ORIGINAL ARTICLE

Farm Environment During Pregnancy and Childhood and Polysensitization at the Age of 31: Prospective Birth Cohort Study in Finland

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Abstract

Background: The farm environment, especially contact with farm animals in early childhood, may prevent allergic sensitization during adulthood. However, prospective associations between exposure to the farm environment and polysensitization have not been studied. Polysensitization is a risk factor for asthma and asthma-related morbidity.
Objective: To investigate whether exposure to a farming environment in early childhood, especially exposure to animals, is associated with sensitization to specific allergens and polysensitization at the age of 31.
Methods: In a prospective birth cohort study, 5509 individuals born in northern Finland in 1966 underwent skin prick testing against birch, timothy, cat, and house dust mite at the age of 31. Prenatal exposure to the farming environment was documented at birth, whereas information on childhood exposure to pets was only collected retrospectively at the age of 31. Data were analyzed using logistic regression.
Results: Being born to a family with farm animals was associated with a reduced risk of sensitization to birch, timothy, and cat (adjusted odds ratio [aOR], 0.55 [95%CI, 0.43-0.70]; aOR, 0.62 [95%CI, 0.48-0.79]; aOR, 0.60 [95%CI, 0.47-0.75]) and polysensitization at the age of 31 (aOR, 0.62 [95%CI, 0.48-0.80]). The number of animal species present during childhood was dose-dependently associated with a reduced risk of sensitization to birch, timothy, and cat, as well as of polysensitization. No association was found with sensitization to house dust mite.
Conclusions: Growing up on a farm and contact with higher numbers of animal species in childhood are associated with less frequent sensitization to birch, timothy, and cat allergens and polysensitization in adulthood, but not with sensitization to house dust mite.

Key words: Atopy. Sensitization. Farm environment. Adults. Polysensitization. Monosensitization.

Resumen

Antecedentes: El ambiente de granja, especialmente el contacto con animales de granja en la primera infancia, puede prevenir la sensibilización alérgica durante la edad adulta. Sin embargo, no se han estudiado las posibles asociaciones entre la exposición al entorno agrícola y la polisensibilización. La polisensibilización es un factor de riesgo para el asma y su morbilidad.
Objetivo: Investigar si el entorno agrícola en la primera infancia, especialmente la exposición a animales, está asociado con la sensibilización a alérgenos específicos y la polisensibilización a la edad de 31 años.
Métodos: En un estudio prospectivo de cohorte de nacimiento, 5.509 sujetos nacidos en el norte de Finlandia en 1966 se sometieron a pruebas cutáneas a la edad de 31 años con abedul, hierba timotea, gato y ácaros del polvo doméstico. La exposición prenatal al ambiente agrícola se documentó al nacer, mientras que la información sobre la exposición infantil a las mascotas solo se recopiló retrospectivamente a la edad de 31 años. Se utilizó La regresión logística en los análisis estadísticos.

Resultados: Nacer en una familia con animales de granja se asoció con un menor riesgo de sensibilización frente a abedul, hierba timotea o gato (odds ratio ajustado, aOR = 0,55 [intervalo de confianza del 95% 0,43-0,70]; aOR = 0,62 [0,48-0,79] ; aOR = 0,60 [0,47-0,75]) y polisensibilización a la edad de 31 años (aOR = 0,62 [0,48-0,80]). La sensibilización frente a abedul, hierba timotea y gato, así como la polisensibilización, se asociaron de forma dependiente e inversa a la dosis con el número de especies animales presentes durante la infancia. No se encontró asociación con la sensibilización frente a los ácaros del polvo doméstico.
Conclusiones: Crecer en una granja y el contacto con un mayor número de especies animales en la infancia se asocia con una menor sensibilización frente al abedul, la hierba timotea, alérgenos de gato y polisensibilización en la edad adulta, pero no con sensibilización frente a los ácaros del polvo doméstico.

Palabras clave: Atopia. Sensibilización. Ambiente agrícola. Adultos. Polisensibilización. Monosensibilización.

Introduction

Living on a farm, mainly in terms of exposure to farm animals and consumption of raw cow's milk in early childhood, has been associated with a lower prevalence of asthma and atopy in children [1]. Compared with urban environments, the farm environment is generally characterized by a more abundant and diverse microbial population than the urban environment [1,2]. Exposure to microbes may stimulate the immune system, affect the development of the immune system and allergic sensitization, and prevent clinical manifestation of allergic diseases [1]. The protective effect of the farm environment in utero and during early childhood may extend to adulthood [3-5], as we previously showed in the prospective birth cohort studied here [6,7].

The protective effect of exposure to the farm environment during infancy against allergic sensitization is not consistent for all allergens. Previous retrospective studies based on exposure and a population ranging between 290 and 1700 showed that growing up on a farm was inversely associated with sensitization to birch, timothy, and/or cat in adulthood [4,8-10]. Findings for sensitization to house dust mite have been contradictory [4,8-10].

Polysensitization has been recognized as a risk factor for morbidity among asthmatic children [11] and has been associated with a risk of asthma in adults [12]. It has also been proposed that mono- and polysensitization are 2 distinct phenotypes within multiple comorbid conditions of allergic diseases in children [13]. A European cross-sectional study of 858 children aged 6-12 years found an inverse association with farming and polysensitization in children [14]. In Greece, urban children were more often polysensitized than children from rural areas, although no differences were found for children who grew up on farms [15]. No such association was found when 101 adult swine breeders and 82 nonbreeders were studied in a cross-sectional study in Italy [16].

Our aim was to investigate the prospective associations between exposure to the farm environment, especially to farm animals in utero and in early childhood. We also investigated specific sensitization to birch, timothy, cat, and house dust mite and polysensitization at the age of 31. This is the first prospective study to investigate the effect of the farm environment during infancy and polysensitization in adulthood.

Methods

The original cohort consisted of 12 058 individuals born between January 1 and December 31, 1966, in the 2 northernmost provinces of Finland, Oulu and Lapland. The study population originally covered 96% of the children born in that region in 1966. In 1997, 8463 survivors still living in Northern Finland or in the area of the capital city received a postal questionnaire and invitation to undergo a clinical examination. A detailed description of the number of participants and flow charts of the 31-year follow-up study are shown on the study website [17]. The University of Oulu Ethics Committee approved the study, and the participants gave their written informed consent.

Assessment at Age 31 Years

During the 31-year follow-up, participants self-completed questionnaires on health and lifestyle factors, sociodemographic factors, and allergic conditions [6]. They also underwent a clinical examination including a skin prick test (SPT).

The SPT was performed using 3 of the most common allergens in Finland (cat, birch, and timothy), as well as house dust mite (*Dermatophagoides pteronyssinus*). Histamine dihydrochloride (10 mg/mL) and the diluent of the allergen extracts were used as positive and negative controls, respectively. Skin reactions to each allergen tested were recorded after 15 minutes as the average of the maximum wheal diameter and the diameter perpendicular to the maximum. Participants with a wheal reaction ≥3 mm to the specific allergen tested were considered sensitized. Those with a positive reaction to the negative control (n=35) or a negative reaction to histamine (<3 mm) were excluded (n=23). Participants who were sensitized against only 1 of the 4 allergens tested were defined as monosensitized. Polysensitization was defined as sensitization to more than 1 of the 4 allergens tested.

Assessment of Antenatal and Childhood Factors

Farm-related determinants and possible confounding factors were collected from women during pregnancy and/or immediately after delivery. The farm-related determinants included were as follows: whether the parents' profession was farming; whether the family had farm animals (species [cows,

Table 1. Adjusted Associations Between Exposure to Farming Environment and Animals In Utero or in Childhood and Sensitization to Common Allergens and House Dust Mite at the Age of 31 Years[a]

	Study Population		Sensitization Against Cat						Sensitization Against Birch						Sensitization Against Timothy						Sensitization Against House Dust Mite					
	N	%	n	%	aOR	95%CI		*P*	n	%	aOR	95%CI		*P*	n	%	aOR	95%CI		*P*	n	%	aOR	95%CI		*P*
Professional farming																										
No	4247	77	767	18.1	1				795	18.7	1				780	18.4	1				278	6.6	1			
Yes	1262	23	118	9.4	0.60	0.47	0.75	<.01	105	8.3	0.55	0.43	0.70	<.01	104	8.2	0.62	0.48	0.79	<.01	93	7.4	1.13	0.84	1.52	.41
Farm animals																										
No	3811	70	724	19.0	1				745	19.6	1				737	19.4	1				258	6.8	1			
Yes	1653	30	151	9.1	0.52	0.41	0.65	<.01	149	9.0	0.56	0.45	0.71	<.01	139	8.4	0.60	0.47	0.76	<.01	109	6.6	0.91	0.67	1.22	.52
Number of cows																										
0	3851	71	729	19.0	1				751	19.5	1				743	19.3	1				263	6.8	1			
1-4	860	16	85	9.9	0.59	0.45	0.77	<.01	85	9.9	0.65	0.49	0.85	.02	77	9.0	0.68	0.51	0.91	.01	49	5.7	0.74	0.52	1.08	.12
≥5	746	14	60	8.0	0.44	0.32	0.60	<.01	58	7.8	0.46	0.34	0.63	<.01	55	7.4	0.49	0.36	0.68	<.01	54	7.2	0.98	0.69	1.40	.90
Maternal work with farm animals during pregnancy																										
No farm animals	3881	70	724	19.0	1				745	19.6	1				737	19.4	1				258	6.8	1			
No maternal work with farm animals	164	3	20	12.2	0.66	0.40	1.08	.10	25	15.2	0.87	0.55	1.37	.53	24	14.6	1.02	0.64	1.63	.93	11	6.7	0.99	0.51	1.90	.97
Maternal work with farm animals with assistance	917	17	82	8.9	0.49	0.37	0.65	<.01	78	8.5	0.51	0.38	0.67	<.01	68	7.4	0.49	0.36	0.66	<.01	65	7.1	0.96	0.68	1.34	.79
Maternal work with farm animals	543	10	49	9.0	0.55	0.39	0.78	<.01	45	8.3	0.56	0.39	0.79	.01	46	8.5	0.67	0.47	0.96	.03	31	5.7	0.74	0.47	1.15	.18
Cats[b]																										
No	2683	51	540	20.2	1				544	20.3	1				552	20.6	1				177	6.6	1			
Yes	2576	49	305	11.8	0.63	0.54	0.75	<.01	322	12.5	0.73	0.62	0.86	<.01	293	11.4	0.64	0.54	0.76	<.01	180	7.0	1.04	0.82	1.31	.77
Dogs[b]																										
No	2411	45	478	19.9	1				497	20.6	1				494	20.5	1				170	7.1	1			
Yes	2909	55	373	12.8	0.69	0.59	0.82	<.01	372	12.8	0.70	0.60	0.82	<.01	358	12.3	0.70	0.60	0.83	<.01	188	6.5	0.82	0.65	1.04	.10
Number of animal species[b,c]																										
0	1428	28	331	23.2	1				339	23.8	1				345	24.2	1				98	6.9	1			
1	1500	30	268	17.9	0.76	0.63	0.92	.01	281	18.7	0.81	0.67	0.97	.02	270	18.0	0.75	0.62	0.91	<.01	98	6.5	0.91	0.68	1.23	.55
2	1017	20	120	11.8	0.48	0.37	0.62	<.01	126	12.4	0.56	0.44	0.72	<.01	120	11.8	0.53	0.41	0.68	<.01	80	7.9	1.01	0.72	1.42	.95
3	645	13	56	8.7	0.35	0.25	0.50	<.01	56	8.7	0.42	0.30	0.59	<.01	53	8.2	0.42	0.29	0.60	<.01	40	6.2	0.76	0.48	1.19	.23
≥4	472	9	38	8.1	0.34	0.23	0.51	<.01	36	7.6	0.38	0.26	0.57	<.01	26	5.5	0.28	0.18	0.45	<.01	30	6.4	0.80	0.49	1.30	.37

Abbreviations: aOR, adjusted odds ratios; N., number of observations; n, the number of cases in the given class; %, percentage of observations in the given class.

[a]Models are adjusted for sex, maternal age, maternal education, smoking during pregnancy, maternal body mass index, place of residence, residential density, current education, current body mass index, paternal asthma, paternal allergy, maternal asthma, maternal allergy, gestational age, mother's age of menarche, parity, and birth height.

[b]Before the age of 7 y.

[c]Includes cows, pigs, sheep, poultry, minks, cats, and dogs. Participants with a wheal reaction ≥3 mm in the skin prick test were considered to be sensitized; the reference group is nonsensitized participants.

pigs, sheep, poultry, and mink] and their counts); whether the mother worked with farm animals during pregnancy (not at all, worked with assistance, or performed all the work by herself); and the place of residence (town, village, or outlying district). In addition, as possible confounders, we recorded maternal factors (education, age, body mass index, smoking during pregnancy from the second month, age of menarche, and parity), child-related factors (gestational age at birth, birth weight and height), and the residential density (the number of people in the household divided by the number of rooms in the household). Information on keeping cats and dogs in childhood (before the age of 7 years) and parental history of allergic diseases was collected retrospectively at the age of 31 years. Exposure to cats and dogs was used not only as an exposure factor itself, but also as a combined exposure to animals (farm animals, cats, and dogs) during early childhood.

Statistical Analysis

The final analysis comprised 5509 individuals who had a positive reaction to histamine, a negative reaction to the control, and sufficient available data on atopic sensitization. The maximum prevalence of missing data was 1.5% for disease outcomes, 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). Logistic regression models were used for statistical analyses. The same confounders as in our previous analysis [6] were selected for the multivariate models, in which the missing data for each confounder were classified as a single category. The reference category was always nonsensitized participants, except where only sensitized participants were analyzed (the polysensitized participants were compared with the monosensitized group). There were no major differences

Table 2. Adjusted Associations Between Exposure to Farming Environment and Animals In Utero or in Childhood and Mono- or Polysensitization at the Age of 31 Years[a]

	Monosensitization							Polysensitization						
	N	n	%	aOR	95%CI		*P*	N	n	%	aOR	95%CI		*P*
Professional farming														
No	3489	667	19	1				3557	735	21	1			
Yes	1152	149	13	0.78	0.62	0.98	.03	1113	110	10	0.62	0.48	0.80	<.01
Farm animals														
No	3088	600	19	1				3190	702	22	1			
Yes	1514	205	14	0.83	0.67	1.04	.10	1446	137	10	0.53	0.42	0.68	<.01
Number of cows														
0	3122	607	19	1				3223	708	22	1			
1-4	785	108	14	0.86	0.66	1.13	.28	750	73	10	0.57	0.42	0.76	<.01
≥5	689	90	13	0.77	0.58	1.01	.06	656	57	9	0.46	0.34	0.64	<.01
Maternal work with farm animals during pregnancy														
No farm animals	3088	600	19	1				3190	702	22	1			
No maternal work with farm animals	145	31	21	1.28	0.83	1.97	.26	133	19	14	0.76	0.45	1.26	.29
Maternal work with farm animals with assistance	843	115	14	0.79	0.61	1.02	.08	802	74	9	0.49	0.37	0.66	<.01
Maternal work with farm animals	497	55	11	0.69	0.49	0.96	.03	486	44	9	0.55	0.38	0.79	<.01
Cats[b]														
No	2160	458	21	1				2212	510	23	1			
Yes	2268	322	14	0.71	0.60	0.84	<.01	2246	300	13	0.66	0.56	0.78	<.01
Dogs[b]														
No	1929	387	20	1				2010	468	23	1			
Yes	2558	406	16	0.85	0.72	1.01	.06	2494	342	14	0.66	0.55	0.78	<.01
Number of animal species[b,c]														
0	1091	228	21	1				1191	328	28	1			
1	1245	272	22	1.09	0.89	1.34	.40	1220	247	20	0.73	0.60	0.89	<.01
2	897	136	15	0.74	0.57	0.95	.02	879	118	13	0.50	0.39	0.64	<.01
3	587	65	11	0.54	0.38	0.76	<.01	578	56	10	0.39	0.27	0.55	<.01
≥4	440	51	12	0.59	0.41	0.86	.01	421	32	8	0.32	0.21	0.48	<.01

Abbreviations: aOR, adjusted odds ratios; N, number of observations; n, the number of cases in the given class; %, percentage of observations in the given class.

[a]Models are adjusted for sex, maternal age, maternal education, smoking during pregnancy, maternal body mass index, place of residence, residential density, current education, current body mass index, paternal asthma, paternal allergy, maternal asthma, maternal allergy, gestational age, mother's age of menarche, parity and birth height. Monosensitization, which is a reference group, is defined as sensitization against only 1 out of 4 tested allergens; polysensitization is defined as sensitization against at least 2 out of 4 tested allergens.

[b]Before the age of 7 y.

[c]Includes cows, pigs, sheep, poultry, minks, cats and dogs; Participants with a wheal reaction ≥3 mm in skin prick test were considered to be sensitized; the reference group is nonsensitized participants.

between the original cohort and participants in the present analysis with respect to general characteristics (Supplemental material, Table E1). All analyses were performed using IBM SPSS Statistics Version 22 (IBM Corp).

Results

A description of the study population stratified by professional farming activity during infancy is shown in the supplemental material (Table E2). Twenty-three percent of the adults who took part of the 31-year follow-up had been born to families in which the parents were farmers, and 27% of the mothers were working with farm animals during pregnancy by themselves or with assistance (Table 1). The prevalence of sensitization in the study population was 16% each for cat, birch, and timothy allergens, 7% for house dust mite, 15% for monosensitization (only 1 positive SPT), and 15% for polysensitization (at least 2 positive SPT results).

Being born to a family in which the parents were farmers, having farm animals in infancy, and being born to a mother who worked with farm animals during pregnancy were associated with a decreased risk of sensitization to cat, birch, and timothy at the age of 31 years (Table 1). The number of cows in infancy and number of different animal species in childhood were dose-dependently and inversely associated with decreased sensitization to cat, birch, and timothy. Farm-related factors during infancy were not associated with sensitization to house dust mite at the age of 31 years (Table 1).

Being born to a family where the parents were farmers, having farm animals in infancy, and being born to a mother who worked with farm animals during pregnancy was inversely associated with the risk of polysensitization (Table 2). The risk of polysensitization was dose-dependently reduced with the number of cows and the number of different animal species. Similar findings were recorded for monosensitization (sensitized against only 1 of the tested allergens), although these were often weaker and nonsignificant (Table 2). The associations between professional farming or farm animals and monosensitization or polysensitization were similar for women and men (*P* value for interaction, >0.2) (data not shown).

Compared with monosensitized participants, the risk of being polysensitized was lower among the participants born to families with farm animals and was also dose-dependently associated with a higher number of cows in infancy (Table 3).

Growing up in a family with cats or dogs (before the age of 7 years) was associated with a decreased risk of sensitization to cat, birch, and timothy (Table 1) and polysensitization (Table 2). Having cats was inversely associated with monosensitization (Table 2). No such protective associations were found with sensitization against house dust mite (Table 1). Compared with monosensitized participants, the risk of polysensitization decreased among those who had a dog(s) in childhood (Table 3).

Discussion

This prospective birth cohort study shows that growing up on a farm, especially one with farm animals, protects from allergic sensitization in adulthood but not against all allergens. The protective effect of farming was associated with sensitization to birch, timothy, and cat, as well as with polysensitization, but not with sensitization to house dust mite. These associations were independent of potential confounders.

This is the first prospective birth cohort study to report associations between growing up on a farm with farm animals and less frequent polysensitization during adulthood. In their cross-sectional study of children, Fuchs et al [14] reported

Table 3. Sensitized Participants (Monosensitized and Polysensitized): Adjusted Associations Between Farming Environment and the Risk of Being Polysensitized at the Age of 31 Years[a]

	Polysensitization						
	N	n	%	aOR	95%CI		*P*
Professional farming							
No	1402	735	52.4	1			
Yes	259	110	42.5	0.78	0.57	1.08	.14
Farm animals							
No	1302	702	53.9	1			
Yes	342	137	40.1	0.62	0.46	0.85	<.01
Number of cows							
0	1315	708	53.8	1			
1-4	181	73	40.3	0.65	0.45	0.95	.03
≥5	147	57	38.8	0.57	0.38	0.86	<.01
Maternal work with farm animals during pregnancy							
No farm animals	1302	702	53.9	1			
No maternal work with farm animals	50	19	38.0	0.62	0.33	1.16	.14
Maternal work with farm animals with assistance	189	74	39.2	0.60	0.41	0.86	.01
Maternal work with farm animals	99	44	44.4	0.76	0.47	1.21	.25
Cats[b]							
No	968	510	52.7	1			
Yes	622	300	48.2	0.93	0.74	1.15	.48
Dogs[b]							
No	855	468	54.7	1			
Yes	748	342	45.7	0.73	0.59	0.91	.01
Number of animal species[b,c]							
0	556	328	59.0	1			
1	519	247	47.6	0.64	0.50	0.83	<.01
2	254	118	46.5	0.63	0.45	0.89	.01
3	121	56	46.3	0.66	0.42	1.05	.08
≥4	83	32	38.6	0.51	0.30	0.87	.01

Abbreviations: aOR, adjusted odds ratios; N, number of observations; n, the number of cases in the given class; %, percentage of observations in the given class.

[a]Models are adjusted for 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. Monosensitization, which is a reference group, is defined as sensitization against only 1 out of 4 tested allergens; polysensitization is defined as sensitization against at least 2 out of 4 tested allergens.

[b]Before the age of 7 y.

[c]Includes cows, pigs, sheep, poultry, minks, cats, and dogs; participants with a wheal reaction ≥3 mm in skin prick test were considered to be sensitized.

similar results, showing that children from farms were more often monosensitized than polysensitized. Furthermore, polysensitization to tested allergens was also dose-dependently and inversely associated with the number of animal species during childhood. These findings suggest that quality and/or quantity of microbial exposure during infancy may also protect from polysensitization. This finding is clinically important, since polysensitization seems to be more strongly associated with the risk of asthma than monosensitization [12,18] and has also been recognized as a risk factor for increased morbidity among asthmatic children [11]. Nevertheless, surprisingly, the preventable risk factors of polysensitization have rarely been studied.

Our study shows that farm-related factors during infancy were consistently associated with a decreased risk of sensitization to birch, timothy, and cat. There was also a dose-dependent and inverse association between the number of animal species present during early childhood and sensitization to these 3 allergens in adulthood. These results are in line with those of previous adult studies [4,5,8,9,19]. Furthermore, the protective effect of a farming environment with sensitization to cat and timothy in our study was similar to that reported in a recent meta-analysis of 29 cross-sectional studies based mainly on exposure to a farm environment before 1 year of age and follow-up until adulthood. The meta-analysis revealed a 40% reduction in the prevalence of atopy [20].

In the present study, contact with a farm environment during infancy did not protect against sensitization to house dust mite during adulthood. This finding is in line with previous adult studies [4,5], although it contrasts with those of a Danish study, which retrospectively assessed childhood exposure to a farm environment and found less sensitization against house dust mite in adulthood [10], and with those of a cross-sectional study performed in European children [14]. In the present study, there was even a weak positive association with house dust mite sensitization among individuals born to farming families, as reported in a previous Finnish adult study [8]. The risk of sensitization to house dust mite seems to be associated with exposure to house dust mite allergen [21,23], but not with exposure to and risk of sensitization to cat allergen [22,23]. Many environmental factors are associated with house dust mite allergen levels [21], and there are large geographical and socioeconomic differences in house dust mite allergen and sensitization levels in Europe. In Nordic countries, which have low temperatures and low indoor relative humidity during winter, house dust mite allergen levels [24] and prevalence of sensitization are relatively low [25]. Furthermore, in nonfarming and urban homes, house dust mite allergen levels are often lower than on farms [26] and in rural homes [27]. House dust mite sensitization rates in our study population were quite similar to those reported in another Finnish study [28] and in other Nordic countries [25], as approximately 7% of participants were sensitized to house dust mite at the age of 31.

Sensitization to house dust mite could also be explained by cross-reactivity with other allergens. House dust mite allergens are known to cross-react with allergens such as shellfish, shrimp, and other invertebrates [21] and also with the storage mite *Lepidoglyphus destructor*, which is common on farms [29]. We cannot rule out the possibility that cross-reactivity could modify the rate of house dust mite sensitization in our study, as we only have skin prick test data on 4 allergens (ie, birch, timothy, cat, and house dust mite).

The hypothesized biological mechanisms behind the protective effect of exposure to a farm environment during infancy against allergic sensitization and allergic diseases are complex [1]. In short, the protective effect of a farm environment, especially contact with farm animals and consumption of farm milk, is hypothesized to be attributable to differences in the quantity, quality, and/or diversity of the microbes an individual is exposed to [1,2]. Exposure to environmental microbes may affect the development of the immune system [30-32] and thereby protect from development of allergic sensitization and from allergic diseases [2,30]. Furthermore, allergic sensitization may develop from a combination of environmental and genetic factors during infancy, since the protective effect seems to be mediated by gene–environment interactions [33,34].

The strength of this study lies its prospective design, with 31 years of follow-up and a high participation rate. Farm-related factors were assessed before or at birth, although there may be some recall bias in the assessment of exposure to pets. Our study is also subject to limitations. Firstly, as it lacked detailed information on exposure to the farm environment during follow-up, the effect of exposure to farming at different time-points could not be assessed. Secondly, some parents may have avoided the farm environment because they experienced allergic or respiratory diseases (healthy worker effect). This potential bias can be partially controlled for by adjusting for parental allergies.

In conclusion, growing up on a farm and contact with higher numbers of animal species in childhood is associated with less frequent sensitization to birch, timothy, and cat allergens and polysensitization in adulthood, although not with sensitization to house dust mite.

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Conflicts of Interest

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References

1. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. Nat Rev Immunol. 2010;10:861-8.
2. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med 2011;364:701-9.
3. House JS, Wyss AB, Hoppin JA, Richards M, Long S, Umbach DM, et al. Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study. J Allergy Clin Immunol. 2017;140:249,256. e14.
4. Leynaert B, Neukirch C, Jarvis D, Chinn S, Burney P, Neukirch F, et al. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood? Am J Respir Crit Care Med. 2001;164:1829-34.
5. Portengen L, Sigsgaard T, Omland O, Hjort C, Heederik D, Doekes G. Low prevalence of atopy in young Danish farmers and farming students born and raised on a farm. Clin Exp Allergy. 2002;32:247-53.
6. Lampi J, Canoy D, Jarvis D, Hartikainen AL, Keski-Nisula L, Järvelin MR, et al. Farming environment and prevalence of atopy at age 31: prospective birth cohort study in Finland. Clin Exp Allergy. 2011;41:987-93.
7. Lampi J, Koskela H, Hartikainen AL, Ramasamy A, Couto Alves A, Järvelin MR, et al. Farm environment during infancy and lung function at the age of 31: a prospective birth cohort study in Finland. BMJ Open. 2015;5:e007350,2014-007350.
8. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Childhood farm environment and asthma and sensitization in young adulthood. Allergy. 2002;57:1130-5.
9. Rennie DC, Lawson JA, Karunanayake CP, Pahwa P, Chen Y, Chu L, et al. Farm Exposure and Atopy in Men and Women: The Saskatchewan Rural Health Study. J Agromedicine. 2015;20:302-9.
10. Elholm G, Linneberg A, Husemoen LL, Omland O, Gronager PM, Sigsgaard T, et al. The Danish urban-rural gradient of allergic sensitization and disease in adults. Clin Exp Allergy. 2016;46:103-11.
11. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Momas I. Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. Pediatr Allergy Immunol. 2016;27:831-7.
12. Toppila-Salmi S, Huhtala H, Karjalainen J, Renkonen R, Mäkelä MJ, Wang DY, et al. Sensitization pattern affects the asthma risk in Finnish adult population. Allergy. 2015;70:1112-20.
13. Anto JM, Bousquet J, Akdis M, Auffray C, Keil T, Momas I, et al. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. J Allergy Clin Immunol. 2017;139:388-99.
14. Fuchs O, Genuneit J, Latzin P, Buchele G, Horak E, Loss G, et al. Farming environments and childhood atopy, wheeze, lung function, and exhaled nitric oxide. J Allergy Clin Immunol. 2012;130:382,8.e6.
15. Priftis KN, Anthracopoulos MB, Nikolaou-Papanagiotou A, Matziou V, Paliatsos AG, Tzavelas G, et al. Increased sensitization in urban vs. rural environment--rural protection or an urban living effect? Pediatr Allergy Immunol. 2007;18:209-16.
16. Galli L, Facchetti S, Raffetti E, Donato F, D'Anna M. Respiratory diseases and allergic sensitization in swine breeders: a population-based cross-sectional study. Ann Allergy Asthma Immunol. 2015;115:402-7.
17. Northern Finland Birth Cohort 1966, 31-year follow-up study. http://www.oulu.fi/nfbc/node/18097 and http://www.oulu.fi/nfbc/node/30344 (June 27th 2019).
18. Bousquet J, Anto JM, Wickman M, Keil T, Valenta R, Haahtela T, et al. Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis. Allergy. 2015;70:1062-78.
19. Koskela HO, Happonen KK, Remes ST, Pekkanen J. Effect of farming environment on sensitisation to allergens continues after childhood. Occup Environ Med. 2005;62:607-11.
20. Campbell BE, Lodge CJ, Lowe AJ, Burgess JA, Matheson MC, Dharmage SC. Exposure to 'farming' and objective markers of atopy: a systematic review and meta-analysis. Clin Exp Allergy. 2015;45:744-57.
21. Calderon MA, Linneberg A, Kleine-Tebbe J, De Blay F, Hernandez Fernandez de Rojas D, Virchow JC, et al. Respiratory allergy caused by house dust mites: What do we really know? J Allergy Clin Immunol. 2015;136:38-48.
22. Dharmage SC, Lodge CL, Matheson MC, Campbell B, Lowe AJ. Exposure to cats: update on risks for sensitization and allergic diseases. Curr Allergy Asthma Rep. 2012;12:413-23.
23. Carlsten C, Dimich-Ward H, Becker AB, Ferguson A, Chan HW, DyBuncio A, et al. Indoor allergen exposure, sensitization, and development of asthma in a high-risk birth cohort. Pediatr Allergy Immunol. 2010;21:e740-6.
24. Zock JP, Heinrich J, Jarvis D, Verlato G, Norback D, Plana E, et al. Distribution and determinants of house dust mite allergens in Europe: the European Community Respiratory Health Survey II. J Allergy Clin Immunol. 2006;118:682-90.
25. Bousquet PJ, Chinn S, Janson C, Kogevinas M, Burney P, Jarvis D, et al. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. Allergy. 2007;62:301-9.
26. Radon K, Schottky A, Garz S, Koops F, Szadkowski D, Radon K, et al. Distribution of dust-mite allergens (Lep d 2, Der p 1, Der f 1, Der 2) in pig-farming environments and sensitization of the respective farmers. Allergy. 2000;55:219-25.
27. Wardzynska A, Majkowska-Wojciechowska B, Pelka J, Korzon L, Kaczala M, Jarzebska M, et al. Association of house dust allergen concentrations with residential conditions in city and in rural houses. World Allergy Organ J. 2012;5:22-7.
28. Remes ST, Koskela HO, Iivanainen K, Pekkanen J. Allergen-specific sensitization in asthma and allergic diseases in children: the study on farmers' and non-farmers' children. Clin Exp Allergy. 2005;35:160-6.
29. Olsson S, van Hage-Hamsten M. Allergens from house dust and storage mites: similarities and differences, with emphasis on the storage mite Lepidoglyphus destructor. Clin Exp Allergy. 2000;30:912-9.

30. Braun-Fahrländer C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med. 2002;347:869-77.
31. Roponen M, Hyvärinen A, Hirvonen MR, Keski-Nisula L, Pekkanen J. Change in IFN-gamma-producing capacity in early life and exposure to environmental microbes. J Allergy Clin Immunol. 2005;116:1048-52.
32. Kääriö H, Huttunen K, Karvonen AM, Schaub B, von Mutius E, Pekkanen J, et al. Exposure to a farm environment is associated with T helper 1 and regulatory cytokines at age 4.5 years. Clin Exp Allergy. 2016;46:71-7.
33. Smit LA, Siroux V, Bouzigon E, Oryszczyn MP, Lathrop M, Demenais F, et al. CD14 and toll-like receptor gene polymorphisms, country living, and asthma in adults. Am J Respir Crit Care Med. 2009;179:363-8.
34. Leynaert B, Guilloud-Bataille M, Soussan D, Benessiano J, Guenegou A, Pin I, et al. Association between farm exposure and atopy, according to the CD14 C-159T polymorphism. J Allergy Clin Immunol. 2006;118:658-65.

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