

Do animals on the farm and in the home reduce the risk of pediatric atopy?

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Recent evidence suggests that proximity to pets and farm animals early in life may decrease the risk of developing atopy. Studies investigating the etiology of atopy and asthma have been especially challenging due to difficulties in ascertaining and classifying incident cases. Nevertheless, cross-sectional and cohort studies described in this paper reported across various populations, among children and adults, tended to demonstrate inverse associations between the presence of indoor cats and dogs or frequent exposure to livestock during the first years of life and sensitization to pet and pollen allergens, hay fever, and to a lesser degree, asthma. The biological mechanisms of this protection is unknown, as are the factors associated with pet keeping and livestock farming that may play a role. In the meantime, it appears that counseling prospective parents that avoidance of exposure to animals in the first years of life will prevent atopy may not be sage advice. *Curr Opin Allergy Clin Immunol* 2:133–139. © 2002 Lippincott Williams & Wilkins.

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Abbreviations

ISAAC	International Study of Asthma and Allergies in Childhood
ECRHS	European and Community Respiratory Health Survey
CI	Confidence Interval

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Introduction

Based on research findings published in the last 2–3 years, exposures associated with the keeping of pets and livestock appear to diminish the probability of the development of sensitization and perhaps asthma in children. However, as in all relationships, apparently timing is everything, and the protection is particularly associated with exposure early in life.

In a review article by Beasley *et al.* [1] the major global findings from both the European Community Respiratory Health Survey (ECRHS) and the International Study of Asthma and Allergies in Childhood (ISAAC) were summarized. The conclusions from these epidemiological studies were that asthma has been increasing worldwide over the last decades, is generally more common in Western, especially English-speaking, countries, is increasing in developing countries as they become more Westernized or urbanized, and the prevalence of other allergic disorders is also increasing worldwide. Studies specific to the United States have likewise demonstrated an increase in the incidence and prevalence of pediatric asthma. [2,3]. From these reports and other work, it has been hypothesized that it is changes in environmental exposures that are influencing an increased susceptibility to the subsequent development of allergies and asthma.

A significant body of literature has been generated regarding the role of common household allergens in atopic conditions, particularly dust mite, cockroach, and pet allergens [4], but it has been difficult to disentangle the relationship of these factors with respect to disease causation versus symptom provocation. Allergic sensitivity to the allergens associated with household pets and dust mites has been consistently demonstrated to be associated with prevalent pediatric asthma, and asthma persisting until adulthood [4–7]. The keeping of household pets has long been recognized as an environmental trigger for asthma, clearly causing symptom exacerbation for many asthmatics. Because of these associations, there has been a general assumption that a higher degree of exposure to animals during early life also increases the risk of the initial development of allergic sensitivity to pet allergen and that continuing exposure to such allergens is associated with airway inflammation leading to the development of asthma in childhood [4]. In other words, the presence of pets in the indoor environment in infancy has been considered to be related to an earlier

and increased level of allergen exposure, which in turn leads to an increased probability of incident atopy and asthma.

Accordingly, exposure to cats and dogs in early life has been thought to increase the risk of subsequent allergy to these animals [8–11]. This assumption is primarily based on a few retrospective studies reporting an increased likelihood of allergic sensitivity following exposure during infancy [9–11]. Due to the difficulties associated with defining asthma clinically and epidemiologically, the majority of studies investigating pet keeping and pet allergen level as risk factors for asthma have utilized prevalent rather than incident cases. Such study designs, however, make it difficult, if not impossible, to distinguish factors that are related to cause versus exacerbation of disease. However, both new cross-sectional studies and recent cohort studies focused on teasing out these differences are consistently demonstrating that early life exposure to pets and other animals decreases, rather than increases, the risk of pediatric atopic conditions, as detailed below.

Exposure to farm animals and pediatric atopy

A flurry of recent work has indicated that farm residence in childhood is associated with a decreased risk of atopy. In a 2000 review of environmental predictors of allergic disease, Von Mutius [12] comments on reports from Switzerland [13], Germany [14] and Austria [15] indicating that hay fever, atopic sensitization and asthma all tended to be less common among children raised on farms. The consistently specific exposure associated with decreased risk was contact with livestock. Kipelaäinen [16] reported results from a survey of over 10 000 Finnish first-year university students. Farm living during the first 6 years of life and a history of physician-diagnosed allergic rhinitis or conjunctivitis was associated with an odds ratio of 0.63 (95% Confidence Interval (CI) 0.5–0.79), adjusted for other major potential confounders. The association for asthma was an odds ratio of 0.70 (95% CI 0.46–1.06).

Ernst *et al.* conducted a cross-sectional study in rural Quebec, surveying 1199 secondary school students using the ISAAC questionnaire [17]. Samples of the subjects who had been raised on a farm and individuals without a history of exposure to a farm environment were given skin prick tests and methacholine challenge. Current wheeze and bronchial hyperreactivity were significantly less common among those adolescents raised on a farm at 17.1% versus 24.7%, $P < 0.002$ and 12.9% versus 17.4%, $P < 0.035$, respectively. Atopy, as defined by a positive skin prick test to one of a battery of 24 inhaled allergens, was also less common among farm-exposed youth (40.8% versus 53.4%. $P < 0.001$). The odds ratio for farm

residency and a positive skin prick test to either cat, dog, *Dermatophagoides pteronyssinus* or *D. farinae* was 0.59 (95% CI 0.46–0.76), adjusting for gender, current smoking and number of siblings.

The association between paternal occupation of farmer and atopic conditions in adults was investigated using a prospective birth cohort from Finland [18•]. A geographically based cohort of 12 058 births was established in 1966, and extensive perinatal data were collected during and immediately after pregnancy. At age 31 years, subjects were surveyed regarding personal history of a physician diagnosis of asthma and parental history of allergies (asthma, allergic rhinitis, atopic eczema), and skin prick tested for cat, birch, timothy and *D. pteronyssinus*. Adjusting for gender, gestation, birth-weight, maternal age, parity and smoking, current body mass index and vocational training, and parental history of allergy, children of farmers were significantly less likely to have at least one positive skin prick test, with an odds ratio of 0.50 (95% CI 0.42–0.60). Paternal farming was also protective for a history of asthma (odds ratio, 0.71; 95% CI 0.53–0.95), and this association was limited to those asthmatics with atopy. Interestingly, this study's main focus was the demonstration of an association between high gestational age and adult atopy, which was stronger among the children of farmers.

Leynaert *et al.* [19•], using data from the ECRHS, also investigated the impact of childhood residence on a farm on the prevalence of adult atopy. Using a two-stage sampling design, a multicenter survey was administered to adults aged 20–44 years, with subsamples invited to undergo clinical examination, methacholine challenge and total and specific immunoglobulin E measurements. Thirteen centers in five countries (Belgium, France, Netherlands, Sweden and New Zealand) surveyed 6251 subjects regarding childhood farm residence. Living on a farm (duration and age undefined) as a child was protective for atopy, defined as positive immunoglobulin E, to at least one of five specific allergens, with an odds ratio of 0.76 (95% CI 0.60–0.97), adjusted for sex, country, parental history of allergy, parental smoking, number of siblings, respiratory infection in childhood, current smoking, and childhood and current pet exposure. Risk estimates were protective for cat immunoglobulin E (odds ratio, 0.63; 95% CI 0.41–0.96), timothy grass immunoglobulin E (odds ratio, 0.68; 95% CI 0.50–0.94) and dust mite immunoglobulin E (odds ratio, 0.81; 95% CI 0.59–1.11), and for hay fever (odds ratio, 0.80; 95% CI 0.64–1.02). These associations were maintained even when excluding those subjects still working on a farm. The protection conferred by childhood farm living was strongest among the youngest subjects, those born after 1960. No multivariate analyses were presented for asthma, defined as having one asthma attack or use of

asthma medications in the previous 12 months, as there was no statistically significant difference in prevalence between those who reported childhood residence on a farm and those who did not (odds ratio, 0.82; 95% CI 0.53–1.27).

An Australian group reported on a cross-sectional study of atopy (as defined by skin prick test results) and asthma among children related to living on a farm [20•]. In a rural region with a high prevalence of allergic diseases, children living in a crop-farming area were compared with children living in an area with both livestock and crop farming. School children aged 7–12 years were given skin prick tests for eight allergens and a self-administered survey was distributed to parents that included questions about farm living, allergy symptoms and asthma diagnosis. Among the children from the livestock farm area, but not the crop farm area, living on a farm for at least 12 months was associated with a lower risk of atopy (odds ratio, 0.44; 95% CI 0.29–0.64). This association was consistent and statistically significant for sensitization to dust mite, rye grass, cat, and *Alternaria* spp. Protective associations were also found for a history of wheezing (odds ratio, 0.55; 95% CI 0.45–0.93), wheezing in the last 12 months (odds ratio, 0.65; 95% CI 0.43–0.98), a history of asthma diagnosis (odds ratio, 0.65; 95% CI 0.45–0.93), and ever use of asthma medications (odds ratio, 0.65; 95% CI 0.46–0.92).

Investigators from Austria, Switzerland and Germany with previous individual studies addressing this issue collaborated on a population based cross-sectional study that took place in 1999 in rural areas of these three countries [21••]. The parents of school children in grades one to six completed surveys based on the ISAAC questionnaire that included detailed questions on environmental factors related to farming. Serum samples for specific immunoglobulin E testing (using radio-allergosorbent test) were collected from the children of farming families and a sample of non-farming families. Using multivariate analyses throughout to adjust for confounders such as family history of atopic conditions, number of siblings and demographic variables, the children of farming families were at lower risk for hay fever symptoms (odds ratio, 0.43; 95% CI 0.24–0.77) and seroatopy (odds ratio, 0.61; 95% CI 0.41–0.92) as defined by positive immunoglobulin E to one or more of the following: house dust mite, storage mite, grass pollen, birch pollen, cat and cow epithelium. Farm children were also less likely to have asthma symptoms, as defined by at least one attack of wheeze in the last 12 months, with an odds ratio of 0.30 (95% CI 0.15–0.61), although there was no difference in the frequency of eczema. The greatest degree of protection was afforded to those children who were exposed to stables, farm milk or both during the first year of life, regardless of whether

they lived on a farm or not. Children of mothers who were active on the farm each day during pregnancy, compared with children not exposed to stables or farm milk in the first year of life, demonstrated an extremely low risk of seroatopy (odds ratio, 0.18; 95% CI 0.06–0.56) and hay fever symptoms (odds ratio, 0.04; 95% CI 0.003–0.53). None of the children of mothers who had daily activity on farms had a physician diagnosis of asthma and only one child had wheezed in the past 12 months (odds ratio, 0.04; 95% CI 0.001–1.30).

In summary, recent literature suggests that factors associated with early exposure to farming life, especially with exposure to livestock, seem to protect against measures of atopy not specific to animal allergens, symptoms of hay fever, and perhaps asthma.

Exposure to pets and pediatric atopy

A number of risk factor studies in the last decade, focusing on household and family characteristics such as house dust mite levels, sibship size and smokers, included the presence of pets as a variable, presumably to be able to control for this factor as a possible confounder due to a positive association with atopy and asthma. Although generally glossed over, dismissed or not noted, measured variables representing the presence of pets have often suggested a protective association [22–25]. Hesselmar and colleagues in Sweden were the first to center their report, in 1999, on early exposure to cats and dogs [26]. In a cross-sectional study of children surveyed at 7–9 and 12–13 years of age, they found that children reported to have had pets in the home during the first year of life were less likely to be skin prick test positive to cat, have allergic rhinitis or asthma. Data on 13 932 adults from the ECRHS indicated that dog ownership in childhood was protective for atopy (specific immunoglobulin E to one or more of the four allergens tested; adjusted odds ratio, 0.82; 95% CI 0.76–0.89) as was cat ownership (adjusted odds ratio, 0.88; 95% CI 0.82–0.95) [27]. This same data set demonstrated that exposure to pets in childhood was associated with a lower risk of sensitization to cat in adulthood, especially among those with parental history of atopy [28]. Moreover, several papers have shown no association between level of exposure to cat allergen and allergic sensitization to cat [29–32].

A recent systematic review and metaanalysis of the literature related to exposure to animals kept in the home and risk for asthma or wheezing was conducted by Apelberg and colleagues [33•]. Thirty-two articles describing cross-sectional (n=20), cohort (n=6) and case-control (n=6) studies published from 1966 to 1999 were included, although all but three were published in the 1990s and nine in 1999. They concluded that pet exposure during the first 2 years of

life tended to slightly increase the risk of asthma and wheezing in children over 6 years of age. Evidence of a slight protection was seen in younger children, although the authors cited the possibility of selection bias since most of the studies yielding these results were cohort studies and there was concern noted that parents with a positive family history would be less likely to keep pets yet have children more susceptible to allergies. However, they summarize their paper by stating that the literature to that date was replete with design flaws and urged the conduct of carefully designed longitudinal studies. Several new studies addressing pet keeping as an etiologic factor have been published in the last year.

Utilizing the Isle of Wight birth cohort study, investigators from the United Kingdom reported in two different papers in 1998 and 2001 [34,35•] on the relationship between pet ownership and sensitization to common allergens, including dog and cat, and atopic conditions. Of the 1456 children recruited in 1989 to 1990, 1218 were surveyed at age 4 years, with 981 receiving a battery of 12 skin prick tests. Concurrent cat or dog ownership was not associated with sensitivity to the respective animal dander, and pet keeping was not associated with the prevalence of any atopic disorder.

Another Swedish cross-sectional study involved surveying the families of 10–11 year old schoolchildren from two different cities and performing skin prick tests to nine allergens [36•]. Cat ownership, both current and previous, was inversely associated with a positive skin prick test to cat dander, with an odds ratio of 0.6 (95% CI 0.4–1.0) for past ownership, although this risk estimate was unadjusted for confounding variables, including current pet keeping. Current pet ownership as a variable is particularly fraught with bias in a cross-sectional study as persons allergic to an animal may be more likely to not keep one. The risk estimate for past cat ownership and atopy, as defined by at least one positive skin prick test and adjusted for family history and study area, had an odds ratio of 0.7 (95% CI 0.5–1.0). Dog ownership was reportedly not associated with sensitization to dog dander, although data were not presented, and there was no mention of other outcomes. Another limitation of this study was a lack of definition for ‘past’ pet ownership.

One of the first prospective studies, by Nafstad *et al.*, utilized the Norwegian Oslo Birth Cohort Study of 3754 children born in 1992 and 1993 [37•]. The children were followed by questionnaire at birth and at 6, 12, 18 and 24 months old, and families were again surveyed when the children turned 4 years. Only the 2531 children with complete information on atopic conditions through to age 4 years were included in the analyses. It appears that questions about pet ownership were asked on each

survey contact, although this was not specified. The authors concluded that their results demonstrated an inverse association between a pet (cat or dog) in the home at the child’s birth and a physician diagnosis of allergic rhinitis and asthma with symptoms in the last 12 months. The odds ratio, adjusted for numerous potential confounders, for allergic rhinitis at age 4 years and a pet in the home at birth was 0.6 (95% CI 0.4–1.0). The corresponding risk estimate for asthma at 4 years had an odds ratio of 0.7 (95% CI 0.5–1.1). The association for asthma was limited to cat ownership, and was stronger for cat keeping in relation to hay fever. Interestingly, exposure to a pet dog at birth was associated with an increased risk of bronchial obstruction during just the first 2 years of life. A limitation of this study was that it was completely survey-based without biological measures of sensitization, and that follow-up was only through to 4 years, stopping short of when asthma can be more definitively diagnosed.

A small study of 100 high risk babies, by virtue of having atopic parents, born in Poole, UK from 1976 to 1977, was followed through to age 22 years [38]. Although the numbers were small, exposure to a cat in the home during the first 5 years of life was associated with a non-statistically significant decreased risk (odds ratio, 0.4; 95% CI 0.04–2.5); such a protective effect, however, was not evident for dog ownership. Platts-Mills *et al.* measured serum immunoglobulin G antibody to Der f 1 and Fel d 1 among 226 samples taken from a cross-sectional study of schoolchildren aged 12–14 years in three U.S. cities [39••]. A high level of cat allergen in house dust samples was associated with a decreased risk for sensitization as determined by skin prick test to cat dander extract or a positive cat-specific serum immunoglobulin E test, but associated with a high level of cat-specific immunoglobulin G.

Remes *et al.* were the first to report results from a long term prospective study, using the Tucson Children’s Respiratory Disease Cohort, evaluating early exposure to pets as a risk factor for frequent wheezing (more than 3 episodes in the preceding 12 months), atopy as measured by skin prick testing, and serum total immunoglobulin E [40••]. The study was based on a birth cohort of 1246 babies born between 1980 and 1984 and followed by questionnaire at 2, 3, 6, 8, 11 and 13 years of age. Information on pet keeping was collected during the first month of life and at 3 and 6 years of age. Skin prick testing was completed on 737 (59.1%) and 613 (49.2%) of the children at 6 and 11 years, respectively and total serum immunoglobulin E was measured for 829 (66.5%), 534 (42.9%) and 462 (37.1%) of the children at 9 months, 6 years and 11 years. Pet ownership did not differ between those families with parents who had a history of asthma or hay fever compared with those who did not.

Both dog and cat ownership decreased the risk of frequent wheeze, although the difference was only statistically significant for dogs. The association for dog keeping was limited to children whose parents did not have asthma, with a relative risk, adjusted for confounders, of 0.53 (95% CI 0.34–0.81). This relationship held for children with and without atopy, with relative risks of 0.47 (95% CI 0.24–0.91) and 0.56 (95% CI 0.32–0.98), respectively. There were no associations evident between cats or dogs in the home during infancy and atopy at either 6 or 11 years of age or total serum immunoglobulin E at 9 months, 6 years, and 11 years.

In summary, exposure to cats and dogs as indoor pets in the first years of life appears to protect against sensitization.

Conclusions

In the last decade there has been an increased emphasis on investigating the theory that patterns of exposure to bacteria and viruses modify the pattern of intestinal colonization in the newborn and exert a protective effect by shifting the immune system from the neonatal T helper 2 allergic phenotype to a T helper 1 non-allergic phenotype, thereby diminishing the likelihood of the development of a clinical allergic diathesis: the so-called Hygiene Hypothesis [41–45]. Pets in the home have been associated with increased levels of bacteria and bacterial products such as endotoxin, a potent T helper 1 stimulator [46–47]. The presence of endotoxins, which are biologically active substances present in gram-negative bacteria, is heightened by the presence of animals. Recent reports have demonstrated that household endotoxin levels were higher in farming households than in non-farming households [48]. Gereda *et al.* [49•] found in metropolitan home environments that the strongest positive association with household endotoxin levels was the number of animals in the home and others have demonstrated a protective association between early endotoxin levels and atopy [50•,51].

An alternative hypothesis, based on findings from a cross-sectional study of school children aged 12–13 years described earlier, is that exposure to the high levels of pet allergen associated with the presence of indoor pets results in a modified T helper 2 cell response manifested by increased levels of immunoglobulins G and G4 and the avoidance of sensitization and asthma [39••]. With either of these paradigms, exposure to animals and household pet keeping can be postulated to decrease, rather than increase, risk for atopic conditions. The keeping of pets and livestock may also be surrogate variables for some other factor that is in the causative pathway for allergies or asthma. Perhaps children in these settings are more likely to be physically active or have particular dietary patterns, both of which have been

changing coincidentally with changes in the prevalence of these conditions. It is likely that the true web of causation is not simple and is in truth an interplay of these factors.

The complexities associated with studying the epidemiology of allergy and asthma render even the evaluation of a seemingly straightforward factor such as pet ownership difficult. Since pet exposure is associated with symptom aggravation, and families may change pet keeping behavior based on symptom prevalence and severity (although most allergists do not find this to be the case), it is critical to identify incident cases of disease in etiologic studies, which requires cohort or case-control methodology. Even with case-control studies, the measurement of exposure is problematic, requiring subjects or their parents to recall exposure to pets during a time that may be very remote. While the optimal design strategy, even cohort studies have to surmount the problem of selection bias in pet ownership. A number of putative risk factors can be correlated, such as socioeconomic status, smoking, birth weight, rural living and pet ownership. Many studies have not had large enough sample sizes to allow for adjusting for multiple potential confounders, including current pet ownership, and arrive at definitive risk estimates with precise confidence intervals.

Despite these difficulties, certain consistencies seem evident across recent studies from varying geographies, which is an important hallmark in epidemiology. Exposure to animals on the farm as livestock or in the home setting as pets appears to protect against sensitization defined by skin prick tests or specific immunoglobulin E. Protection is associated with general atopy, not just sensitization to cat and dog allergens. While this inverse association is strongest and most often seen for sensitization as an outcome, there is some evidence that early pet keeping also decreases risk for wheeze and asthma. Results of some studies have varied by whether the subjects did or did not have a family history of atopic conditions. It is unknown what biological or social factors associated with pet keeping afford this protection. Definitive answers await the conduction of large prospective birth cohort studies with careful measurement of environmental and hereditary factors and outcomes. However, as Marks remarked in his recent *Journal of Allergy and Clinical Immunology* editorial [52], at this point in time it may not be prudent for clinicians to advise new parents wishing to prevent allergies and asthma in their children to rid their homes of pets [52].

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