Check for updates

REVIEW

Recent Understandings of Pet Allergies [version 1; peer review: 2 approved]

Dennis Ownby¹, Christine Cole Johnson²¹Georgia Regents University, Augusta, GA, USA²Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA**V1** First published: 27 Jan 2016, 5(F1000 Faculty Rev):108
<https://doi.org/10.12688/f1000research.7044.1>Latest published: 27 Jan 2016, 5(F1000 Faculty Rev):108
<https://doi.org/10.12688/f1000research.7044.1>**Abstract**

Allergic reactions to pets have been recognized for at least a hundred years. Yet our understanding of the effects of all of the interactions between pet exposures and human immune responses continues to grow. Allergists, epidemiologists, and immunologists have spent years trying to better understand how exposures to pet allergens lead to allergic sensitization (the production of allergen-specific immunoglobulin class E [IgE] antibodies) and subsequent allergic disease. A major new development in this understanding is the recognition that pet exposures consist of not only allergen exposures but also changes in microbial exposures. Exposures to certain pet-associated microbes, especially in the neonatal period, appear to be able to dramatically alter how a child's immune system develops and this in turn reduces the risk of allergic sensitization and disease. An exciting challenge in the next few years will be to see whether these changes can be developed into a realistic preventative strategy with the expectation of significantly reducing allergic disease, especially asthma.

Keywords

Pet Allergies , Allergic reactions , IgE antibodies , allergic sensitization ,

Open Peer Review**Approval Status**

	1	2
version 1 27 Jan 2016

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Wanda Phipatanakul**, Boston Children's Hospital, Boston, USA
2. **David Lang**, Cleveland Clinic Foundation, Cleveland, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Dennis Ownby (downby@gru.edu)

Competing interests: Neither of the authors has any commercial competing interests related to the ideas and opinions expressed in this manuscript.

Grant information: The authors are funded by the National Institutes of Allergy and Infectious Disease for studies related to the relationships between the human gut microbiome and allergic disease.

Copyright: © 2016 Ownby D and Johnson CC. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Ownby D and Johnson CC. **Recent Understandings of Pet Allergies [version 1; peer review: 2 approved]** F1000Research 2016, 5(F1000 Faculty Rev):108 <https://doi.org/10.12688/f1000research.7044.1>

First published: 27 Jan 2016, 5(F1000 Faculty Rev):108 <https://doi.org/10.12688/f1000research.7044.1>

Introduction

Many families in the US and other countries keep a variety of pets. The American Pet Products Association estimates that 65% of US households own a pet, an increase of 3% from 2010 to 2015. Although this estimate may be high, there is little doubt that approximately half of all American families have a pet and the vast majority of these pets are furry^{1,2}. It is also well known that when there is a high prevalence of pet-keeping in a community, pet allergens are found in relatively high concentrations in public places such as schools. These “second-hand” exposures to pet allergens have been shown to exacerbate disease in sensitive children³. The purpose of this review is to provide an understanding of some of the recent studies related to pet allergies and potential health consequences. The areas to be explored include the following: the changing prevalence of all types of allergic diseases, how people’s interactions with pets have changed, new concepts of how the human immune system responds to pet allergens, and especially the growing understanding of how this immune response relates to the microbial ecology of the gut. The potential economic costs of pet allergies will also be briefly explored. There are many excellent reviews focusing on the precise mechanisms of human immune responses to pets^{4–9}.

This review will focus on scientific research related to human allergic responses to pets. However, it is important to recognize that pet allergy can be a very emotionally sensitive topic. Every practicing allergist has repeatedly heard a family say that “if ‘X’ person in the family is allergic to the pet, then ‘X’ goes and the pet stays in the home!”. This statement is always meant to be humorous but it clearly comes from strong feelings about the pet’s place in the family. This is but one example of how pets are commonly considered members of the family and considerable angst is generated if there is a conflict between the potential health of a family member and the love of the pet. The point to be made is that strong emotions may lead to strongly held beliefs that have little factual basis. The internet has widely spread information on topics such as “low” or “hypoallergenic” pets when there is little supporting scientific evidence^{10,11}.

This review will focus on cats and dogs since these are the most popular pets in the US and many other developed countries. Because cats and dogs are the most prevalent household pets, there are many more studies of how they relate to allergic disease. Although reactions to other animals will not be examined in detail, allergic responses to other animals are believed to be similar to those elicited by cats and dogs after considering the relative intensity and duration of exposures, and many studies have shown that the majority of pet allergens come from the same protein family^{12,13}. An important cross-over area is occupational exposure versus in-home exposure to animals. For example, in both settings, exposure to mice or rats can be desired (pets or reared animals) or unwanted (vermin). The literature in these areas is voluminous but beyond the scope of this review.

An important topic that is beyond this review is the relationship between exposure to cats and dogs and the risk of allergic disease. This subject has been widely debated and subjected to numerous reviews but will not be included herein^{4,14–19}.

Temporal increase in prevalence of allergies

Many studies over the previous two to three decades have suggested that allergic diseases have increased in frequency²⁰. Most notable has been the increase in asthma over the past three decades. Although some would argue that there have been epidemics of different allergic diseases at different times, it is difficult to discern how many of these changes were related to gradually improving recognition and diagnosis of new diseases²⁰. However, there is little doubt that asthma has nearly tripled in prevalence among youth in the US since the 1970s and that food allergies have at least doubled in the same period^{21,22}. The reasons for the increase in the prevalence of allergies have been widely debated and investigated but there is no consensus on the precise cause. Among the many hypotheses are improving hygiene, global warming, increasing use of antibiotics (especially in food), and reduced physical activity. One of the few agreed-upon assumptions is that the increase has occurred during one or two generations, making genetic evolution highly improbable; however, a new area of inquiry is epigenetic change, which is the heritable change in gene expression that does not involve changes to the underlying DNA sequence. There are at least three mechanisms of epigenetic change: DNA methylation, histone modification, and non-coding RNA-associated gene silencing²³. Epigenetic changes have been linked to asthma in some studies^{24–27}.

Changing relationships of people to pets

Objective data concerning how persons view their pets and the role of pets in families over multiple generations are extremely hard to find. A study by Kennedy and McGarvey took an interesting approach to examining this question of whether the relationship between pets and their families has changed over time²⁸. They examined 1,348 advertisements including both people and pets which had appeared in popular US women’s magazines from the 1920s through the 1980s and coded the ads for seven themes such as whether the pet was depicted indoors or outdoors, was on a leash, or was used to depict companionship (i.e. touching or holding the pet). They concluded that over the time interval studied, pets have moved from outdoor protectors to indoor family members²⁸.

The increasingly close contact between persons and pets and the resulting higher allergen exposures occurred over the same decades during which all allergic diseases appeared to be increasing. This combination has been thought to be a major reason for the increase in pet allergies. Unfortunately, data supporting this hypothesis are not robust. In the US, skin test results from the NHANES (National Health and Nutrition Examination Survey) II and III studies were compared. NHANES II was conducted from 1976 through 1980, and NHANES III was from 1988 through 1994. There were six allergens common to both studies, allowing comparison of results in a representative sample of the non-institutionalized, US population, from ages 6 to 59 years. The probability of reacting to at least one allergen skin test was higher in NHANES III compared with II: 41.9% (standard error [SE] 1.23) and 21.8% (SE 0.94), respectively, slightly more than a doubling. Reactivity to cat, the only pet allergen tested in both NHANES II and III, increased 5.5-fold (3.1% to 17.0%) compared with an average increase of 2.6-fold for the other five in common allergens (rye and Bermuda grasses, short ragweed, oak, and *Alternaria alternata*). Tempering this finding is

the possibility that the cat allergen used in NHANES III was more potent, thus increasing reactivity; however, studies from Europe suggest similar changes²⁹.

Immune response to pet allergens

Allergy has always been defined by the presence of immunoglobulin class E (IgE) antibodies immunologically specific for individual antigens. Initially, the minute quantities of IgE present in humans could be detected only by allergen skin testing. Now laboratory tests for cat allergens are essentially as sensitive as skin tests, but the results of skin and *in vitro* tests are not always identical^{29,30}. Antigens eliciting IgE responses are referred to as allergens. Although IgE antibodies have been most extensively studied, humans do produce other immune responses to allergens. Immune responses are initiated by specialized antigen-presenting cells such as dendritic cells, which present the allergen to T cells. Attempts have been made to identify the small portions of the major cat allergen (*Felix domesticus* 1, abbreviated Fel d 1) presented to T cells, in the hope of using these peptides to induce hypo-responsiveness to Fel d 1 as a treatment for cat allergy^{31,32}. Recent studies have identified how the cysteine-rich portion of the major cat allergen, Fel d 1, is bound on cells through a mannose receptor³³. Some have suggested that Fel d 1 is uniquely able to induce an IgG subclass 4 (IgG4) response in many individuals and that high concentrations of Fel d 1-specific IgG4 can block IgE responses^{34,35}. However, other studies have not found a relationship between cat-specific IgE and IgG4 levels and symptoms^{36,37}. Multiple studies, including those of allergen immunotherapy with cat and other allergens, all suggest that repeated relatively high-dose exposure to any allergen leads to IgG4 production^{7,38,39}.

Interestingly, the allergens characterized from furry animals thus far have all belonged to three broad groups of proteins: secretoglobins, lipocalins, and kallikreins. Whereas Fel d 1 is a secretoglobin of unknown function, more than 50% of allergens from furry animals have been identified as lipocalins^{12,13}. These animal allergens are found in dander, saliva, and urine. They are commonly on small particles that allow airborne dispersion and also dispersion by adherence to surfaces such as clothing^{2,40}. The apparent constant circulation of pet allergens on shoes and clothing through public areas and into homes has made it very difficult to control symptoms from pet allergens by avoidance measures such as air cleaning^{41,42}.

Microbial exposures related to pets and other animals

Probably the most dramatic change in understanding the relationships between pet exposure and pet allergy is the realization that pet exposure involves more than just exposure to the allergens shed by the pet⁴³. Multiple studies have shown that early life exposure to pets and to farm animals is associated with a reduced risk of subsequent allergic disease^{44–46}. Although other studies have disputed these findings, the results of systematic reviews and meta-analyses have typically shown either a reduction or no increase in risk associated with infantile exposure to furry pets^{47–50}. The hypothesis developed to explain why animal exposure could be associated with a decreased prevalence of allergy postulates that animals increase the diversity of microbes to which a child is exposed, and that this more diverse exposure leads to the development of

an immune system less likely to develop allergic responses to antigens. Two studies have demonstrated that cats or dogs in the home increase the diversity of the microbiota of the home^{43,51}. Another study showed that the stool microbiota of children living with pets differed from those without pet exposure. Studies in homes of farmers also suggest a broader diversity of microbes^{52–54}. Several investigations have been directed toward understanding the dominant exposures of farm living leading to a lower prevalence of allergic disease. One important factor in farm living is consumption of farm (i.e. unpasteurized) milk^{55–57}. The assumption is that farm milk contains many live bacteria that can alter the gut microbiota of the child, or that unpasteurized milk contains substances supporting the growth of specific microbes. This hypothesis is supported by studies showing that the amount of bacterial contamination in surface water used for drinking is directly correlated with a lower risk of allergic disease⁵⁸. Variables that appear relatively consistent in all of these studies are (1) that the exposure to diverse bacteria must occur in during the first year of life and perhaps in the first weeks of life, and (2) that the types of bacteria which appear to be protective are common soil bacteria or bacteria found in the gastrointestinal tracts of mammals. This increasing knowledge related to microbial exposure has led some to suggest that we shift from the “hygiene” to the “microbial” hypothesis of allergen protection^{59,60}. The critical question is whether this knowledge can be developed into a medically valuable preventive strategy such as supplementing mothers or infants with live bacteria at a critical stage of development.

Although the full demonstration of this animal-microbe-gut-immune development hypothesis has not been achieved, multiple human and animal studies strongly support the hypothesis. Several early studies have shown that there are differences in stool microbes between children in certain countries and that these changes are associated with the risk of asthma⁶¹. One of the most supportive mouse studies was by Fujimura *et al.*⁶². These investigators first compared gavage young adult mice with slurries of house dust from homes with and without dogs. The mice were then immunized with cockroach allergen by using a protocol designed to induce allergic sensitivity and asthma-like airway reactivity. The mice given the dust from homes with a dog were strongly protected from sensitization and airway disease compared with mice given the house dust from homes without dogs. An analogous experiment using challenge with respiratory syncytial virus (RSV) again showed strong protection of the mice given dust from homes with dogs. When the microbial communities of the caeca of the gavage mice were examined, several different microbes were in much higher abundance in the mice given dust from homes with dogs. One of these bacteria, *Lactobacillus johnsonii*, was cultured and given to groups of mice. The mice given gavages with live *L. johnsonii* were again significantly protected from both allergen-induced and RSV infection-induced airway disease, but gavages with killed bacteria were not effective. It has been shown that supplementing high-risk infants with *Lactobacillus casei* subsp. Rhamnosus (LGG) does alter the development of the gut microbiome and so it may be possible to use supplementation as a disease prevention strategy in humans⁶³. Others have shown similar protective effects from *Lactobacillus reuteri* in mice⁶⁴. There are also suggestions that vitamins and other diet elements may play roles in altering the gut microbiome and the subsequent function of the immune system^{65,66}.

While the hypothesis of infants acquiring a different gut microbiome from animal exposure has been developing, there are other findings that suggest this hypothesis is missing essential elements. An alternative hypothesis is that pregnant women living with pets or closely associated with farm animals may over time develop different gut and vaginal microbiomes and that these pet-associated maternal gut microbiomes are inoculated into infants during normal vaginal birth. This would fit with the studies showing that birth by C-section carries a higher risk of childhood asthma than vaginal birth, presumably because an infant does not acquire a large inoculum of maternal vaginal and gut microbes at birth^{67–69}. Another study related to this hypothesis is the finding that the prenatal presence of dogs in homes has a stronger effect on the development of total serum IgE in infants delivered by C-section than those born vaginally⁷⁰. It could be argued that if pets were associated with an alteration of the maternal gut or vaginal microbiome, a stronger effect would have been expected in infants born vaginally. An alternative argument is that infants born by C-section have a suboptimal initial maternal inoculum, which allows a greater impact by environmental microbes such as those in house dust on early colonization^{68,71,72}.

A common argument against the hygiene and microbial hypotheses related to allergy is the frequently quoted high prevalence of asthma among inner-city residents^{73–75}. However, a recent study from the Inner-City Asthma Consortium found a clear interrelationship between allergen exposure, microbe exposure, and risk of disease¹⁸. In that study, children with the greatest exposure to allergens and bacteria in specifically the first year of life had the lowest risk of recurrent wheeze and allergic sensitization, again suggesting the protective effect from exposure to a high diversity of bacteria. Unfortunately, that study was racially homogenous and so potential effects of race could not be evaluated.

An important element to consider in all studies of pets and of microbes is the timing of exposure related to immune development. As already suggested, the effects of pets on the development of the infant gut microbiome are likely to be much larger in the first weeks and months of life than in later childhood. The one-year age cutoff found in many studies may be an artifact of how data were collected rather than a biological horizon.

A common question related to the apparent protective effect of early pet exposure on allergy is whether this is of clinical significance and if so how the information should be used. The current level of understanding is inadequate at best. If our hypothesis that early pet exposure may alter an infant's developing microbiota and lead to a reduced risk of some immune diseases is correct, then the critical question is whether this knowledge can be transformed into a therapeutic strategy. Clearly, exposing all children to pets is not possible and probably not desirable. There are many questions related to owning a pet to consider: costs of food, veterinary care, possible zoonotic infections, etc. These are questions that persons should carefully consider before obtaining a pet. However, if a pregnant woman has a pet when she finds that she is pregnant, we believe that there is no increased risk of allergic disease and probably a

decreased risk if she continues to keep the pet through the birth of her child and the child's first year. After the first year of life, the data become inconsistent. Some studies suggest that continued pet exposure after the first year of life provides additional protection from atopy whereas other studies do not find any benefit after the first year^{76–78}. The more important question is whether knowledge of the interaction of pet and human microbiota can be used to provide a preventive option such as a probiotic supplement. Although such trials have been conducted with mixed results, it appears that much more study and understanding are necessary before there will be consistent success with such approaches^{79,80}. Other potentially simple approaches to allergy reduction that may be related to microbial exposures, such as hand washing of dishes and licking pacifiers, seem to be helpful with minimal risks^{81,82}.

Health-care costs related to pet allergy

The potential allergy-related health-care costs of keeping pets are rarely discussed in the medical literature, partially because these costs are difficult to objectively assess. One question is whether pet-keeping by pet-allergic individuals with asthma substantially increases costs of asthma care. A study estimated that the increased number of visits for acute asthma care among dog-allergic adults, who chose to live with dogs, might add as much as \$0.5 to 1.0 billion per year to costs of care in 2010⁸³. This estimate suggests a substantial increase in health-care cost for adults but does not include indirect costs such as lost work days which would drive the estimate even higher⁸³. Unfortunately, there have not been any similar estimates of how pet allergy might increase the cost of asthma care for children. However, Almqvist *et al.* showed that even indirect exposure to cat dander, brought into classrooms on the clothes of children living with cats, increased symptoms and medication use in cat-allergic children with asthma⁸⁴. The increased costs of new-onset asthma in a child are also difficult to estimate but substantial. A longitudinal study of 3,535 school children in California identified only three risk factors for new-onset asthma in these children: a humidifier (relative risk [RR] 1.7, confidence interval [CI] 1.2–2.4), any pet (RR 1.6, CI 1.0–2.5), and having a dog in the home (RR 1.4, CI 1.0–2.0)⁸⁵. Similarly, in other studies, sensitization to cats or dogs has been identified as a risk factor for new-onset reactive airway disease^{86,87}. The presence of a dog in the home also increased ozone exposure-related asthma symptoms in a study⁸⁸. In total, these studies suggest that allergic sensitivity to pets and pet exposure are significant contributors to the overall costs of asthma care.

The combination of the studies summarized in this review shows a somewhat paradoxical relationship of pets and allergy. Exposure to the microbes associated with pets in the first few months of life appears to be associated with a substantial reduction in the risk of allergic disease and asthma. This effect appears to last at least until early adulthood⁷⁸. Only one longitudinal study has shown that continuing exposure to dogs was required for continuing protection at least until 7 years of age⁷⁶. Others have not shown any apparent effect after the first year⁷⁷. A few studies have shown that sensitization to cats or dogs is a risk factor for new-onset asthma later in life, and one study has shown that the presence of a dog in the home was a risk factor for new-onset asthma.

Summary

Pets are an important source of health benefits to many individuals. But close contact with pets, such as when they live in homes, can be associated with a variety of risks, including medically significant allergic diseases. Adding confusion to our understanding of the relationship of pets to allergic disease has been the discovery that infantile exposure to furry pets appears to be associated with a substantial reduction of allergy and asthma risks in childhood; however, it is possible that continuing pet exposure may become a risk for allergies and asthma at some stage of life. The apparent allergy-protective effect of pets appears to be mediated through exposure to a more diverse microbial community in the home. The discovery of this microbe-related protective effect will hopefully lead to allergy

prophylactic options in the coming years without requiring direct pet or other animal exposure.

Competing interests

Neither of the authors has any commercial competing interests related to the ideas and opinions expressed in this manuscript.

Grant information

The authors are funded by the National Institutes of Allergy and Infectious Disease for studies related to the relationships between the human gut microbiome and allergic disease.

References

- Zane JP: **Pets of the golden years.** New York Times. New York, 2015.
- Arbes SJ Jr, Cohn RD, Yin M, *et al.*: **Dog allergen (Can f 1) and cat allergen (Fel d 1) in US homes: results from the National Survey of Lead and Allergens in Housing.** *J Allergy Clin Immunol.* 2004; **114**(1): 111–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Almqvist C, Larsson PH, Egmar AC, *et al.*: **School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes.** *J Allergy Clin Immunol.* 1999; **103**(6): 1012–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Dharmage SC, Lodge CL, Matheson MC, *et al.*: **Exposure to cats: update on risks for sensitization and allergic diseases.** *Curr Allergy Asthma Rep.* 2012; **12**(5): 413–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Simpson A: **Effect of household pet ownership on infant immune response and subsequent sensitization.** *J Asthma Allergy.* 2010; **3**: 131–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Konradsen JR, Nordlund B, Onell A, *et al.*: **Severe childhood asthma and allergy to furry animals: refined assessment using molecular-based allergy diagnostics.** *Pediatr Allergy Immunol.* 2014; **25**(2): 187–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Akdis CA, Akdis M: **Mechanisms and treatment of allergic disease in the big picture of regulatory T cells.** *J Allergy Clin Immunol.* 2009; **123**(4): 735–46; quiz 747–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Böttcher I, Bellinghausen I, König B, *et al.*: **Different regulation of T helper 1- and T helper 2-promoting cytokine signalling factors in human dendritic cells after exposure to protein versus contact allergens.** *Immunology.* 2008; **123**(1): 139–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Burton OT, Oettgen HC: **Beyond immediate hypersensitivity: evolving roles for IgE antibodies in immune homeostasis and allergic diseases.** *Immunol Rev.* 2011; **242**(1): 128–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Nicholas CE, Wegienka GR, Havstad SL, *et al.*: **Dog allergen levels in homes with hypoallergenic compared with nonhypoallergenic dogs.** *Am J Rhinol Allergy.* 2011; **25**(4): 252–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Butt A, Rashid D, Lockey RF: **Do hypoallergenic cats and dogs exist?** *Ann Allergy Asthma Immunol.* 2012; **108**(2): 74–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Nilsson OB, van Hage M, Grönlund H: **Mammalian-derived respiratory allergens - implications for diagnosis and therapy of individuals allergic to furry animals.** *Methods.* 2014; **66**(1): 86–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Díaz-Perales A, González-de-Olano D, Pérez-Gordo M, *et al.*: **Allergy to uncommon pets: new allergies but the same allergens.** *Front Immunol.* 2013; **4**: 492.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lodge CJ, Allen KJ, Lowe AJ, *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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lodge CJ, Lowe AJ, Gurrin LC, *et al.*: **Pets at birth do not increase allergic disease in at-risk children.** *Clin Exp Allergy.* 2012; **42**(9): 1377–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kelly LA, Erwin EA, Platts-Mills TA: **The indoor air and asthma: the role of cat allergens.** *Curr Opin Pulm Med.* 2012; **18**(1): 29–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Korppi M, Hyvärinen M, Kotaniemi-Syrjänen A, *et al.*: **Early exposure and sensitization to cat and dog: different effects on asthma risk after wheezing in infancy.** *Pediatr Allergy Immunol.* 2008; **19**(8): 696–701.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lynch SV, Wood RA, Boushey H, *et al.*: **Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children.** *J Allergy Clin Immunol.* 2014; **134**(3): 593–601.e12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Carlsten C, Dimich-Ward H, Becker AB, *et al.*: **Indoor allergen exposure, sensitization, and development of asthma in a high-risk birth cohort.** *Pediatr Allergy Immunol.* 2010; **21**(4 Pt 2): e740–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Platts-Mills TA: **The allergy epidemics: 1870–2010.** *J Allergy Clin Immunol.* 2015; **136**(1): 3–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sicherer SH, Muñoz-Furlong A, Burks AW, *et al.*: **Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey.** *J Allergy Clin Immunol.* 1999; **103**(4): 559–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sicherer SH, Leung DY: **Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2010.** *J Allergy Clin Immunol.* 2011; **127**(2): 326–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lim PS, Li J, Holloway AF, *et al.*: **Epigenetic regulation of inducible gene expression in the immune system.** *Immunology.* 2013; **139**(3): 285–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Breton CV, Byun HM, Wang X, *et al.*: **DNA methylation in the arginase-nitric oxide synthase pathway is associated with exhaled nitric oxide in children with asthma.** *Am J Respir Crit Care Med.* 2011; **184**(2): 191–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Hollingsworth JW, Maruoka S, Boon K, *et al.*: **In utero supplementation with methyl donors enhances allergic airway disease in mice.** *J Clin Invest.* 2008; **118**(10): 3462–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Selgrade MK, Blain RB, Fedak KM, *et al.*: **Potential risk of asthma associated with in utero exposure to xenobiotics.** *Birth Defects Res C Embryo Today.* 2013; **99**(1): 1–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Virani S, Dolinoy DC, Halubai S, *et al.*: **Delivery type not associated with global methylation at birth.** *Clin Epigenetics.* 2012; **4**(1): 8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Kennedy PF, McGarvey MG: **Animal-companion depictions in women's magazine advertising.** *Journal of Business Research.* 2008; **61**(5): 424–30.
[Publisher Full Text](#)

29. Konradsen JR, Fujisawa T, van Hage M, *et al.*: **Allergy to furry animals: New insights, diagnostic approaches, and challenges.** *J Allergy Clin Immunol.* 2015; 135(3): 616–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. **F** Fernández C, Cárdenas R, Martín D, *et al.*: **Analysis of skin testing and serum-specific immunoglobulin E to predict airway reactivity to cat allergens.** *Clin Exp Allergy.* 2007; 37(3): 391–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
31. Briner TJ, Kuo MC, Keating KM, *et al.*: **Peripheral T-cell tolerance induced in naive and primed mice by subcutaneous injection of peptides from the major cat allergen Fel d 1.** *Proc Natl Acad Sci U S A.* 1993; 90(16): 7608–12.
[PubMed Abstract](#) | [Free Full Text](#)
32. **F** Herre J, Grönlund H, Brooks H, *et al.*: **Allergens as immunomodulatory proteins: the cat dander protein Fel d 1 enhances TLR activation by lipid ligands.** *J Immunol.* 2013; 191(4): 1529–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
33. **F** Emara M, Royer PJ, Abbas Z, *et al.*: **Recognition of the major cat allergen Fel d 1 through the cysteine-rich domain of the mannose receptor determines its allergenicity.** *J Biol Chem.* 2011; 286(15): 13033–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. Platts-Mills T, Vaughan J, Squillace S, *et al.*: **Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study.** *Lancet.* 2001; 357(9258): 752–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Platts-Mills TA, Woodfolk JA, Erwin EA, *et al.*: **Mechanisms of tolerance to inhalant allergens: the relevance of a modified Th2 response to allergens from domestic animals.** *Springer Semin Immunopathol.* 2004; 25(3–4): 271–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Burnett M, Wegienka G, Havstad S, *et al.*: **Relationship of dog- and cat-specific IgE and IgG₄ levels to allergic symptoms on pet exposure.** *J Allergy Clin Immunol Pract.* 2013; 1(4): 350–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Jarvis D, Zock JP, Heinrich J, *et al.*: **Cat and dust mite allergen levels, specific IgG and IgG₄, and respiratory symptoms in adults.** *J Allergy Clin Immunol.* 2007; 119(3): 697–704.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. **F** Burks AW, Jones SM, Wood RA, *et al.*: **Oral immunotherapy for treatment of egg allergy in children.** *N Engl J Med.* 2012; 367(3): 233–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. **F** Meiler F, Klunker S, Zimmermann M, *et al.*: **Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors.** *Allergy.* 2008; 63(11): 1455–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
40. Enberg RN, Shemie SM, McCullough J, *et al.*: **Ubiquitous presence of cat allergen in cat-free buildings: probable dispersal from human clothing.** *Ann Allergy.* 1993; 70(6): 471–4.
[PubMed Abstract](#)
41. Wood RA, Johnson EF, Van Natta ML, *et al.*: **A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy.** *Am J Respir Crit Care Med.* 1998; 158(1): 115–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Sublett JL, Seltzer J, Burkhead R, *et al.*: **Air filters and air cleaners: rostrum by the American Academy of Allergy, Asthma & Immunology Indoor Allergen Committee.** *J Allergy Clin Immunol.* 2010; 125(1): 32–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Fujimura KE, Johnson CC, Ownby DR, *et al.*: **Man's best friend? The effect of pet ownership on house dust microbial communities.** *J Allergy Clin Immunol.* 2010; 126(2): 410–2, 412.e1–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Braun-Fahrlander C, Lauener R: **Farming and protective agents against allergy and asthma.** *Clin Exp Allergy.* 2003; 33(4): 409–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. **F** 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(8): 963–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
46. Bacharier LB, Strunk RC: **Pets and childhood asthma—how should the pediatrician respond to new information that pets may prevent asthma?** *Pediatrics.* 2003; 112(4): 974–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. **F** Langan SM, Flohr C, Williams HC: **The role of furry pets in eczema: a systematic review.** *Arch Dermatol.* 2007; 143(12): 1570–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
48. **F** Lodrup Carlsen KC, 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(8): e43214.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. **F** Pelucchi C, Galeone C, Bach JF, *et al.*: **Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies.** *J Allergy Clin Immunol.* 2013; 132(3): 616–622.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
50. **F** Takkouche B, González-Barcala FJ, Etminan M, *et al.*: **Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis.** *Allergy.* 2008; 63(7): 857–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. **F** Dunn RR, Fierer N, Henley JB, *et al.*: **Home life: factors structuring the bacterial diversity found within and between homes.** *PLoS One.* 2013; 8(5): e64133.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. Alenius H, Pakarinen J, Saris O, *et al.*: **Contrasting immunological effects of two disparate dusts - preliminary observations.** *Int Arch Allergy Immunol.* 2009; 149(1): 81–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Debarry J, Garn H, Hanuszkiewicz A, *et al.*: **Acinetobacter Iwoffii and Lactococcus lactis strains isolated from farm cowsheds possess strong allergy-protective properties.** *J Allergy Clin Immunol.* 2007; 119(6): 1514–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. **F** Ege MJ, Mayer M, Normand AC, *et al.*: **Exposure to environmental microorganisms and childhood asthma.** *N Engl J Med.* 2011; 364(8): 701–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. Perkin MR, Strachan DP: **Which aspects of the farming lifestyle explain the inverse association with childhood allergy?** *J Allergy Clin Immunol.* 2006; 117(6): 1374–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. **F** Waser M, Michels KB, Bieli C, *et al.*: **Inverse association of farm milk consumption with asthma and allergy in rural and suburban populations across Europe.** *Clin Exp Allergy.* 2007; 37(5): 661–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
57. **F** Lluís A, Depner M, Gaugler B, *et al.*: **Increased regulatory T-cell numbers are associated with farm milk exposure and lower atopic sensitization and asthma in childhood.** *J Allergy Clin Immunol.* 2014; 133(2): 551–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. **F** von Hertzen L, Laatikainen T, Pitkanen T, *et al.*: **Microbial content of drinking water in Finnish and Russian Karelia - implications for atopy prevalence.** *Allergy.* 2007; 62(3): 288–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
59. Penders J, Stobberingh EE, van den Brandt PA, *et al.*: **The role of the intestinal microbiota in the development of atopic disorders.** *Allergy.* 2007; 62(11): 1223–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Penders J, Gerhold K, Thijs C, *et al.*: **New insights into the hygiene hypothesis in allergic diseases: mediation of sibling and birth mode effects by the gut microbiota.** *Gut Microbes.* 2014; 5(2): 239–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Björkstén B, Naaber P, Sepp E, *et al.*: **The intestinal microflora in allergic Estonian and Swedish 2-year-old children.** *Clin Exp Allergy.* 1999; 29(3): 342–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. Fujimura KE, Demoor T, Rauch M, *et al.*: **House dust exposure mediates gut microbiome Lactobacillus enrichment and airway immune defense against allergens and virus infection.** *Proc Natl Acad Sci U S A.* 2014; 111(2): 805–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. **F** Cox MJ, Huang YJ, Fujimura KE, *et al.*: **Lactobacillus casei abundance is associated with profound shifts in the infant gut microbiome.** *PLoS One.* 2010; 5(1): e8745.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
64. **F** Forsythe P, Inman MD, Bienenstock J: **Oral treatment with live Lactobacillus reuteri inhibits the allergic airway response in mice.** *Am J Respir Crit Care Med.* 2007; 175(6): 561–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
65. Ly NP, Litonjua A, Gold DR, *et al.*: **Gut microbiota, probiotics, and vitamin D: interrelated exposures influencing allergy, asthma, and obesity?** *J Allergy Clin Immunol.* 2011; 127(5): 1087–94; quiz 1095–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Weiss ST, Litonjua AA: **Vitamin D, the gut microbiome, and the hygiene hypothesis. How does asthma begin?** *Am J Respir Crit Care Med.* 2015; 191(5): 492–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. **F** Debley JS, Smith JM, Redding GJ, *et al.*: **Childhood asthma hospitalization risk after cesarean delivery in former term and premature infants.** *Ann Allergy Asthma Immunol.* 2005; 94(2): 228–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. **F** Dominguez-Bello MG, Costello EK, Contreras M, *et al.*: **Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns.** *Proc Natl Acad Sci U S A.* 2010; 107(26): 11971–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
69. **F** Renz-Polster H, David MR, Buist AS, *et al.*: **Caesarean section delivery and the risk of allergic disorders in childhood.** *Clin Exp Allergy.* 2005; 35(11): 1466–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
70. Havstad S, Wegienka G, Zoratti EM, *et al.*: **Effect of prenatal indoor pet exposure on the trajectory of total IgE levels in early childhood.** *J Allergy Clin Immunol.* 2011; 128(4): 880–885.e4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

71. Kuitunen M, Kukkonen K, Juntunen-Backman K, *et al.*: **Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort.** *J Allergy Clin Immunol.* 2009; **123**(2): 335–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. Almqvist C, Cnattingius S, Lichtenstein P, *et al.*: **The impact of birth mode of delivery on childhood asthma and allergic diseases—a sibling study.** *Clin Exp Allergy.* 2012; **42**(9): 1369–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Busse WW: **The National Institutes of Allergy and Infectious Diseases networks on asthma in inner-city children: an approach to improved care.** *J Allergy Clin Immunol.* 2010; **125**(3): 529–37; quiz 538–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. Togias A, Fenton MJ, Gergen PJ, *et al.*: **Asthma in the inner city: the perspective of the National Institute of Allergy and Infectious Diseases.** *J Allergy Clin Immunol.* 2010; **125**(3): 540–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Bryant-Stephens T, West C, Dirl C, *et al.*: **Asthma prevalence in Philadelphia: description of two community-based methodologies to assess asthma prevalence in an inner-city population.** *J Asthma.* 2012; **49**(6): 581–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
76. Remes ST, Castro-Rodriguez JA, Holberg CJ, *et al.*: **Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy.** *J Allergy Clin Immunol.* 2001; **108**(4): 509–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
77. Wegienka G, Johnson CC, Havstad S, *et al.*: **Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years.** *Clin Exp Allergy.* 2011; **41**(7): 979–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. Wegienka G, Johnson CC, Havstad S, *et al.*: **Indoor pet exposure and the outcomes of total IgE and sensitization at age 18 years.** *J Allergy Clin Immunol.* 2010; **126**(2): 274–9, 279.e1–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Dotterud CK, Avershina E, Sekelja M, *et al.*: **Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child?** *J Pediatr Gastroenterol Nutr.* 2015; **61**(2): 200–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
80. Gern JE: **Promising candidates for allergy prevention.** *J Allergy Clin Immunol.* 2015; **136**(1): 23–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. Hesselmar B, Sjöberg F, Saalman R, *et al.*: **Pacifier cleaning practices and risk of allergy development.** *Pediatrics.* 2013; **131**(6): e1829–37.
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Hesselmar B, Hicke-Roberts A, Wennergren G: **Allergy in children in hand versus machine dishwashing.** *Pediatrics.* 2015; **135**(3): e590–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Ownby DR: **Pet dander and difficult-to-control asthma: The burden of illness.** *Allergy Asthma Proc.* 2010; **31**(5): 381–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Almqvist C, Wickman M, Perfetti L, *et al.*: **Worsening of asthma in children allergic to cats, after indirect exposure to cat at school.** *Am J Respir Crit Care Med.* 2001; **163**(3 Pt 1): 694–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
85. McConnell R, Berhane K, Gilliland F, *et al.*: **Indoor risk factors for asthma in a prospective study of adolescents.** *Epidemiology.* 2002; **13**(3): 288–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
86. Litonjua AA, Sparrow D, Weiss ST, *et al.*: **Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness. The Normative Aging Study.** *Am J Respir Crit Care Med.* 1997; **156**(1): 23–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
87. Hedman L, Andersson M, Bjerg A, *et al.*: **Environmental risk factors related to the incidence of wheeze and asthma in adolescence.** *Clin Exp Allergy.* 2015; **45**(1): 184–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
88. McConnell R, Berhane K, Molitor J, *et al.*: **Dog ownership enhances symptomatic responses to air pollution in children with asthma.** *Environ Health Perspect.* 2006; **114**(12): 1910–5.
[PubMed Abstract](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **David Lang**

Department of Allergy and Clinical Immunology, Cleveland Clinic Foundation, Cleveland, OH, USA

Competing Interests: No competing interests were disclosed.

2. **Wanda Phipatanakul**

Boston Children's Hospital, Boston, MA, USA

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research