

Farm environment in childhood prevents the development of allergies

M. KILPELÄINEN, E. O. TERHO, H. HELENIUS* and M. KOSKENVUO†

Departments of Pulmonary Diseases and Clinical Allergology, *Biostatistics and †Public Health, University of Turku, Finland

Summary

Background A protective effect of infections in early life might explain the firmly reported finding of an inverse association between atopic disorders and large sibships.

Objective To study the effect of childhood farm, rural non-farm and urban environment, as well as family size and other factors on the occurrence of asthma, wheezing and atopic disorders up to young adulthood.

Methods Data on lifetime prevalence of physician-diagnosed asthma, allergic rhinitis and/or allergic conjunctivitis, atopic dermatitis, as well as self-reported episodic wheezing from 10 667 Finnish first-year university students aged 18–24 years were collected by a postal questionnaire. Associations of lifetime prevalence of the diseases with living on a farm, in a rural non-farm and urban environment during childhood were estimated by logistic regression analysis. Adjustment was made for potential confounding by gender, parental atopy, parental education, number of older siblings, day care outside the home and passive smoking.

Results The childhood farm environment independently reduced the risk for physician-diagnosed allergic rhinitis and/or allergic conjunctivitis (adjusted odds ratio 0.63, 95% CI 0.50–0.79, $P < 0.001$), and for diagnosed asthma and episodic wheezing analysed together (OR 0.71, 95% CI 0.54–0.93, $P < 0.05$), but not for atopic dermatitis during lifetime. Urban childhood environment did not show independent increased risk when compared with rural non-farm residence. The inverse association of sibship size with the occurrence of allergic rhinitis and/or allergic conjunctivitis was found among subjects with one (OR 0.86, 95% CI 0.77–0.96, $P < 0.01$) or at least four older siblings (OR 0.47, 95% CI 0.26–0.84, $P < 0.05$).

Conclusion Childhood farm environment seems to have a protective effect against allergic rhinitis and/or conjunctivitis, and more weakly against asthma and wheezing irrespective of family size. Environmental exposure to immune modulating agents, such as environmental mycobacteria and actinomycetes, favouring manifestation of a nonatopic phenotype could explain the finding.

Keywords: allergic conjunctivitis, allergic rhinitis, asthma, atopic dermatitis, epidemiology, family size, farm environment, rural, urban

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Introduction

The inverse association of sibship size with occurrence of atopic sensitization [1–5], nasal allergies [2,6–9] and in

some studies with asthma [2,10,11] has been repeatedly reported, but the finding is more inconsistent with respect to atopic eczema [2,5,12]. Moreover, in large studies the negative relationship of birth order with atopic disorders [2,4,6–8,11] has been assessed. It is obvious that some environmental, rather than genetic, factor lies behind this finding. The theory of the protective role of childhood

Correspondence: M. Kilpeläinen, Department of Pulmonary Diseases and Clinical Allergology, Turku University Central Hospital, Kiinamyllynkatu 4–8, FIN-20520 Turku, Finland (e-mail: maritta.kilpelainen@utu.fi).

infections has been suggested and could be based on knowledge of T-lymphocyte differentiation into TH1 and TH2 subsets [13,14]. In addition, there is epidemiological evidence on the effect of specific infections to support this 'hygiene' theory [15–17]. However, family size and structure seem not to be the only explanation for the rise in occurrence of asthma and atopic sensitization in Western countries [18,19]. Studies on effects of outdoor environment, based on comparisons of urban-rural differences within countries [20,21] and between countries with different 'lifestyles' [20,22–24] have given conflicting results as regards the theory of the harmful effect of air pollution.

In Finland, change from an agricultural to an industrialized society is apparently the main structural change over recent decades. In 1930s 66.0% of the workforce was engaged in farming, but nowadays the number is one tenth of that (6.6%) [25]. In addition to changes in family size and structure, the impact of change in environment could be crucial in the development of allergies.

We investigated the effect of childhood farm environment, family structure and status on the development of asthma, episodic wheezing and atopic disorders in a cross-sectional questionnaire study among young Finnish adults.

Materials and methods

Study population

A postal questionnaire study of possible risk factors for asthma and atopic diseases was carried out in winter 1995–96 among all the Finnish first-year university students ($N=14\,202$) studying in 22 universities situated in all parts of the country.

Questionnaire

The questionnaire was based on the Tuohilampi Questionnaire [26] developed in Finland for population studies of hypersensitivity diseases. Data were collected on diagnosis and symptoms suggestive of asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis. Questions investigating background factors related to the development of asthma and atopy, such as characteristics of the household and residential environment at different periods of life, were included.

We assessed the lifetime prevalence rates of physician-diagnosed asthma and atopic diseases with positive answers to the following questions (1) Asthma: Have you ever had asthma? If yes, has a doctor diagnosed your asthma? (2) Allergic rhinitis: Have you had 'hay fever' or other allergic nasal symptoms (sneezing, itchy, runny nose from, e.g. pollen or animals)? If yes, has 'hay fever' or nasal allergy been diagnosed by a doctor? (3) Allergic conjunctivitis:

Have you had allergic eye symptoms (watering, itching, redness, swelling of eyelids, etc.) from, e.g. pollen or animals? If yes, has allergic eye condition been diagnosed by a doctor? (4) Atopic dermatitis: Have you ever had an itchy rash called atopic eczema, or eczema in the folds of the elbows or behind the knees? If yes, has eczema been diagnosed by a doctor? (5) Self-reported wheezing during lifetime included subjects without diagnosed asthma and with positive responses to following questions: Have you at any time during your life had attacks of shortness of breath with wheezing? If yes, has your breathing been normal between the attacks? If yes, Have you had these attacks also during times you did not have a cold, 'flu' or other chest infection?

The validity of the questions was assessed in a clinical examination of a sample of 195 subjects who, according to the questionnaire, had had asthma or asthma-like symptoms at any time, and a random sample of as many subjects with no symptoms suggestive of asthma. The participation rates were 78 and 66%, respectively. We validated the disease-related questions against criteria of 'current diseases' including an interview by a chest physician and a dermatologist, and objective measures of sensitization (skin prick tests and specific serum immunoglobulin E) and lung function (spirometry with a bronchodilation test and methacholine challenge). Finally, the validity measures were calculated to adjust for proportions of asthma and non-asthma groups in the original questionnaire study. The specificity of physician-diagnosed asthma during lifetime against criteria of 'current asthma' was 99 and sensitivity 36%, and of attacks of shortness of breathing with wheezing (breathing normal between the attacks and apart from respiratory infection) 95 and 39%, respectively. When validated against 'current diseases' the corresponding values for physician-diagnosed allergic rhinitis during lifetime were 98 and 52%, for allergic conjunctivitis 98 and 30%, and for lifetime atopic dermatitis against 'current atopic dermatitis in examination' 76 and 50% (Kilpeläinen *M et al.* manuscript submitted).

Background factors

To examine the effect of childhood residential environment, we used a categorical variable on three levels: (a) living on a farm at age 0–6 years, (b) living in a rural area (scattered settlement) at age 0–6 years but never on a farm (rural non-farm category), as well as (c) living in an urban area at age 0–6 years.

Family size was included in the analysis as the number of older siblings in five categories: 0, 1, 2, 3 and 4 or more and comparisons were made between those without any older siblings and the other four categories. The socioeconomic status of the family was defined according to the educational

level of the head of the household, and was divided into three levels. The lowest level included basic education, the middle level included nonuniversity graduates and the high level university graduates. Parental asthma or atopy was defined as either of the parents ever having had asthma, allergic rhinitis, allergic conjunctivitis or atopic dermatitis.

Because day care outside the home is uncommon in farming families, it was included in the final analysis as a two-scaled parameter: day care at home and outside the home at age 0–2 years. Child care in kindergarten or in other children's families (family care) formed the outside the home category. Passive smoking of the subject was considered to have occurred if at least one of the household members had smoked daily indoors at home when the subject had been aged 0–2 years.

Statistical analysis

Initially, univariate analyses between lifetime occurrence of physician-diagnosed asthma, of attacks of shortness of breath with wheezing, of allergic rhinitis and/or conjunctivitis and of atopic dermatitis, and a large set of background variables were performed. There was substantial overlapping in the diagnosis of allergic rhinitis and allergic conjunctivitis: 42.2% (757/1794) of allergic rhinitis patients had also diagnosed allergic conjunctivitis, and 81.3% (174/931) of patients with allergic eye condition suffered from allergic nasal symptoms. Thus, the allergic nasal and eye diagnoses were combined in the analysis, and included subjects with either allergic rhinitis or allergic conjunctivitis, or both diagnoses.

Multiple logistic regression was used to assess the independent effect of remarkable variables, found in the univariate analyses ($P < 0.05$) to be associated with occurrence of asthma or allergic diseases. The variables included in the final model were: farm, rural non-farm, and urban childhood environment, parental education, number of older siblings, day care outside the home and passive smoking, as well as gender, and parental asthma or atopic disease. The 95% confidence intervals (95% CI) for the odds ratios (OR) were calculated. P -values 0.05 or below were considered to be statistically significant. The test of trends was calculated for the relation between number of older siblings and physician-diagnosed disease, if there seemed to be linearity between sibship size and the diseases. The statistical analysis was performed with the SAS system for Windows, release 6.12/1996 (SAS Institute Inc. 1996) [27].

The entire study design was approved by the Ethics Committee of the University of Turku.

Results

Data were obtained from 10 667 students aged 18–24 years,

4164 were men (39.0%) and 6503 women (61.0%). After three mailings, the response rate was 75.0% among the whole study population. Non-responders were more often men than women: 66.5% of men and 81.8% of women returned the questionnaire. In general, the response rate was lower among students studying commercial and technical subjects. The age range of the students was 18–24 years. Mean age was 20.9 years ($SD \pm 1.6$ years).

The lifetime prevalence of physician-diagnosed asthma was 4.6%. In addition, 6.8% reported episodes of shortness of breath with wheezing. Thus, the lifetime occurrence of doctor-diagnosed asthma together with episodic wheezing was 11.4%. The lifetime prevalence of allergic rhinitis and/or conjunctivitis was 21.5%, and of atopic dermatitis 18.2%.

The impact of living on a farm or in an urban area at age 0–6 years was analysed in relation to living in a rural non-farming residence. The unadjusted lifetime prevalence of physician-diagnosed asthma (Table 1), of episodic wheezing (data not shown), of allergic rhinitis and/or allergic conjunctivitis (Table 2) and of atopic dermatitis were lowest among students who had lived on a farm compared with rural non-farm or urban childhood residence. In the univariate analysis, the protective effect of the farm environment compared with rural non-farm environment was significant among the students who had allergic rhinitis and/or conjunctivitis (13.9 vs 22.4%, $P < 0.001$), but the association was insignificant among asthmatics (3.7 vs 4.5%, $P = 0.156$), and in subjects with atopic dermatitis (16.4 vs 18.6%, $P = 0.200$, not shown in Tables). When diagnosed asthma and wheezing (without asthma diagnosis) were analysed together the lifetime prevalence rates differed marginally significantly (farm 9.3 vs rural non-farm 12.7%, $P = 0.031$). There was only a slight difference in lifetime prevalence rates between students from urban and rural non-farming residence: asthma was more common among students coming from non-farming rural homes and allergic rhinitis and/or conjunctivitis more common among those who had lived in an urban home (Tables 1,2). The differences in lifetime prevalence rates between urban and rural non-farm environment did not reach statistical significance. The last year prevalence rates (symptomatic during the last year) were somewhat lower, but their distribution was equal to the lifetime prevalence rates in the three categories of childhood residential environment.

The greatest differences in distribution of background variables used in the analyses were shown between farm and urban childhood environment. Of the respondents with childhood farm environment 63.0% were women, compared with 59.5% of those with urban background. There were more children in farming families compared with urban families (4.1 vs 0.7% with four or more children), and more exposure to tobacco smoke at age 0–2 (24.8 vs 20.5%). Compared with urban background the childhood farm

Table 1. Association of physician-diagnosed asthma during lifetime with background factors in young Finnish adults. Adjustment performed by logistic regression model for all the other factors in the table and parental education

	Total N*	Prevalence (%)*	Crude OR*	95% CI	P-value	Adjusted OR†	95% CI	P-value
<i>Place of residence at age 0–6 years</i>								
Rural non-farm	1243	5.3	1.00			1.00		
Farm	1095	3.7	0.68	0.45–1.01	NS	0.70	0.46–1.06	NS
Urban	7276	4.5	0.81	0.64–1.10	NS	0.81	0.61–1.07	NS
<i>Day care outside the home at age 0–2 years</i>								
No	9324	4.5	1.00			1.00		
Yes	1127	5.1	1.14	0.86–1.52	NS	1.09	0.80–1.49	NS
<i>Passive smoking at age 0–2 years</i>								
No	8292	4.3	1.00			1.00		
Yes	2257	5.6	1.32	1.07–1.62	<0.01	1.30	1.03–1.64	<0.05
<i>Gender</i>								
Male	4142	5.1	1.00			1.00		
Female	6488	4.2	0.81	0.67–0.97	<0.05	0.72	0.59–0.88	<0.01
<i>Parents' asthma or atopy</i>								
No	6258	2.9	1.00			1.00		
Yes	4299	6.9	2.46	2.04–2.97	<0.001	2.32	1.89–2.84	<0.001
<i>Number of older siblings</i>								
0	5672	4.9	1.00			1.00		
1	3597	4.3	0.88	0.72–1.08	NS	0.94	0.76–1.17	NS
2	920	4.0	0.82	0.58–1.16	NS	0.91	0.62–1.33	NS
3	256	3.5	0.71	0.36–1.40	NS	0.74	0.36–1.53	NS
≥ 4	144	3.5	0.70	0.29–1.73	NS	0.90	0.36–2.25	NS

* Using all available information.

† For subjects with complete data on all the background variables.

environment associated with lower prevalence of parental atopy (37.0 vs 41.3%), of highest level of education (13.7 vs 39.1%), and of day care attendance at age 0–2 (3.7 vs 12.0%).

In the multiple logistic regression analysis, adjusted by the other variables, the risk for allergic rhinitis and/or conjunctivitis (OR 0.63, 95% CI 0.50–0.79) during lifetime among those who had lived on a farm at age 0–6 years was significantly lower when compared with rural non-farm residence (Table 2). The decreased risk failed to reach significance with respect to physician-diagnosed asthma (OR 0.68, 95% CI 0.46–1.06, Table 1), but when subjects with wheezing (without diagnosis) were included lower risk was weakly demonstrated (OR 0.71, 95% CI 0.54–0.93, not shown in the Tables). Residential environment in childhood had no significant association with physician-diagnosed atopic dermatitis (farm vs rural non-farm OR 0.93, 95%

CI 0.75–1.17, data not shown in Tables). There were not significant differences in odds ratios between living in an urban and rural non-farming residence in childhood (Tables 1 and 2).

The impact of farm environment on the diseases was also analysed separately according to atopic inheritance (parental asthma or atopy vs no parental asthma or atopy), and a similar highly significant protective effect of farm environment among subjects with and without atopic inheritance was found (data not shown).

In the univariate model the lifetime prevalence of physician-diagnosed asthma and allergic rhinitis and/or allergic conjunctivitis were inversely related to the number of older children in the household (Tables 1 and 2). The association seemed to be most linear among asthmatics, but in the logistic model adjusted by confounding factors no statistical significance could be found (*P*-value for test of trends 0.07).

Table 2. Association of physician-diagnosed allergic rhinitis and/or allergic conjunctivitis during lifetime with background factors in young Finnish adults. Adjustment performed by logistic regression model for all the other factors in the table and parental education

	Total N*	Prevalence (%)*	Crude OR*	95% CI	P-value	Adjusted OR†	95% CI	P-value
<i>Place of residence at age 0–6 years</i>								
Rural non-farm	1248	20.8	1.00			1.00		
Farm	1098	13.9	0.61	0.49–0.77	<0.001	0.63	0.50–0.79	<0.001
Urban	7307	22.4	1.10	0.95–1.27	NS	1.08	0.92–1.26	NS
<i>Daycare outside the home at age 0–2 years</i>								
No	9365	20.5	1.00			1.00		
Yes	1129	25.2	1.30	1.13–1.51	<0.001	1.22	1.04–1.42	<0.05
<i>Passive smoking at age 0–2 years</i>								
No	8325	21.0	1.00			1.00		
Yes	2269	20.6	0.98	0.87–1.09	NS	1.03	0.91–1.17	NS
<i>Gender</i>								
Male	4168	21.9	1.00			1.00		
Female	6509	20.2	0.90	0.82–0.99	<0.05	0.82	0.74–0.91	<0.001
<i>Parents' asthma or atopy</i>								
No	6283	15.4	1.00			1.00		
Yes	4318	28.9	2.23	2.03–2.45	<0.001	2.25	2.03–2.49	<0.001
<i>Number of older siblings</i>								
0	5697	22.3	1.00			1.00		
1	3610	19.5	0.85	0.76–0.94	<0.01	0.86	0.77–0.96	<0.01
2	924	20.4	0.89	0.75–1.06	NS	0.99	0.82–1.19	NS
3	258	19.8	0.86	0.63–1.17	NS	0.99	0.71–1.37	NS
≥ 4	144	9.0	0.35	0.20–0.61	<0.001	0.47	0.26–0.84	<0.05

* Using all available information.

† For subjects with complete data on all the background variables.

However, the independent protective impact of large sibships was established with respect to allergic rhinitis and/or conjunctivitis if there had been one (OR 0.86, 95% CI 0.77–0.96); or four or more older children in the family (OR 0.47, 95% CI 0.26–0.84). The association did not reach significance in atopic dermatitis or in wheezing.

In the multivariate model, parental history of atopic disease or asthma was the most powerful risk factor for asthma (OR 2.32, 95% CI 1.89–2.84, Table 1), for allergic rhinitis and/or conjunctivitis (OR 2.25, 95% CI 2.03–2.49, Table 2), and for atopic dermatitis (OR 1.71, 95% CI 1.54–1.91, data not shown in Tables). Male gender was an independent risk factor for physician-diagnosed asthma and allergic rhinitis and/or conjunctivitis (Tables 1 and 2). There was no gender difference when subjects with diagnosed asthma and wheezing were combined (OR 0.96, 95% CI 0.84–1.10, not shown in Tables). Female gender

associated positively with physician-diagnosed atopic dermatitis (OR 1.51, 95% CI 1.34–1.69, data not shown in Tables).

After adjustment for the other background variables, passive exposure to tobacco smoke at the age of 0–2 years was slightly positively associated with asthma (OR 1.30, 95% CI 1.03–1.64, Table 1), but not with atopic nasal, eye or skin disorders. Day care attendance at age 0–2 years was a weak risk factor for allergic rhinitis and/or conjunctivitis (OR 1.22, 95% CI 1.04–1.42, Table 2) but not for asthma (OR 1.09, 95% CI 0.80–1.49, Table 1).

In the multivariate model, we also tested the impact of family socioeconomic status, which was defined according to education of the head of the household on three levels, and found no independent associations with diagnosed asthma and allergies. The impact of parental education has therefore not been shown in the Tables.

Discussion

In the present cross-sectional study among 10 677 university students aged 18–24 years, from all over Finland, we found a protective effect of childhood farm environment on the development of allergic rhinitis and/or allergic conjunctivitis during lifetime, but not on diagnosed asthma or atopic dermatitis. When subjects with lifetime asthma diagnosis were analysed together with subjects having lifetime episodic wheezing symptoms, the protective impact could also be demonstrated. On the other hand, we found no independent increased risk of asthma or atopic diseases among subjects with urban childhood environment when compared with rural non-farm residence. The result was confirmed after adjustment for confounding factors related to farming, such as sibship size, parental education, smoking indoors, day care outside the home and parental atopy.

The protective impact of farm environment was demonstrated also in separate analysis among subjects with atopic and nonatopic inheritance. Thus, selection of nonatopic subjects as farmers seemed not to bias the result towards greater protective effect.

In the present study, the response rate was lower among male students (66.5 compared with 81.8% in female students), which may lead to response bias. If symptomatic men were more willing to respond, it might explain the higher lifetime prevalence rate of asthma among men. However, when subjects with wheezing were analysed together with diagnosed asthmatics, no gender difference was shown, which above all suggests under-diagnosis among women.

In this kind of a cross-sectional study a recall bias is possible. In the present study it is most probable concerning the question on smoking of family members indoors. Although those with asthma could better remember their exposure to tobacco smoke, the finding that passive smoking at early age increases the risk of subsequent asthma is in line with earlier studies with different methodology [28]. On the other hand, problems in recalling the other early event, day care at age 0–2 years, may not differ among atopics and nonatopics, and thus does not cause differential recall bias leading to overestimation of the risk.

Possibilities for consulting a doctor, and thus getting diagnosis, might differ between rural and urban areas. In Finland, the widely spread health care centre system created at the beginning of the 1970s gives equal access to medical services [29]. In fact, an equal reduced risk was found when questions referring to symptoms of allergic nasal or eye symptoms, without further definition 'diagnosed by a doctor', were analysed in the multiple regression model. In a sample subjected to detailed clinical studies, subjects coming from farming families (29/291) had less often allergic rhinoconjunctivitis (31.0 vs 49.6%) and also

asthma (13.8 vs 30.4%), but the differences did not reach significance due to the small sample size. Originally we regarded physician-diagnosed diseases more suitable for use in risk factor analysis because of their higher specificity. Taken together, differences in diagnostic labelling do not appear to be a relevant explanation for our finding.

Traditionally high socioeconomic status of the family has been related to the increased prevalence of atopic disorders [30–33], but we found no association of a three-level variable based on the educational level of the head of the household with atopic disorders in the multivariate model.

Sibship size [1–11] and in some studies also number of older siblings compared with younger [2–4,6] and even opposite sex of sibling (brothers) [5,7] have been of importance. The inverse association of the number of older siblings with the occurrence of allergic rhinitis and/or conjunctivitis was not as linear as in other studies with a different methodology [2,3,5–8]. However, the variable we used in this study is relevant to analyse the effect of sibship size. The trend for decreasing occurrence of asthma as sibship size increased was similar, but not significant even if wheezers were included. Similar results, in fact, were reported by Räsänen *et al.* among Finnish adolescent twins [9]. An inverse relation between family size and occurrence of asthma or wheezing has been reported from British populations with a possible explanation that prevalence rates of asthma or wheezing have been higher [2,10]. Moreover, an interesting finding in this study is that the independent protective effect of the number of older siblings was clearly weakened when the farm environment was included in the analysis and the latter, as well as the other variables, in fact explained much of the sibship size effect.

It has been assumed that in large families more infections occur during childhood, and that these infections may prevent the development of allergies [6,14]. Indeed, comparative population studies from Western and Eastern Europe [20,22] give support to this theory. In those studies, asthma and allergies, as well as IgE-mediated sensitization were less common, but symptoms related to infection were more frequent in Eastern Europe. On the other hand, no association was found between reported infections in childhood and subsequent allergies in adulthood in a longitudinal study [8]. However, a clear negative association between early infections and development of allergic diseases has been reported in measles [15], tuberculosis [16], and hepatitis A [17]. Thus at least these infections seem to prevent IgE-mediated allergic sensitization. The mechanism of the protective effect may be that these infections, especially tuberculosis, may favour a TH1 rather than TH2 lymphocyte response [13]. Increased TH1-response leads to increased secretion of interferon- γ that prevents the formation of IgE antibodies and the development of IgE-mediated allergies.

We found a discrepancy in the theory of the protective effect of early infections on allergic diseases in that day care outside the home at age 0–2 years even seemed to be associated with somewhat greater occurrence of allergic rhinitis and/or conjunctivitis (Table 2), although epidemics of respiratory infections do occur in kindergartens. This apparent discrepancy might also be explained by some kind of 'dose–response' relationship between pathogenic microbes and possible prevention of atopy. When measles infection spreads within the family, the number of viruses in the diseased cases is much greater and the clinical course of the disease more severe than if the infection has occurred outside the home [34]. Thus, the immunological consequences of the infection may be more pronounced when the infection spreads within the family from one sibling to another than in the kindergarten from one child to another. Recently a protective effect of early onset of day care (from 6 to 11 months) was demonstrated to reduce the risk of atopic sensitization in small, but not in large families [35]. Our result, however, is in line with most of the other studies, that have reported weak and conflicting results as regards to day care attendance [3,24,36] and atopic disorders.

Several studies have reported differences in occurrence of asthma and atopic diseases between rural and urban areas within the same country [20,21] but the findings are not consistent [30]. In the present study, no significant difference was found between urban and rural non-farm childhood residence. In fact, the low risk of allergic rhinitis and/or conjunctivitis, as well as asthma in combination with wheezing that related to the farm environment seemed to explain the 'urban-rural' difference. Our result confirms the earlier report on low risk of allergic rhinitis among Swedish conscripts who had lived in a farmhouse [19]. Furthermore, it is in line with a recent Swiss study among rural children with farming as a parental occupation, reporting that prevalence of atopic sensitization, as well as sneezing attacks during pollen season, were lower among farmers' children [37]. The negative association of farming with wheezing, however, was not confirmed in that study after adjusting for covariates.

We suggest that 'infection theory' could be a unifying explanation for the effect of sibship size and farm environment. People living in a farm environment are exposed to microbes like actinomycetes [38], and environmental mycobacteria that immunologically favour the development of a TH1-response [39,40]. Massive repeated exposures to actinomycetes on a farm are known to lead to the development of extrinsic allergic alveolitis, which seems to be a CD8⁺ T-lymphocyte-associated disease [39]. On the other hand, CD8⁺ cells secrete TH1-type cytokines, which inhibit the IgE response [39]. *Mycobacterium vaccae* infection was recently shown to suppress serum IgE and production of typical TH2-cytokine, interleukin (IL) -5, in

ovalbumin-sensitized mice [41]. In addition, intranasal inoculation of *Mycobacterium bovis*-Bacillus Calmette-Guérin (BCG) was found to inhibit ovalbumin-induced airway eosinophilia and production of IL-5 in mice [41]. Furthermore, tolerance induction by possibly greater exposure to allergens on farms could be included in the mechanisms that explain our finding [14,42].

In conclusion, we have shown that there is a real 'protective farm factor' that works independently on the development of allergic rhinoconjunctivitis and more weakly on asthma analysed together with wheezing, but not as clearly on atopic dermatitis. Our results give further support that increased exposure to immune modulating agents, such as environmental mycobacteria and fungi related to farming might explain this finding. Experimental studies on the interactions between exposure to microbes and allergens are clearly indicated.

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