

Original article

Childhood farm environment and asthma and sensitization in young adulthood

Background: Farm environment in childhood may protect against sensitization, allergic rhinitis, and asthma.

Methods: Subjects were obtained from 10 667 Finnish first-year university students who responded to a questionnaire survey on IgE-mediated diseases. Two random samples were selected from 1631 respondents in Turku: subjects with asthma or wheezing, and subjects without asthmatic symptoms. A total of 296 subjects (72%) participated. Skin prick tests (SPT), measurements of IgE-antibodies, methacholine challenge, and bronchodilation tests were performed. Weighted occurrence of current asthma and sensitization among students from “childhood farm” and “childhood nonfarm” environments were analyzed.

Results: Current asthma was found in 3.1% of subjects with childhood farm environment, and in 12.4% with nonfarm environment (odds ratio (OR) 0.22; 95% confidence interval (CI) 0.07–0.70). There were fewer positive SPT to birch (8.3 vs. 24.2%, OR 0.28, 95% CI 0.07–1.15) and timothy pollen (12.6 vs. 30.3%, OR 0.33, 95% CI 0.09–1.20) among subjects with childhood farm environment, but more sensitization to house-dust mite (22.0 vs. 4.9%, OR 5.43, 95% CI 1.60–18.46). Sensitization to cat (RAST class ≥ 3) was less common in subjects with farm compared to nonfarm environments in childhood (1.5 vs. 13.1%; OR 0.10, 95% CI 0.02–0.47).

Conclusions: Farm environment in childhood protects against adult asthma and sensitization—especially to cat—the most important asthma related allergen. In contrast, sensitization to house-dust mite was more common in farming subjects.

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A few studies have documented a protective effect of farms on the development of IgE-mediated allergic diseases (1), allergic rhinitis (2–6), sensitization (2, 4, 6) and on reported asthma and wheeze (3–6) among children (2–4) and young adults (5) who have lived on a farm, compared to either nonfarm rural (2–5) or urban (5) residents. Therefore, farm environment has been suggested as a model to study the mechanism of sensitization and asthma in western society.

We have previously reported lower occurrence of physician-diagnosed allergic rhinitis and/or conjunctivitis (but not as clearly for asthma up to age 18–24 years) among first-year Finnish university students from childhood farm environments, compared to subjects with nonfarm rural and urban backgrounds (5).

In the present study, the effect of childhood farm environment on current asthma and sensitization was investigated in a clinical subsample of 296 questionnaire respondents. Weighted occurrence (by sampling) of current asthma, defined by interview and lung

function tests, skin prick tests (SPT) and specific serum IgE to common inhaled and food allergens were analyzed in relation to childhood farm and nonfarm environments.

Material and methods

Subjects

A total of 10 667 Finnish first-year university students aged 18–25 years responded to a questionnaire survey on asthma and atopic diseases and possible risk factors. Of these subjects, 39% were men and 61% women. The response rate was higher among women than among men: 82% and 66%, respectively.

Originally, for the validation of the questionnaire, 200 subjects with history of asthma or wheezing during their lifetime, were randomly selected from the 1631 questionnaire respondents in the three universities of Turku. We expected that nonsymptomatic people would not participate as eagerly as symptomatic ones. The 218 respondents without asthma or wheezing were randomly selected and stratified by sex, so that the sex distribution in the symptomatic and nonsymptomatic groups was the same. Five symptomatic subjects were later excluded for various reasons (such as moving abroad). The two random gender-matched samples finally invited for clinical examination are shown in Fig. 1.

* Conflicts of interests: none.

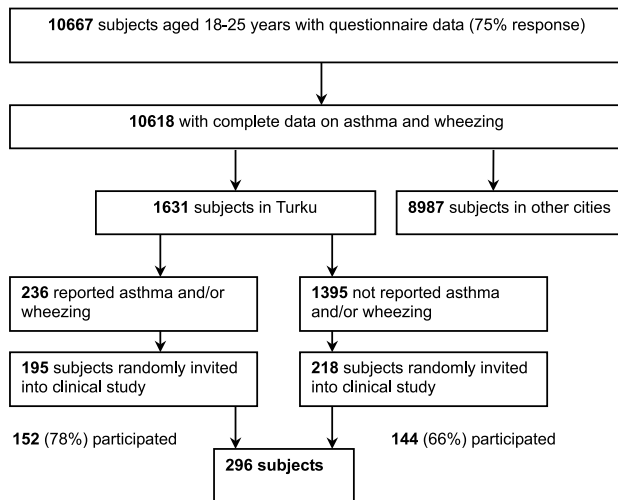


Figure 1. Selection of the clinical sample. The 236 subjects who reported asthma or attacks of shortness of breath with wheezing. Of the final 296 subjects, six did not have methacholine challenge, one did not have skin prick tests, and two did not have blood tests for specific IgE.

A total of 296 (72%) subjects were interviewed and tested in the winter of 1996–1997. The participation rate was 78% ($n = 152$) among students with history of asthma or wheezing, and 66% ($n = 144$) among those without (Fig. 1). The percentage of female participants was 68% and 62%, respectively. The mean age of the clinical study respondents was 21.5 years (range 18.7–26.6).

In the original questionnaire study, the occurrence of asthma and allergic rhinitis/or conjunctivitis was similar among subjects with childhood nonfarm-rural and urban environments at age 0–6 years. Therefore, these were analyzed together as a nonfarm population, against childhood farm population. To correct for unequal sampling, prevalence rates weighted by sampling proportions were used in the analyses to compare farm and nonfarm childhood environments.

The proportion of subjects with farm environment at the age of 0–6 years were similar for the questionnaire survey respondents and the clinical study participants, 10.3% (1098/10637) and 9.8% (29/296), respectively.

Clinical examination

Interview. Pulmonary disease specialist (M.K.) and dermatologist (Leena Mattila, MD, The Finnish Student Health Service, Turku, Finland) examined and interviewed the patients, and supervised the tests. A structured questionnaire was used to collect information at interview. The doctors were blinded to the original questionnaire responses, to both the symptoms and the background factors such as farming environment.

Lung function tests. Flow-volume spirometry and a bronchodilation test (7) by standard spirometer (Vitalograph Compact, Vitalograph, UK) was performed. Anti-inflammatory medication for asthma was allowed, but β -agonists were withheld for 12 h before the test. An increase of 15% in forced expiratory volume in 1 s (FEV_1) 15 min after inhalation of 0.4 mg of salbutamol was regarded as a positive bronchodilation response. Methacholine challenge was carried out on separate occasion, using a dosimeter nebulization method (8). After three inhalations of physiological saline for baseline FEV_1 , methacholine was delivered by nebuliser

(Spira-Elektro-5, Hengityshoitokeskus, Finland) in five cumulative doses up to 2.9 mg. The provocative dose causing a 20% fall (PD_{20}) in FEV_1 was determined on a logarithmic scale and the test was regarded positive if $PD_{20} FEV_1$ was equal to or below the cumulative dose of 2.9 mg of methacholine. Subjects with FEV_1 below 60% of the normal value were not challenged.

Current asthma definition

At the pulmonary disease specialist's interview, current asthma was confirmed if the subject had had symptoms suggestive of asthma, such as wheezing, shortness of breath, cough with wheezing, in association with typical provoking factors, such as exercise or animals, during the last 12 months, and at the same time fulfilled at least one of the following lung function criteria:

- 1) $PD_{20} FEV_1 \geq 2.9$ mg in methacholine challenge
- 2) $FEV_1 <$ reference value minus 1.96 SD
- 3) $FEV_1/FVC <$ reference value minus 1.96 SD (where FVC is forced vital capacity)
- 4) FEV_1 shows a rise of at least 15% after bronchodilation.

A total of 290 subjects with complete data on lung function tests were analyzed.

Skin prick tests. The allergen panel included standardized antigens of birch, timothy grass and mugwort pollens, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Pityrosporum ovale*, cat, dog, and horse epithelium, as well as house-dust mite *D. pteronyssinus* (Soluprick, Allergologisk Laboratorium, Copenhagen, Denmark) and latex (Stallergenes, France). Food allergens tested were kiwi fruit, egg ovalbumin, and celery, using the prick-prick method, and wheat in 10% saline suspension (9). Histamine chloride 10 mg/ml was used as a positive control, and diluent solution as a negative control. Antihistamine medication was withheld for 5 days prior to testing. The same nurse carried out the tests in duplicate, on the volar side of both forearms. The wheal reaction was expressed as a mean diameter, and the negative diluent controls were subtracted. Thereafter, the mean of the two wheals tested with the same antigen was calculated, and reactions of at least 3 mm were regarded positive (10). One student was excluded from the tests due to pregnancy, thus 295/296 subjects were tested.

The specific IgE Pharmacia CAP System (Pharmacia, Upjohn, Sweden) was used to assay serum IgE antibodies against common airborne allergens (cat, dog, horse, birch, timothy, mugwort, *D. pteronyssinus* and *Cladosporium* antigens, Phadiatop) and food allergens (milk, wheat, soy, egg white, codfish, and peanut) (Fxs5, Pharmacia, Upjohn, Sweden) (11). Subjects with positive (> 0.35 kU/l) results in Phadiatop or Fxs5 were further tested by specific antigens, and those with negative results were regarded as specific-IgE negatives. Different cutoff points for IgE antibodies, radioallergosorbent test (RAST) class 1–2 and ≥ 3 values were analyzed separately. Two subjects missed the blood tests, thus 294/296 samples were analyzed.

Statistical analysis

Data was weighted by original-questionnaire survey proportions of the randomized sex matched samples (12), and calculated by STATA STATISTICAL SOFTWARE (13). This method was chosen to show the real occurrence of asthma or sensitization, because in the non-weighted analyses the prevalence rates of asthma and sensitization would have been higher than in the questionnaire survey because of the sampling procedure. Multiple logistic regression analysis was performed to analyze the impact of farm environment on asthma and sensitization, adjusted by early childhood pet-keeping (sas

system for WINDOWS, version 6.12). Adjustment for sex was not performed, because the sex distribution of farm and nonfarm subject was equal. *P*-values < 0.05 were regarded significant. *Weighting by sampling did not change the results of risk factor analyses.*

Results

Asthma and bronchial hyperreactivity

In the weighed clinical sample 10.7% had current asthma and 11.9% had bronchial hyperreactivity (methacholine PD₂₀ FEV₁ ≥ 2.9 mg). Of subjects with farm environment at age 0–6 years, 3.1% had current asthma, and of subjects with nonfarm environment 12.4% (OR 0.22, 95% CI 0.07–0.70) (Table 1). There was no difference in occurrence of bronchial hyperreactivity (12.0 vs. 11.8%). On the other hand, there was a trend showing more moderate or severe bronchial hyperreactivity (methacholine PD₂₀ FEV₁ ≤ 600 µg) among subjects with childhood nonfarm environment (Table 1).

IgE sensitization

In the weighted clinical sample, 28.1% had positive SPT to timothy pollen, 22.4% to birch pollen, 18.3% to cat, 14.3% to dog, 8.4% to horse, and 6.8% to house-dust mite. Of the tested foods, sensitization to celery (8.0%) and kiwi fruit (6.4%) were most common.

Among subjects with childhood farm environment there were fewer positive SPT, not quite reaching significance, to timothy pollen (12.6 vs. 30.3%, OR 0.33, 95% CI 0.09–1.20), birch pollen (8.3% vs. 24.2%, OR 0.28, 95% CI 0.07–1.15) and cat dander (12.6 vs. 20.2%, OR 0.57, 95% CI 0.16–2.08) than among subjects with childhood nonfarm environment (Table 2). On the contrary, occurrence of positive SPT against house-dust mite was significantly more common among subjects with childhood farm environment (22.0% vs. 4.9%, OR 5.43, 95% CI 1.60–18.46; Table 2).

In the weighted data of the clinical sample the occurrence of serum IgE *specific* to airborne allergens was comparable to SPT results (data not shown). Because symptomatic allergy most clearly occurs with higher

levels than needed for sensitization criteria, RAST classes 1–2 and ≥3 *only*, were analyzed separately (Table 3). Cat-specific IgE was significantly negatively associated with childhood farm environment, 1.5 vs. 13.1% (OR 0.10, 95% CI 0.02–0.47, Table 3), when high levels of IgE antibodies were analyzed. House-dust mite specific IgE was negatively associated with childhood farm environment when the lowest level of IgE antibodies was regarded (RAST class ≥ 1 vs. 0, OR 3.29, 95% CI 1.21–8.96), but the difference did not reach significance when the high level of antibodies (RAST class ≥ 3 vs. < 3) was analyzed (Table 3). The result did not change after adjusting for pet-keeping at age 0–2 in multiple regression analysis (data not shown).

In a separate analysis of current asthmatics with childhood farm and nonfarm environment, 25% of farm and 69% of nonfarm asthmatics were SPT-positive to cat (*P* value 0.07, weighted data). On the other hand, sensitization to horse (75 vs. 24%, *P* = 0.03) and to birch pollen (100 vs. 46%, *P* = 0.07), most clearly related to current asthma among subjects with childhood farm environment. Sensitization to house-dust mite, however, was as strongly related to current asthma in subjects with childhood farm and nonfarm environment (25 vs. 19%, *P* = 0.79). This data, however, is originally based on only four farm asthmatics, and 75 nonfarm asthmatics.

Discussion

Adult asthma, mainly allergic asthma in the present study, occurred clearly less often among subjects with childhood farm environment than among subjects with childhood nonfarm environment. There was a negative association between high levels of IgE antibodies specific to cat and childhood farm environment, and a similar trend for sensitization to birch and timothy pollen measured by SPT. In general, consistently lower figures for specific sensitization were shown among subjects with childhood farm environment, although statistical significance was not reached, evidently due to low number of subjects from farms. However, the analysis regarding

Table 1. Current asthma at clinical examination, and bronchial hyperreactivity among 282 Finnish university students who had lived in farm and nonfarm environments at age 0–6 years (percentages weighted for original proportions in the questionnaire survey)

	Farm %	Nonfarm %	Odds ratio	95% Confidence interval
Current asthma*	<i>n</i> = 29 3.1	<i>n</i> = 253 12.4	0.22	0.07–0.70*
Bronchial hyperreactivity	<i>N</i> = 29	<i>n</i> = 248‡		
PD ₂₀ FEV ₁ ≤ 2900 µg	12.0	11.8	1.02	0.27–3.77
PD ₂₀ FEV ₁ ≤ 1600 µg	7.2	7.8	0.91	0.20–4.22
PD ₂₀ FEV ₁ ≤ 600 µg	1.5	3.8	0.25	0.08–1.92

* Symptoms suggestive of asthma during the last year and obstructive spirometry or bronchial hyperreactivity (methacholine PD₂₀ FEV₁ ≤ 2900 µg).

** *P* < 0.01.

‡ Five subjects missing the methacholine challenge.

Table 2. Occurrence and odds ratios for positive skin prick tests (≥ 3 mm) among 281 Finnish university students who had lived on farm or nonfarm environments at age 0–6 years (percentages weighted for original proportions in the questionnaire survey)

	Farm % <i>n</i> = 28	Nonfarm % <i>n</i> = 253	Odds ratio	95% Confidence interval	<i>P</i> value
Timothy	12.6	30.3	0.33	0.09–1.20	0.09
Birch	8.3	24.2	0.28	0.07–1.15	0.08
Mugwort	11.0	5.7	2.05	0.45–9.31	0.35
Cat	12.6	20.2	0.57	0.16–2.08	0.39
Dog	22.8	13.7	1.86	0.62–5.56	0.27
Horse	12.6	8.3	1.59	0.42–6.08	0.68
House-dust mite	22.0	4.9	5.43	1.60–18.46	0.01
<i>Cladosporium</i>	0	1.2	–	–	–
<i>Aspergillus</i>	0	0	–	–	–
<i>Pityrosporum ovale</i>	11.8	5.3	2.42	0.55–10.65	0.24
Egg white	0	0.1	–	–	–
Kiwi fruit	2.4	5.8	0.40	0.10–1.57	0.18
Celery	5.9	8.0	0.72	0.11–4.65	0.73
Wheat	1.6	2.6	0.62	0.10–3.66	0.59

Table 3. Occurrence and odds ratios of IgE sensitization among 289 Finnish university students who had lived on farm or nonfarm environments at age 0–6 years (percentages weighted for original proportions in the questionnaire survey)

	RAST class	Farm % <i>n</i> $\geq$ 29	Nonfarm % <i>n</i> $\geq$ 260	Odds ratio RAST $\geq$ 1†	95% Confidence interval	Odds ratio RAST $\geq$ 3‡	95% Confidence interval
Timothy	1–2	6.4	14.8	0.56	0.20–1.55		
	$\geq$ 3	16.9	20.4			0.79	0.25–2.54
Birch	1–2	16.1	8.9	0.99	0.35–2.80		
	$\geq$ 3	7.2	14.5			0.45	0.10–2.07
Mugwort	1–2	15.4	14.1	1.28	0.43–3.81		
	$\geq$ 3	6.4	3.7			1.75	0.30–10.15
Cat	1–2	10.5	5.0	0.62	0.17–2.24		
	$\geq$ 3	1.5	13.1			0.10	0.02–0.47**
Dog	1–2	21.0	11.3	1.44	0.54–3.86		
	$\geq$ 3	7.2	10.1			0.68	0.15–3.14
Horse	1–2	10.5	6.8	1.04	0.28–3.87		
	$\geq$ 3	1.5	4.8			0.31	0.06–1.51
House-dust mite	1–2	21.0	8.3	3.29	1.21–8.96*		
	$\geq$ 3	11.3	4.3			2.80	0.66–11.95
<i>Cladosporium</i>	1–2	4.8	3.3	1.12	0.92–9.52		
	$\geq$ 3	0	1.1			–	–
Egg white	1–2	5.6	0.6	4.44	0.52–37.53		
	$\geq$ 3	0	0.7			–	–
Peanut	1–2	14.6	4.9	1.78	0.49–6.45		
	$\geq$ 3	0.8	4.4			0.17	0.02–1.44
Soy	1–2	9.7	5.5	1.85	0.41–8.41		
	$\geq$ 3	0.8	0.5			1.64	0.17–15.6
Milk	1–2	0	2.8	–	–		
	$\geq$ 3	0	0.1			–	–
Fish	1–2	0	0.7	0.59	0.07–4.89		
	$\geq$ 3	0.8	0.6			1.31	0.14–11.93
Wheat	1–2	5.6	5.6	1.03	0.19–5.73		
	$\geq$ 3	0.8	0.6			1.31	0.14–11.93

† RAST (radioallergosorbent test) $\geq$ 1 compared to RAST $\geq$ 0.‡ RAST $\geq$ 3 compared to RAST $<$ 3.* $P < 0.05$.** $P < 0.01$.

sensitization to specific allergens with low prevalence of sensitization, such as soy and wheat, may not be reliable. In contrast, the occurrence of house-dust mite sensitiza-

tion, especially, when low levels of IgE antibodies were analyzed, was more common among subjects with childhood farm environment.

In the present study, we analyzed weighted occurrence reflecting the “real” occurrence, because of unequal sampling based on lifetime asthmatic or nonasthmatic symptoms. The weighting, however, did not change the effect of exposure factors. However, when multiple endpoints, such as bronchial hyperreactivity and specific sensitization are analyzed, multiple problems with comparison can lead to some false associations. Moreover, false significant associations (type I errors) seem to be unlikely because most data point to the “protective” effect of childhood farm, supporting also the results of an earlier questionnaire study.

Previous studies have documented a lower occurrence of reported asthma and wheeze (3–6) among children living in farm environments. In the original questionnaire study among first-year Finnish university students the *lifetime* occurrence of physician-diagnosed asthma was 4.6%, and that of episodic wheezing 6.8% (5). In the present clinical sample of students, the weighted prevalence of *current* asthma—measured by lung function tests and physician’s interview—was 10.7%, suggesting that many of the subjects with wheezing in fact had asthma. The questionnaire study showed a significant protective farm effect on physician-diagnosed asthma and self-reported episodic wheezing analyzed *together* (5). In line with that finding, in the present clinical sample current asthma was less common among subjects with childhood farm environment.

Occurrence of bronchial hyperreactivity, however, was not related to childhood residential environment. This could be explained by the fact that subjects with more severe asthma were having anti-inflammatory asthma medication to relieve bronchial hyperreactivity. Furthermore, bronchial hyperreactivity as an only measure of asthma does not correlate well with asthma diagnosis made by a physician (14). On the other hand, there was a trend for lower occurrence of severe bronchial hyperreactivity among subjects with childhood farm environments, that corresponds to the similar finding with asthma.

In an Austrian study of rural children, lower occurrence of positive SPT to timothy and birch pollens, but not as clearly to animals, house-dust mites or storage mites, was documented among farm children (4). Similarly, in the present adult population, the occurrence of positive SPT against common allergens, such as timothy (30.3 vs. 12.6%) and birch pollen (24.2 vs. 8.3%) were approaching significance.

In contrast, IgE sensitization to house-dust mite was clearly more common among subjects with childhood farm environment, and the result was confirmed by specific-IgE measurements when low levels of IgE antibodies to house-dust mite was analyzed (Table 3). Sensitization to house-dust mite is related to exposure and, furthermore, house-dust mite antigen is a strong sensitizing agent (15). The present high occurrence of sensitization to house-dust mite could be explained by

partly cumulative exposure to cross-reactive storage mites (16), abundant in farm environments (17). At least low levels of IgE antibodies could be related more to exposure than clinical allergy. Interestingly, the present finding on high occurrence of IgE sensitization to mites is more like the results obtained among farmers (18), than in the farmer’s children (4), supporting the fact that the “window” for IgE sensitization to house-dust mite is wide, and lasts at least up to young adulthood.

Moreover, IgE antibodies to house-dust mite *were* common among current asthmatics with childhood farm or nonfarm environments, suggesting that when exposure lasts until young adulthood, the risk of asthma is not increased in relation to subjects with nonfarm environments. This finding, however, should be interpreted cautiously, because the analysis is based on only four farm asthmatics.

In contrast, there was significantly less cat allergy among subjects from childhood farm environments, when high levels of IgE antibodies to cat (RAST class ≥ 3) were analyzed against lower levels.

IgE sensitization to cat and dog amongst adult Swedish farmers was lower than in the general population, although exposure to these pet allergens was abundant in farm environments (18). A recent study documented that high exposure to cat allergen among children was associated with a high quantity of IgG₄ antibodies to cat (altered Th2 response), possibly inducing tolerance among children with high exposure to cat allergen, compared to moderate or low exposure (19). In the same study, a similar effect of high exposure to house-dust mite allergen and IgG-response was not detected. In the present study, however, low occurrence of IgE antibodies to cat on farms did not change after adjusting for pet-keeping at age 0–2 years (data not shown), suggesting that animal exposure *per se* does not explain the low prevalence of sensitization.

In the study among rural Austrian children, the difference in IgE sensitization to cat and house-dust mite between farm and nonfarm children was more clear, if higher quantities of IgE antibodies, possibly correlating better with clinical allergy, were analyzed (20). In line with that, we found that small quantities of IgE specific to pollen and animal dander were common among the farm population, which could be related to great exposure to these agents rather than to clinical allergy.

It is interesting that amongst subjects with childhood farm environments, IgE sensitization to cat was significantly less common, when high levels of IgE antibodies were analyzed, and that adjustment for early childhood pet-keeping did not change the results. Few studies in Northern (21) and Central Europe (22) have documented that sensitization to cat allergen—not exposure *per se*—is a strong risk factor for asthma. Similarly, our finding of low occurrence of cat sensitization and, further, the lower occurrence of cat sensitization among

current asthmatics with childhood farm vs. nonfarm environments, could explain the low prevalence of asthma among subjects who have lived on a farm as a child. Additionally, low occurrence of sensitization on farms could be related to exposure to endotoxins (23,24) and environmental mycobacteria (25) in farm environments, that strengthen the antiallergic Th1-lymphocyte response.

In conclusion, in young adults who have lived on a farm in childhood we have shown a lower occurrence of current asthma and a lower occurrence of IgE antibodies to cat, and a trend for low levels of IgE antibodies to

other allergens except house-dust mite. The farm environment, protecting against IgE-mediated disorders, is worth investigating further to elucidate the mechanisms of sensitization and asthma.

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