Does Early Exposure to Animals Alter Risk of Childhood Asthma?

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Summary

In this cohort study, the association between early exposure to dogs and farm animals and the risk of asthma was evaluated and included all children born in Sweden. The association was assessed as the odds ratio (OR) for a current diagnosis of asthma at age 6 years for school-aged children and as the hazard ratio (HR) for incident asthma at ages 1 to 5 years for preschool-aged children. The primary outcome was childhood asthma diagnosis and medication used. Of the 1 011 051 children born during the study period, 376 638 preschool-aged (53 460 [14.2%] exposed to dogs and 1729 [0.5%] exposed to farm animals) and 276 298 school-aged children (22 629 [8.2%] exposed to dogs and 958 [0.3%] exposed to farm animals) were included in the analyses. Of these, 18 799 children (5.0%) in the preschool-aged children's cohort experienced an asthmatic event before baseline, and 28 511 cases of asthma and 906 071 years at risk were recorded during follow-up (incidence rate, 3.1 cases per 1000 years at risk). In the school-aged children's cohort, 11 585 children (4.2%) experienced an asthmatic event during the seventh year of life. Dog exposure during the first year of life was associated with a decreased risk of asthma in school-aged children (OR, 0.87; 95% CI, 0.81-0.93) and in preschool-aged children 3 years or older (HR, 0.90; 95%CI, 0.83-0.99) but not in children younger than 3 years (HR, 1.03; 95% CI, 1.00-1.07). Farm animal exposure was associated with a reduced risk of asthma in both school-aged children and preschool-aged children (OR, 0.48; 95%CI, 0.31-0.76, and HR, 0.69; 95%CI, 0.56-0.84), respectively. The authors conclude that exposure to dogs and farm animals during the first year of life reduce the risk of asthma in children at age 6 years.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: The origin and/or basis of childhood asthma have intrigued researchers for decades. About a quarter of a century back, Strachan observed a negative relationship between size of families and the development of atopic conditions [1]. He later suggested that higher levels of personal and household cleanliness were responsible for this, rather than small family size alone. In smaller families, there is less opportunity for 'unhygienic' contact between children and their older sibling(s) resulting in lowered incidence of infections but higher risk of atopic/allergic conditions [2]. This concept gained popularity as the 'hygiene hypotheses' wherein reduced exposure to microbes (through greater cleanliness, better sanitation facilities, widespread vaccination and antibiotic usage) is associated with greater risk of developing allergy/atopy. The proposed biologic explanation is the relative deficiency of a Th1 type immune response (which is associated with infections) that drives the immune system to a predominant Th2 type response which is associated with release of allergic mediators [3,4].

Some investigators explored other aspects of hygiene (or its lack) through exposure to pet animals, farm environments, farm animals etc; with variable conclusions. A recent series of systematic reviews suggested that contact with pet animals particularly dogs could reduce the risk of developing atopic dermatitis or eczema [5-7]. Similarly another systematic review documented a protective effect of early childhood (*i.e.*, before 1 year) farm exposure on development of allergic sensitization [8]. In contrast, a detailed analysis across multiple birth cohorts in European countries failed to identify any relationship between exposure to pet animals in early childhood and later development of asthma or allergy [9]. This is contradictory to another review that suggested a protective effect of exposure to pet animals [10]. An older systematic review conversely suggested that exposure to dogs may actually increase the risk of developing asthma [11]. Of course, there are several reasons for contradictory conclusions from various reviews, including limitations with the original studies in terms of definitions, sample size, tools for outcome measurement, etc. Against this backdrop, the recent publication [12] of a large cohort study examining

the relationship of exposure to pet dogs and farm animals (*I=Intervention/ Exposure*) in early childhood (*P=Population*), to later diagnosis of asthma (*O=Outcome*), is both timely and relevant.

Critical appraisal: ***Table*** **I** presents a formal critical appraisal of the study. In addition, there are some methodological refinements worth noting. In addition to the stringent inclusion and exclusion criteria, the authors

TABLE I. CRITICAL APPRAISAL OF THE STUDY

Criteria	*Report*
Did the study address a clearly focused issue?	Yes. This study included the entire birth cohort of Sweden over a ten year period. The investigators used clear and objective definitions for determining the risk factors (exposure to dogs or farm animals) and outcomes (diagnosis of asthma).
Did the authors use an appropriate method to answer their question?	Yes. An intervention study randomizing infants to be exposed to the risk factors (*i.e* pet dogs or farm animals) is limited by logistic, technical and financial difficulties. Therefore a prospective cohort study with a large sample size is perhaps the ideal study design, especially as it allows statistical adjustment for potential confounders. Of course, a more economical (in terms of time and resources) alternative could be the case-control design, but it is methodologically inferior.
Was the cohort recruited in an acceptable way?	Yes. The cohort comprised the entire Swedish birth cohort over a 10 year period, who were identified through national population-based registers. This obviated potential for selection bias, and lack of representativeness (which are frequent limitations in cohort studies).
Was the exposure accurately measured to minimize bias?	Yes. Exposure to dogs was attributed by determining family ownership of dogs (ascertained from official registers maintained for the purpose). The investigators also determined that over 80% dogs in Sweden are registered through this system. However they explicitly acknowledged the limitations of being unable to determine changes in ownership of dogs and/or cessation of original ownership through demise of the animals. Exposure to farm animals was attributed somewhat indirectly 7 by linking parental occupation/employment as 'animal producers' rather than confirmation of direct exposure to the animals. Obviously it could be argued that both definitions could be erroneous as pet ownership or parental occupation need not be synonymous with 'exposure'; however, this is perhaps the best that can be done in such a situation. On the plus side, the same definitions were used for the entire cohort (*i.e* no mid-term changes).
Was the outcome accurately measured to minimize bias?	Asthma was defined by extracting data from multiple official registers. These included registers recording diagnosis (based on ICD-10 classifications), pharmacy-based registers, either of the two, or both of them. This method of determining outcome has strengths as well as limitations. While the definition itself is objective, the data of individual children could be subjective, creating a bias. It is also unclear whether the method has been actually validated for the purpose, i.e there is no independent ascertainment to document whether the system misses or mis-classifies children as asthma. This is likely because the clinical definition of asthma and/or medications prescribed for asthma, have been undergoing changes in recent years, especially among children less than 5 years [13,14]. One great strength of this system is that the ascertainment is blinded *i.e* there is no prior knowledge of exposure to the risk factors. In addition to the main outcome of asthma, the investigators included secondary outcomes *viz* diagnosis of pneumonia and lower respiratory tract infections. This is particularly useful to explore the hygiene hypothesis.
Have the authors identified all important confounding factors?	Yes. The authors considered multiple potential confounders *a priori* viz. education level of parents, socio-economic status, parental history of asthma (but not atopy), birth order, etc. The last two are especially important as parental asthma and/or older siblings with asthma could influence parental perceptions of asthma and health-care seeking behavior as well as alter the pattern of pet ownership. Statistical treatment of data to take care of confounders was undertaken.
Was the follow up of subjects complete and long enough?	The age chosen for prevalence of asthma (7^{th} year) is appropriate as the potential effects of the risk factors would have had enough time to manifest. However, the exclusion of children who died or emigrated could potentially create a bias since some of these could have been related to the outcome.
What are the results of this study? How precise are the results?	The authors presented data as odds ratio (95% CI). In summary, they demonstrated lower odds of having asthma with early exposure to dogs (adjusted OR 0.87, 95% CI 0.81, 0.93) and farm animals (adjusted OR 0.48, 95% CI 0.31, 0.76). The 'beneficial effect' of farm animals was evident in

	school children as well as pre-schoolers. These results were insensitive (*i.e* robust) with respect to presence or absence of parental asthma. The investigators also documented a statistically significant higher risk of developing pneumonia and a trend towards more frequent lower respiratory tract infection with exposure to dogs.
Do you believe the results?	The study methodology and quality provide compelling data that cannot be ignored. Some of the Bradford Hill criteria [15] to attribute causality are demonstrable *viz* Temporality, Consistency, Theoretical Plausibility, and Coherence. However the odds of developing asthma appear to be much lower with exposure to farm animals than pet dogs. The stronger association with the former (even though the children need not have been in direct contact with farm animals) suggests that there may be other factors (besides the hygiene related issues) influencing the outcome. Clearly, this study cannot demonstrate the criteria of 'Specificity in the causes' (*i.e* the outcome has more than one potential cause) and Dose Response Relationship.
Can the results be applied to to the local population?	Please see section on Extendibility.
Do the results of this study fit with other available evidence?	The previous pieces of evidence suggest an equivocal effect of exposure to dogs, with different studies suggesting beneficial effect, no effect, as well as harmful effect. In contrast, "farm exposure" (the term is variably defined in different studies) is associated with protective effect. This study adds an oft-ignored bit of information *viz.* dog exposure was associated with a higher risk of pneumonia and other types of lower respiratory infections.

tried to minimize design effect by including only one child per family in the main analysis. They also attempted to identify the effect of cessation of dog exposure among those who did and did not develop asthma. Three sensitivity analyses based on timing of exposure to dogs were conducted. Multiple additional sensitivity analyses based on definition of asthma, parental asthma status and birth order were also undertaken, making it possible to tease out some of the confounding effects observed in previous studies.

Some limitations are also worth mentioning. The methods used to ascertain exposure to the risk factors did not consider exposure to additional pets (furry or otherwise); which could also have a bearing on the outcome. The study also did not offer the opportunity to examine the effect (if any) of the so-called hypoallergenic pets. Although it may have been possible to study the effect of both risk factors together, this was not done.

The investigators could determine asthma in the seventh year, as well as pre-school age group separately; however they did not report whether the children in the latter group continued to have asthma by the seventh year of life. This would have been relatively easy, and added considerable academic and clinical value especially because the protective effects observed in this study appeared limited to older children (>3 years) despite early exposure (i.e before 1 year) to the risk factors. Although not an intended objective, this study provides valuable confirmation of asthma prevalence in Swedish children and also an estimate of incidence among pre-school age group. It also demonstrates a 2.5 fold higher prevalence of asthma among children whose parents had asthma.

Extendibility: The authors themselves point to the immediate generalizability of their results to Sweden, and potential application to European countries. However there are several challenges in extrapolating these data to India. First, the proportion of 'asthma' attributable to atopy versus non-atopic mechanisms is unclear. Further India represents considerable diversity in terms of living conditions, environmental exposures, and access to health-care, making it difficult to replicate this type of study across the nation. Further, the relatively unregulated use of antibiotics, vaccines, and medications for asthma could further confound the discourse on the potential emphasis of the hygiene hypothesis in our setting.

Conclusions: This well-designed nation-wide cohort study suggests that exposure to dogs in early infancy could be associated with lower prevalence of asthma at the onset of school years, although these children had higher risk of developing pneumonia. Exposure to farm animals appeared to have consistent beneficial effects.

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Pediatric Pulmonologist's Viewpoint

Relevance: Asthma is a chronic respiratory disorder that has become substantially more common over the past decades. One environmental factor for which particularly strong associations with asthma and allergic diseases have been described is exposure to farming environments in childhood [1]. Recent studies have identified new ways in which viral and microbial exposures in early life interact with host genetic background/variants to modify the risk for developing asthma and allergic diseases [2]. In this nationwide cohort study, a search is made for the association between early exposure to dogs and farm animals and the risk of asthma and included all first born children in Sweden in ten years.

Critical Appraisal: This study shows dog exposure during the first year of life was associated with a decreased risk of asthma in school-aged children (OR, 0.87; 95%CI, 0.81-0.93) and in preschool-aged children 3 years or older (HR, 0.90; 95%CI, 0.83-0.99) but not in children younger than 3 years (HR, 1.03; 95%CI, 1.00-1.07). Statistically, the variations in CI, OR and HR are very marginal to suggest a definite hypothesis. It is also not explained why children younger than 3 years age did not got the protection from animal exposure. (HR, 1.03; 95%CI, 1.00-1.07).It is not clear why secondary outcomes of bronchiolitis, pneumonia and lower respiratory tract infections were considered. These diagnoses were not relevant in this study! The authors speculated that dog exposure may increase an infant's overall exposure to microorganisms and allergens, some of which increase the risk for respiratory tract infections and others that modulate the immune system in such a way that decreases the risk of allergy-related asthma in school-aged children. This speculation has no proved support shown in this study. The limitation in the study are 1) details of different asthma phenotypes were not studied , 2) dog registry and family history of asthma and allergy were not fully covered and 3) children only during their seventh year of age were examined leaving children at other ages unevaluated.

Discussion: Susceptibility to asthma and allergic diseases is complex and involves genetic variants and environmental exposures (bacteria, viruses, smoking, and pet ownership), alteration of our microbiome and potentially large-scale manipulation of the environment over the past century [2]. Pooled analysis of individual participant data of 11 prospective European birth cohorts in 1990 showed that pet ownership in early life did not appear to either increase or reduce the risk of asthma or allergic rhinitis symptoms in children aged

6–10 years. Missing from all these studies of childhood exposures is a comprehensive longitudinal study that follows children exposed to both livestock and crop farming into their adult years. This type of study is particularly necessary, because studies have reported an increased risk of respiratory disease in adult farmers compared to non-farmers. It is currently not clear if the apparent protective effect of farm exposures in childhood persists into adulthood [3].

Clinical Application: The age-old "hygiene hypothesis" is highly debated. Based on these observations, it is not feasible to accept the inference of this study to be used in clinical practice at present. There is a need of a robust longitudinal, multi-centric (stratified through different economic and environmental conditions) trial on effect of farm animal exposure in early life in the future outcome on asthma.

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Children's Health and Environment Viewpoint

The respiratory and immune systems both continue to develop after birth and are vulnerable to both pre and post-natal environmental exposures that act on underlying genetic predisposition to asthma [1]. Family history of allergies and asthma is a major risk factor for persistent asthma. Environmental risk factors include frequent respiratory viral infections, sensitization to aeroallergens from household/ambient air pollution, second hand tobacco smoke or bio-aerosols [2]. A majority of all mammalian allergens are spread as airborne particles, and several have been detected in environments where furry animals are kept. The Can F I allergens found in canines can often induce an IgE response in humans. Among domestic pets, allergic reactions to cats are the most common [3]. The verdict on allergy to dogs and farm animals is less clear and equivocal. The association between early exposure to animals and subsequent risk for asthma is at best inconsistent and most reviews report substantial heterogeneity. The authors acknowledge that differences in study designs, age of outcome measurements, and how confounders, exposures and outcomes are assessed influence the results of the studies. An important determinant of lung function and capacity is physical environment. Children living in farms have more physical activity and less ambient air pollution which can explain better lung capacities, but this social mileu is rarely adjusted for in large cohort studies that rely on population data bases with information available on limited socio-demographic and environmental variables. Another important confounder is history of allergy to fur animals in the family. Those families with history of allergy to canines are less likely to have canine pets. Therefore it is unclear whether early exposure to canines reduces the likelihood of asthma or whether those families who have these genetic allergies are less to have pets. Individual genetic predisposition, social mileu, nutritional qualities are likely contributors to an individual child's susceptibility to environment toxicants. So a rigorous environmental history in pediatric practice should include family history of environmental triggers, including allergies to canines.

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