Can f 2, Can f 4, and Can f 6 are associated with asthma severity in dog dander sensitized children. Molecular allergy diagnostics may thus help the clinicians to evaluate the impact of allergic sensitization on asthma morbidity (29).

Ubiquity of pet allergens

Cat and dog allergens should be considered as ubiquitous because they are found not only in indoor environments where these animals are kept, but also in other indoor private or public places where they have never been kept (27). Public spaces include nurseries, offices, hospitals, hotels, schools and means of public transport (e.g. buses, cars, airplanes) (20). These indoor environments, contaminated by pet allergens, are able to induce allergic sensitization in susceptible individuals and trigger respiratory symptoms in already highly sensitized subjects (30). In fact, in these contaminated environments, especially schools, the amount of pet allergens is higher than threshold values generally recognized as sufficient to induce sensitization (1 µg of allergen/g) or trigger respiratory symptoms (8-10 µg of allergen/g) for dust (31). In developed countries, the consequence of pet allergen ubiquity is a persistent stimulation of airways like the one induced by dust mite, that may increase the risk of allergic sensitization either directly or by a cross- reaction mechanism involving albumins and lipocalins (15, 32).

Indirect exposure

Accumulation of pet allergens in indoor environments without animals has been demonstrated to correlate with the number of visitors owning a pet or with those who are in regular contact with these animals. Therefore, the higher the frequency of pet ownership in a community, the higher the presence of pet allergens in apparently pet-free spaces (33). We and others have shown that clothing and other items, such as human hair, constitute a means of transferring pet allergens into pet-free indoor environments (34, 35).

As previously described, the percentage of pet allergens carried on small particles (about 0.5-2 µm) becomes easily airborne under common domestic ventilation and it constitutes the real risk either for allergic sensitization or, in some circumstances, exacerbation of symptoms in already sensitized patients (27). However, it has been shown that the indirect modality of exposure to allergens of domestic animals can also include other species, such as rabbits (36) or horses (37, 38).

Cross reactivity between Can f 5 and human prostate-specific antigen (PSA)

Can f 5, a newly described dog allergen, is a prostatic kallicrein, an androgen-regulated protein expressed in the prostate and detectable only in male dogs (39). Some studies have shown that the frequency of a prevalent or exclusive allergic sensitization to Can f 5 is high, ranging from 37% to 52%

(40). A high rate of allergic sensitization to Can f 5 has been recorded in the North East of Italy. Specifically, 69.02% of dog-sensitized patients showed IgE against Can f 5, and 57.92% were exclusively sensitized to Can f 5 (41). Moreover, we have also shown that mono-sensitization to Can f 5 is strongly associated to a prevelent esposure to male dogs, compared to female dogs (42). A moderate potential for cross-reaction between Can f 5 and human Prostate Specific Antigen (PSA), contained in human semen, has been demonstrated, and this cross-reaction may be clinically significant (although very rare) after sexual intercourse in women allergic to dogs (43, 44).

Inducers of anaphylaxis
Pets have been reported to induce anaphylaxis after contact or inhalation of allergens (45, 46), as well as following a bite (47, 48). Anaphylaxis is more frequent in the literature after laboratory animals' bites (mostly mice and rats), compared to pets (49, 50).
Recently, an anaphylactic shock due to a slow loris' bite has been described (51). Slow loris is a venomous monkey, sometimes kept as a pet, that combines its brachial gland exudate (which serves as a defensive tool) with saliva and bites to deliver the venom (51). Interestingly, it has been shown homology between this brachial gland protein and the main allergen of cat dander (52). Laboratory data demonstrate that Fel d 1 may satisfy some criteria to be considered a toxin and thus suggesting the possibility that cat-induced reactions could also include a form of toxic reaction (53). A similar model is provided by hymenoptera stings, possibly leading to allergic or non-allergic (e.g. toxic) severe reactions (54).

Occupational asthma
Allergy to common pets (or other furry animals) may also occur in some occupational settings where workers are intensively exposed to animal dander during most of their working time (55, 56). We have also described a case of respiratory allergy induced by an unusual occupational exposure to rabbit in a part-time magician (57). In fact, a few minutes after the rabbit was pulled out from the top hat, the patient experienced the onset of upper and lower airway symptoms, and in some occasions, he was forced to stop the show and to use short acting $\beta_2$agonists and intramuscular steroids (57). In case of contact with domestic and non-domestic animals, workers should apply prevention measures to avoid the passive transport of allergens from workplaces to private homes, for the consequent risk of allergic sensitization of family members (58).

Animals as pests
Among animals defined as "pests", cockroaches and rodents (mouse and rat) represent the most common cause of airway allergic sensitization and bronchial asthma worldwide (2).
It has been shown that residence in poor and urban areas, exposure to outdoor / indoor pollutants and tobacco smoke, poverty, material hardship, poor-quality housing, differences in health care quality contribute to increase pest-related allergic sensitization and asthma morbidity (2).
Liccardi et al.(59) found that although their prevalence in Italy is lower compared with other countries, it is not negligible for cockroaches (8%) while for mouse and rat is rather low (3% and 1% respectively). The risk factors for sensitization to pests, in Italy, are completely comparable to those found in other geographical areas (59).

Modest efficacy of Allergen Immunotherapy (AIT)
Liccardi et al.(60) conducted an online survey encompassing both manufacturing companies and allergy centers evenly distributed across Italy. The trends of pet AIT prescriptions, over the last decade, were notably higher for cat allergy, compared to dog. Clinical efficacy is reported as more favorable in patients receiving cat allergenic extracts than those receiving dog allergenic extracts.

The limited standardization of allergenic materials, especially for dogs, remains the primary factor contributing to the overall unsatisfactory clinical efficacy of traditional AIT, AIT with modified allergens, as well as intralymphatic allergen-specific immunotherapy (ILAIT) (55,56) 61).

Concluding remarks

The data presented in this review show that, from a strictly allergological point of view, the "negative" aspects resulting from exposure to domestic / non-domestic animals outweigh the "positive" aspects (Figure 1). Different negative aspects (such as the transmission of infectious agents, invasiveness due to overpopulation, etc.) or positive ones (such as service or pet therapy animals, etc.) were obviously not considered. It has been well established that allergic sensitization to animals, particularly -but not only- to dogs and cats, is a complex puzzle influenced by many different factors related to individuals, living environments, modes of exposure, and the animals themselves.

Considering the high percentage of atopic subjects in the general population and the importance of maintaining the human-animal relationship for ethical, behavioral, social, and psychological reasons, among others, it is up to humans to seek new ways to balance the pros and cons of pet relationship. There is a clear need for further studies encompassing prevention aspects, standardization of pet allergens, improvement of the efficacy of various AIT modalities as well as new immunological approaches (e.g. the use of anti-Fel d 1 monoclonal antibodies in humans, immunization of cats to induce neutralizing antibodies against Fel d 1, and feline diet with an egg product containing anti-Fel d 1 IgY antibodies). We hope that the findings of these research areas will allow the best possible coexistence between subjects at risk of allergy and domestic and non-domestic animals.

Contributions

All authors contributed equally to this work

Conflict of interest and funding. All authors declare that they have no conflict of interest. The study has been carried out without any financial support.

References

1. Thirty-fourth Institute of Political, Economic and Social Studies (EURISPES) Report 2022. www.eurispes.eu
2. Liccardi G, Bilò MB, Calzetta L, Milanese M, Martini M, Bresciani M, Cilia M, Cucinelli F, D'Angelo R, Feliziani A, Filon FL, Longo R, Losappio L, Manzotti G, Minale P, Modica S, Murzilli F, Musarra A, Pingitore G, Polillo BR, Puggioni F, Quercia O, Rapone C, Rogliani P. Pest sensitization to cockroach, mouse, and rat: An Italian multicenter study. Allergy. 2023 May;78(5):1360-1363. doi: 10.1111/all.15586. Epub 2022 Nov 26. PMID: 36398484
3. Phillips JF, Lockey RF. Exotic pet allergy. J Allergy Clin Immunol. 2009 Feb;123(2):513-5. doi: 10.1016/j.jaci.2008.09.019. Epub 2008 Nov 2. PMID: 18980777
4. Curin M, Hilger C. Allergy to pets and new allergies to uncommon pets. Allergol Select. 2017 Aug 4;1(2):214-221. doi: 10.5414/ALX01842E. eCollection 2017.PMID: 30402618
5. Garn, H.; Potaczek, D.P.; Pfefferle, P.I. The Hygiene Hypothesis and New Perspectives-Current Challenges Meeting an Old Postulate. Front. Immunol. 2021 Mar 18:12:637087. doi: 10.3389/fimmu.2021.637087. e Collection 2021.
6. Indolfi C, D'Addio E, Bencivenga CL, Rivetti G, Bettini I, Licari A, Manti S, Mori F, Miraglia Del Giudice M, Klain A. The Primary Prevention of Atopy: Does Early Exposure to Cats and Dogs Prevent

the Development of Allergy and Asthma in Children? A Comprehensive Analysis of the Literature. Life (Basel). 2023 Sep 2; 13(9):1859. doi: 10.3390/life13091859
7. Chun Y, Do A, Grishina G, Arditi Z, Ribeiro V, Grishin A, Vicencio A, Bunyavanich S. The nasal microbiome, nasal transcriptome, and pet sensitization. J Allergy Clin Immunol. 2021 Jul;148(1):244-249.e4. doi: 10.1016/j.jaci.2021.01.031. Epub 2021 Feb 13. PMID: 33592204
8. Mäki JM, Kirjavainen PV, Täubel M, Piippo-Savolainen E, Backman K, Hyvärinen A, Tuoresmäki P, Jayaprakash B, Heinrich J, Herberth G, Standl M, Pekkanen J, Karvonen AM. Associations between dog keeping and indoor dust microbiota. Sci Rep. 2021 Mar 5;11(1):5341. doi: 10.1038/s41598-021-84790-w.PMID: 33674692
9. Park MJ, Lee SY, Song KB, Lee SH, Choi KY, Lee KW, Jung S, Suh DI, Sheen YH, Kim KW, Ahn K, Hong SJ. Dog Ownership in Early Life Increased the Risk of Nonatopic Asthma in Children. Int Arch Allergy Immunol. 2021;182(10):980-988. doi: 10.1159/000516057. Epub 2021 Ma 6. PMID: 33957625
10. Okabe H, Hashimoto K, Yamada M, Ono T, Yaginuma K, Kume Y, Chishiki M, Sato A, Ogata Y, Imaizumi K, Murata T, Kyozuka H, Shinoki K, Yasumura S, Nishigori H, Fujimori K, Hosoya M; Japan Environment and Children's Study (JECS). Associations between fetal or infancy pet exposure and food allergies: The Japan Environment and Children's Study. PLoS One. 2023 Mar 29;18(3): e0282725. doi: 10.1371/journal.pone.0282725. eCollection 2023
11. Qin L, Tang L-F, Cheng L, Wang H-Y (2022) The clinical significance of allergen-specific IgG4 in allergic diseases. Front Immunol 2022 Oct 25:13:1032909. doi:10.3389/fimmu.2022.1032909. eCollection 2022
12. Woodrow JS, Sheats MK, Cooper B, Bayless R. Asthma: The Use of Animal Models and Their Translational Utility. Cells. 2023 Apr 5; 12(7):1091. doi: 10.3390/cells12071091.PMID: 37048164
13. Tew S, Taicher BM. A Dog Is a Doctor's Best Friend: The Use of a Service Dog as a Perioperative Assistant. Case Rep Pediatr. 2016; 2016:9013520. doi: 10.1155/2016/9013520. Epub 2016 Oct 23. PMID: 27843665
14. van Hage M, Käck U, Asarnoj A, Konradsen JR. An update on the prevalence and diagnosis of cat and dog allergy - Emphasizing the role of molecular allergy diagnostics. Mol Immunol. 2023 May; 157:1-7. Doi : 10.1016/j.molimm.2023.03.003.
15. Dramburg S, Hilger C, Santos AF, de Las Vecillas L, Aalberse RC, et al. EAACI Molecular Allergology User's Guide 2.0. Pediatr Allergy Immunol. 2023 Mar;34 Suppl 28: e13854. doi: 10.1111/pai.13854.PMID: 37186333
16. Dávila I, Domínguez-Ortega J, Navarro-Pulido A, Alonso A, Antolín-Amerigo D, González-Mancebo E, Martín-García C, Núñez-Acevedo B, Prior N, Reche M, Rosado A, Ruiz-Hornillos J, Sánchez MC, Torrecillas M. Consensus document on dog and cat allergy. Allergy. 2018 Jun;73(6):1206-1222. doi: 10.1111/all.13391. Epub 2018 Feb 13. PMID : 29318625
17. Sudharson S, Kalic T, Hafner C, Breiteneder H. Newly defined allergens in the WHO/IUIS Allergen Nomenclature Database during 01/2019-03/2021. Allergy. 2021 Nov;76(11):3359-3373. doi: 10.1111/all.15021. Epub 2021 Aug 5. PMID: 34310736
18. Roger A, Lazo C, Arias N, Quirant B, Albert N, Gómez M, Schayman W. Using Component-Resolved Diagnosis to Characterize the Sensitization to Specific Cat and Dog Allergens in Patients with Allergic Respiratory Diseases in Catalonia, Spain. Int Arch Allergy Immunol. 2023; 184 (5):440-446. doi: 10.1159/000528643.
19. Özuygur Ermis SS, Borres MP, Basna R, Ekerljung L, Malmhäll C, Goksör E, Wennergren G, Rådinger M, Lötvall J, Kankaanranta H, Nwaru BI. Sensitization to molecular dog allergens in an adult population: Results from the West Sweden Asthma Study. Clin Exp Allergy. 2023 Jan;53(1):88-104. doi: 10.1111/cea.14216.
20. Liccardi G, Triggiani M, Piccolo A, Salzillo A, Parente R, Manzi F, Vatrella A. Sensitization to Common and Uncommon Pets or Other Furry Animals: Which May Be Common Mechanisms? Transl Med UniSa. 2016 May 16; 14: 9-14.

21. Zhu H, Huang Z, Liu T, An N, Gan H, Huang D, Hao C, Luo W, Sun B. Sensitization to Furry Animals in Patients with Suspected Allergic Disease in China: A Multicenter Study. J Asthma Allergy. 2022 Nov 24; 15: 1701-1712. Doi: 10.2147/JAA.S390473.
22. Kang SY, Yang MS, Borres MP, Andersson M, Lee SM, Lee SP. The association between specific IgE antibodies to component allergens and allergic symptoms on dog and cat exposure among Korean pet exhibition participants. World Allergy Organ J. 2022 Oct 12; 15(11):100709.doi: 10.1016/j.waojou.2022.100709.
23. Ramírez-Mateo E, Fernández-Lozano C, De-Andrés-Martín A, González-De-Olano D. A Case of Transient Pediatric Pork-Cat Syndrome Caused by Sensitization to Albumin. J Investig Allergol Clin Immunol. 2024 Jun;34(3):209-211. doi: 10.18176/jiaci.0959.PMID: 38888583
24. Arkestål K, Sibanda E, Thors C, Troye-Blomberg M, Mduluza T, Valenta R, Grönlund H, van Hage M.Impaired allergy diagnostics among parasite-infected patients caused by IgE antibodies to the carbohydrate epitope galactose-alpha 1,3-galactose. J Allergy Clin Immunol. 2011 Apr;127(4):1024-8. doi: 10.1016/j.jaci.2011.01.033. Epub 2011 Mar 3. PMID: 21376382
25. Wilson JM, Schuyler AJ, Workman L, Gupta M, James HR, Posthumus J, McGowan EC, Commins SP, Platts-Mills TAE. Investigation into the alpha-Gal Syndrome: Characteristics of 261 Children and Adults Reporting Red Meat Allergy. J Allergy Clin Immunol Pract. 2019 Sep-Oct;7(7):2348-2358.e4. doi: 10.1016/j.jaip.2019.03.031. Epub 2019 Mar 30.PMID: 30940532
26. Hossenbaccus L, Linton S, Ramchandani R, Burrows AG, Ellis AK. Study of Cat Allergy Using Controlled Methodology-A Review of the Literature and a Call to Action. Front Allergy. 2022 Mar 17;3: 828091. doi: 10.3389/falgy.2022.828091. eCollection 2022.PMID: 35386639
27. Liccardi G, D'Amato G, Russo M, Canonica GW, D'Amato L, De Martino 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 Sep;132(1):1-12. doi: 10.1159/000073259.PMID: 14555853
28. Zeidler MR, Goldin JG, Kleerup EC, Kim HJ, Truong DA, Gjertson DW, Kennedy NJ, Newman KB, Tashkin DP, Silverman JM, Corren J. Small airways response to naturalistic cat allergen exposure in subjects with asthma. J Allergy Clin Immunol. 2006 Nov;118(5):1075-81. doi: 10.1016/j.jaci.2006.06.042. Epub 2006 Sep 8. PMID: 17088132
29. Käck U, van Hage M, Grönlund H, Lilja G, Asarnoj A, Konradsen JR. Allergic sensitization to lipocalins reflects asthma morbidity in dog dander sensitized children. Clin Transl Allergy. 2022 May 2;12(5):e12149. doi: 10.1002/clt2.12149. eCollection 2022 May.PMID: 3551007
30. 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 Apr; 97(4):907-14. doi: 10.1016/s0091-6749(96)80064-9.
31. Chapman MD, Wood RA. The role and remediation of animal allergens in allergic diseases. J Allergy Clin Immunol 2001 Mar; 107(3 Suppl): S414-21. doi: 10.1067/mai.2001.113672.
32. 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 Oct; 11(5):421-6. doi: 10.1007/s11882-011-0214-7.
33. Heinrich J, Bedada GB, Zock JP, Chinn S, Norbäck D, Olivieri M, Svanes C, Ponzio M, Verlato G, Villani S, Jarvis D, Luczynska C; Indoor Working Group of the European Community Respiratory Health Survey II. Cat allergen level: its determinants and relationship to specific IgE to cat across European centers. J Allergy Clin Immunol.2006 Sep; 118(3):674-81. doi: 10.1016/j.jaci.2006.06.012. Epub 2006 Jul 24. PMID: 16950287
34. 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 Apr; 99(4):577-8. doi: 10.1016/s0091-6749(97)70088-5.
35. 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 Jun; 137(2):141-4. doi: 10.1159/000085793. Epub 2005 May 13.

36. 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 Nov;59(11):1237-8. doi: 10.1111/j.1398-9995.2004.00599.x.PMID: 15461612
37. Liccardi G, Dente B, Senna G, De Martino M, D'Amato L, D'Amato G. Sensitization to horse allergens without apparent exposure to horse. Report of two cases. Eur Ann Allergy Clin Immunol.2005 Nov; 37(9):350-2. PMID: 16453968
38. Liccardi G, Emenius G, Merritt AS, Salzillo A, D'Amato M, D'Amato G. Direct and indirect exposure to horse: risk for sensitization and asthma. Curr Allergy Asthma Rep. 2012 Oct;12(5):429-37. doi: 10.1007/s11882-012-0280-5.PMID: 22717671
39. Mattsson L, Lundgren T, Everberg H, Larsson H, Lidholm J. Prostatic kallikrein: a new major dog allergen. J Allergy Clin Immunol 2009; 123:362-368
40. Basagaña M, Luengo O, Labrador M, Garriga T, Mattsson L, Lidholm J, et al. Component-Resolved Diagnosis of dog allergy. J Investig Allergol Clin Immunol 2017; 27:185-187
41. Villalta D, Milanese M, Da Re M, Sabatino G, Sforza M, Calzetta L, Liccardi G. Frequency of allergic sensitization to Can f 5 in North East Italy. An analysis of 1403 ISACs 112 (Component Resolved Diagnosis) collected retrospectively. Eur Ann Allergy Clin Immunol.2019 Jul; 51 (4):186-189. Doi: 10.23822/EurAnnACI.1764-1489.89.
42. Liccardi G, Calzetta L, Bilò MB, Brusca I, Cecchi L, Costantino MT, Da Re M, Buzzulini F, Giani M, Lombardi C, Meneguzzi G, Meriggi A, Milanese M, Onida R, Patella V, Pignatti P, Quercia O, Ridolo E, Sabatino G, Sacerdoti C, Savi E, Scala E, Steinhilber G, Villalta D, Passalacqua G, Rogliani P; Italian Allergic Respiratory Diseases Task Force. A prevalent exposure to male dog is a risk factor for exclusive allergic sensitization to Can f 5: An Italian multicenter study. J Allergy Clin Immunol Pract. 2020 Jul-Aug; 8(7):2399-2401. Doi: 10.1016/j.jaip.2020.02.041.
43. Ukleja-Sokolowska N, Lis K, Żbikowska-Gotz M, Adamczak R, Bartuzi Z. Analysis of allergen profile in patients sensitized to canine allergen and potential Can f 5 cross-reactivity with human PSA. Int J Immunopathol Pharmacol. 2021 Jan-Dec; 35:20587384211023670. doi: 10.1177/20587384211023670.PMID: 34116601
44. Liccardi G, Caminati M, Senna G, Calzetta L, Rogliani P. Anaphylaxis and intimate behaviour. Curr Opin Allergy Clin Immunol. 2017 Oct; 17(5):350-355. doi: 10.1097/ACI.0000000000000386.PMID: 28742538
45. Prince E, Zacharisen MC, Kurup VP. Anaphylaxis to rabbit: a case report. Ann Allergy Asthma Immunol.1998 Sep; 81(3):272-3. doi: 10.1016/S1081-1206(10)62825-6. PMID: 9759807
46. Gawlik R, Pitsch T, Dubuske L. Anaphylaxis as a manifestation of horse allergy. World Allergy Organ J. 2009 Aug; 2(8):185-9. doi: 10.1097/WOX.0b013e3181b2fe51.PMID: 23283110
47. Stave GM. Animal bite anaphylaxis, rarely diagnosed but underappreciated. Allergol Select. 2023 Aug 22;7: 149-153. doi: 10.5414/ALX02421E. eCollection 2023.PMID: 37705675
48. Guida G, Nebiolo F, Heffler E, Bergia R, Rolla G. Anaphylaxis after a horse bite. Allergy. 2005 Aug; 60(8):1088-9. doi: 10.1111/j.1398-9995.2005.00837.x.PMID: 15969694
49. Niitsuma T, Tsuji A, Nukaga M, Izawa A, Okita M, Maruoka N, Morita S, Tsuyuguchi M. Two cases of anaphylaxis after dwarf hamster bites. Allergy. 2003 Oct;58(10):1081. doi: 10.1034/j.1398-9995.2003.00242.x.PMID: 14510738
50. Stave GM, Lee EH, Darcey DJ. Laboratory Animal Bite Anaphylaxis: A National Survey: Part 1: Case Series and Review of the Literature. J Occup Environ Med. 2017 Aug;59(8):728-738. doi: 10.1097/JOM.0000000000001005.PMID: 28796663
51. Inoue F, Inoue A, Tsuboi T, Ichikawa T, Suga M, Ishihara S, Nakayama S. Severe Anaphylactic Shock Following a Slow Loris Bite in a Patient with Cat Allergy. Intern Med. 2021 Sep 15;60(18):3037-3039. doi: 10.2169/internalmedicine.6775-20. Epub 2021 Mar 29. PMID: 33776006
52. Scheib H, Nekaris KA, Rode-Margono J, Ragnarsson L, Baumann K, Dobson JS, Wirdateti W, Nouwens A, Nijman V, Martelli P, Ma R, Lewis RJ, Kwok HF, Fry BG. The Toxicological Intersection between Allergen and Toxin: A Structural Comparison of the Cat Dander Allergenic

Protein Fel d1 and the Slow Loris Brachial Gland Secretion Protein. Toxins (Basel). 2020 Jan 28;12(2):86. doi: 10.3390/toxins12020086.PMID: 32012831
53. Ligabue-Braun R. Hello, kitty: could cat allergy be a form of intoxication? J Venom Anim Toxins Incl Trop Dis 2020 Dec 14: 26: e20200051. doi: 10.1590/1678-9199-JVATITD-2020-0051.
54. Bilò MB, Danieli MG, Moroncini G, Martini M. Hymenoptera Venom Allergy and Anaphylaxis. Curr Pharm Des. 2023; 29(3):165-177. doi: 10.2174/1381612828666220817091039.PMID: 35980057
55. Hudson TW, Stave GM. Laboratory Animal Allergy Prevention-10-Year National Survey Follow-up Shows Little Progress; We Urgently Need to Address This. J Occup Environ Med. 2023 Jun 1;65(6): e440. doi: 10.1097/JOM.0000000000002827. Epub 2023 Mar 9. PMID: 36893058
56. Kesici GG, Karataþ A, Ünlü Y, Tutkun E. Occupational allergy to dog among police dog trainers. Eur Ann Allergy Clin Immunol. 2019 Nov;51(6):265-273. doi: 10.23822/EurAnnACI.1764-1489.102.
57. Liccardi G, Billeri L, Foglia M, Sapio C, De Giglio MA, D'Amato G. An unusual case of occupational asthma in a part time magician. He has got an allergy surprise from his top hat! Eur Ann Allergy Clin Immunol. 2014 Sep;46(5):178-80. PMID: 25224948
58. Krakowiak A, Szulc B, Górski P. Allergy to laboratory animals in children of parents occupationally exposed to mice, rats and hamsters. Eur Respir J. 1999 Aug;14(2):352-6. doi: 10.1034/j.1399-3003.1999.14b19.x.PMID: 10515413
59. Liccardi G, Martini M, Bilò MB, Milanese M, Calzetta L, Laitano R, Rogliani P. A narrative review on asthma and pest sensitization (cockroach, mouse and rat allergens): a social issue besides the medical problem. J Asthma. 2023 Oct;60(10):1800-1808. doi: 10.1080/02770903.2023.2200844. Epub 2023 Apr 23. PMID: 37042228
60. Liccardi G, Martini M, Bilò MB, Cecchi L, Milanese M, Brussino L, Motta E, Rogliani P. Why is Pet (cat/dog) allergen immunotherapy (ait) such a controversial topic? current perspectives and future directions. Eur Ann Allergy Clin Immunol. 2024 Feb 13. doi: 10.23822/EurAnnACI.1764-1489.330. Online ahead of print. PMID: 38348623
61. Uriarte SA, Grönlund H, Wintersand A, Bronge J, Sastre J. Clinical and Immunologic Changes due to Subcutaneous Immunotherapy With Cat and Dog Extracts Using an Ultrarush Up-Dosing Phase: A Real-Life Study. J Investig Allergol Clin Immunol.2022 Apr 19; 32 (2):133-140 DOI: 10.18176/jiaci.0656.

Table 1. Main cat/dog allergens.

Allergens source	Allergen	Biochemical family	Prevalence of specific IgE in patients (%)	MW (kDa)
Cat (*Felis domesticus*)	Fel d 1	Secretoglobin	> 90	18
	Fel d 2	Serum albumin	14-23	69
	Fel d 3	Cystatin	10	11
	Fel d 4	Lipocalin	63	22
	Fel d 5	Immunoglobulin	20-40	400
	Fel d 6	Immunoglobulin	/	800-1,000
	Fel d 7	Lipocalin	38	17.5
	Fel d 8	Latherin	19	24
Dog (*Canis familiaris*)	Can f 1	Lipocalin	50-90	23-25
	Can f 2	Lipocalin	22-35	19
	Can f 3	Serum albumin	25-60	69
	Can f 4	Lipocalin	35-59	18-23
	Can f 5	Kallicrein	31-76	8
	Can f 6	Lipocalin	56	27-29
	Can f 7	Nieman Pick type C2	10-14	14
	Can f 8	Cystatin	10-14	14

Figure 1. Positive/negative role of domestic non-domestic animals in allergy.