

Original article

Small nonspecialized farming as a protective factor against immediate-type occupational respiratory allergy?

Background: In Poland small, nonspecialized farms, growing different crops and raising usually a few animals of various species constitute the majority.

Objective: The aim of the case-control study was to evaluate the risk factors of work-related respiratory symptoms and occupational asthma and/or rhinitis in Polish farmers and investigate whether the farming characteristics may have influence on the prevalence of atopy and allergic diseases.

Methods: The study groups comprised 100 cases who were farmers reporting work-related asthmatic and/or rhinitis symptoms from randomly selected family doctors practices (80 of 353) and 102 healthy controls. All subjects were examined by means of a questionnaire, skin prick tests (SPT) to common and occupational allergens, total serum immunoglobulin (Ig)E level and the presence of specific IgE and allergen-specific inhalation challenge tests were performed. The provocation tests were monitored with the spirometry, histamine challenge test and evaluation of nasal symptoms score and nasal washings.

Results: Respiratory allergic disease was recognized in 68 symptomatic patients, including 41 cases because of occupational allergens (asthma $n = 38$, rhinitis $n = 41$). Step-wise logistic regression analysis confirmed the protective role of small farms against the development of work-related symptoms (OR 0.23; 95% CI 0.11, 0.47) as well as the significance of positive SPT to cereals (OR 5.55; 95% CI 1.6, 19.21) and storage mites (OR 3.73; 95% CI 1.27, 10.96) as a risk factor of these symptoms. Cereal farming (OR 13.75; 95% CI 2.39, 78.83) and positive SPT to cereals (OR 26.92; 95% CI 5.33, 135.9) and storage mites (OR 44.07; 95% CI 8.40, 231.1) were found to be significant risk factors of occupational asthma and/or rhinitis.

Conclusions: Cereal farming and hypersensitivity to cereals plays the significant role in the development of occupational asthma among Polish farmers. It also seems that working on small farms may protect farmers against work-related respiratory symptoms that are mostly because of allergy.

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Farmers are exposed to a variety of allergens from plants, animals, moulds and insects, hence a high prevalence of allergy can be expected among them. However, a number of studies brought puzzling results concerning the prevalence of atopy and allergic diseases in the rural environment. It was demonstrated that the risk of asthma, hay fever and atopy in children from farming families was lower, as compared with their peers from nonfarming families (1–5).

Moreover, in adult farmers, allergic diseases were not found to be more frequent than in the general population. For instance, a cross-sectional study in subjects farming cereals, pigs and cattle, conducted in Saskatchewan, Canada, revealed that the prevalence of asthma was lower (5.9% males and 4.6% females) than in the general population (6.5%) (6). The respective parameter for farmers in New Zealand was 11.8% compared with 15%

in the general population. In that study, being a horse breeder/groomer, pig or poultry farmer and handling oats were significant risk factors of asthma (7). The prevalence of self-reported asthma in a French population of dairy farmers was 5.3% and was similar to that found in the general population (8).

On the contrary, farming is one of the occupations with the highest risk of asthma in nonatopic subjects (9). The prevalence of respiratory symptoms among farmers is considered to be high, especially in grain workers and pig breeders (10–12). According to the Finnish Registry of Occupational Diseases, animal epithelia, hairs and secretions or flours, grains and fodders accounted for 60% of the total cases of occupational asthma (13).

In Poland, there are no epidemiological data concerning either the prevalence or the risk factors of asthma and allergic rhinitis. However, the structure of the Polish

agriculture differs from that in other European countries. Working on small, nonspecialized farms, growing different crops and raising a few different species of livestock are the typical characteristics. The present study was undertaken to evaluate the risk factors of work-related respiratory symptoms and allergic diseases in the population of Polish farmers, in relation to the specific farming conditions.

Materials and methods

Study population

That was case-control study. The farmers were recruited from 80 of 353 randomly selected family doctors' practices in the Lodz district. The study group comprised 100 randomly selected cases reporting work-related respiratory symptoms suspected to be due to occupational, immediate-type hypersensitivity (rhinitis, attacks of cough and dyspnoea). One subject did not agree to take part in the study. A hundred and two healthy subjects were the controls. They were randomly selected from the same surgeries in the district. The persons to be enrolled as controls had to be farmers and could not receive treatment for any chronic disease. We had previously selected 110 patients but two of them were found to suffer from chronic rhinitis and another six subjects did not respond.

The study protocol was approved by the Regional Biomedical Ethics Committee. All the participants gave their informed consent prior to the study.

Questionnaire

The questionnaire, administered by a physician, was an adaptation of the instrument developed by the International Union against Tuberculosis and Lung Disease (IUATLD) (14). Before performing the study the questionnaire had been validated. It included a history of physician-diagnosed allergic diseases, personal and family history of atopy; tobacco smoking status; description of occupational exposure and farming characteristics (small nonspecialized farm, cereal farming, animal breeding, fruit farming). Small nonspecialized farm was defined as a farm with an area of up to 10 ha, characterized by crop farming and breeding of at least three different species of livestock. Symptoms suggestive of asthma included wheezing, chest tightness, and shortness of breath or cough under usual conditions or induced by exercise, exposure to cold air, smoke, dust or strong odours. Smoking was considered in three categories: current smokers, ex-smokers and nonsmokers. Smokers were defined as subjects who reported smoking tobacco at present. Ex-smokers were the subjects who had smoked daily and quit at least a month before the survey. Nonsmokers were those who had never smoked. Passive smoking was defined as a nonsmoker's exposure to tobacco smoke through living with one or more smokers.

Skin prick tests

Skin prick tests (SPT) were performed on the volar part of the forearm with a standard battery of common and occupational allergens including tree and grass pollens, *Dermatophagoides pteronyssinus*, *D. farinae*, moulds, feathers, wheat, straw, hay and barn dust, cow fur, threshings, cereals and storage mites (Allergopharma, Reinbek, Germany). The negative control was allergen diluent (commercially available, containing 9 mg NaCl, 4 mg phenol and

563 mg glycerol/ml) and the positive one – histamine dihydrochloride solution of 1 mg/ml. The SPTs were performed according to standardized techniques (15). The largest wheal diameter was assessed after 15 min. A positive reaction was defined as a wheal diameter of at least 3 mm in the absence of reaction to the diluent and in the presence of a positive reaction to histamine.

Total and specific IgE

Total serum immunoglobulin (IgE) was evaluated using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). Total IgE level > 100 KU/l was considered elevated.

The Pharmacia CAP System, RAST FEIA (Pharmacia Diagnostics) was used to quantify specific IgE antibodies against 25 allergens: sheep and pig epidermis, pig urine protein, cat, dog, horse, and cow furs, goose, chicken, turkey and duck feathers, grass and cereal pollens, house dust mites (*D. pteronyssinus*, *D. farinae*), storage mites (*Acarus siro*, *Lepidoglyphus destructor*, *Gastrophilus intestinalis*), nonstinging insects (*G. intestinalis*, *Sitophilus granarius*) and moulds (*Aspergillus fumigatus*, *Alternaria alternata*, *Penicillium notatum*, *Cladosporium herbarum*, *Helminthosporium halodes*). The results were expressed quantitatively in kilounits per litre and considered positive at values higher than 0.35 KU/l.

Inhalation challenge tests

Specific inhalation challenge tests were performed in all cases and controls. At first, all subjects were challenged with placebo (potato flour) for 30 min. Three days later, provocation tests with grain dust, animal epidermis, furs and feathers were performed in a worksite simulation (room space 6 m², temperature 22–25°C) with patients' own samples for 30 min. The patients were challenged with different agents separately, in a week intervals, always starting with the most probable allergens, i.e. to which the patient had skin or serum specific IgE.

The evaluation of nasal symptoms

The number of sneezes and the degree of mucosal oedema, rhinorrhea and itching were evaluated. Total symptom score ranged from 0 to 8 and represented the sum of the scores for sneezing (0 sneezes – 0 points, 1–4 sneezes – 1 point, > 4 sneezes – 2 points), rhinorrhea (none – 0 points, mild – 1 point, abundant – 2 points), mucosal oedema (none – 0 points, mild – 1 point, nasal block – 2 points) and itching (none – 0 points, itching of the nose or throat – 1 point, itching of the nose and throat – 2 points) (16).

An analysis of cell count and proportion and biochemical composition (permeability index i.e. albumin to total protein ratio) of nasal washings was performed. All the procedures were similar as in the 'nasal pool' method (17). Nasal washings were collected immediately before the provocation and 30 min, 4 and 24 h afterwards. The processing of nasal washings has been described in detail elsewhere (18).

Pulmonary function

Resting spirometry (Vicat 2A, Mijnhardt, The Netherlands) was performed in all subjects. Bronchial response was measured by serial monitoring of forced expiratory volume in 1 s (FEV₁) and peak expiratory flow rate (PEFR) before and 5 min, 30 min, 1 h, 2 h, 4 h, 6 h and 24 h after the provocation. All the subjects were instructed beforehand how to use the peak flow meter for hourly PEFR measurements.

Histamine challenge was performed according to Cockcroft before the challenge tests, 24 h after the placebo and 24 h after the specific provocation test (19).

Diagnostic criteria

Work-related symptoms included rhinitis, cough, wheezing or dyspnoea induced by occupational exposure.

Diagnosis of occupational allergic rhinitis (20) was based on questionnaire data and positive nasal response to provocation test i.e. total score of more than 3 points (16) and significant increase in the proportion of eosinophils and in the permeability index (18).

Occupational asthma (20) was recognized in subjects reporting work-related chest symptoms, for whom a specific challenge test was found to induce an early or dual asthmatic reaction (at least a 20% decrease in FEV₁) or a three-fold increase in nonspecific bronchial hyperreactivity.

Statistical analysis

Continuous variables were expressed as mean values $\pm$ standard deviations (SD) while the nominal variables, as numbers and percentages. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for all studied risk factors, separately for the two outcomes i.e. work-related symptoms and occupational respiratory disease (EGRET statistical software). The analysis of risk factors of work-related symptoms included the group of 100 cases, and the controls were 102 healthy persons. The analysis of the risk factors of occupational respiratory allergy covered the group of cases, 41 persons with recognized occupational allergic rhinitis and/or asthma, and 102 controls. The variables included in the logistic regression model (step-wise analysis) for work-related symptoms were as follows: having a small nonspecialized farm, animal breeding, cereal farming, positive SPT to common and occupational allergens (also separately for hay dust, cereals and storage mites). The analysis of risk factors of occupational respiratory allergy included such variables as: having a small nonspecialized farm, cereals farming, elevated total IgE level, positive SPT to common allergens and to hay dust, cereals, animal allergens and storage mites. The variable – present or past smoking – was included as a confounding factor.

Results

Description of study groups

The subjects were 100 farmers (48 males, 52 females, mean age 46.5 ± 9.3 years) reporting work-related respiratory symptoms and 102 healthy farmers (52 males, 50 females, mean age 45.8 ± 8.64 years) as the controls. Active smoking was reported by 8% of symptomatic farmers and 52.9% of the controls, while smoking in the past by 47 and 13.7%, respectively. Forty-nine cases as well as 86 controls possessed small nonspecialized farms.

Respiratory symptoms and allergological tests

Table 1 shows the prevalence of respiratory symptoms reported by symptomatic subjects. Rhinitis was the most frequently reported symptom (92%). The mean latency

Table 1. Reported symptoms and medical diagnosis in the group of 100 farmers with work-related respiratory symptoms

Symptoms/outcome	Cases the number of subjects	Controls
Cough	83	0
Dyspnoea	79	0
Wheezing	19	0
Rhinitis	92	0
Conjunctivitis	38	0
Respiratory allergic (immediate-type)	68	0
disease caused by		
Occupational allergens	41	
Grain dust	28	
Cow	11	
Pig	1	
Poultry	1	
Asthma caused by	43	0
Occupational allergens	38	
Grain dust	26	
Cow	10	
Pig	1	
Poultry	1	
Allergic rhinitis caused by	63	0
Occupational allergens	41	
Grain dust	28	
Cow	11	
Pig	1	
Poultry	1	

period of the reported symptoms was 7.8 ± 6.1 years. The primary agents that intensified the symptoms were reported to be grain dust (75%) and hay dust (67%). Contact with the livestock induced respiratory symptoms less frequently: cows in 36%, pigs – 11%, horses – 3% and poultry – 10%.

Positive SPT to at least one allergen was found in 59% of symptomatic subjects and 16% of the controls, both with respect to common allergens (37% vs 11.8%) and occupational allergens (47% vs 8.8%). The frequency of positive SPT to occupational allergens is shown in Table 1.

The mean total IgE level was 278.6 ± 572.7 kU/l in farmers with respiratory symptoms and 71.9 ± 109.2 kU/l in controls. Specific IgE was found in four symptomatic subjects for animal allergens, 18 for grass and cereal pollens and 25 assays for storage mites. In addition, specific anti-grass and anti-cereal pollens were found in four controls and anti-storage mites IgE in two subjects.

Specific inhalation challenge test induced positive results in 38 patients: early reaction in 23 and biphasic reaction in 15 subjects. Moreover, the challenge with occupational allergens induced allergic changes in nasal lavage fluid in 41 patients. None of the controls displayed either spirometric or nasal changes. The agents inducing positive results were grain dust ($n = 28$), as well as cow ($n = 11$), pig ($n = 1$) and poultry allergens ($n = 1$).

Table 2. Odds ratio (OR) of work-related respiratory symptoms in Polish farmers (100 cases and 102 controls)

Factor	Group with work-related symptoms		Control group		OR (95% CI)
	<i>n</i>	Rate/100	<i>n</i>	Rate/100	
Type of farming					
Small nonspecialized farm	49	49	86	84.31	0.17 (0.09; 0.35)*
Animal breeding	21	21	8	7.84	3.12 (1.31; 7.44)*
Cereal farming	25	25	8	7.84	3.91 (1.67; 9.18)*
Fruit-trees cultivation	12	12	18	17.64	0.63 (0.28; 1.40)
Active smoking	8	8	54	52.94	0.15 (0.08; 0.30)*
Past or present smoking	55	55	68	66.67	0.61 (0.35; 1.08)
Environmental tobacco smoke exposure	47	47	44	43.14	1.10 (0.67; 2.04)
Family history of atopy	27	27	16	15.69	1.90 (0.99; 3.97)
Total IgE > 100 KU/l	36	36	26	25.49	1.64 (0.89; 3.01)
Positive SPT to					
Common allergens	37	37	12	11.76	4.41 (2.13; 9.11)*
Occupational allergens	47	47	9	8.82	9.16 (4.16; 20.17)*
Hay and straw dust	35	35	6	5.88	8.62 (3.42; 21.65)*
Animal allergens	7	7	1	0.98	3.70 (0.76; 18.58)
Cereals	22	22	4	3.92	6.90 (2.28; 20.89)*
Storage mites	16	16	5	4.90	3.60 (1.29; 10.52)*
All	100		102		
Logistic regression (step-wise) analysis					
Small nonspecialized farm	<i>P</i> < 0.001				0.23 (0.11; 0.47)*
Positive SPT to cereals	<i>P</i> = 0.007				5.55 (1.6; 19.21)*
Positive SPT to storage mites	<i>P</i> = 0.017				3.73 (1.27; 10.96)*

* Indicates *P* < 0.05

SPT, skin prick test; IgE, immunoglobulin E.

Table 3. Odds ratio (OR) of occupational asthma and/or rhinitis in Polish farmers (41 cases and 102 controls)

Factor	Group with occupational respiratory disease		Control group		OR (95% CI)
	<i>n</i>	Rate/100	<i>n</i>	Rate/100	
Type of farming					
Small nonspecialized farm	19	46.34	86	84.31	0.16 (0.07; 0.39)*
Animal breeding	7	17.07	8	7.84	2.01 (0.65; 6.22)
Cereal farming	15	36.59	8	7.84	6.78 (2.59; 17.73)*
Fruit-trees cultivation	5	12.19	24	17.64	0.65 (0.22; 1.88)
Active smoking	3	7.31	54	52.94	0.07 (0.01; 0.25)*
Past or present smoking	19	46.34	68	66.67	0.58 (0.27; 1.21)
Environmental tobacco smoke exposure	22	53.66	44	43.14	0.88 (0.42; 1.82)
Family history of atopy	13	31.7	16	15.69	2.22 (0.94; 5.25)
Total IgE > 100 KU/l	23	56.09	26	25.49	3.74 (1.74; 7.99)*
Positive SPT to					
Common allergens	25	60.97	12	11.76	11.72 (4.91; 27.97)*
Occupational allergens	30	73.17	9	8.82	28.18 (10.66; 74.52)*
Hay and straw dust	25	60.97	6	5.88	27.73 (9.79; 78.56)*
Animal allergens	7	17.07	1	0.98	10.29 (2.04; 51.96)*
Cereals	17	41.46	4	3.92	19.17 (5.92; 62.07)*
Storage mites	11	26.83	5	4.90	7.11 (2.29; 22.10)*
All	41		102		
Logistic regression (step-wise) analysis					
Grains cultivation	<i>P</i> = 0.003				13.75 (2.39; 78.83)*
Positive SPT to cereals	<i>P</i> < 0.001				26.92 (5.33; 135.9)*
Positive SPT to storage mites	<i>P</i> < 0.001				44.07 (8.40; 231.1)*

* Indicates *P* < 0.05.

SPT, skin prick test; IgE, immunoglobulin E.

Respiratory allergic disease, including 41 cases caused by occupational allergens, was recognized in 68 patients (Table 1). Occupational asthma was diagnosed in 38 farmers and rhinitis in 41 subjects.

Statistical analysis of risk factors

Univariate analysis revealed that cereal farming, animal breeding, positive SPT to common and occupational allergens were significant risk factors of work-related respiratory symptoms (Table 2). Moreover, cereal farming, elevated IgE level, positive SPT to common and occupational allergens were also the significant risk factors of occupational respiratory allergic disease (Table 3). Possessing a small nonspecialized farm had the protective effect both against the work-related respiratory symptoms and respiratory allergy (Tables 2 and 3). Likewise, active smoking was found to be a protective factor against respiratory symptoms and allergy; however, the significance of this variable was not confirmed when analysing past or present smoking altogether (Tables 2 and 3). Step-wise logistic regression analysis confirmed the protective role of small farms against the development of work-related symptoms as well as the significance of positive SPT to cereals and storage mites as a risk factor of these symptoms (Table 2). The same analysis performed for occupational respiratory allergy as an outcome confirmed a significant role of cereal farming, positive SPT to cereals and storage mites (Table 3).

Discussion

As the study group comprised the patients of randomly selected family doctors, we can assume they can be regarded as a representative sample of farmers from Central Poland. The controls were also recruited from the same population of patients. Both groups were very similar with respect to the mean age and gender proportions. The only criterion for the selection of the symptomatic patients was the suspicion of immediate-type respiratory allergy at the family doctor's level, based on the history, physical examination, spirometry and chest radiography. However, in more than 30% of the study group, we did not recognize allergic disease and the symptoms may, at least partially, be explained by the manifestation of asthma-like symptoms. The diagnosis of respiratory allergy was based on the results of specific inhalation challenge considered to be a gold standard in occupational asthma. The test was performed in a worksite simulation. To some disadvantage of this test is the lack of standardization and the plurality of the provocation materials but these derived from the patient's own farm and were supplied by himself. The application of nasal lavage examination in the cases with accompanying rhinitis made it possible to differentiate between

allergic and irritative effect (21), which was extremely important in the case of farmers allergens.

The most striking finding of this study is the protective role of having a nonspecialized farm. This was revealed by univariate analysis for both outcomes (work-related symptoms and occupational allergy) and confirmed in the logistic regression model for work-related symptoms. The lack of significance in the model for occupational allergy may be due to the small number of cases. The farms in Poland are usually small and run by family members. All of them had been living there since their birth and none of the examined subjects was a farm worker. All of these farm owners had cattle, pigs, poultry and were farming cereals, usually wheat or rye. From late autumn to spring, the farm animals are kept in stables, which results in specific conditions of the farmer's work environment. A number of studies performed in Europe, Canada and Australia confirmed that the presence of livestock was an essential element of the protective 'farm effect' (3, 4, 22, 23). For instance, a recent study in Australia revealed that regular contact with livestock or poultry was the factor most strongly associated with a reduced risk of allergic sensitization in children living on a farm (22). Hence, there is a possibility that the 'farm effect' may result from elevated exposures to bacterial compounds in the microbial environment of farm stables. As expected, the highest endotoxin concentrations were found in stables, but also among families of children with regular contact with livestock, higher endotoxin levels were found in the mattress as compared with control households (23). The mechanisms by which endotoxin exposure may protect against the development of IgE-mediated sensitization and diseases are not fully understood. The LPS engages with antigen-presenting cells via CD14 ligation eliciting strong IL-12 responses, which in turn is an obligatory signal for the maturation of naive T cells into Th1-type cells (24, 25). Predominant Th1-type immune response may divert the development of atopy, as well as pathologic remodelling processes in asthma (26). Cereal farming was found to be a significant risk factor of respiratory allergy. Chronic inhalation of grain dust has been shown to cause acute and chronic airway injury characterized by bronchitis and airway obstruction (27). In contradistinction to asthma-like syndromes induced by grain dust inhalation, the frequency of bronchial asthma is low – it has been estimated to be about 1.6% of exposed subjects (28). The presence of specific IgE has been demonstrated in up to 40% of exposed workers with clinical lower respiratory symptoms (29). On the contrary, in some patients with positive results of specific challenge tests, specific IgE could not be found, which might indicate the involvement of other immunological or nonimmunological mechanisms (30). Although there have been some speculations on the role of IgG, the possibility of specific IgG₄ as a sensitizing antibody seemed to be very low (30). Most researchers – similarly as our results – suggest flour and storage mites as the main sensitizing agents in the

grain dust (31, 32). Among 28 patients with positive inhalation challenge with grain dust, 17 were sensitized to wheat and rye flours, all to hay and straw dust and 10 to storage mites. Kronqvist et al. (31) found that almost one-fifth of the farmers were sensitized to mites. Furthermore, mites were the most prevalent allergens among subjects with asthma and rhinoconjunctivitis. Sixteen per cent of our patients with work-related respiratory symptoms and 26.8% of those with respiratory allergy, as well as 4.9% of the controls were sensitized to storage mites.

About one-third (12 of 41) of cases with occupational respiratory diseases was because of animal allergens, mainly cow allergens. In Finland, Terho et al. (32) demonstrated that 50 of 70 farmers with allergic rhinitis had a positive reaction upon nasal challenge with cow dander. Also in Swedish farmers, sensitization to cow dander was the most common (4.2%) among animal danders (31). Sensitization to other animal allergens (pig, poultry) in our study was rare. Pig farmers have the highest risk of work-related symptoms, but respiratory allergy does not seem to be predominant in them (33). Their symptoms are often described as 'asthma-like syndrome'. Indeed, among our patients only in one of 11 subjects reporting respiratory symptoms when working in swine confinements, we confirmed IgE mediated disease. Similarly, only one of 10 farmers with poultry-related symptoms had suffered from allergic rhinitis. There are a few studies on poultry farmers. In New Zealand, an increased prevalence of wheezing was noted among poultry farmers (7). Radon et al. (33) found nasal allergies in half of the poultry farmers complaining about asthma and/or work-related wheezing. Müller et al. (34) described a high prevalence of sensitization and respiratory symptoms in a group of 339 poultry farmers.

Logistic regression analysis confirmed that positive SPT to occupational allergens was a significant risk factor of work-related respiratory symptoms and allergic disease. In univariate analysis, also SPT to common allergens was significantly associated with respiratory symptoms and allergy. In Kronqvist et al. (31) study,

sensitization to pollens and mites was a significant risk factor for any respiratory symptoms and asthma. Also in Dalphin et al. (8) study, asthma and asthma-related symptoms positively and significantly correlated with indicators of IgE-mediated allergy.

The protective role of active smoking found in the univariate analysis is contrary to other reports (35) and may be surprising. However, assuming that people suffering from respiratory symptoms may have quit smoking and that the anamnesis from patients who claim for compensation may not always be fully reliable we decided to perform an analysis for the factor 'smoking at present or in the past'. The analysis did not confirm this finding. Therefore, the variable 'active smoking' was not included into the logistic regression model and the variable 'past or present smoking' was included as the confounding factor.

There are two interesting findings of our study. The first one, rather of regional implication, is the significant role of cereal farming and hypersensitivity to cereals in the development of occupational asthma among Polish farmers. However, the most interesting observation is the possible protective effect of small farms. It seems that the conditions that are very close to natural environment are beneficial to the health condition of the exposed subjects. Probably, the presence of endotoxin plays the key role here. We presume that such a cause-effect relationship could be observed only because our farmers had been living in these conditions since their birth. It is known that once asthma and allergic diseases are established, the relationship is generally the opposite: microbial exposures worsen the course of the disease (36). Further studies would be necessary to estimate the concentration of endotoxins in small farms and to compare it with the levels found in larger, highly specialized farms.

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