

Very Low Prevalence of Asthma and Allergies in Schoolchildren From Rural Beijing, China

Yu Ma, MD,¹ Jing Zhao, MD,¹ Z.R. Han, MD,¹ Yuzhi Chen, MD,¹ Ting F. Leung, MD,² and Gary W.K. Wong, MD^{2*}

Summary. Background: The prevalence of asthma is relatively low in the Chinese population. There is consistent evidence that growing up on a farm is associated with protection against the subsequent development of asthma. Objective: To compare the prevalence of asthma in schoolchildren from urban and rural China and to assess the possible protection associated with agricultural and livestock farming. Methods: Random samples of schoolchildren aged 13–14 years from urban Beijing and rural area around Beijing were studied using the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III protocol. Subjects were studied by questionnaires ($n = 7,077$) and skin-prick tests ($n = 2,126$). Results: The prevalence rates of wheeze in the past year and physicians' diagnosis of asthma were 1.0% and 1.1% in the rural area, and these were significantly lower than 7.2% and 6.3% found in the urban children ($P < 0.0001$). For the video questionnaire, only 0.3% of rural children reported wheeze in the past year compared with 3.1% in urban children ($P < 0.0001$). Atopy was 3.22 times higher in urban children compared with rural children ($P < 0.0001$). For rural schoolchildren, 1,453 (41%) have always been living on agricultural farms since birth and the prevalence rates of their asthma symptoms and atopic sensitization were not significantly different from those who have exposed to livestock farming. Conclusion: Using the same validated ISAAC questionnaire and objective skin-prick tests, the prevalence rates of asthma and atopic sensitization in rural Chinese children were significantly lower than urban children. Exposure to agricultural farming conferred the same protection as livestock farming. **Pediatr Pulmonol.** © 2009 Wiley-Liss, Inc.

Key words: asthma; allergies; rural; children; Chinese.

INTRODUCTION

Asthma has become one of the most common chronic childhood disorders in developed countries. Many studies from around the world have documented increasing prevalence of asthma and related atopic disorders.^{1–5} Such increase is most likely due to environmental changes resulting in manifestations of the disease in genetically susceptible individuals. There have also been a few recent reports showing a plateau or even a decline in the trend of asthma prevalence.^{6–8} In the last decade, studies in Europe, American, and Australia suggest that living on a farm is associated with protection against the subsequent development of atopic diseases.^{9–16} The exact reasons explaining such protection remain unclear. Studies from central Europe have provided further evidence that exposure to microbes or their components might modify the immune system leading to a reduction of the risk in developing asthma and allergies.^{11,15} As documented by the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence rates of asthma and

allergies are relatively lower in Chinese children.^{17,18} In ISAAC Phase I, the 12-month prevalence rate of wheeze in 13–14 schoolchildren in Beijing city was only 3.3% as identified by the ISAAC video questionnaire.¹⁸ Many regions in China are undergoing rapid urbanization.

¹Capital Institute of Pediatrics, Beijing, China.

²Department of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China.

Grant sponsor: Hong Kong Research Grant Council; Grant number: CUHK4512/06M.

*Correspondence to: Dr. Gary W.K. Wong, MD, Department of Pediatrics, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region, China. E-mail: wingkinwong@cuhk.edu.hk

Received 15 March 2009; Revised 26 April 2009; Accepted 27 April 2009.

DOI 10.1002/ppul.21061

Published online in Wiley InterScience
(www.interscience.wiley.com).

However, over 90% of its population is still living in rural areas and there has not been any comparative asthma epidemiology study of children from urban and rural China.

Beijing city was one of the participating centers in the Phase I study of ISAAC. Around the Beijing city, there are rural communities engaging in various forms of farming activities including agricultural and livestock farming. The common livestock being raised in these nearby farms includes poultry, sheep, pigs, and cows. Corn, Chinese herbal plants, and different types of vegetables and fruits such as peach are the common types of crops being grown. In order to determine whether living in rural China may protect children from developing asthma and allergies, a cross-sectional study of secondary schoolchildren aged 13–14 years from both urban and rural Beijing using the ISAAC Phase III protocol was performed in 2003–2004. The results were compared with those in Phase I using the identical ISAAC Core questionnaires performed in 1994–1995.¹⁸ Schoolchildren from the rural Tongzhou district were recruited for comparison. Tongzhou district is a rural area approximately 70 km east of Beijing. Almost all the farms in this area are small-scaled and family-owned. We determine whether the farming environment or the types of farming activities have protection against asthma and allergies when compared with children from urban area.

METHODS

Study Population

Schoolchildren aged 13–14 years were targeted for this study following the ISAAC Phase III protocol.¹⁹ In participating schools, 2 school years (second and third year of high school) with the highest proportion of children aged 13–14 years were recruited for this study. All schoolchildren in the classes of the respective school years were invited. The urban area is the Chaoyang district located on the east side of Beijing city. Children participated in the ISAAC Phase I were also recruited from this district. There were a total of 87 and 46 high schools from the urban (Chaoyang) and rural (Tongzhou) districts with approximately 30,000 and 16,000 children of the target range in the two districts, respectively. Similar to Phase I, schools were individually allocated a number, and by computer randomization, a minimum of 10 schools were recruited from each district. Eleven schools from the urban district participated in the study and were able to provide 3,609 schoolchildren of the target age as potential subjects. Ten schools from the rural area were recruited with 3,568 potential subjects. Informed consent was obtained from parents or guardians before the study. A total of 3,531 and 3,546 from the urban and rural areas agreed to participate, representing an overall response rate of 98%.

Questionnaire

Each subject was given an ISAAC Phase III written questionnaire to complete, followed by video questionnaire at the same session in school. The written questionnaire was translated into Chinese following the ISAAC protocol as described previously.¹⁷ “Current” symptoms referred to symptoms in the past 12 months; “asthma ever” was defined as having been diagnosed with asthma by a physician in the subjects’ lifetime; “rhino-conjunctivitis” was defined as sneezing or having a runny nose or blocked nose accompanied by itchy-watery eyes when the subject did not have an upper respiratory tract infection; “flexural eczema” was defined as an itchy rash which was coming and going for at least 6 months affecting the folds of elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes. The ISAAC video questionnaire has five scenes showing young persons of different races with wheezing at rest, wheeze after exercise, night waking with wheeze, night waking with cough, and severe asthma attack. In addition, a parental questionnaire was added to determine the timing and types of farming activities of the families during different periods of early life of the children and these periods are: under 1 year of age, 1–5 years, >5 years, and the current farming activities.

Skin-Prick Test

A random sample of four schools from both the rural and urban areas was invited for skin-prick testing. In the urban district, the four schools were able to provide 1,145 students in the target age group and 999 subjects agreed to participate representing a response rate of 87%. In the four schools from the rural district with a total of 1,264 target subjects, 1,127 agreed to be tested (89%). The sensitivity to eight common aeroallergens in the locality was assessed as described previously.¹⁷ These allergens are *Dermaphagoides pteronyssinus*, *D. farinae*, cat, mixed tree pollen, mixed grass pollen, American cockroach, German cockroach, and mixed moulds. Standardized allergen extracts and control solutions were obtained from ALK (Hørsholm, Denmark). Histamine (10 mg/ml) and diluent were used as positive and negative control. A drop of each allergen extract was brought into the skin of the volar side of the left forearm using ALK lancets. After 15 min, the weal reaction was measured as the mean of the longest diameter and the length of the perpendicular line through its middle. A weal size ≥ 3 mm after subtraction of the negative control is considered positive. Subjects with one or more positive reactions were considered atopic.

The study protocol was approved by the Clinical Research Ethics Committees of the Chinese University of Hong Kong and Capital Institute of Pediatrics. Written informed consent was obtained from the children’s parents or legal guardians.

Analysis of Data

All data were entered into a computer using double data entry by two independent persons. Data were categorized and analyzed using Statistical Package for Social Sciences (SPSS) version 14.0 (SPSS, Inc.; Chicago, IL). 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 ratios (ORs) and 95% confidence intervals (95% CIs) where appropriate. *P* values less than 0.05 were considered significant.

RESULTS

The age and sex distribution of participating children in Phase I, Phase III urban and rural regions are similar as shown in Table 1. The response rates were excellent varying from 98% to 99%. Table 2 shows the responses to various questions on asthma and atopic symptoms in the urban district of the two surveys, Phase I and III. In a span of 8 years between Phase I and Phase III, there has not been any significant increase in the prevalence of physicians' diagnosis of asthma (6.9% vs. 6.3%). The prevalence of wheeze in the past year was reported to have increased significantly from 5.1% to 7.2% by the written questionnaire only ($P < 0.01$). In addition, there was also a significant increase in the prevalence rate of symptoms of rhinoconjunctivitis (8.5% and 10.3%, $P < 0.01$). For the results of the video questionnaires, the prevalence rates of various symptoms remained unchanged except for an increase in exercise-induced wheeze in the past year.

Table 3 shows the comparison of responses between schoolchildren recruited from the urban and rural regions in Phase III. All asthma and atopic symptoms were significantly higher in schoolchildren from the urban district. The prevalence of physician diagnosis of asthma was sixfold higher in children from the urban area. Furthermore, there were 7- and 10-fold differences in the prevalence of current wheeze as documented by the written and video questionnaires. Current symptoms of rhinoconjunctivitis and flexural eczema were 10.3% and

1.2% in urban children compared with 3.3% and 0.5% in rural children ($P < 0.0001$). Table 4 shows the comparison of prevalence of atopic sensitization between urban and rural subjects. Atopy as defined as having at least one positive skin-prick test was significantly higher in urban children than rural children (OR 3.22; $P < 0.0001$). Depending on the allergen, the ORs of being sensitized were 2.8 to almost ninefold higher in urban children when compared with rural children.

Among the subjects recruited from the rural area, only 21 (0.6%) children reported that they have never lived on a farm and 1,453 children (41%) reported that they have always been living on agricultural farms since birth. Among these 1,453 children, 338 underwent skin-prick testing. A total of 2,072 subjects have been exposed to livestock farming and 1,699 (82%) have been exposed in the first year of life. Of these 2072 subjects, 789 underwent skin-prick testing. Table 5 shows the comparison of atopic symptoms and atopic sensitization between children who have always been living on agricultural farms and those who have been exposed to livestock farming. The prevalence of atopic symptoms, asthma diagnosis, and atopic sensitization were not significantly different between these two groups of children.

DISCUSSION

The present study was the first comparative study of urban and rural Chinese schoolchildren using the same standardized ISAAC protocol including both written and video questionnaires. Validation studies of the Chinese version of the ISAAC questionnaire have been performed in Chinese schoolchildren.^{20,21} Both written and video questionnaires were found to have similar sensitivity and specificity in predicting asthma-associated BHR. Having a physician diagnostic label of asthma had a sensitivity of 0.88 and specificity of 0.90 in predicting asthma-associated BHR.^{20,21} Our results demonstrated a markedly lower prevalence of asthma and wheeze in rural children when compared with urban children. The prevalence of current wheeze in rural schoolchildren was only 0.3% as documented by the video questionnaire and this rate is among the lowest reported in the world.^{22,23} Furthermore, the prevalence of asthma and allergies was similar among children who have always been on agricultural farms when compared with children who have been exposed to livestock farming. Such protection was also confirmed by objective skin-prick testing (Tables 4 and 5). In the urban area, our results did not demonstrate any consistent increase of asthma symptoms between Phase I and Phase III (Table 2).

In the past decade, there have been many reports suggesting the protective role of farming environment against the development of asthma and related atopic conditions.^{9–15} Braun-Fahrlander et al.⁹ first reported a

TABLE 1—Demographic Data of Recruited Subjects in ISAAC Phase I and Phase III

	Phase I urban	Phase III urban	Phase III rural
N	4,167	3,531	3,546
Sex, N (%)			
Boys	2,088 (50.1)	1,820 (51.5)	1,807 (50.9)
Girls	2,079 (49.9)	1,711 (48.5)	1,739 (49.1)
Age (years)			
Mean	14.3	14.0	14.2
Median	14.2	13.9	14.2
SD	0.8	0.8	0.7
Response rate (%)	99	98	99

TABLE 2—Responses to Written and Video Questionnaires: Comparison of Two Surveys in Urban Beijing (Chaoyang District)

	Phase I		Phase III		<i>P</i>
	%	95% CI	%	95% CI	
Written questionnaire					
Wheeze ever	9.2	8.4–10.1	12.4	11.3–13.5	<0.01
Current wheeze	5.1	4.4–5.8	7.2	6.4–8.0	<0.01
Current speech limiting wheeze	0.9	0.7–1.3	1.0	0.7–1.4	NS
Current exercise induced wheeze	25.2	23.9–26.6	25.6	24.1–27.0	NS
Asthma ever	6.9	6.2–7.7	6.3	5.6–7.2	NS
Current rhinoconjunctivitis	8.5	7.7–9.4	10.3	9.3–11.4	<0.01
Current flexural eczema	2.3	1.8–2.8	1.2	0.9–1.7	<0.01
Video questionnaire: current symptoms					
Wheeze at rest	3.3	2.8–3.9	3.1	2.5–3.7	NS
Wheeze after exercise	4.7	4.0–5.4	6.2	5.4–7.0	<0.01
Night waking with wheeze	0.7	0.4–0.9	—	—	—
Night waking with cough	6.8	6.1–7.6	6.3	5.5–7.1	NS
Severe asthma attack	1.4	1.0–1.8	1.6	1.3–2.1	NS

NS, not significant; 95% CI, 95% confidence interval.

study of 1,620 Swiss children showing farming as a parental occupation was significantly associated with lower rates of symptoms of allergic rhinitis and atopic sensitization. This finding of such possible protection has been replicated in other countries including Germany, Austria, Australia, Canada, and Finland.^{10–14} In these urban–rural comparative studies, there is always a possibility of the so-called “healthy farmer effect” that people with allergies might have moved away from the farms to work in the urban areas. This might result in higher prevalence of asthma and allergies in subjects recruited from the urban areas. We have not enquired about possible migration in our sample of urban children.

However, previous similar study showed that less than 5% schoolchildren recruited from urban Beijing were born in rural areas and migrated to the city.¹⁷ Such low percentage of migration is unlikely to introduce any significant bias in our results.

The exact farming-related factors conferring protection are still unclear but several have suggested that exposure to livestock may be an important factor.^{9,11} Furthermore, the farming environment is associated with higher exposure to bacterial endotoxin and other microbial products.^{24–26} A large cross-sectional study of schoolchildren from Germany, Switzerland, and Austria has documented an inverse relationship of the levels of

TABLE 3—Prevalence of Asthmatic Symptoms and Atopic Sensitization in Schoolchildren: Comparison of Urban and Rural Beijing (Phase III)

	Urban Chaoyang, n = 3,531		Rural Tongzhou, n = 3,546		OR	<i>P</i>
	%	95% CI	%	95% CI		
Written questionnaire						
Wheeze ever	12.4	11.3–13.5	4.5	3.8–5.2	3.03	<0.0001
Current wheeze	7.2	6.4–8.0	1.0	0.7–1.4	7.53	<0.0001
Current exercise induced wheeze	25.6	24.1–27.0	12.5	11.4–13.6	2.42	<0.0001
Asthma ever	6.3	5.6–7.2	1.1	0.8–1.5	6.09	<0.0001
Current rhinoconjunctivitis	10.3	9.3–11.4	3.3	2.8–4.0	3.34	<0.0001
Current flexural eczema	1.2	0.9–1.7	0.5	0.3–0.7	2.78	<0.0001
Video questionnaire: current symptoms						
Wheeze at rest	3.1	2.5–3.7	0.3	0.2–0.5	10.2	<0.0001
Exercise induced wheeze	6.2	5.4–7.0	1.4	1.1–1.9	4.51	<0.0001
Night waking with wheeze	0	—	0	—	—	—
Night waking with cough	6.3	5.5–7.1	1.2	0.9–1.6	5.57	<0.0001
Severe asthma attack	1.6	1.3–2.1	0.1	0.0–0.2	14.8	<0.0001
Skin-prick test						
Atopy, ≥1 positive skin test	36.5	33.5–39.6	11.4	9.6–13.3	3.22	<0.0001

OR, odds ratio.

TABLE 4—Atopy and Allergic Sensitization: Comparison of Subjects From Urban and Rural Areas (Phase III)

Allergen	Urban Chaoyang (n = 999)		Rural Tongzhou (n = 1,127)		OR	P
	%	95% CI	%	95% CI		
Atopy, ≥ 1 positive skin test	36.5	33.5–39.6	11.4	9.6–13.3	3.22	<0.0001
<i>D. pteronyssinus</i>	16.9	14.6–19.3	2.7	1.8–3.8	6.36	<0.0001
<i>D. farinae</i>	20.4	17.9–23.0	3.7	2.7–5.0	5.48	<0.0001
Cat	10.8	9.0–12.9	1.2	0.6–2.1	8.70	<0.0001
German cockroach	11.0	9.1–13.1	3.8	2.8–5.0	2.89	<0.0001
American cockroach	8.3	6.7–10.2	2.9	2.0–4.1	2.84	<0.0001
Mixed tree	4.0	2.9–5.4	0.5	0.2–1.2	7.52	<0.0001
Mixed grass	3.9	2.8–5.3	0.5	0.2–1.2	7.33	<0.0001
Mixed moulds	3.1	2.1–4.4	0.5	0.2–1.2	6.81	<0.0001

endotoxin and the prevalence of hay fever, atopic asthma, and atopic sensitization.^{24,26} In addition, stimulated cytokines production of peripheral blood lymphocytes such as interleukin-10 showed an inverse relationship with endotoxin level in the dust samples obtained from the subjects' home.²⁴ Therefore, high endotoxin exposure in early life may modulate the immune system and reduce the subsequent development of atopic disorders such as allergic asthma.

Consumption of farm milk or unpasteurized milk has also been implicated as one of the protective factors.^{11,26,27} Riedler et al.²⁶ evaluated the relationship of consumption of farm milk and allergies in schoolchildren from the ALEX study. Consumption of unpasteurized farm milk in the first year of life was associated with a reduced prevalence of atopic sensitization (OR, 0.43; 95% CI, 0.24–0.77) and wheeze attack in past year (OR, 0.43;

95% CI, 0.20–0.92). There was no protective effect for farm milk consumption beyond the first year of life. A recent study from England also documented that consumption of unpasteurized milk was associated with reduction of atopy, lower total IgE, and higher production of interferon- γ .²⁷ However, exposure to livestock farming and consumption of farm milk are not the likely explanations for the very low prevalence of asthma and allergies in rural Beijing. Our results showed that children who have been exposed to livestock farming ever since a very young age have similar prevalence of asthma symptoms when compared with children who have always been exposed to agricultural farming. The prevalence rates of objective marker of atopy, skin-prick sensitization, were also similar in the two groups. Furthermore, none of the subjects from the rural area gave a history of consumption of unpasteurized farm milk. In addition to

TABLE 5—Prevalence of Symptoms and Atopic Sensitization in Rural Subject: Comparison of Children From Agricultural and Livestock Farming Background

	Agricultural farming (n = 1,453)		Livestock farming (n = 2,072)		P
	%	95% CI	%	95% CI	
Written questionnaire					
Current wheeze	1.2	0.7–1.9	2.0	1.3–2.7	0.55
Current rhinoconjunctivitis	2.7	1.9–3.7	3.7	2.7–4.7	0.09
Current flexural eczema	0.4	0.2–0.9	0.5	0.2–0.9	0.98
Asthma ever	1.2	0.7–1.9	1.1	0.7–1.6	0.86
Video questionnaire: current symptoms ¹					
Wheeze at rest	0.2	0.04–0.06	0.3	0.1–0.7	0.69
Exercise induced wheeze	1.3	0.7–2.0	1.4	0.9–1.9	0.96
Atopic sensitization ²					
Number of subjects tested		338		789	
Atopy, ≥ 1 positive skin test	9.8	6.8–12.8	12.0	9.8–14.5	0.28
<i>D. pteronyssinus</i>	2.7	1.2–5.0	2.7	1.6–4.0	0.99
<i>D. farinae</i>	3.0	1.4–5.4	4.1	2.7–5.6	0.47
Cat	1.5	0.5–3.4	1.1	0.5–2.2	0.86
German cockroach	3.3	1.6–5.0	4.1	2.7–5.6	0.63
American cockroach	2.7	1.2–5.0	3.1	1.9–4.4	0.88

¹Prevalence of other symptoms.

²Sensitization to other allergens tested were very low (data not shown) and not significantly different between the two groups.

investigations of the possible protective role of exposure to bacteria, recent studies have shown that exposure to fungal products and grass pollens may also be important in explaining the protective farming effect.^{15,28,29} Another recent study comparing schoolchildren from Russia and Finland suggested that exposure to high microbial load via drinking water may be a potential protective factor for asthma and atopy.³⁰ As the majority of our subjects (82%) with exposure to livestock farming occurred in the first year of life, our study did not have enough power to determine effect of timing of exposure on the subsequent development of asthma and allergies. Furthermore, we cannot rule out possible exposure to livestock in those children from agricultural farms as they might have visited and played in their neighbors' farm periodically. Our previous study of urban Chinese schoolchildren revealed that frequent consumption of fruits and raw vegetables was one of the factors explaining the disparity of asthma prevalence between Hong Kong and mainland China.³¹ Ongoing studies of various environmental and dietary factors are underway to investigate the possible environmental exposures which may explain the markedly lower prevalence of asthma and allergies in rural China.

In conclusion, using a standardized and validated study protocol, we have documented an extremely low prevalence of asthma and wheeze in rural China and such protective effect was found in children exposed to both agricultural and livestock farming. Additional protective factors other than exposure to microbes via contact with livestock or consumption of farm milk are likely to be important in rural China. Further studies are needed to evaluate the possible protective factors that may explain the farming effect on the development of asthma and allergies.

ACKNOWLEDGMENTS

The authors wish to thank the children, parents and staff of the schools for their participation in the survey.

REFERENCES

1. Leung R, Wong GW, Lau J, Ho A, Chan JK, Choy D, Douglass C, Lai CK. Prevalence of asthma and allergy in Hong Kong schoolchildren: an ISAAC study. *Eur Respir J* 1997;10:354–360.
2. Downs SH, Marks GB, Sporik R, Belosouva EG, Car NG, Peat JK. Continued increase in the prevalence of asthma and atopy. *Arch Dis Child* 2001;84:20–23.
3. Burney P. The changing prevalence of asthma? *Thorax* 2002;57:II36–II39.
4. Toelle BG, Ng K, Belousova E, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *BMJ* 2004;328:386–387.
5. Lai CK, Douglass C, Ho SS, Chan J, Lau J, Wong GW, Leung R. Asthma epidemiology in the Far East. *Clin Exp Allergy* 1996; 26:5–12.
6. Anderson HR, Ruggles R, Strachan DP, Austin JB, Burr M, Jeffs D, Stranding P, Steriu A, Goulding R. Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey. *BMJ* 2004;328:1052–1053.
7. Ronchetti R, Villa MP, Barreto M, Rota R, Pagani J, Martella S, Falasca C, Paggi B, Guglielmi F, Ciofetta G. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. *Eur Respir J* 2001;17:881–886.
8. Wong GW, Leung TF, Ko FW, Lee KK, Lam P, Hui DS, Fok TF, Lai CK. Declining asthma prevalence in Hong Kong Chinese schoolchildren. *Clin Exp Allergy* 2004;34:1550–1555.
9. Braun-Fahrlander C, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, Vuille JC, Wuthrich B. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. *Clin Exp Allergy* 1999;29:28–34.
10. Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. *Am J Respir Crit Care Med* 2000;161:1563–1566.
11. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000;30:187–193.
12. Downs SH, Marks GB, Mitakakis TZ, L  ppli JD, Car NG, Peat JK. Having lived on a farm and protection against allergic diseases in Australia. *Clin Exp Allergy* 2001;31:570–575.
13. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000;30:194–200.
14. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. *Clin Exp Allergy* 2000;30:201–208.
15. Schram-Bijkerk D, Doekes G, Douwes J, Boeve M, Riedler J, Ublagger E, von Mutius E, Benz MR, Pershagen G, van Hage M, Scheynius A, Braun-Fahrlander C, Waser M, Brunekreef B, PARSIFAL Study Group. Bacterial and fungal agents in house dust and wheeze in children: the PARSIFAL study. *Clin Exp Allergy* 2005;35:1272–1278.
16. Wong GW, Chow CM. Childhood asthma epidemiology: insights from comparative studies of rural and urban populations. *Pediatr Pulmonol* 2008;43:107–116.
17. Wong GW, Hui DS, Chan HH, Fok TF, Leung R, Zhong NS, Chen YZ, Lai CK. Prevalence of respiratory and atopic disorders in Chinese schoolchildren. *Clin Exp Allergy* 2001;31:1225–1231.
18. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;12:315–335.
19. ISAAC Steering Committee. Phase Three manual of the International Study of Asthma and Allergies in Childhood (ISAAC). Auckland: ISAAC; 2000.
20. Lai CK, Chan JK, Chan A, Wong GW, Ho A, Choy D, Lau J, Leung R. Comparison of the ISAAC video questionnaire (AVQ3.0) with the ISAAC written questionnaire for estimating asthma associated with bronchial hyperreactivity. *Clin Exp Allergy* 1997;27:540–545.
21. Wong GW, Li ST, Hui DS, Fok TF, Zhong NS, Chen YZ, Lai CK. Individual allergens as risk factors for asthma and bronchial hyperresponsiveness in Chinese children. *Eur Respir J* 2002;19: 288–293.
22. Asher MI, Montefort S, Bj  rkst  n B, Lai CK, Strachan DP, Weiland SK, Williams H, ISAAC Phase Three Study Group.

- Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
23. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C, the ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007;62:758–766.
24. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A, Lauener RP, Schierl R, Renz H, Nowak D, von Mutius E. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–877.
25. Gehring U, Strikwold M, Schram-Bijkerk D, Weinmayr G, Genuneit J, Nagel G, Wickens K, Siebers R, Crane J, Doekes G, Di Domenicantonio R, Nilsson L, Priftanji A, Sandin A, El-Sharif N, Strachan D, van Hage M, von Mutius E, Brunekreef B, ISAAC Phase Two Study Group. Asthma and allergic symptoms in relation to house dust endotoxin: Phase Two of the International Study on Asthma and Allergies in Childhood (ISAAC II). *Clin Exp Allergy* 2008;38:1911–1920.
26. Riedler J, Braun-Fahrlander CH, Eder W, Schreuer M. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;358:1129–1133.
27. Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? *J Allergy Clin Immunol* 2006;117:1374–1381.
28. Eduard W, Douwes J, Omenaas E, Heederik D. Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers. *Thorax* 2004;59:381–386.
29. Douwes J, van Strien R, Doekes G, Smit J, Kerkhof M, Gerritsen J, Postma D, de Jongste J, Travier N, Brunekreef B. Does early indoor microbial exposure reduce the risk of asthma? The Prevention and Incidence of Asthma and Mite Allergy birth cohort study. *J Allergy Clin Immunol* 2006;117:1067–1073.
30. von Hertzen L, Laatikainen T, Pitkanen T, Vlasoff T, Mäkelä MJ, Vartiainen E, Haahtela T. Microbial content of drinking water in Finnish and Russian Karelia—implications for atopy prevalence. *Allergy* 2007;62:288–292.
31. Wong GW, Ko FW, Hui DS, Fok TF, Carr D, von Mutius E, Zhong NS, Chen YZ, Lai CK. Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey. *BMJ* 2004;329:486–488.