

ORIGINAL ARTICLE

Farming environment and prevalence of atopy at age 31: prospective birth cohort study in Finland

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Summary

Background Cross-sectional studies have shown an association between the farming environment and a decreased risk of atopic sensitization, mainly related to contact with farm animals in the childhood.

Objective Investigate the association of a farming environment, especially farm animal contact, during infancy, with atopic sensitization and allergic diseases at the age of 31.

Methods In a prospective birth cohort study, 5509 subjects born in northern Finland in 1966 were followed up at the age of 31. Prenatal exposure to the farming environment was documented before or at birth. At age 31, information on health status and childhood exposure to pets was collected by a questionnaire and skin prick tests were performed.

Results Being born to a family having farm animals decreased the risk of atopic sensitization [odds ratio (OR) 0.67; 95% confidence interval (CI) 0.56–0.80], atopic eczema ever (OR 0.77; 95% CI 0.66–0.91), doctor-diagnosed asthma ever (OR 0.74; 95% CI 0.55–1.00), allergic rhinitis at age 31 (OR 0.87; 95% CI 0.73–1.03) and allergic conjunctivitis (OR 0.86; 95% CI 0.72–1.02) at age 31. There was a suggestion that the reduced risk of allergic sensitization was particularly evident among the subjects whose mothers worked with farm animals during pregnancy, and that the reduced risk of the above diseases by farm animal exposure was largely explained by the reduced risk of atopy. Having cats and dogs in childhood revealed similar associations as farm animals with atopic sensitization.

Conclusion and Clinical Relevance Contact with farm animals in early childhood reduces the risk of atopic sensitization, doctor-diagnosed asthma and allergic diseases at age 31.

Keywords allergy, asthma, atopy, farm animals, farming

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Introduction

Cross-sectional studies have suggested that a farm environment in infancy may protect against atopic sensitization and allergic diseases in childhood [1–3]. This protective effect may persist into adult life [4]. It has been hypothesized that high microbial exposure on a farm, either through contact with farm animals [1–3] or via consumption of unpasteurized milk [1, 2, 5], promotes the development of the non-allergic phenotype by effects on the development of the immune system, particularly T-helper and T-regulatory cells [6]. This effect may occur as a result of maternal exposure during pregnancy [2, 7]. Nevertheless, the me-

chanism is not fully understood. Prospective associations between exposure to a farm environment in early life and atopic sensitization in adulthood are even less clear. The present prospective birth cohort offered an exceptional opportunity to investigate the effect of farming environment in infancy, especially farm animal contact, with reported allergic disease and atopic sensitization measured by skin prick tests (SPTs), at the age of 31 years.

Methods

The original cohort consisted of 12 058 live births from the two northernmost provinces of Finland, Oulu and

Lapland, and covered 96% of the children born in that region between January 1 and December 31, 1966. In 1997, 8463 survivors still living in Northern Finland or in the capital city area received a postal questionnaire and invitation to clinical examinations; 6007 attended the examinations. The University of Oulu Ethics Committee approved the study and the participants gave written informed consent.

Assessment at age 31 years

During follow-up at age 31 years, participants underwent a clinical examination and a SPT to assess sensitivity to three of the most common allergens in Finland, i.e. cat, birch and timothy, and sensitivity to the house dust mite (*Dermatophagoides pteronyssinus*). Histamine dihydrochloride (10 mg/mL) and a diluent of the allergen extracts were used as positive and negative controls, respectively. Skin reactions to each allergen tested were recorded after 15 min as the average of the maximum weal diameter and the diameter perpendicular to the maximum. Subjects with a weal reaction ≥ 3 mm to one or more of the four allergens tested were considered as atopic. Subjects with a positive reaction to the negative control or a negative reaction to histamine (< 3 mm) were excluded. Weight and height were measured and body mass index (BMI) was calculated as weight/height².

At the 31-year follow-up, participants also filled in questionnaires, which included questions on health and lifestyle factors, socio-demographic factors, as well as allergic conditions. Allergic rhinitis (AR), allergic conjunctivitis, atopic eczema and doctor-diagnosed asthma were based on self-report and were asked separately for the last 12 months (labelled 'current' in the present analyses) and ever having had the condition. We analysed current rhinitis, conjunctivitis and asthma, but due to low numbers of current asthma and atopic eczema, we also analysed asthma ever and atopic eczema ever. We also identified those who reported a parental history of AR, atopic eczema and asthma. Moreover, we asked about cat and dog ownership before the age of 7 years.

Assessment of antenatal factors

Childhood information about parental professional farming, having farm animals (species and counts), maternal work with farm animals during pregnancy, place of residence, residential density, maternal education, maternal age, maternal BMI, smoking during pregnancy from the second month, mother's age of menarche and parity number, gestational age at birth, birth weight and height were collected during pregnancy and/or immediately after delivery. Residential density was defined as the number of subjects in the household divided by the number of rooms in the household. Maternal work with farm animals

during pregnancy is a subquestion for having farm animals in which subjects with farm animals during infancy were divided into three groups based on their mother's participation in work with farm animals during pregnancy.

Statistical analyses

We included in the final analyses those 5509 subjects who had non-missing SPT data on all allergens, and who had a positive reaction to histamine and a negative reaction to control. Among these subjects, the maximum prevalence of missing data for disease outcomes was 1.5%, 1.3% for farm characteristics collected during pregnancy and 4.5% for data on pet ownership collected at the 31-year follow-up. The highest prevalence of missing information for the confounders was 12.8% (paternal allergy). Univariate analyses were carried out using the χ^2 test and multivariate models were run using logistic regression. To select confounders for multivariate models, we identified *a priori* the list of potential confounders, i.e. sex, maternal age, maternal education, mother's smoking during pregnancy, maternal BMI, place of residence, residential density, current education, current BMI, current smoking, paternal asthma, paternal allergy, maternal asthma, maternal allergy, gestational age, mother's age of menarche, parity, birth height and weight. Current BMI, maternal BMI, birth weight and height were categorized in the analyses. In the multivariate models, missing data for each confounder listed above were classified as its own category. For the final models, we included all variables that were associated with either atopy or doctor-diagnosed asthma at $P < 0.2$ level. Only current smoking and birth weight were not significantly associated with either outcome and were therefore not adjusted for. All analyses were conducted using SPSS 15.0

Results

In our study population, there were 1262 (23%) subjects whose parents were professional farmers. In contrast to many modern Finnish farms, the field sizes of the farms were relatively small (64% below 8 ha). There were 1653 (30%) subjects who were born to a family with farm animals. Among the subjects living in homes with farm animals in infancy, 98% had cows, 21% pigs, 18% sheep, 13% poultry and 10% minks. However, many of these homes had only a few farm animals (54% had less than or equal to four cows, 54% had only one pig, 71% had less than or equal to four sheep, 63% had less than or equal to 16 chickens and 86% had less than or equal to 50 minks), which was a typical feature of the farms in the Northern Finland at that time.

Significantly decreased risks of atopy were seen in subjects born in villages, especially outlying districts,

Table 1. Adjusted associations between farm-related factors in infancy and atopic sensitization at age 31

Farm-related factors in infancy	Study population		Atopy*				
	N	%	n	%	aOR	95% CI	CI
Place of residence							
City	1813	33	685	38	1		
Village	1375	25	455	33	0.86	0.74	1.01
Outlying districts	2321	42	544	23	0.59	0.51	0.69
Professional farming							
No	4247	77	1425	34	1		
Yes	1262	23	259	21	0.69	0.58	0.83
Family had farm animals							
No	3811	70	1323	35	1		
Yes	1653	30	344	21	0.67	0.56	0.80
Number of cows							
0	3851	71	1336	35	1		
1–4	860	16	183	21	0.71	0.57	0.87
> 5	746	14	147	20	0.60	0.48	0.75
Pigs							
No	5118	94	1610	32	1		
Yes	343	6	57	17	0.59	0.43	0.79
Sheep							
No	5168	95	1611	31	1		
Yes	293	5	56	19	0.74	0.55	1.02
Poultry							
No	5246	96	1629	31	1		
Yes	215	4	38	18	0.65	0.45	0.94
Minks							
No	5296	97	1629	31	1		
Yes	159	3	37	23	0.91	0.62	1.34
Maternal work with farm animals during pregnancy							
No farm animals	3811	70	1323	35	1		
No maternal work with farm animals	164	3	50	31	1.01	0.70	1.44
Maternal work with farm animals with assistance	917	17	189	21	0.63	0.51	0.77
Maternal work with farm animals	543	10	101	19	0.62	0.48	0.80
Family had cats [†]							
No	2683	51	981	37	1		
Yes	2576	49	630	25	0.68	0.60	0.78
Family had dogs [†]							
No	2411	45	869	36	1		
Yes	2909	55	757	26	0.75	0.66	0.85
Number of animal species ^{†,‡}							
0	1428	28	565	40	1		
1	1500	30	527	35	0.88	0.75	1.03
2	1017	20	256	25	0.59	0.49	0.72
3	645	13	123	19	0.45	0.35	0.59
≥4	472	9	83	18	0.43	0.32	0.58

aOR: adjusted with sex, maternal age, maternal education, smoking during pregnancy, maternal BMI, place of residence, residential density, current education, current BMI, paternal asthma, paternal allergy, maternal asthma, maternal allergy, gestational age, mother's age of menarche, parity and birth height.

*Subjects with a weal reaction ≥ 3 mm to one or more of the four allergens tested were considered to be atopic.

[†]Before age of seven.

[‡]Includes cows, pigs, sheep, poultry, minks, cats and dogs.

CI, confidence interval; BMI, body mass index.

those having a parent who was a professional farmer during infancy and those being born to a family having farm animals (Table 1). There was evidence of decreasing risk with increasing exposure to cows. Decreased risk of

atopy was particularly evident among subjects whose mothers worked with farm animals during pregnancy. Having a cat or a dog in childhood reduced the risk of atopy at age 31. Taken together, contact with increasing

number of animal species in childhood was dose dependently and inversely associated with a decreased risk of atopic sensitization in adulthood.

Further adjustment for family's professional farming in infancy had little effect on the strength or the significance of the association of the farm animal-related factors with atopy, except on poultry [odds ratio (OR) 0.75 95% confidence interval (CI) 0.52–1.09], which became non-significant. When each animal species from Table 1 was considered as a separate exposure in the same model with potential confounders and socio-economic factors, only contact with cows (OR 0.76 95% CI 0.61–0.93), cats (OR 0.75 95% CI 0.65–0.86) and dogs (OR 0.77 95% CI 0.68–0.88) remained significantly associated with a decreased risk of allergic sensitization. Contact with pigs (OR 0.76 95% CI 0.54–1.06) and poultry (OR 0.85 95% CI 0.57–1.27) became non-significant.

Similar, but somewhat weaker associations were observed between farm-related factors in infancy and allergic diseases at the age of 31 (Table 2). Being born to a family having farm animals was associated with a decreased risk of doctor-diagnosed asthma (current and ever), AR, allergic conjunctivitis and atopic eczema ever (although some of the associations were not nominally significant) at age 31. An inverse trend between the number of animal species in childhood and the risk of allergic diseases in adulthood was also detected. Having dogs in childhood was significantly associated with a decreased risk of doctor-diagnosed asthma ever, and having cats with the decreased risk of AR and conjunctivitis in adulthood. Maternal work with farm animals during pregnancy was not as consistently associated with the risk of allergic diseases (Table 2) as with the risk of atopy (Table 1).

To explore whether the associations in Table 2 are mediated via atopy, the associations in Table 2 of having farm animals and the number of animal species were further adjusted for atopy. This clearly weakened all the observed associations and no significant ORs were observed with the number of animal species. Having farm animals in infancy remained significantly associated only with atopic eczema ever (OR 0.81 95% CI 0.69–0.95), but not with doctor-diagnosed asthma ever (OR 0.83 95% CI 0.61–1.12).

We also explored whether atopy modifies the association between having farm animals and asthma, AR or atopic eczema. We observed a significant interaction ($P < 0.05$) only for AR. However, the OR for having farm animals was very similar among atopics (OR 0.92 95% CI 0.68–1.25) and non-atopics (OR 1.05 95% CI 0.83–1.33).

Discussion

Our prospective study shows that being born to a family having farm animals decreased the risk of atopic sensi-

tization at age 31. There was a suggestion that this decreased risk of atopic sensitization is restricted to subjects with maternal work with farm animals during pregnancy. In addition, contact with a cat or a dog in childhood reduced the risk of atopic sensitization in adulthood. Similar but weaker associations were detected between farm-related factors and allergic diseases at age 31. Atopic sensitization explained most of these disease-related associations.

Although cross-sectional studies have suggested that a farming environment, especially farm animal contact, in childhood may protect against atopic sensitization and allergic diseases in childhood [1–3] or possibly in adulthood [4], there is a lack of prospective studies. This first prospective longitudinal study over 30 years until adult age shows that a farming environment, especially having farm animals in infancy, significantly decreases the risk of atopic sensitization in adulthood. This association remained independent of professional farming, socio-economic differences and other potential confounders between subjects. Previously, it has been reported that both having had a farm childhood and being a farmer decrease the risk of atopic sensitization [8]. Because our study lacked information on current or more recent farm animal contact as well as intermediated assessments of allergic diseases, detailed assessments of the farm animal effect in different time-points could not be performed. Therefore, we cannot definitely separate the effect of perinatal exposure from current exposure. However, our study underscores the importance of perinatal farm animal contact as the protective effect was only seen among those children whose mothers worked with farm animals during pregnancy. Also, the lack of information about farm milk consumption was a limitation in our study.

Similar but weaker, farm-related factors in infancy were associated with a decreased risk of allergic diseases and doctor-diagnosed asthma in adulthood. However, most of the associations were explained by atopic sensitization, although e.g. of asthma little more than half is attributable to atopy [9]. These observations are compatible with the hypothesis [1] that microbial exposure in the farming environment may influence the risk of atopic sensitization. Further, atopy may drive the observed associations of allergic diseases.

The preventive effect of farming environment and especially farm animal contact is hypothesized to be related to high microbial exposure to which the farmers and their children are subjected to. Studies have reported that high microbial exposure, particularly subjects exposed to bacterial endotoxin (LPS, Gram-negative bacterial cell wall component), is related to a decreased risk of atopic sensitization [10, 11]. However, a wide variety of microbes are present and these correlate highly [11], which makes the identification of the causal microbial exposure difficult. Microbial exposure may alter the gene

Table 2. Adjusted associations between farm-related factors in infancy and asthma, allergic rhinitis (AR), allergic conjunctivitis and atopic eczema at age 31

Farm-related factors in infancy	Study population				Doctor-diagnosed asthma ever				AR*				Allergic conjunctivitis*				Atopic eczema†			
	N	%	n	%	aOR	95% CI	CI	n	%	aOR	95% CI	CI	n	%	aOR	95% CI	n	%	aOR	95% CI
Professional farming																				
No	4247	77	347	8	1			1267	30	1			1171	28	1		1646	39	1	
Yes	1262	23	90	7	0.96	0.72	1.29	292	23	0.79	0.66	0.94	272	22	0.83	0.70	434	35	0.81	0.69
Family had farm animals																				
No	3811	70	327	9	1			1151	31	1			1075	29	1		1499	40	1	
Yes	1653	30	103	6	0.74	0.55	1.00	399	25	0.87	0.73	1.03	360	22	0.86	0.72	565	35	0.77	0.66
Maternal work with farm animals during pregnancy																				
No farm animals	3811	70	327	9	1			1151	31	1			1075	29	1		1499	40	1	
No maternal work with farm animals	164	3	5	3	0.39	0.15	0.96	47	29	1.04	0.72	1.49	40	25	1.00	0.68	51	31	0.66	0.46
Maternal work with farm animals																				
Maternal work with farm animals with assistance	917	17	59	7	0.78	0.55	1.10	216	24	0.82	0.67	1.00	208	23	0.88	0.72	321	36	0.81	0.67
Maternal work with farm animals																				
Maternal work with farm animals with assistance	543	10	39	7	0.87	0.57	1.31	132	25	0.92	0.72	1.18	109	20	0.79	0.61	186	34	0.80	0.64
Family had cats‡																				
No	2683	51	224	9	1			836	32	1			768	29	1		1026	39	1	
Yes	2576	49	196	8	0.90	0.72	1.12	668	26	0.84	0.74	0.96	614	24	0.85	0.74	967	38	0.98	0.87
Family had dogs‡																				
No	2411	45	211	9	1			745	31	1			694	29	1		948	40	1	
Yes	2909	55	212	7	0.81	0.65	1.00	772	27	0.89	0.78	1.01	707	25	0.89	0.78	1072	37	0.94	0.83
Number of animal species‡,§																				
0	1428	28	131	9	1			491	35	1			448	32	1		577	41	1	
1	1500	30	123	8	0.85	0.65	1.11	431	29	0.81	0.69	0.96	417	28	0.88	0.75	566	38	0.90	0.77
2	1017	20	83	8	0.81	0.59	1.11	270	27	0.74	0.61	0.90	234	23	0.71	0.58	405	40	0.98	0.82
3	645	13	41	6	0.61	0.40	0.95	160	25	0.71	0.56	0.92	142	22	0.71	0.55	223	35	0.78	0.61
≥4	472	9	26	6	0.56	0.34	0.92	112	24	0.68	0.52	0.90	105	23	0.74	0.55	158	34	0.73	0.56

aOR: adjusted with sex, maternal age, maternal education, smoking during pregnancy, maternal BMI, place of residence, residential density, current education, current BMI, paternal asthma, paternal allergy, maternal asthma, maternal allergy, gestational age, mother's age of menarche, parity and birth height.

*Self-reported in past 12 months.

†Self-reported ever.

‡Before age of seven.

§Includes cows, pigs, sheep, poultry, minks, cats and dogs.

CI, confidence interval; BMI, body mass index.

expression of receptors of the innate immunity [7, 12], interact with genes coding receptors of the innate immunity [13] and alter the T cell responses of the immune system [6, 10, 14], thereby leading to a decreased risk of allergic sensitization and allergic diseases. The present study suggests a strong dose dependent and inverse association between contact with both increasing number of animal species and the total number of cows during infancy with atopic sensitization in adulthood. A similar suggestion has been reported in another cross-sectional study [3]. Thus, the quantity and/or the quality of microbial exposure in childhood may influence the risk of atopic sensitization.

Cross-sectional studies have suggested that contact with farm animals may reduce the risk of allergic sensitization also in the uterus. It is possible that the effect of microbial exposure may be most evident at the time of immune system priming, particularly during the first years of life or even at the time of fetal development [2, 7]. Interestingly, our study also suggests that a decreased risk of atopic sensitization in adulthood is particularly evident among subjects whose mothers were working with farm animals during pregnancy. However, as our study only has information on stable work during pregnancy, it is impossible to disentangle the effects of a subjects pre- and postnatal sensitization, which should be considered as a limitation of our study.

There is evidence that dog ownership may protect from allergic sensitization; for cat ownership, however, there is no consistent evidence [15]. Previous studies have reported that cat ownership may either decrease or increase the risk of atopic sensitization [15]. Our study suggests that having a cat or a dog in the household during childhood prevents from atopic sensitization at age 31, independent of farm animal contact. A similar suggestion of the protective effect of pet ownership against asthma and AR has been reported, but with no consistent evidence. Cat exposure has been reported to prevent from asthma while dog exposure increased the risk of asthma [16]. In our study, allergic diseases in adulthood were not significantly associated with childhood pet ownership, except cat ownership, which reduced the risk of AR and conjunctivitis at age 31, and dog ownership, which reduced the risk of doctor-diagnosed asthma ever at age 31. However, our data on childhood pet ownership were limited to retrospective data only until the age of 7 years.

To our knowledge, the present study is the first prospective cohort study on the association of a farming environment in infancy with atopic sensitization and allergic diseases at age 31. In this large population-based cohort, we were able to collect detailed information about subjects' farming environment during infancy without possible recall bias. However, even in this prospective cohort study, we cannot rule out the possibility that some parents of the children selected other occupations or otherwise avoided a farm environment. The potential effect is only partly controlled by adjustment for parental allergies. When the farm environment information was collected in 1966, Finland was still in many respects an agricultural society. At that time, farm animal ownership was not restricted to subjects whose parents were professional farmers. Typically, a family where the husband was working mainly as, for example, a lumberjack may also have had a few cows taken care of by the wife. In the multivariate analysis, we adjusted the effect of having farm animals for both place of residence and professional farming. This weakened the effect of having farm animals and may in fact overadjust, but the adjustment did not abolish the effect. Hence, we were able to disentangle the effect of having farm animals in infancy and being born to a family practicing professional farming. Thus, heterogeneous study population was a major strength of our study.

Clinical relevance

In conclusion, farm animal contact in infancy reduces the risk of atopic sensitization, doctor-diagnosed asthma and allergic diseases at age 31. Further studies should be carried out to reveal protective factors beyond farm animal contact and associated gene-environment interactions.

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Conflicts of interest statement: we declare that we have no conflicts of interest.

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