

Prevalence of Atopy and Allergic Diseases in Korean Children: Associations with a Farming Environment and Rural Lifestyle

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Key Words

Allergic disease • Atopy • Farming • Hygiene hypothesis • Rural lifestyle

Abstract

Background: The results of recent studies suggest that factors in rural environments may protect against the development of allergic diseases, but the underlying mechanisms are not well understood. The aim of this study was to investigate the prevalence of allergic diseases, to establish if this prevalence is influenced by migration from rural to urban areas and to identify environmental risk factors associated with these diseases. **Methods:** A cross-sectional study of children aged 9–12 years from a rural village, a rural town and an urban city in Korea was conducted. Demographic and disease-related information was obtained via a detailed questionnaire, and skin prick tests were performed. **Results:** There were significant differences in lifestyle and environmental factors between children from the rural village, the rural town and the urban children. The prevalence of allergic diseases and atopy was higher in urban children. A lower prevalence of allergic diseases and atopy was associated with farming parents, contact with farm animals during

pregnancy, owning pets or a stable, breast-feeding and having older siblings. A comparison of rural village and rural town children revealed no evidence of an association of allergic diseases and atopy with farming parents, contact with farm animals during pregnancy or owning a stable. On the other hand, having older siblings and antibiotic use during infancy were significantly associated with allergic diseases and atopy in these children. **Conclusions:** Protective factors associated with a farming environment and/or rural lifestyle may influence the prevalence of allergic diseases and atopy in Korean children.

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The past several decades have seen an increase in the prevalence of allergic diseases in most westernized countries. In Korea, the prevalence of allergic diseases steadily increased in children and adolescents from 1995 to 2000 [1]. It has been suggested that improvements in hygiene are responsible for the increased prevalence of allergic diseases observed in many industrialized countries [2]. Until recently, research in this area has focused primarily on the possible link between atopy and microbial exposure [3]. Investigations of other factors such as

changes in diet and other shifts in lifestyle that could explain the current trends have been conducted in parallel.

The prevalence of allergic diseases is lower in rural areas than in urban areas [4, 5]. The results of numerous studies suggest that being raised in a farm environment confers protection against allergic diseases and atopic sensitization among children [6–8]. Cross-sectional studies of farm children have shown that exposure to farm animals and high indoor endotoxin levels are inversely associated with an incidence of aeroallergen sensitization, allergic rhinitis (AR) and asthma [9, 10]. However, the assertion that microbial exposure in rural environments is associated with the incidence of allergic diseases is inconsistent with the observation of an increased risk of asthma where there is a low degree of ‘cleanliness’ in the home among inner-city populations in North America [11, 12]. In fact, comparative studies have shown that there are a number of significant differences in immediate environment and lifestyle between children reared on farms versus urban and rural nonfarming environments, including family size, mode of delivery, use of antibiotics, dietary habits and exposure to livestock, pets, dampness, mold and environmental tobacco smoke [13, 14].

Previous studies have examined some of the risk factors for allergic diseases among children in East Asia [15–17]. An important and currently unresolved issue is whether risk factors in East Asia are similar to or different from those reported in Europe, and particularly whether the constellation of risk factors is consistent with the hygiene hypothesis. We hypothesized that the prevalence of allergic diseases and atopic sensitization would be lower among rural children in Korea due to differences in environment and lifestyle.

The objective of the study was to compare the prevalence of allergic diseases and atopic sensitization among Korean schoolchildren in an urban city, a rural town and a rural village. We investigated the association of putative risk and protective factors (including those linked to the hygiene hypothesis) with allergic diseases and atopic sensitization in these children. The reason for comparing 3 regions in this thesis, i.e. not only the city and a rural village, was because the environment or lifestyle of a rural town is somewhere between these two, as is the likelihood of the prevalence of allergic diseases like asthma.

Methods

Children aged 9–12 years and attending local schools were recruited from 3 different environments: a traditional rural village of Jeongeup, the nearby rural town of Jeongeup city, and a large,

fully urbanized city, Seoul. Jeongeup (127°E, 30°N) occupies an area of 692.93 km² and is located in the center of Korea. There is no heavy industry in this area and road traffic is light. The populations of the rural village and rural town were 53,000 and 75,000, respectively. Various types of farming were carried out in the village community, including agricultural and livestock farming. The most common livestock raised on the farms nearby were poultry, pigs, goats and cows. The rural village of Jeongeup is located on the outskirts of the rural town, Jeongeup city. Rural children were defined as those children living in the rural village and in the rural town.

Ten schools from the urban and rural areas participated in the study with a total of 1,828 schoolchildren within the target age range. Of the 1,828 potential subjects, 1,749 (95.7%) returned the questionnaires.

The approval to conduct the study was obtained from the human ethics committees of Hallym University and from the principals of the schools attended by the children. Written informed consent was obtained from the parents of all the children.

Questionnaire Data

Demographic factors, potential explanatory and confounding factors and the prevalence of diseases and symptoms were assessed by a questionnaire issued to the parents. The questions were taken from the International Study of Asthma and Allergies in Childhood (ISAAC) [18] and the Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study [19]. The written questionnaire was translated into Korean according to the ISAAC protocol (Phase 1). The questionnaires were distributed and collected from July to October, 2008.

Definitions of disease were based on answers or combinations of answers to specific questions, e.g. ‘Ever had wheezing?’, ‘Ever had a doctor’s diagnosis of asthma?’, ‘Current asthma?’ and ‘Wheezing during the last 12 months?’

Each subject was given an ISAAC Phase III written questionnaire to complete, which was followed by a video questionnaire at school. The ISAAC video questionnaire consisted of 5 scenes showing young people of different races (1) wheezing at rest, (2) wheezing after exercise, (3) waking at night with wheezing, (4) waking at night with a cough and (5) experiencing a severe asthma attack. In addition, the parents of each subject were given a parent questionnaire to complete, which included questions on social background, the family history of allergic diseases, exposure to a farm environment, types of animal exposure, pet ownership and a history of vaccinations and parasite infection.

Skin Prick Test

Skin prick tests (SPTs) were performed on the volar surface of the arm on skin that was of normal appearance using standardized allergen extracts and control solutions from Allergopharma (Reinbek, Germany). Subjects were tested for sensitivity to the following 16 allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, dog epithelium, cat epithelium, cockroach, grass, mixed tree pollen 1 and 2, *Alternaria*, *Aspergillus*, ragweed, mugwort, milk, egg white, peanut and soybean. A positive skin reaction was defined as a wheal ≥ 3 mm in size, after the subtraction of a negative control. SPTs were performed on 1,507 children (82.4%). One or more positive reactions were considered atopy.

Table 1. Prevalence of allergic diseases and atopic sensitization

	Rural village	Rural town	Urban area	p value
Wheezing, in the last 12 months	19/457 (4.2)	28/518 (5.3)	24/649 (3.7)	0.614
Asthma diagnosis, ever	30/454 (6.6)	51/511 (10.0)	54/637 (8.5)	0.345
Current asthma ¹	8/454 (1.8)	13/511 (2.5)	13/631 (2.1)	0.794
Wheezing symptoms ever by VQ ²	27/453 (6.0)	35/464 (7.5)	67/727 (9.2)	0.041
Exercise-induced wheezing by VQ	37/453 (8.2)	59/464 (12.7)	96/727 (13.2)	0.012
AR symptoms, in the last 12 months	98/425 (23.1)	141/495 (28.5)	227/624 (36.4)	<0.001
AR diagnosis, ever	57/431 (13.2)	96/496 (19.4)	216/613 (35.2)	<0.001
Current AR ¹	36/419 (8.6)	69/477 (14.5)	141/551 (25.6)	<0.001
Itchy rash, in the last 12 months	43/439 (9.8)	64/506 (12.6)	102/663 (15.4)	0.007
AD diagnosis, ever	82/449 (18.3)	119/512 (23.2)	182/650 (28.0)	<0.001
Current AD ¹	30/421 (7.1)	53/484 (11.0)	82/599 (13.7)	0.001
Atopic sensitization ³	159/448 (35.5)	171/441 (38.8)	286/618 (46.3)	<0.001
Sensitization, ≥ 2 positive SPT	110/448 (24.6)	130/441 (29.5)	213/618 (34.5)	0.003

Values in parentheses are percentages. Statistical analysis was performed using the χ^2 test. ¹ Defined as having allergic symptoms within the last 12 months and a doctor's diagnosis of allergic disease. ² Lifetime prevalence of wheezing symptoms based on video questionnaire (VQ). ³ Atopic sensitization to one or more common allergens, as indicated by SPT.

Laboratory Tests

The levels of total IgE in serum were measured using the UniCAP fluoroenzyme immunoassay (Pharmacia Diagnostics, Uppsala, Sweden). The number of blood eosinophils was determined using an automatic blood cell counter (XE-2100; Sysmex, Tokyo, Japan). Total IgE level and eosinophil count (%) were obtained for 1,478 children from all 3 areas.

Statistical Analysis

Data were categorized and analyzed using SPSS version 14.0. (SPSS, Inc., Chicago, Ill., USA) The χ^2 test was used to compare prevalence rates of various symptoms and atopic sensitization between groups and subgroups of children. Results are presented as odds ratio (OR) and 95% confidence interval (CI). Logistic regression analyses were performed to calculate adjusted OR for the association of allergic diseases or atopy with specific environmental factors. Multivariate models evaluating the effect of environmental factors on allergy outcomes were adjusted for predefined covariates, including sex, age, history of allergic disease (mother and father), income, environmental tobacco smoke and body mass index. A p value of <0.05 was considered significant.

Results

Population Characteristics

Demographic data and risk factors associated with allergic diseases in children living in 3 different environments (rural village, rural town and urban city) are presented in online suppl. table 1 (for all online suppl. material see www.karger.com/doi/10.1159/000330820). There

were clear differences between the 3 groups in terms of lifestyle factors. A history of parental allergic diseases was significantly more common in the urban and rural town groups. Subjects who lived in the rural village were more likely to have a dog or a cat and had more siblings. Breast-feeding was more common in the rural village than in the town or urban environment, as was helminth infection. High body mass index, birth by Cesarean section, antibiotic use during infancy and vaccinations were more common in the urban population.

Total IgE levels and eosinophil percentage were significantly higher in rural children. All 3 groups exhibited a normal distribution of total IgE (log total IgE, data not shown).

Allergic Diseases and Atopic Sensitization

Table 1 shows the prevalence of allergic diseases among rural village, rural town and urban children. The prevalence of asthma symptoms (based on a written questionnaire filled out by the parents) did not differ significantly among the 3 groups. Based on the video questionnaire by the subject, the lifetime prevalence of wheezing at rest and exercise-induced wheezing were lower in the rural village group than in the rural town and urban group. All symptoms of AR and atopic dermatitis (AD) were significantly higher in urban children compared to those from the other 2 environments.

Among rural village children, 35.5% were sensitized to one or more allergen, compared to 46.3% of the urban children. Among rural village children, 24.6% were sensitized to two or more allergens compared to 29.5% of the rural town children and 34.5% of the urban children.

Protective and Risk-Associated Rural Factors of Allergic Diseases

The results of multivariate logistic regression analysis of potential risk factors for allergic diseases and atopic sensitization are shown in online supplementary table 2. A doctor's diagnosis of asthma (based on answers in the written questionnaire) was significantly associated with having older siblings (OR 0.582, 95% CI 0.391–0.867) and antibiotic use during infancy (OR 1.928, 95% CI 1.262–2.945). A doctor's diagnosis of AR was associated with agricultural or livestock farming parents (OR 0.642, 95% CI 0.439–0.940), stable ownership (OR 0.565, 95% CI 0.330–0.96), pet ownership (OR 0.567, 95% CI 0.389–0.824), older siblings (OR 0.491, 95% CI 0.375–0.642) and antibiotic use during infancy (OR 1.535, 95% CI 1.139–2.069). Similarly, current AR was associated with agricultural or livestock farming parents, pet ownership, older siblings and antibiotic use during infancy. A doctor's diagnosis of AD was associated with farm animal contact during pregnancy (OR 0.217, 95% CI 0.050–0.941), stable ownership (OR 0.571, 95% CI 0.345–0.945) and antibiotic use during infancy (OR 1.597, 95% CI 1.193–2.136). Farm animal contact, older siblings and antibiotic use during infancy were associated with current AD. Atopic sensitization was associated with breast-feeding (OR 0.685, 95% CI 0.540–0.868) and older siblings (OR 0.691, 95% CI 0.545–0.877) (see also fig. 1).

Effects of Factors on Children in the Rural Village and Rural Town

The rural village of Jeongeup is located in the area outside Jeongeup city. We investigated the effects of certain risk factors on children in these two rural areas only. Table 2 shows the results of multivariate logistic regression analysis of potential risk factors for allergic diseases and atopic sensitization in the combined groups of rural village and rural town children. Having older siblings was related to a doctor's diagnosis of asthma (OR 0.478, 95% CI 0.282–0.809), a doctor's diagnosis of AR (OR 0.427, 95% CI 0.290–0.629), current AR (OR 0.435, 95% CI 0.277–0.683), a doctor's diagnosis of AD (OR 0.703, 95% CI 0.495–0.998) and atopic sensitization (OR 0.550, 95% CI 0.399–0.757). Antibiotic use during infancy was significantly associated with a doctor's diagnosis of asthma

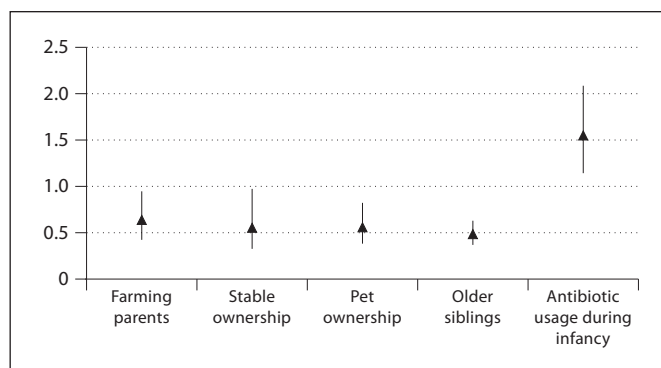


Fig. 1. Multivariate logistic regression analysis of potential risk factors (adjusted OR, 95% CI) for AR diagnosis, ever.

(OR 1.945, 95% CI 1.007–3.515), AR (OR 1.832, 95% CI 1.173–2.863) and AD (OR 2.021, 95% CI 1.343–3.040), current AR (OR 1.694, 95% CI 1.008–2.854) and current AD (OR 1.854, 95% CI 1.012–3.364). There was no protective effect due to agricultural or livestock farming parents, farm animal contact during pregnancy and stable ownership in the development of allergic diseases and atopy in these children.

Discussion

In an effort to identify potential protective factors for allergic diseases, we assessed differences in the prevalence of these diseases among rural village, rural town and urban schoolchildren in Korea. The results indicated that a rural village environment confers the greatest protection against allergic sensitization, wheezing symptoms (based on the video questionnaire), AR and AD. Differences in prevalence were also observed between rural town and urban children. Analysis of atopic sensitization attested to the impact of these associations. Overall, the current findings suggest that factors associated with a farm environment and a rural lifestyle may protect against the development of allergic diseases and atopy in Korean schoolchildren.

The prevalence of allergic diseases and atopic sensitization in East Asia has previously been addressed mainly through population-based studies [15–17]. The prevalence of allergic diseases specifically among rural children in Korea has not been reported. Studies done in East Asia, China and elsewhere may not be applicable to the farming population of Korea, where farming and the attendant lifestyle are most likely different. Furthermore,

Table 2. Multivariate logistic regression analysis of risk factors (adjusted¹ OR, 95% CI) for allergic diseases and atopy in rural village and rural town environments

	Asthma Symptom, ever (VQ) ²	Asthma diagnosis, ever	Current asthma ³	AR diagnosis, ever	Current AR	AD diagnosis, ever	Current AD	Atopy
Agricultural or livestock farming parents	1.240 (0.665–2.313)	0.847 (0.467–1.535)	0.757 (0.231–2.481)	0.800 (0.519–1.233)	0.693 (0.412–1.164)	0.910 (0.621–1.333)	1.100 (0.632–1.916)	0.940 (0.671–1.315)
Farm animal contact during pregnancy	1.593 (0.341–7.436)	0.672 (0.082–5.521)	–	0.293 (0.036–2.393)	0.409 (0.050–3.342)	0.339 (0.072–1.591)	0.464 (0.057–3.784)	1.073 (0.352–3.262)
Farm animal contact, now	1.243 (0.629–2.456)	1.100 (0.598–2.024)	1.366 (0.343–5.444)	0.909 (0.586–1.411)	0.802 (0.543–1.184)	1.184 (0.796–1.760)	2.086 (1.138–3.824)	1.367 (0.963–1.942)
Stable ownership	0.906 (0.389–2.109)	0.788 (0.358–1.731)	1.286 (0.339–4.875)	0.926 (0.531–1.615)	1.128 (0.614–2.074)	0.689 (0.405–1.172)	0.705 (0.319–1.555)	1.256 (0.816–1.933)
Pet ownership	1.330 (0.679–2.605)	0.703 (0.353–1.402)	0.314 (0.066–1.496)	0.679 (0.409–1.127)	0.726 (0.408–1.290)	1.115 (0.732–1.699)	0.894 (0.463–1.726)	1.059 (0.727–1.543)
Breast-feeding	1.073 (0.587–1.959)	0.717 (0.424–1.215)	1.434 (0.481–4.274)	0.890 (0.604–1.312)	0.902 (0.572–1.421)	0.942 (0.664–1.338)	1.013 (0.600–1.713)	0.722 (0.527–0.990)
Birth by Cesarean section	1.059 (0.556–2.014)	0.645 (0.349–1.191)	0.794 (0.263–2.397)	0.875 (0.568–1.435)	0.875 (0.533–1.435)	0.829 (0.698–1.212)	0.994 (0.574–1.723)	0.719 (0.580–1.016)
Older siblings	0.665 (0.366–1.211)	0.478 (0.282–0.809)	0.515 (0.184–1.400)	0.427 (0.290–0.629)	0.435 (0.277–0.683)	0.703 (0.495–0.998)	1.440 (0.819–2.531)	0.550 (0.399–0.757)
Antibiotic use during infancy	1.262 (0.585–2.724)	1.945 (1.007–3.515)	2.433 (0.808–7.323)	1.832 (1.173–2.863)	1.694 (1.008–2.854)	2.021 (1.343–3.040)	1.845 (1.012–3.364)	1.443 (0.974–2.140)
Helminth infection	0.816 (0.284–2.340)	2.003 (0.787–5.098)	9.062 (1.781–46.103)	1.380 (0.654–2.912)	1.368 (0.579–3.232)	1.286 (0.625–2.645)	1.230 (0.414–3.652)	1.086 (0.562–2.098)

¹ Adjusted for age, sex, parental income, parental history of allergic diseases, BMI and exposure to tobacco smoke. ² Lifetime prevalence of wheezing symptoms defined by video questionnaire (VQ). ³ Defined as having allergic symptoms within the last 12 months and a doctor's diagnosis of allergic disease.

potential protective factors such as older siblings and breast-feeding, as well as risk factors such as antibiotic use during infancy, have been identified in rural environments. This study is the first to compare urban and rural children in East Asia to determine whether associations predicted by the hygiene hypothesis hold true for allergic diseases and atopic sensitization.

Unlike AR and AD, there was no clear difference in the prevalence of asthma symptoms (assessed via written questionnaire) among urban and rural children. These results are in agreement with the results of other national children's studies within the framework of the ISAAC study [20, 21]. Cross-sectional studies conducted in Europe suggest a protective rural effect on asthma symptoms [22, 23], whereas a study performed in the USA indicated a protective urban effect [24]. Based on a video questionnaire (completed by the study subjects), the lifetime prevalence of wheezing and exercise-induced wheezing were significantly higher in urban schoolchildren.

Results from the ISAAC study have suggested that the video questionnaire may be more objective than the written questionnaire, even taking into account translation or interpretation problems [25]. Thus, our findings using the video questionnaire likely reflect the true prevalence of asthma in Korean children. In contrast to asthma, an increased prevalence of AR was consistently observed in urban children as compared to rural village and rural town children [13, 17].

One possible explanation for the lower prevalence of allergic diseases in rural areas might be a lack of awareness of symptoms, due to fewer opportunities to interact with a medical caregiver; thus, assessment of allergic sensitization and video questionnaires are important as objective markers of allergic diseases. The prevalence of allergic sensitization was 35.5% in the rural village, 38.8% in the rural town and 46.3% in the urban city. Our results are in line with earlier observations suggesting a lower prevalence of allergic sensitization, measured by SPT or

IgE levels, in rural subjects as compared to urban subjects [13, 26]. In contrast to allergic sensitization, total IgE levels were significantly higher in the rural town and rural village. These findings are in agreement with previous results [27]. At present, it is not clear why high levels of total IgE would correlate with a low prevalence of allergic sensitization in certain rural areas. We observed a higher prevalence of parasitic infection and cat ownership in the rural town and rural village environments, which suggests that differences between total IgE levels and sensitization to a specific allergen may be due in part to parasite and *Toxoplasma gondii* infection.

The results of this study confirm several well-known associations between suspected risk and protective factors and allergic outcomes, namely the increased risk associated with antibiotic use during infancy and the reduced risk associated with having older siblings, owning pets, breast-feeding and farming. We also confirmed the results of previous studies [28, 29] showing that having older siblings has a greater protective effect than younger siblings. Interestingly, farming-related factors do not appear to be protective against allergic diseases in rural village and rural town children. One possibility for this is that the questionnaire we used was not sufficient to accurately measure a farming background and its associated exposures. In addition, we cannot rule out possible exposure to livestock as a result of visiting and/or playing on a nearby farm. Alternatively, the reported protective effects of European farms may not extend to Korean children, as agricultural practices in Korea are likely to be very different from the European farm environment.

The specific farming-related factors that confer protection are not known, but several groups have suggested that exposure to livestock may be important [19, 30]. Furthermore, the farming environment is associated with higher exposure to bacterial endotoxins and other microbial products [6, 31]. However, certain findings suggest that there is a protective effect of 'rurality' that is not related to exposure to microbial products. The PARSIFAL study focused on 2 groups of children in which there is a lower prevalence of allergic diseases and sensitization: farm children [19, 32] and children in families with an anthroposophic lifestyle [33]. The anthroposophic way of life involves practices and customs that were common in the general population many decades ago, including a restrictive use of antibiotics, antipyretics and vaccinations, as well as certain dietary habits. Previous studies were unable to identify any single lifestyle factor as a primary factor in the lower prevalence of atopy in this population, because the behavioral characteristics of the anthroposophic lifestyle

were strongly correlated [33]. It is worth noting that the lifestyle of rural children in Korea is similar to the anthroposophic lifestyle. Therefore, a farm environment and to a lesser extent a rural lifestyle may confer protection against both allergic diseases and sensitization in childhood.

It is likely that there is no single factor in the farm and/or rural environment that prevents children from developing allergic diseases. Rather, protective effects are probably the result of complex interactions between various environmental and lifestyle factors. Alternatively, it may be that a more traditional lifestyle is more prevalent in rural communities, even those that are not farming based. Recently, it was shown that an urban diet is associated with an increased likelihood of a positive SPT [34].

In summary, the prevalence of allergic diseases and atopic sensitization is lower among rural village children than among rural town and urban children in Korea, suggesting that there are factors unique to the rural environment that may confer protective effects in these children. Our results also suggest that there are elements of the rural lifestyle as well as the farm environment that are associated with the development of allergic diseases. While these results do not demonstrate a causal relationship, they support moving forward with additional studies to identify specific protective mechanisms and risk factors. These include dietary and other environmental factors as well as the gene-environmental interactions associated with farming and a rural lifestyle that impact upon the development of allergic diseases.

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Table S1. Demographic data and risk factors for allergic diseases in children grouped according to living environment (rural village, rural town and urban area)

	Rural village	Rural town	Urban area	p-value
Number (%)	478	567	783	
Age (Year)	11.17±0.88	11.16±0.89	10.94±0.85	< 0.001
Sex (Male, %)	242(50.6%)	276(48.7%)	377(48.1%)	< 0.05
BMI*	18.97±3.21	18.76±3.29	19.38±3.30	0.003
Parental history of allergic diseases	85/466(18.2%)	111/545(20.4%)	202/614(32.9)%	< 0.001
Eosinophil (%)	3.85±2.92	3.73±2.73	3.40±2.51	0.015
Total IgE (IU/mL)	281.69±472.08	311.96±536.88	150.94±286.02	< 0.001
Number of allergen sensitization	159/448 (35.5%)	171/441 (38.8%)	286/618 (46.3%)	< 0.001
Economic state				< 0.001
Low	192(46.7%)	131(26.7%)	76(12.3%)	
Middle	208(50.6%)	315(64.3%)	475(76.7%)	
High	11(2.7%)	44(9.0%)	68(11.0%)	
Current dog owner	203/394(51.5%)	142/437(32.5%)	113/596(19.0%)	< 0.001
Current cat owner	39/368(10.6%)	25/409(6.1%)	26(4.5%)	0.001
Older siblings	311/471(66%)	324/554(58.5%)	353/753(46.9%)	< 0.001
Younger siblings	234/469(49.9%)	247/554(44.6%)	296/761(38.9%)	0.001
Birth by Cesarean section	131/446(29.4%)	159/509(31.2%)	248/663(37.4%)	0.010
Breast feeding	295/448(65.8%)	295/517(57.1%)	366/664(55.1%)	0.001

ETS exposure	246/447(55%)	230/505(45.5%)	250/650(38.5%)	< 0.001
Antibiotic use during infancy	56/436(12.8%)	113/508(22.2%)	206/667(30.9%)	< 0.001
Helminth infection	31/346(9.0%)	30/421(7.1%)	27/568(4.8%)	0.011
Routine vaccination	376/445(84.5%)	439/516(85.1%)	616/667(92.4%)	0.016
Agricultural or livestock farming parents	207/445(46.5%)	79/507(15.6%)	22/634(3.5%)	< 0.001
Agricultural or livestock farming mother (during pregnancy)	51/444(11.7%)	17/514(3.3%)	8/661(1.2%)	< 0.001
Consumption of whole milk	12/429(2.9%)	7/503(1.4%)	11/640(1.7%)	0.233
Farm animal contact				
Pregnancy	56/303(18.5%)	25/364(6.9%)	23/514(4.5%)	< 0.001
Aged < 1 yr	75/467(16.1%)	20/545(3.7%)	2/656(0.3%)	< 0.001
Current	74/467(15.8%)	20/545(2.8%)	3/656(0.5%)	< 0.001

Values represent the means $\pm$ SD or n (%)

Statistical analysis was performed using the chi-square test

BMI, body mass index; ETS, environmental tobacco smoking

Table S2. Multivariate logistic regression analysis of risk factors (adjusted* odds ratio, 95% CI) for allergic diseases and atopy

	Asthma symptom ever (VQ) †	Asthma diagnosis, ever	Current asthma‡	Allergic rhinitis diagnosis ever	Current allergic rhinitis	Atopic dermatitis diagnosis ever	Current atopic dermatitis	Atopy
Agricultural or livestock farming parents	1.031 (0.604-1.759)	0.834 (0.490-1.420)	0.572 (0.190-1.728)	0.642 (0.439-0.940)	0.582 (0.368-0.920)	0.783 (0.555-1.105)	0.878 (0.542-1.424)	0.910 (0.672-1.233)
Farm animal contact during pregnancy	0.896 (0.205-3.921)	0.394 (0.051-3.066)	-	0.553 (0.178-1.714)	0.388 (0.085-1.768)	0.217 (0.050-0.941)	0.279 (0.037-2.127)	0.828 (0.332-2.063)
Farm animal contact, current	1.363 (0.826-2.251)	0.836 (0.506-1.380)	0.582 (0.186-1.824)	0.855 (0.614-1.190)	0.802 (0.543-1.184)	1.182 (0.867-1.611)	1.767 (1.151-2.713)	1.280 (0.962-1.703)
Stable ownership	0.879 (0.410-1.884)	0.835 (0.405-1.720)	1.187 (0.337-4.174)	0.565 (0.330-0.965)	0.712 (0.397-1.277)	0.571 (0.345-0.945)	0.542 (0.256-1.150)	1.028 (0.685-1.545)
Pet ownership	1.227 (0.735-2.050)	0.768 (0.447-1.319)	0.740 (0.275-1.988)	0.567 (0.389-0.824)	0.567 (0.366-0.877)	0.971 (0.698-1.351)	0.784 (0.475-1.295)	0.925 (0.682-1.253)
Breast milk feeding	0.792 (0.523-1.201)	0.722 (0.487-1.070)	1.513 (0.670-3.416)	0.904 (0.691-1.183)	0.930 (0.680-1.273)	0.913 (0.706-1.181)	1.063 (0.734-1.539)	0.685 (0.540-0.868)

Birth by Cesarian section	1.160 (0.749- 1.797)	0.845 (0.552- 1.294)	0.951 (0.425- 2.218)	1.121 (0.846- 1.485)	1.074 (0.771- 1.496)	0.918 (0.698- 1.206)	0.941 (0.639- 1.385)	1.092 (0.850- 1.402)
Older siblings	0.714 (0.469- 1.087)	0.582 (0.391- 0.867)	0.643 (0.295- 1.403)	0.491 (0.375- 0.642)	0.556 (0.407- 0.761)	0.812 (0.627- 1.052)	1.539 (1.042- 2.273)	0.691 (0.545- 0.877)
Antibiotic use during infancy	1.221 (0.748- 1.994)	1.928 (1.262- 2.945)	1.824 (0.794- 4.189)	1.535 (1.139- 2.069)	1.727 (1.231- 2.431)	1.597 (1.193- 2.136)	1.585 (1.057- 2.379)	1.231 (0.931- 1.631)
Helminth infection	0.816 (0.284- 2.340)	1.355 (0.558- 3.295)	3.357 (0.869- 12.964)	1.169 (0.637- 2.145)	1.442 (0.745- 2.793)	0.761 (0.395- 1.464)	0.577 (0.203- 1.639)	1.222 (0.702- 2.216)

* Adjusted for age, sex, parental income, parental history of allergic diseases, BMI, and exposure to tobacco smoke.

† Lifetime prevalence of wheezing symptoms defined by video questionnaire (VQ)

‡ Defined as having allergic symptoms within the last 12 months and doctor diagnosis of allergic disease