

Early Exposure to Pets: Good or Bad?

Jeremy D. Bufford, MD, and James E. Gern, MD

Corresponding author

James E. Gern, MD

University of Wisconsin Hospital and Clinics, 600 Highland Avenue, K4/918, CSC Box 9988, Madison, WI 53792, USA.

E-mail: gern@medicine.wisc.edu

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Although pet exposure is known to trigger or worsen allergy symptoms and asthma in patients sensitized to pets, data from recent years has shown that pet exposure in early childhood may actually prevent the development of allergic sensitization and allergic diseases including allergic rhinitis, asthma, and atopic dermatitis. The concept of a protective pet effect remains controversial because these findings have not been duplicated in all studies. Moreover, some studies suggest that pet exposure promotes allergic disease. The protective pet effect may be influenced by multiple factors including type of pet; timing, duration, and intensity of exposure; and genetic factors. The mechanisms behind the protective pet effect remain under investigation but may include alterations in immune development, pet-specific tolerance, and exposure to innate immune stimuli.

Introduction

Exposure to environmental allergens has long been implicated in the development of allergic sensitization and other manifestations of atopy including allergic rhinitis, asthma, and atopic dermatitis. Pet exposure has been shown to promote allergen sensitization and worsen allergic diseases, especially asthma [1,2], in subjects sensitized to these animals. This led to the belief that the avoidance of allergen exposure in early life might prevent the development of allergic diseases [3]. In contrast to this well-established dogma, more recent evidence indicates that exposure to pets, especially in early childhood, may confer a protective benefit on the development of allergic sensitization, allergic rhinitis, asthma, and atopic dermatitis [4–7]. Reports of protective effects of pet exposure on the development of atopic diseases were initially published as epidemiologic studies; however, confirmatory data from prospective birth cohort studies have been published more recently. Studies to evaluate alterations in immune development associated with pets and associated microbial

exposure have provided clues about mechanisms responsible for protective effects of pets. These studies suggest that the effect of pet exposure and the development of allergic disease may depend not only upon stimulation of innate immune responses by factors associated with pets, but also the timing, quantity, and duration of exposure, as well as personal genetics and family history (Fig. 1). The aim of this paper is to present seminal concepts and recent data surrounding the presumed protective pet effect, specifically early childhood exposure.

Evidence that Pets Are Bad

Allergic sensitization

Early pet exposure, specifically cat, in childhood has been shown to increase the risk of cat-specific sensitization based on both skin prick testing and allergen-specific immunoglobulin (Ig) E testing, although this is not observed in all studies [8]. This effect has been demonstrated for both cat ownership and exposure levels of Fel d 1, the major cat allergen. In the Multicenter Atopy Study, a prospective birth cohort study of German children followed during the first 3 years of life, Wahn et al. [3] demonstrated a dose-response relationship between exposure to Fel d 1 measured in settled dust samples from carpet at 6 and 18 months of age and sensitization to cat (allergen-specific serum IgE). Children with a positive family history of allergy were sensitized by exposure to lower cat allergen levels. These findings prompted the authors to conclude that allergen avoidance, including pets, should be implemented in infancy to prevent allergen-specific sensitization later in life [3]. In addition, a dose-dependent effect on cat-specific sensitization has also been demonstrated for both increasing Fel d 1 levels and increasing cat exposure in the first 2 years of life in a study of Swedish children ages 1 to 4 years with asthma [9]. In contrast, Custovic et al. [10] demonstrated a bell-shaped, nonlinear dose-response curve between cat allergen exposure and sensitization in adults with an increased risk of cat-specific sensitization being attributed to moderate Fel d 1 exposure compared with the lowest and highest exposure levels. Data from the Prevention and Incidence of Asthma and Mite Allergy prospective birth cohort study of children from the Netherlands with or without a maternal history of atopy demonstrated that cat allergen exposure at 3 months of age is positively associated with pet-specific serum sensitization at age 4 years [11]. In the prospective, prenatally randomized National Asthma Campaign Manchester Asthma and Allergy birth cohort

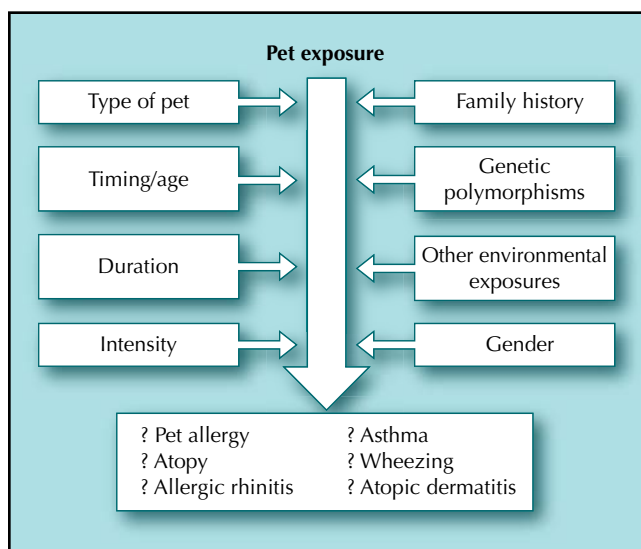


Figure 1. Pet exposure may prevent the development of atopic diseases; however, multiple factors may influence or modify this protective pet effect.

study, which was designed to determine the effects of allergen avoidance on allergy and asthma, Custovic et al. [12] demonstrated a positive association between cat ownership and cat sensitization (odds ratio [OR] 24.6 [3.04–199.05]) in the portion of the birth cohort classified as high risk based on a parental history of atopy in both parents.

There is no clear evidence to suggest that dog exposure in early life increases the risk of dog-specific sensitization. On the contrary, the studies looking into this effect have found either no association or a protective effect between dog exposure and dog-specific sensitization [3,8,9,11]. In addition, there is no evidence to suggest that early pet exposure, including cats or dogs, is a risk for the development of allergic sensitization to other indoor or outdoor allergens.

Asthma

Pet exposure among adult asthmatics sensitized to dogs or cats causes more severe disease as indicated by increased symptoms and medication use, reduced lung function, and increased bronchial hyperresponsiveness [1,2]. These relationships are quite reproducible and engender little debate. A separate question is whether pet exposure may be a risk factor for the development of wheezing or asthma. Salo et al. [13] demonstrated that pet exposure in early childhood before age 6 was associated with an increased risk of physician-diagnosed asthma and respiratory symptoms in a population-based cross-sectional study of ninth-grade students from China. In a population-based case control study of children in Beijing, China, where asthma prevalence is lower than Western countries, Zheng et al. [14] demonstrated that the current presence of both a cat and a dog in the home was associated with an increased risk of asthma in

children ages 6 to 10 years (OR 1.5 [1–2.3]). This effect was not seen for either dog or cat ownership alone and suggests that the intensity of pet exposure may influence outcomes. In a meta-analysis of studies pertaining to pet exposure and the development of asthma or wheezing, Apelberg et al. [15] concluded that early pet exposure increases the risk of asthma and wheezing in children older than 6 years, but may protect against asthma and wheezing in younger children. These studies suggest that the influence of pet exposure on asthma and perhaps other clinical outcomes may depend on both the age of exposure and the age when the outcome is measured.

The family history has affected the relationship between pet exposures and asthma in some studies. In a prospective birth cohort study conducted in the Netherlands, there were nonsignificant trends between both Fel d 1 and Can f 1 (the major dog allergen) and persistent wheeze at age 4 years, but the trend for Can f 1 exposure was present only in children without a maternal history of atopy [11]. In a birth cohort study conducted in the United States and involving families with at least one atopic parent, the effect of cat, but not dog, exposure on wheezing outcomes varied with maternal atopic status [16]. Cat exposure reduced the risk of wheezing from age 1 to age 5 in children born to mothers without a history of atopy (RR 0.6 [0.4–0.9]), but increased the risk of wheezing from age 3 to 5 years in children with a maternal history of atopy (RR 2.4 [1.3–4.5]). Similarly, in the prospective Asthma Multicenter Infants Cohort Study, Polk et al. [17] reported an interaction between Fel d 1 levels in household dust and maternal asthma on wheezing at age 4 (RR 2.77 [1.19–6.46]) ($P = 0.018$). These studies suggest that heredity or genetics may modify the effect of pet exposure on wheezing outcomes.

Only a few studies have investigated the effect of pet exposure on objective measures of lung function. Using the National Asthma Campaign Manchester Asthma and Allergy Study birth cohort, Lowe et al. [18•] have investigated the effect of pet ownership and pet allergen levels on lung function in preschool children at age 3 years. There was a positive correlation between airway resistance and dog allergen levels, but only among children sensitized to dog ($r = 0.45$, $P = 0.03$). Similarly, in the Childhood Asthma Management Program (CAMP) study, methacholine sensitivity was stronger among cat-sensitive children exposed to significant amounts of Fel d 1 ($> 8 \mu\text{g/g}$ of dust) compared to nonexposed children [19].

Evidence that Pets Are Good

Exposure to furred pets, especially cats and dogs, in early childhood has been shown to protect against the development of atopic diseases including allergic sensitization, allergic rhinitis, atopic dermatitis, and asthma/wheezing. These findings have been found in both epidemiologic studies and longitudinal cohort studies, including prospec-

tive birth cohort studies. Prospective studies have allowed researchers the opportunity to follow pet exposure, other environmental exposures, and clinical and immunologic outcomes over time.

Pet sensitization

In a study of 7- to 8-year-old Swedish children followed prospectively for 3 years, Perzanowski et al. [20] demonstrated inverse associations between cat or dog ownership by age 8 years and allergic sensitization (skin prick test) to cat and dog, respectively; however, these effects were limited to children with at least one parent with allergy symptoms. Cat, but not dog, ownership was also associated with a decreased risk of asthma among children with a family history of asthma. Similarly, in a case-control study of 10- to 11-year-old New Zealand children with high dust mite level exposure and a high prevalence of cat ownership (60%), Erwin et al. [21] demonstrated that exposure to cats is associated with cat-specific tolerance. Cat ownership ever in life was associated with a decreased risk of sensitization to cats (20/141 vs 21/83, $P = 0.04$), but not dust mites. The effect of cat was still present after the authors accounted for children whose families practiced cat-avoidance behavior.

Sensitization to other allergens

Although numerous studies have demonstrated the protective pet effect on allergic sensitization to cats and dogs specifically, one of the more intriguing features of the protective pet effect is the ability of pet exposure to modulate atopic outcomes beyond pet-specific sensitization. In one of the first population-based prospective birth cohort studies to investigate the relationship between early environmental exposures and allergic sensitization and asthma, Ownby et al. [4] demonstrated that exposure to two or more cats or dogs in the first year of life was associated with a decreased risk of allergic sensitization at ages 6 and 7 years based on skin prick testing (atopy) and allergen-specific IgE (seroatopy). These findings suggest that pet exposure might interfere with the development of allergic sensitization in general because exposure to two or more pets reduced allergic sensitization to both indoor and outdoor aeroallergens as well. In this population the prevalence of atopy was 33.6% among children with no pets, 34.3% among children with one pet, and 15.4% among children with two or more pets ($P = 0.005$). The effects of pet exposure in infancy were also evaluated in the Childhood Origins of ASThma (COAST) birth cohort study, which consists of families that include at least one parent with asthma or atopy. Home exposure to dogs, but not cats, in the first year of life at birth was associated with a decreased risk of allergic sensitization to food and aeroallergens at age 1 year (19% vs 33%, $P = 0.02$) [22••].

Asthma

Among 1246 children followed prospectively from birth to age 13 in the Tucson Children's Respiratory Study, the

presence of at least one indoor dog, but not cat, at birth was associated with a decreased risk of frequent wheeze by age 13 ($P = 0.004$) [6]. This protective effect was limited to children without a parental history of asthma. This is one of the first studies to investigate longitudinally changes in pet ownership over time, and Remes et al. [6] found the lowest risk for wheezing among children with continuous dog exposure throughout childhood, although the highest risk was found among children never exposed to dogs. Changes in dog ownership resulting in removal of the dog by age 3 or age 6 resulted in an increased risk of frequent wheeze compared to children with continuous exposure. In a cross-sectional questionnaire study of German children 5 to 7 years old, Oberle et al. [23] found no relationship between pet exposure at birth or current exposure at age 5 to 7 years and atopic outcomes; however, continuous exposure to furred pets (cats, dogs, guinea pigs, rabbits, or hamsters) from birth to 5 to 7 years was associated with a decreased risk of atopic asthma (OR 0.58 [0.33–0.96]) at age 5 to 7 years. When stratified by specific pets, continuous exposure only to cats was associated with decreased risk of physician-diagnosed asthma and atopic asthma, but only among children who allowed cats in their bedroom. The authors suggested that allowing cats in the bedroom was a marker of more intensive exposure. These two studies suggest that the protective effect of pets on wheezing and asthma may depend upon early and prolonged exposure.

Although numerous studies have reported a protective effect of pet exposure on asthma and wheezing, few studies have found effects on objective markers of airway obstruction. Ownby et al. [4] have demonstrated a decrease in the prevalence of methacholine sensitivity at ages 6 to 7 years among boys, but not girls, with increasing exposure to cats or dogs in the first year of life, but they failed to find an association between pet exposure and asthma. There was also a dose-response increase in mean percent predicted forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) among boys in relation to increasing pet exposure.

Atopic dermatitis

Several studies have reported a link between early exposure to pets and reduced atopic dermatitis, including two large European birth cohorts. Zirngibl et al. [24] found that the keeping of any pet, especially dogs, was associated with a reduced risk of atopic dermatitis in the first 2 years of life in a large German cohort. In a large study of Danish children, Benn et al. [25] found that pet exposure in early childhood decreased the risk of atopic dermatitis by 18 months of age, alone and in combination with other exposures that increase microbial exposure including siblings, day care, and farm residence. Similar relationships for dog exposure were reported in cohort studies from Boston, MA [26••] and Madison, WI [22••], although one study found that cats are associated with reduced

atopic dermatitis. Purvis et al. [27] evaluated pet exposure in the Auckland Birthweight Collaborative study of low-birth-weight infants that included a normal-birth-weight control population to determine environmental risk factors associated with the development of atopic dermatitis at 3.5 years. There was an inverse association between atopic dermatitis and ownership of cats, but not dogs, at age 3.5 years in a multivariate analysis adjusting for other environmental factors and family history (adjusted odds ratio [aOR] 0.45 [0.21–0.97]).

Multiple atopic outcomes

A number of studies have reported that the keeping of pets is associated with multiple health benefits. In the Oslo Birth Cohort Study, one of the first population-based birth cohorts to evaluate the effects of early pet exposure and atopy-related conditions, Nafstad et al. [28] followed Norwegian children to age 4 and found that exposure to any pet in the home at birth was associated with decreased risk of asthma at age 4 (OR 0.7 [0.5–1.1]), allergic rhinitis at age 4 (OR 0.6 [0.4–1.0]), and atopic dermatitis at 0 to 6 months (OR 0.7 [0.5–0.9]), with the latter effect being limited to children with atopic parents. With the exception of a protective effect of cat at birth on atopic dermatitis, there were no significant risks of cat or dog individually on these outcomes. In Sweden, the keeping of a cat or dog in the home in first year of life was associated with a lower prevalence of allergic rhinitis at 7 to 8 years (5.9% vs 9.5%, $P = 0.016$) and a lower prevalence (3.3% vs 10%, $P < 0.001$) and cumulative incidence (8.6% vs 13.3%, $P = 0.03$) of asthma at 12 to 13 years [5]. Furthermore, cat ownership during the first year of life was associated with a decreased skin prick test to cat at age 12 to 13 (6% vs 14.3%, $P = 0.016$). In German schoolchildren, regular contact with dogs, but not cats, in first year of life was inversely associated with cumulative prevalence of hay fever (OR 0.61 [0.39–0.95]), eczema (OR 0.76 [0.61–0.94]), itchy rash (OR 0.76 [0.61–0.94]), and pollen sensitization (radioallergosorbent test [RAST] $\geq$ class 4; OR 0.56 [0.38–0.82]) [29]. These inverse associations were stronger for children with a parental history of atopy. In a cross-sectional study of 8- to 13-year-old children in the Netherlands, de Meer et al. [30] found that keeping a cat or a dog before age 2 was associated with a decreased risk of atopic sensitization (skin prick testing and serum-specific IgE) to indoor and outdoor allergens (OR 0.78 [0.61–0.99]) and a decreased risk of atopic rhinitis (OR 0.65 [0.46–0.92], $P < 0.05$) and atopic symptoms in general (OR 0.74 [0.54–1.0], $P = 0.05$). Pet keeping did not influence current symptoms of wheezing, rhinitis, dermatitis, or asthma in nonatopic children.

The associations with atopic outcomes may vary with age. For example, in a population-based birth cohort of 1228 Swedish children followed to age 4 years, Sandin et al. [31] found that dog keeping in the first year of life was associated with an increased risk of early-onset transient wheeze among

children with parental history of asthma, but a decreased risk of pollen sensitization at age 4 (OR 0.3 [0.1–0.9]) and late-onset wheezing by age 4 (OR 0.4 [0.2–1]).

Pet ownership and atopic outcomes among adults

Analysis of the European Community Respiratory Health Survey (ECRHS), a cross-sectional study of adults age 20 to 44 from 16 countries, has revealed some interesting and unexpected relationships between pet ownership, personal atopy, the prevalence of pets in a community, and allergic outcomes. First, both dog and cat keeping in childhood were found to be inversely related to seroatopy, although the effect of cat ownership was observed only in subjects with a parental history of allergy [32]. Second, the prevalence of cat ownership in the community was positively related to cat sensitization, respiratory symptoms, and asthma among those who did not currently own pets, suggesting that higher community prevalence is a risk factor for sensitization of non-pet owners [33]. Third, cat ownership in childhood was associated with an increased risk of asthma in atopic adults, an association that was stronger among individuals from communities with a lower prevalence of cat keeping [34]. Finally, a history of dog ownership in childhood was associated with an increased risk of adult asthma in nonatopic subjects, and conversely, was protective of adult hay fever among atopic subjects [34]. These are interesting concepts that may begin to explain the inconsistencies in clinical studies of the associations between pet ownership and allergic diseases.

Oryszczyn et al. [35] conducted a cross-sectional study of adults to explore the effect of the timing of pet exposure on allergic outcomes. The researchers found that childhood pet exposure was associated with decreased risk of allergic sensitization based on skin prick testing to any allergen (OR 0.16 [0.06–0.4]), including cat allergen (OR 0.3 [0.12–0.76]), but only among those whose exposure started before 2 years of age. Pet exposure before the onset of asthma was also associated with less atopy, especially if the pet was present before age 2. Furthermore, subjects with longer pet exposure had a lower risk of atopy. These findings provide further evidence that the protective pet effect might depend on the timing (early childhood) and duration of pet exposure.

Ubiquity of Pet Allergens

One criticism of studies on the effect of pet exposure on atopic outcomes has been that the absence of pet ownership does not necessarily mean the complete absence of pet exposure. A difficulty in performing these studies has been developing accurate methods for quantifying pet exposure. Studies have shown that cat and dog allergens are ubiquitous, even in homes where pets are not kept and in public buildings such as schools, day care centers, office buildings, and hospitals where pets are not commonly

allowed [36–39]. In addition, children are commonly exposed to pets outside the home, including the homes of friends and relatives and in-home day care centers. In a prospective birth cohort study of Stockholm children, Almqvist et al. [40] sought to determine the effects of direct and indirect pet exposure on atopic outcomes. They demonstrated that early (median age 2 months) cat exposure at home or at the homes of relatives increased the risk of cat sensitization (OR 1.44). This association was not present for dog exposure and dog sensitization; in fact, dog ownership was associated with a reduced risk of sensitization to other aeroallergens (OR 0.36) and asthma (OR 0.5) at age 4 years. Indirect cat exposure, defined as regular contact with relatives who owned cats, was associated with an increased risk of cat-specific sensitization but a decreased risk of sensitization to other aeroallergens. The findings prompted the authors to conclude that cat and dog exposure may have differential effects on the developing immune system. These findings also suggest that these clinical outcomes may also depend on the frequency and intensity of pet exposure.

Reverse Causation

A potential barrier to understanding the true relationship between pets and allergic diseases is the concept of *reverse causation* or *selective avoidance bias*. Opponents of the protective pet effect feel that this phenomenon can be explained by the pet-keeping practices of the study subjects, including avoidance behavior. In short, children and adults without a personal or family history of atopy disease are able to keep pets, although those with a personal history of atopy, specifically pet allergy, or children with a paternal history of atopic disease are not able to keep pets, sometimes for fear that pet exposure may promote allergic disease. As a result, these studies give the appearance that pets protect from allergies, when, in reality, a history of allergies may preclude pet ownership. Several studies have examined the effects of reverse causation on the results of pet keeping studies.

In a cross-sectional study of 7- to 12-year-old Dutch primary school children, Anyo et al. [7] found that current pet ownership was associated with a reduced risk of hay fever and sensitization to allergens, including cat and dog. In contrast, past pet ownership was associated with an increased risk of sensitization to indoor allergens in the unadjusted analysis and asthma in the adjusted analysis. The authors suggested that an apparent protective pet effect may be due to selective pet avoidance by allergic families. This study, however, was unable to detect a selective avoidance effect due to parental asthma or hay fever, and did not inquire into the reasons behind pet-avoidance or pet-removal behaviors.

The reasons for pet avoidance behavior were assessed in a cross-sectional study of 1- to 6-year-old Swedish children conducted by Bornehag et al. [41]. Of the study

subjects, 8.5% got rid of pets due to a family history of allergy, and 27.3% reported avoidance behavior due to a family history of allergy. Pet keeping (cat, dog, hamster, rabbit) at birth was associated with reduced asthma, allergic rhinitis, and symptoms in the whole-population unadjusted analysis. A high rate of allergic disease was reported by children who had pets in the home at the time of birth, and then subsequently were without pets. The authors also demonstrated a dose-response relationship between number of furred pets at birth and symptoms later in life. The authors concluded that their study provides evidence for a “healthy pet-keeping effect,” in that allergic families preferred to live without pets [41].

Data from a 9-year follow-up of the European Community Respiratory Health Survey has shown that asthma and allergies in childhood and adulthood might influence subsequent pet keeping, with subjects with asthma and allergies exhibiting selective avoidance behaviors concerning pet ownership later in life [42•]. Childhood asthma influenced cat ownership in children 5 to 15 years of age without a parental history of asthma or allergy, although adult asthma symptoms negatively influenced the decision to obtain a cat in adulthood. A similar effect of smaller magnitude was demonstrated for subsequent acquisition of a dog. The authors confirmed that selective pet avoidance may have a small effect on the protective pet phenomenon and concluded that this effect may explain part, but not all, of the protective pet phenomenon. This selective pet avoidance may depend upon the type of pet, type of symptoms, timing of symptoms, previous pet ownership, and parental history [42•]. In addition to these studies, the protective pet effects demonstrated in some of the studies previously mentioned in this paper remained significant after adjusting for avoidance behavior [21], although the protective pet effects seen in other studies are no longer significant after adjusting for pet avoidance [5]. Collectively, these findings indicate that studies of pets and allergic diseases need to consider reverse causation in the experimental design and analysis plan.

Reasons for Inconsistencies

Research into the role of pet exposure in the development of atopic diseases has yielded some inconsistencies. Reasons behind these inconsistencies include differences in study design, subject characteristics (eg, age, atopic history), location, and even the prevalence of pet keeping in the community. These studies also differ in the clinical outcomes measured and ascertainment of pet exposure (timing, duration, recall). Few studies have investigated changes in ownership over time. Some studies try to avoid selection bias by adjusting for pet avoidance behaviors within individuals and their families. These studies are also complicated by other concurrent environmental exposures and conditions.

Mechanisms

Initial studies of the protective pet effect focused on clinical outcomes. The focus has now shifted from clinical outcomes to potential mechanisms responsible for the protection against atopic diseases, and several theories have been proposed. Platts-Mills et al. [43] have provided evidence that chronic exposure to high levels of cat antigen may induce a modified helper T (Th) 2 cell response that results in the downregulation of cat-specific IgE and an increase in cat-specific IgG, particularly IgG4. This modified Th2 response, which has been demonstrated in some [21,44] but not all [45] studies, may provide a form of immunologic tolerance; however, a clear protective effect of IgG4 on atopic outcomes including asthma, allergic sensitization, and allergic rhinoconjunctivitis has yet to be demonstrated [5,44,46]. Modified Th2 responses to dog proteins have not been directly demonstrated.

Pet exposure may have effects on the balance between Th1 and Th2 responses. In a longitudinal birth cohort study of children growing up in an agricultural area of California, Duramad et al. [47] demonstrated that pet exposure in the first year of life was associated with a 35% increase in Th1 cells based on whole-blood phorbol 12-myristate 13-acetate (PMA)/ionomycin-induced cytokine expression at age 2 years, although asthma and wheezing were associated with increased Th2 levels. This is one of the first studies to correlate pet and other environmental exposures with Th1/Th2 status using interferon (IFN)- γ and interleukin (IL)-4 responses as markers of Th1 and Th2 cells, respectively. In the COAST birth cohort study, dog exposure at birth modified cytokine responses by increasing phytohemagglutinin (PHA)-induced peripheral blood mononuclear cell IL-10 and IL-13 responses at age 1 year [22••]. In addition, the effects of dog exposure on the expression of atopic dermatitis in the first year of life depended on CD14 genotype, suggesting a mechanism involving innate immune stimulation. Other researchers have demonstrated gene-by-environment interactions between cat exposure in early childhood and genetic polymorphisms in genes for IL-1 α and IL-10 on the induction of cat-specific tolerance [48]. These studies provide evidence that pet exposure in early childhood is associated with alterations in immune development, and these changes may be further modified by genetics.

Many have hypothesized that pet exposure is a surrogate marker not only for allergens, but for microbial antigens as well. The inconsistent findings between pet exposure and atopic outcomes, including pet-specific sensitization and allergic sensitization in general, suggest that there might be other factors unrelated to pet allergen exposure that modify the immune system and influence the development of atopic diseases. Indoor dogs and cats have been shown to increase exposure to lipopolysaccharide or endotoxin [45,49,50], a component of gram-negative bacterial cell walls; however, it is likely that the magnitude of this effect is small because it has not been demonstrated

in all studies [21,46]. A number of other innate immune stimuli have the potential to affect immune development; however, there are no studies to date investigating whether indoor pets increase the exposure to these substances.

Because exposure to endotoxin has been shown to have protective effects on allergic sensitization [51,52], allergic rhinitis [29,52], atopic asthma [52], and atopic dermatitis [26••,53], there has been particular interest in determining whether endotoxin is responsible for some or all of the protective effects of pet exposures. Litonjua et al. [54] reported that both exposure to higher cat allergen levels and dog ownership at baseline were associated with a decreased risk of wheezing. The authors found that these effects were independent of endotoxin levels in settled house dust. Similarly, in the cross-sectional Allergy and Endotoxin (ALEX) study of German, Swiss, and Austrian children (mean age 9.4 years), protective effects of current dog exposure on allergic outcomes were also independent of current endotoxin levels in settled dust [45]. Investigators in the Cincinnati Childhood Asthma and Air Pollution have taken a different approach [55•]. In this study, wheezing and aeroallergen sensitivity at age 1 in a high-risk prospective birth cohort were not associated with pet allergen levels or endotoxin levels individually; but the prevalence of wheezing and recurrent wheezing were reduced among children exposed to two or more dogs and high endotoxin levels. These findings suggest that dog exposure and endotoxin may modify wheezing outcomes synergistically. Additional studies are needed to further evaluate this possibility.

Conclusions

Pet exposure in early childhood appears to influence immune development and the development of atopic diseases in childhood, and these effects may persist into adulthood. Although there is certainly strong evidence to support the concept of a protective pet effect, this topic remains controversial because the results have not been replicated in all studies. The benefits of early pet exposure seem to be the consequence of multiple factors including the complex interplay of the type of pet exposure, timing of exposure, duration of exposure, genetics, and heredity (Fig. 1). Although these findings have not yet led to recommendations suitable for the clinic, advances in understanding the mechanisms underlying these effects are bringing us closer to this goal. Data are emerging that suggest pet exposure modulates the specific immune response to pet proteins and may cause alterations in immune development in general through changes in cytokine responses. Further studies relating to the mechanisms of the protective pet effect are needed to determine the specific factors related to pet exposure that are responsible for these immunologic changes and clinical outcomes. Identification of those factors may lead to therapeutic interventions that could have a major impact on the incidence of atopic diseases.

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- Of importance
- Of major importance

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