

Early exposure to cats, dogs and farm animals and the risk of childhood asthma and allergy

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Abstract:

Background: Synergistic role of exposure to cats, dogs, and farm animals during infancy on the risk of childhood asthma and allergy remains unknown.

Objectives: To investigate independent and synergistic associations between exposure to indoor pets and farm animals during infancy and the risk of asthma and allergy by age 5.

Methods: We studied 3781 children participating in the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) nutrition study. At age 5, a validated version of the International Study of Asthma and Allergies in Childhood questionnaire was administered to collect information on asthma and allergic disease; and exposure to indoor pets and farm animals during the first year of life. Allergen-specific IgE antibodies were analyzed from serum samples. Statistical analyses employed Cox proportional hazards- and logistic regression.

Results: Having a dog in the house was inversely associated with the risk of asthma (HR 0.60; 95%CI, 0.38-0.96); allergic rhinitis (OR 0.72; 95%CI, 0.53-0.97); and atopic sensitization (OR 0.77; 95%CI, 0.63-0.96). Having a cat was associated with decreased risk of atopic eczema (OR 0.68; 95%CI, 0.51-0.92). Farm animals were neither independently nor in synergy with indoor pets associated with the outcomes.

Conclusion: Having a dog or cat in the house during the first year of life may protect against childhood asthma and allergy. We did not find a synergistic association between cat, dog and farm animal exposure on the risk of childhood asthma and allergy. Future research should identify specific causative exposures conferred by indoor pets and whether they could be recommended for allergy prevention.

Keywords: *Asthma; Allergic Rhinitis; Atopic Eczema; Cats; Children; Dogs; Farm animals*

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Main text:

Background

The presence of domestic pets and farm animals and exposure to environments rich in microorganisms during early life appear to protect against asthma and allergy in childhood ^{1,2}. However, conclusions from studies on birth cohorts and systematic reviews have been inconsistent ^{3,4}. While some evidence has shown a reduced risk ⁵, others have demonstrated an increased risk ^{6,7}, and yet others have not shown any associations ⁸. In their review, Ownby and Johnson ⁹ concluded that systematic reviews and meta-analyses on early life exposure to pets and farm animals showed either a reduction; or no increase in the risk of subsequent allergic disease.

Interaction between environmental exposures in early life may add complexity to the risk of asthma and allergic disease ^{6,7,10}. Single exposures are invariably contaminated by other exposures ⁶, and the risk-exposure curve may not be linear ¹¹. Whether the association between exposure to pets and farm animals and the risk of asthma and allergy in children act independently or in synergy remains largely unknown ^{6,11}. Any dose-response effect regarding the number and variety of these exposures on the risk of childhood asthma, therefore, needs to be elucidated ^{3,12}.

We sought to investigate the independent and synergistic roles of exposure to an indoor cat; indoor dog; and farm animals during the first year of life in the development of asthma and allergy in children by the age of 5 years.

Methods

Study Setting and Population

The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study is a prospective population-based birth cohort study that started in 1994, aimed at exploring means to predict and prevent type 1 diabetes. All newborn infants with HLA-conferred susceptibility to type 1 diabetes are recruited from the University Hospital areas of Turku, Oulu, and Tampere and monitored at 3-12

months' intervals for type 1 diabetes-related auto-antibodies¹³. In 1996 in Oulu and 1997 in Tampere, a nutrition part was initiated within the DIPP study (DIPP Nutrition Study). The DIPP nutrition study examines the role of maternal diet during pregnancy and lactation and child's diet during infancy and childhood in the development of type 1 diabetes, allergic diseases, and asthma¹⁴.

Between September 1996 and September 2004, 7782 children born in Oulu and Tampere University Hospitals were invited to the DIPP Nutrition Study. At the age of 5 years, 4075 children still participating in the dietary follow up were invited to take part in the allergy component of the DIPP Nutrition Study. A total of 3781 children (93%) took part through parental completion of the allergy study questionnaire and/or by giving a blood sample for the analysis of serum immunoglobulin E (IgE) levels. Of these, 3143 children returned the modified International Study of Asthma and Allergies in Children (ISAAC) questionnaire. Serum IgE levels to food and inhalant allergens were analyzed in a sub-sample of 3675 children blind to clinical and demographic data. The local ethics committees approved the study procedures and the parents provided written informed consent. The flow diagram of the study population is presented in Figure 1.

Outcome Assessment

At the age of 5 years, a questionnaire modified from ISAAC was administered to the parents of the participating children to capture the child's history of allergic symptoms and asthma. A blood sample was obtained for each child for the measurement of circulating immunoglobulin E (IgE) antibodies to food and inhalant allergens. Asthma was defined as physician-diagnosed asthma with wheezing symptoms and/or the use of asthma medication in the preceding year. Allergic rhinitis was defined as sneezing, nasal congestion, or rhinitis other than that caused by respiratory infections, accompanied by itching of the eyes and tearing during the previous year. Atopic eczema was defined as atopic eczema ever diagnosed by a physician. Atopic sensitization was assessed through the measurement of the child's allergen-specific IgE levels from serum specimens. Positivity was defined

as values of ≥ 0.35 KU/L to any of the allergens measured: egg, cow's milk, fish, wheat, house dust mite, cat, timothy grass, and birch allergens.

Exposure Assessment

Information on whether there was a dog or cat in the house; farm animals (cows, horses, sheep, goats, hens, other) in a building outside of the house; and visits to a building housing farm animals during the child's first year of life; was collected using the modified ISAAC questionnaire completed by the parents when the child reached the age of 5 years. These were all coded as yes/no responses. In addition to types of pets living mainly inside the house, the questionnaire also collected information on the frequency of weekly visits to a cowhouse or building where farm animals are kept; whether allergies affected house furnishing or decisions to buy and keep pets; and whether the child had avoided contact with animals.

Socio-demographic and potential confounding factors

Information on the duration of gestation, mode of delivery, birth weight, and maternal smoking during pregnancy was retrieved from the medical birth registries of Oulu and Tampere University Hospitals. Information on the child's sex, maternal age, parity, maternal professional educational level, and the number of siblings was recorded in a structured questionnaire completed by the parents after delivery. Home municipality urbanization level was categorized according to Statistics Finland guidelines as rural, semi-urban, and urban. Parental history of asthma and allergic rhinitis; and farming occupation of the family during the first year of life were also assessed in the modified ISAAC allergy questionnaire.

Statistical Analyses

The Pearson Chi-square test or the Fisher's exact test was used to examine the association between demographic characteristics and allergy and asthma outcomes. Logistic regression was used to study the associations between the exposure variables and the allergy outcomes (allergic

rhinitis, atopic eczema, and atopic sensitization), while Cox proportional hazards regression was used to study the association between the exposure variables and asthma. The possible dependence among siblings was accounted for by using the generalized estimating equations with the sandwich estimator of variance to estimate regression coefficients in logistic regression analyses. In the Cox models, dependence among siblings was considered by performing a marginal analysis with a working independence assumption and a robust sandwich estimator of variance. Potential confounders adjusted in the models were child's sex, place of birth (Tampere/Oulu), maternal professional educational level (none, professional education/course, secondary professional education, university), age (<25, 25-29, 30-34, and ≥35 years) and smoking during pregnancy (yes/no), duration of gestation (<37 and ≥37 weeks), mode of delivery (vaginal/cesarean section), number of siblings (0, 1, 2 and ≥3), home municipality urbanization level (rural, semi-urban and urban), maternal history of asthma or allergic rhinitis (yes/no) and farming as a primary or secondary occupation of the family during the first year of life (yes/no). Statistical significance was taken as two-sided $P < 0.05$. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA)

Results:

We analyzed data from 3781 children. Of these, 45% were the first child in the family, and slightly more than half were boys (53%). Forty-five percent of the mothers reported a history of asthma or allergic rhinitis. Eight percent of the mothers smoked during pregnancy, and 6% of the children were delivered pre-term. A majority of the children (77%) resided in an urban municipality. About 4% of children had parents who reported farming as either a primary or secondary occupation during the child's first year of life. (Table 1). Nine hundred fifty-four (31%) children had any pet in the house, 592(19%) had an indoor dog while 374(12%) had a cat in the house during the first year of life.

Six percent of the children had asthma, 14% allergic rhinitis, 25% atopic eczema, and 37% were sensitized to an allergen. Asthma, allergic rhinitis and atopic eczema were more common among boys than girls. Asthma and allergy were more common among children whose mothers had a history of asthma or allergic rhinitis. (Table 1)

In unadjusted analyses, having a cat in the house during the first year of life was associated with a decreased risk of developing atopic eczema at the age of 5 years, compared to not having a cat in the house. In comparison with not having one, having a dog in the house was associated with decreased risk of atopic sensitization to any allergen by the age of five years. (Supplement 1)

In adjusted analyses, compared to those without, having a dog in the house was associated with 40% reduced risk of developing asthma (HR 0.60; 95%CI, 0.38-0.96); 28% reduced odds of allergic rhinitis (OR 0.72; 95%CI, 0.53-0.97); and 23% reduced odds of atopic sensitization to any allergen (OR 0.77; 95%CI, 0.63-0.96) by the age of 5 years. Visiting a stable, cowhouse, or any building housing farm animals during the first year of life was not associated with any of the outcomes. Furthermore, there was no synergistic association of having both a dog and a cat in the house; or having any of these pets in the house and visiting a stable or buildings where animals are kept with any of the outcomes. (Supplement 1)

Discussion

This relatively large birth cohort study shows that having a dog in the house in the first year of a child's life is associated with a reduced risk of developing asthma and allergic diseases by the age of 5 years. The same was true for having a cat in the house in relation to atopic eczema. However, exposure to farm animals in cowhouses and stables during the child's first year of life was not associated with asthma or any of the allergy outcomes. Moreover, we did not find any synergism in the association between having a cat; a dog; and visiting a stable or cowhouse; and any of the outcomes in this population.

Study Strengths and Limitations

Families that avoid keeping pets due to familial history of allergies have been shown to have higher risks of developing asthma and allergy compared to families without this pet-avoidance behavior, inferring that pet-keeping may have a protective effect ^{6,10,15–17}. In the present study, we did not account for this ‘healthy pet-keeping effect’, which may have under- or over-estimated the association seen between pet-keeping and the risk of asthma and allergy in children. However, some studies have shown that parental asthma did not modify the effect of exposure to dogs or farm animals on the risk of asthma in childhood, and pet avoidance may not be a major factor ^{5,16,17}.

We did not differentiate between children whose parents both work and live on farms versus those working on farms not located close to their homes. This could lead to misclassification and an underestimate of the farm effect ⁵. Our questionnaire did not collect information regarding the frequency and length of exposure to pets and farm animals, or the type of dog or cat owned, e.g., fur shedding vs. non-shedding dogs. Consequently, we could not ascertain the density of exposure to the risk factors. Furthermore, we did not assess gender disparity in exposure to the farm animals and our outcomes. Though there could be gender modification in the relationship between asthma and a farming environment ¹⁸, others have also shown that gender did not modify the effect of living on a farm on allergic rhinitis ¹⁹.

It would appear that pet-keeping is protective in regions with high awareness of risks associated with keeping pets, but a risk factor in regions with less awareness ¹⁰. Others have also suggested that the effect of pet ownership may be related to the prevalence of pet-keeping and community exposure to pet allergens such that those without pets benefit from passive exposure ¹⁵. As such, counseling for lifestyle modifications could be important, more so for families with a genetic predisposition to asthma and allergy²⁰. We did not assess these factors in the current study. We can, therefore, cannot discount any residual confounding due to such factors.

Our study population had HLA-conferred susceptibility to type 1 diabetes, which may limit the generalizability of our findings to children without HLA-conferred risk of type 1 diabetes. Additionally, 23% of the invited families declined participation, leading to the possibility of selection bias. However, the association between HLA genes and asthma remains mixed as both increased risk and reduced risk have been reported ²¹. Furthermore, the absolute risk of type 1 diabetes up to the age of 15 years in the DIPP nutrition study is 3-4 times that of the general Finnish population ^{21,22}

Our well-defined birth cohort with a relatively large sample size drawn from two university hospitals where large proportions of births occur in Finland was not based on a positive familial history of asthma. These minimize the potential selection bias toward those at high risk for allergy. The cumulative incidence of asthma in the DIPP nutrition study also compares with the general Finnish population of children this age. ²² Moreover, our modified ISAAC questionnaire has also been validated to capture asthma compared with clinical diagnosis reliably. ²³ These, together with our high retention rates, strengthen the internal validity of our study and provides a reliable picture of findings among similar populations. We had small sample sizes in some cells, and though this could have affected the precision of our estimates, it is unlikely to have led to spurious positive association given the narrow confidence intervals in the observed associations. However, as with any other observational epidemiologic studies, caution should be taken when making any causal inferences from our findings.

Comparison with other studies

Contention still surrounds the association between exposure to pets and childhood asthma and allergy ^{7,12}. While some studies among school-aged children have shown that exposure to cats is associated with an increased risk of asthma and allergies ^{7,24}; others have shown exposure to dogs to be associated with a reduced risk ^{2,5,25}; and yet still others, no association of asthma with any pet exposure ^{15,26}. In their study among children aged 6-18 years, Song *et al.* found that exposure to dogs was associated with higher prevalence of allergic diseases than exposure to cats ⁷. On the other

hand, Collin *et al.* showed a protective association of cats on repeated episodes of wheezing, but exposure to dogs did not show such an association in children aged seven years¹². In our study, having a dog living in the house during the first year of life was inversely associated with asthma, allergic rhinitis, and atopic sensitization at the age of 5 years. Having a cat living in the house in the first year of life was also inversely associated with atopic eczema later in childhood. Similar findings following exposure to dogs and cats have been demonstrated by other research work¹⁶.

Findings from our study are in tandem with previous studies that showed no difference in symptom reporting among children of the same age as those in our study, following exposure to both dog and cat, compared to exposure to either dog or cat alone^{8,17}. In contrast, others have demonstrated an increased risk of asthma and allergic diseases in school-aged children following exposure to both dog and cat¹⁶.

We did not find any association between exposure to farm animals or visiting a cowhouse or any building where animals are kept, and the risk of asthma and allergy. Similar findings have been seen in other studies that did not find differences in the prevalence of allergic diseases among children living on farms and conducting activities such as visiting barns, riding horses, and feeding livestock²⁷. However, it has generally been observed that children living in such farm environments have fewer allergic diseases compared to those in non-farm settings. This would suggest that activities in a farming environment, including cultivation-farming, contact with farm animals and stables, and consumption of raw cow's milk may be protective against asthma and allergic diseases in childhood^{2,5,6,15,28}. These findings have been heterogeneous, though, suggesting that particular farm characteristics may have greater effects than others²⁸⁻³⁰. The beneficial effect of the farm environment has been ascribed to the consumption of raw cow's milk, . There are efforts to isolate the relevant cowshed-associated bacterial flora and examine their specific roles in the protective effect of the farm environment

While some researchers ³¹ have not found any dose-response relationship between pet-keeping and allergic rhinitis, others have posited that the amount of exposure to microbial antigens in the farm environment ^{27,32} and gene regulatory mechanisms ³³ also have a role to play in the protection against asthma and allergy in children exposed to a farm environment during early childhood. In the present study, we did not find evidence for a synergistic effect of exposure to indoor pets and farm animals on the risk of asthma and allergic diseases. It is unclear whether the cumulative diversity of the farm environment is more important than exposure to single factors for immune responses resulting in allergy in children ³⁰. To our knowledge, only one previous study ³² has demonstrated that the protective effect of growing up on a farm on the incidence of rhinitis in atopic subjects was further augmented when combined with exposure to any pet in childhood.

Conclusion and Recommendations

Children who lived with a dog in the house in the first year of life had a lower risk of developing asthma and allergy later in childhood, compared to children who did not have a dog living in the house. Similar observations were made among children living with a cat, in relation to atopic eczema. Farm animals were neither independently nor in synergy with a dog or cat in the house, associated with asthma and allergy in this population.

While our observations add to the body of evidence showing that having pets in the house during infancy subsequently reduces the risk of allergy later in childhood; future research should focus effort on identifying the specific causative exposures conferred by indoor pets and whether they could be recommended for allergy prevention.

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Table 1: Study population characteristics by asthma, allergic rhinitis, atopic eczema and atopic sensitization, at age 5

years									
Characteristic	Total (N=3143)	Asthma (n=194)		Allergic Rhinitis (n=442)		Atopic Eczema (n=785)		Atopic Sensitization [†] (n=1161)	
	(%)	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value
Gestational age at birth (weeks)									
<37	192(6)	21(11)	0.005	22(11)	0.25	42(22)	0.29	57(30)	0.06
≥37	2920(93)	172(6)		418(15)		738(26)		1093(39)	
Missing information	31(1)								
Sex									
Male	1646(52)	121(7)	0.004	262(16)	0.002	432(27)	0.07	642(41)	0.001
Female	1497(48)	73(5)		180(12)		353(24)		519(36)	
Mode of delivery:									
Vaginal	2701(86)	161(6)	0.19	382(14)	0.96	681(26)	0.55	1002(39)	0.42
Caesarean section	420(13)	32(8)		59(14)		100(24)		151(37)	
Maternal age									
≤24	466(15)	35(8)	0.39	66(15)	0.84	106(23)	0.07	174(39)	0.59
25-29	1099(35)	68(6)		157(14)		301(28)		414(39)	
30-34	973(31)	61(6)		141(15)		243(25)		351(38)	
≥35	605(19)	30(5)		78(13)		135(23)		222(38)	
Number of siblings:									
0	1417(45)	86(6)	0.06	224(16)	0.002	380(27)	0.04	537(39)	0.28
1	988(31)	67(7)		138(14)		246(25)		365(38)	
2	421(13)	27(6)		52(12)		97(23)		148(37)	
>3	258(8)	6(2)		18(7)		48(19)		88(35)	
Missing information	59(2)								
Maternal history of asthma or allergic rhinitis									
Yes	1377(44)	128(9)	<0.001	272(20)	<0.001	409(30)	<0.001	583(44)	<0.001
No	1665(53)	61(4)		156(10)		347(21)		544(34)	
Missing information	111(3)								
Maternal smoking during pregnancy									
Yes	229(7)	14(6)	0.95	34(15)	0.71	59(26)	0.79	91(40)	0.31
No	2812(89)	175(6)		398(14)		704(25)		1031(38)	
Missing information	102(3)								
Home municipality urbanization:									
Rural	400(13)	28(7)	0.60	43(11)	0.09	98(25)	0.59	157(41)	0.56
Semi-Urban	305(10)	16(5)		47(16)		68(23)		112(39)	
Urban	2416(77)	149(6)		351(15)		615(26)		884(38)	
Farming as family occupation									
Yes	127(4)	7(6)	0.75	18(14)	0.98	31(25)	0.91	46(38)	0.95
No	3007(96)	187(6)		423(14)		752(25)		1113(38)	

[†] To any of the following allergens: inhalant, food, egg, milk, fish, wheat, dust mite, cat, Timothy grass, birch

**Figure 1: Flow diagram of the study population for the Allergy component of the DIPP Study
Supplement 1: Exposure to indoor dogs, cats, and farm animals in the first year of life and the risk of
asthma and allergy by age 5 years.**