

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Poultry exposure and environmental protection against asthma in rural children

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Abstract

Background: Asthma is one of the most common chronic diseases in childhood, and the prevalence has been increasing over the past few decades. One of the most consistent epidemiological findings is that children living in a farming or rural environment are protected from development of asthma and allergies, but the protective factors in rural China are not clear.

Methods: A community-based, cross-sectional epidemiological study was performed in a total of 17,587 children aged 5–8 years, 3435 from Hong Kong (urban) and 14,152 from Conghua (rural county in southern China). Asthma and allergic symptoms as well as environmental exposures were ascertained by using a standardized and validated questionnaire.

Results: The prevalence of current wheeze was significantly lower in rural Conghua than that of urban Hong Kong (1.7% vs. 7.7%, $p < 0.001$). A lower rate of asthma ever was also reported in rural children compared with their urban counterparts (2.5% vs. 5.3%, $p < 0.001$). After adjusting for confounding factors, exposure to agricultural farming (adjusted odds ratio 0.74, 95% confidence interval: 0.56–0.97) and poultry (0.75, 0.59–0.96) were the most important factors associated with the asthma-protective effect in the rural area. Further propensity score-adjusted analysis indicated that such protection conferred by living in the rural environment was mainly attributable to poultry exposure.

Conclusions: We confirmed that the prevalence of asthma and atopic disorders was significantly lower in rural children when compared with their urban peers. Exposure

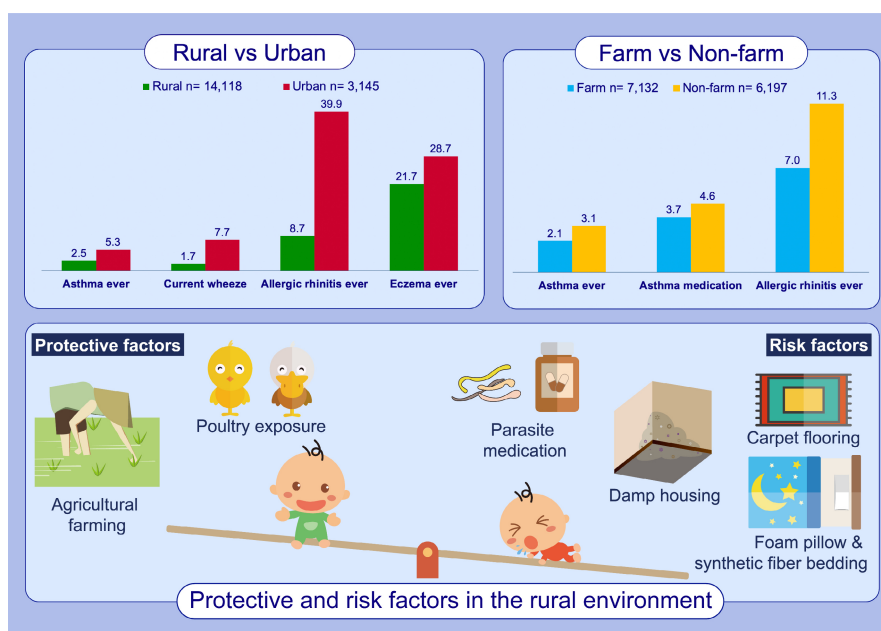
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to poultry and agricultural farming are the most important factors associated with asthma protection in the rural area.

KEYWORDS

asthma, environmental protection, poultry exposure, rural, urban



GRAPHICAL ABSTRACT

The prevalence of asthma and related atopic disorders was significantly lower in rural children when compared with their urban counterparts. Farm living provided further protection against asthma among rural children. Poultry exposure was the most important factor associated with asthma protection conferred by living in the rural area.

1 | INTRODUCTION

Asthma is one of the most common chronic diseases in childhood, and the prevalence of asthma has been increasing significantly over the past few decades.^{1,2} Although the exact causes of asthma remain largely unknown, the disease has been associated with affluence and urbanization.^{3,4} One of the most consistent findings of epidemiological studies conducted in different regions of the world is that children growing up on traditional farms are protected from the development of asthma and related allergies in line with the hygiene hypothesis.⁵⁻¹² Studies in Alpine regions demonstrated the strong protective effects of exposure to farm animals and consumption of farm milk against the development of asthma.⁵⁻⁸ The importance of the environment was lent further support by comparative studies of two U.S. farming populations originated from Germany/Switzerland, the Amish and the Hutterites, who share highly similar genetic background. However, the Amish retains the traditional farming practice with frequent contact with farm animals, whereas the Hutterites embrace modern farming techniques using farm machinery. Prevalence of asthma and allergic sensitization was 4–5 times higher in the Hutterite children than that of the Amish children.⁹ A recent study performed in South Africa corroborated with

the findings in Europe and the United States demonstrating that the rural protection against asthma and allergies was likely associated with exposure to an environment rich in microbial components.¹⁰

Over the past three decades, China has undergone huge socio-economical changes. In parallel, there was a rapid rise in the prevalence of childhood asthma and allergic diseases.¹³ For example, the prevalence of asthma among adolescents has doubled in a southern Chinese city of Guangzhou over a 15 years period.¹⁴ Compared with other Chinese cities, a higher prevalence of asthma and allergies has been consistently reported in Hong Kong, a densely populated metropolis with very high degree of urbanization. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase II survey revealed that asthmatic symptoms in 10-year-old Hong Kong children were three times more common than their mainland (Guangzhou and Beijing) counterparts.¹⁵ Conghua, a rural county of southern China, is located approximately 200 kilometers northwest of Hong Kong and shares a similar subtropical climate. It has a typical agriculture-dominated farming environment, growing primarily the fruit lychee and other related crops. The prevalence of physician-diagnosed asthma in Conghua children aged 13–14 years was 3.4%,¹² which was markedly lower than the 10.2% in Hong Kong.¹⁶ Such urban–rural disparity was also observed in Beijing, northern China,

where only 0.3% of rural children had wheeze in the past 12 months compared with 3.1% in children from urban Beijing.¹¹ Given the similar ethnic background,¹⁷ differences in asthma prevalence were likely to be explained by environmental factors rather than genetic differences. In contrast with the small-scaled farms with the presence of many large farm animals in Central Europe, the farming environment in China is primarily agricultural in nature. The potential protective factors in the Chinese farms are not known.

In this study, we aimed to compare the prevalence of asthma and related atopic disorders in children from Hong Kong (urban area) and Conghua (rural area) using the validated ISAAC Phase III questionnaires, and to identify environmental factors that may confer protection against development of asthma in rural China.

2 | METHODS

2.1 | Study design and population

This is a community-based, cross-sectional epidemiological study of children 5–8 years of age from Hong Kong and Conghua. The recruitment process of study population is shown in Figure 1. There were a

total of 515 and 99 kindergartens and primary schools in Hong Kong and Conghua, respectively. Each kindergarten/school was allocated a unique number. Eighteen primary schools/kindergartens in Hong Kong were selected by computer randomization, in proportion to the population distribution throughout the four geographic districts of Hong Kong (New Territories East, $n = 7$; New Territories West, $n = 5$; Kowloon, $n = 4$; and Hong Kong Island, $n = 2$). All children in the targeted age groups in the recruited schools were approached for consent of study. With a participation rate of at least 80%, a minimum of 3000 children would be successfully recruited from Hong Kong. As the prevalence of childhood asthma in Conghua was expected to be low, all the kindergartens and primary schools ($n = 99$) were approached. A total of at least 14,000 children from Conghua would be recruited. The prevalence of current wheeze was estimated to be 8% in Hong Kong and 2% in Conghua. Our sample size would have a power of greater than 99% in detecting a difference of prevalence of current wheeze of 6% at a 95% level of confidence.

The study protocol was approved by the ethics review board of the Chinese University of Hong Kong (No. 2013220) and the First Affiliated Hospital of Guangzhou Medical University (No. 2012049). Informed consent was obtained from parents/guardians of each study subject.

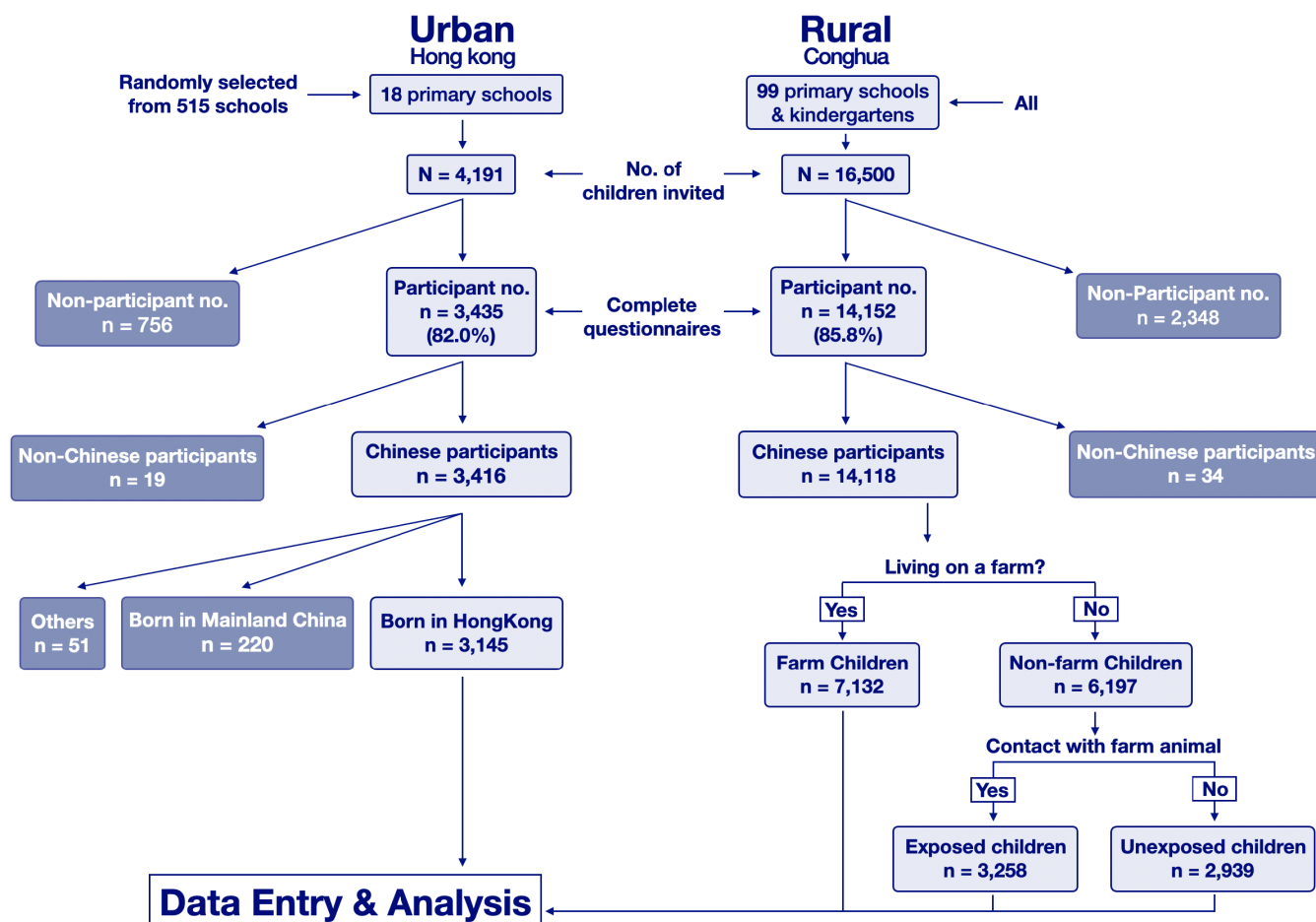


FIGURE 1 Study population and design

2.2 | Outcome and other variables

Written ISAAC Phase III questionnaires were distributed to all children aged 5–8 years in the invited kindergartens/schools and were completed by their parents (or guardians) at home. The questionnaire was developed based on the ISAAC Phase III questionnaire translated into Chinese using the standardized protocol.¹⁸ “Current” symptoms refer to symptoms in the past 12 months; “asthma ever” was defined as having been diagnosed with asthma by a physician in the subjects’ lifetime; other atopic symptoms and diagnosis such as “allergic rhinitis (AR),” “rhino-conjunctivitis,” and “flexural eczema” were defined in accordance with previous studies.^{11,19} “Asthma ever” was used as the outcome variable, and its association with various environmental and lifestyle factors was evaluated. Previous validation studies of the Chinese version of ISAAC questionnaire showed that a parental reported diagnosis of asthma had a sensitivity of 0.88 and specificity of 0.90 in predicting asthma-associated bronchial hyperresponsiveness.^{20,21} For our analysis of asthma medication usage, bronchodilators, oral or inhaled corticosteroids, and leukotriene receptor antagonists were considered as asthma medications. Each parent or guardian was also asked to complete an environmental questionnaire. The environmental questionnaire was developed based on pilot interviews with pregnant mothers, parents with young infants, and children in Conghua to reflect the potential environmental protective or risk factors in rural Conghua. Exposure factors investigated in this study included family history of atopic diseases, parental level of education, cigarette smoking, duration of breastfeeding, worm infestation, previous use of parasite medications, pet ownership, household dampness and mold exposure, cooking fuels, flooring materials, types of bedding, farm characteristics (livestock or agricultural farming or combination of both), contact with pets (dogs, cats, other furry animals, and birds) and farm animals (cattle, pigs, poultry, horses, sheep/goats, and rabbits/hares), and involvement of farming activities. We further divided Conghua children into farm and non-farm subgroups based on whether they had ever lived on a farm and engaged in any farming activities. Some of the “non-farm” children also reported having contact with farm animals, for example, by visiting their neighbors who run a farm or playing with other farm children, and this group of children was categorized as “exposed children.” As AR/hay fever often coexists with asthma and may affect asthma development,²² we also evaluated the association between AR and asthma and the potential impact of AR on environmental factors affecting asthma in the study population.

2.3 | Statistical analysis

Data were entered by two researchers independently (double data entry) and analyzed using SPSS software version 22.0 (SPSS Inc.,) and RStudio version 1.3.959 (RStudio, PBC.). Chi-square tests were used to compare prevalence rates of asthma and atopic disorders between urban and rural children. The results are presented as point

prevalence with 95% confidence intervals (95%CI) where appropriate. To determine the potential risk or protective factors in the rural environment, logistic regression analyses were performed to assess the associations between asthma and exposure factors with adjustment for co-variables when necessary. Multivariate analyses stratified by status of AR were also conducted to evaluate the influence of AR on relationship between various exposure factors and asthma. A propensity score was created to estimate the adjusted exposure effect of farming. We adopted a stepwise modeling approach to investigate the “protective farm effect” in the rural environment. An unadjusted farm effect was estimated in the initial model. In each subsequent step, an exposure factor was added to the model to evaluate the residual protection of the farming environment for asthma and AR.

3 | RESULTS

3.1 | Demographic characteristics of study population

Overall, 14,152 Conghua (rural) children and 3435 Hong Kong (urban) children took part in the survey, representing a participation rate of 85.8% and 82.0%, respectively. After excluding the non-Chinese participants, 14,118 Conghua and 3145 Hong Kong children were included in the final analysis. Demographic characteristics of study subjects from the two regions are shown in Table 1. Age and gender were well-balanced between urban and rural children, with a mean age of 6.5 (± 0.7) years and 6.6 (± 1.1) years (Hong Kong vs. Conghua, $p = 0.79$) and 52.6% (95CI%: 50.8–54.3) and 53.5% (95CI%: 52.7–54.3) being boys (Hong Kong vs. Conghua, $p = 0.43$), respectively.

3.2 | Asthma and allergic disorders were more common among urban children

Table 1 summarized the prevalence of childhood asthma and allergies in urban and rural children. Asthma and related allergic symptoms were generally more common in Hong Kong than that in Conghua. 7.7% of urban children reported wheezing episodes during the past 12 months, whereas only 1.7% of rural children had such symptom (odds ratio [OR] = 4.86, $p < 0.001$). Compared with rural children, a significantly larger proportion of urban children experienced sleep-disturbing wheeze (0.5% vs. 3.4%), exercise-induced wheeze (6.9% vs. 10.5%), symptoms of rhino-conjunctivitis (2.7% vs. 22.2%), and flexural eczema (4.3% vs. 8.4%), or used asthma medication (1.7% vs. 14.8%, all p values < 0.001) in the previous year. Similarly, lifetime diagnosis of asthma (asthma ever) was 2.19 times more prevalent among urban children than their rural counterparts (5.3% vs. 2.5%, $p < 0.001$). More urban children reported having a history of wheeze (16.9% vs. 5.8%), AR (39.9% vs. 8.7%) or eczema (28.7% vs. 21.7%), or ever used asthma medication (25.5% vs. 4.0%) in comparison with rural children (all p values < 0.001).

TABLE 1 Comparison of the prevalence of asthma and allergic disorders in children from Hong Kong and Conghua

	Hong Kong (n = 3145)		Conghua (n = 14,118)		Hong Kong vs. Conghua	
	No. of children	Prevalence, % (95% CI)	No. of children	Prevalence, % (95% CI)	OR*	p value
Mean age (years $\pm$ SD)		6.5 ($\pm$ 0.7)		6.6 ($\pm$ 1.1)		0.79
No. of boys (%)	1654	52.6 (50.8–54.3)	7535	53.5 (52.7–54.3)	0.99	0.43
Symptoms during the last 12 months						
Current wheeze	242	7.7 (6.8–8.7)	238	1.7 (1.5–1.9)	4.86	<0.001
Wheezing attack in the last year						
1–3 episodes	183	5.8 (5.0–6.7)	203	1.4 (1.2–1.6)	4.24	<0.001
4–12 episodes	35	1.1 (0.8–1.5)	35	0.2 (0.2–0.3)	4.53	<0.001
>12 episodes	19	0.6 (0.4–0.9)	9	0.1 (0–0.1)	9.53	<0.001
Current sleep-disturbing wheeze	106	3.4 (2.8–4.1)	69	0.5 (0.4–0.6)	7.10	<0.001
Current speech-limiting wheeze	19	0.6 (0.4–0.9)	28	0.2 (0.1–0.3)	3.06	<0.001
Current exercise-induced wheeze	331	10.5 (9.5–11.6)	970	6.9 (6.5–7.3)	1.59	<0.001
Current asthma medication	466	14.8 (13.6–16.1)	242	1.7 (1.5–1.9)	9.97	<0.001
Current rhino-conjunctivitis	699	22.2 (20.8–23.7)	384	2.7 (2.5–3.0)	10.22	<0.001
Current flexural eczema	265	8.4 (7.5–9.5)	604	4.3 (4.0–4.6)	2.06	<0.001
Symptoms ever						
Physician-diagnosed asthma	167	5.3 (4.6–6.2)	352	2.5 (2.2–2.8)	2.19	<0.001
Wheeze ever	533	16.9 (15.7–18.3)	814	5.8 (5.4–6.2)	3.34	<0.001
Asthma medication ever	803	25.5 (24.0–27.1)	568	4.0 (3.7–4.4)	8.18	<0.001
Allergic rhinitis ever	1256	39.9 (38.2–41.7)	1224	8.7 (8.2–9.1)	7.00	<0.001
Eczema ever	904	28.7 (27.2–30.4)	3067	21.7 (21.0–22.4)	1.45	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

*Unadjusted OR.

3.3 | Rural children from farm families were further protected from asthma

To determine the effect of exposure to farming in the rural area, we investigated whether rural children from families engaging in farming activities had further protection from allergic disorders. 7132 children (50.5%) were from families with farming activities. Significant differences in lifetime prevalence of asthma and related symptoms were observed between those who ever lived on a farm and those who did not (Table 2). Only 2.1% of farm children were ever diagnosed by a physician to have asthma, compared to that of 3.1% of non-farm children (OR = 0.67, $p < 0.001$). Furthermore, farm children were less likely to have used asthma medication compared with non-farm children (3.7% vs. 4.6%, OR = 0.81, $p = 0.01$). A further reduction in AR ever was also documented in farm children (OR = 0.59, $p < 0.001$). Among rural non-farm children, children who had farming exposure by visiting their neighbor has significantly lower life-long prevalence of AR and asthma medication usage than unexposed children (10.0% vs. 12.8%, OR = 0.75, $p < 0.001$; 4.0% vs. 5.2%, OR = 0.77, $p = 0.03$, respectively). However, prevalence of current eczema and eczema ever was slightly higher in farm children

than that of non-farm children (4.9% vs. 3.9%, OR = 1.26, $p = 0.008$; 23.6% vs. 22.1%, OR = 1.09, $p = 0.04$, respectively).

3.4 | Environmental exposures associated with asthma in rural children

As asthma and AR were closely related (aOR = 4.06, 95%CI: 3.17–5.20, Table S1), we conducted stratification analyses to evaluate the potential influence of AR on various exposure factors affecting asthma. Table 3 shows the association between physician-diagnosed asthma and various demographic and environmental factors in the rural population. After adjusting for gender, age, and co-variables including maternal smoking, maternal education level, breastfeeding, and parental asthma, two environmental exposures were found to be protective factors for asthma in the multivariate model, namely agricultural farming (adjusted odds ratio [aOR] = 0.74, 95% CI: 0.56–0.97) and poultry exposure (aOR = 0.75, 95% CI: 0.59–0.96). Of note, aORs of agricultural farming and poultry exposure for asthma in rural children without AR (aOR = 0.73, 95% CI = 0.53–1.01; aOR = 0.76, 95% CI = 0.56–1.03, respectively) were very similar to those of the

TABLE 2 Comparison of the prevalence of asthma and allergic symptoms in farm and non-farm children from Conghua

	Non-farm children				Farm vs. Non-farm children		Exposed vs. Unexposed Non-farm children	
	Farm children (n = 7132)	All (n = 6197)	Exposed (n = 3258)	Unexposed (n = 2939)	OR*	P value	OR*	p value
	Prevalence, % (95%CI)							
Symptoms in the past 12months								
Current wheeze	1.7 (1.5-2.1)	1.8 (1.5-2.2)	1.7 (1.2-2.2)	2.0 (1.5-2.6)	0.97	0.81	0.83	0.34
Current asthma medication	1.7 (1.4-2.0)	1.9 (1.5-2.2)	1.6 (1.2-2.1)	2.1 (1.6-2.7)	0.89	0.38	0.78	0.18
Current rhino-conjunctivitis	1.0 (0.8-1.3)	2.0 (1.7-2.4)	1.7 (1.3-2.2)	2.3 (1.8-3.0)	0.52	<0.001	0.72	0.07
Current flexural eczema	4.9 (4.4-5.4)	3.9 (3.4-4.4)	4.2 (3.5-4.9)	3.6 (3.0-4.4)	1.26	0.008	1.16	0.27
Symptoms ever								
Physician-diagnosed asthma	2.1 (1.8-2.4)	3.1 (2.7-3.6)	2.6 (2.1-3.3)	3.6 (3.0-4.4)	0.67	<0.001	0.73	0.03
Wheeze ever	6.4 (5.8-7.0)	5.5 (5.0-6.1)	5.4 (4.7-6.3)	5.6 (4.8-6.5)	1.16	0.05	0.96	0.73
Asthma medication ever	3.7 (3.3-4.2)	4.6 (4.1-5.1)	4.0 (3.4-4.8)	5.2 (4.4-6.1)	0.81	0.01	0.77	0.03
Allergic rhinitis ever	7.0 (6.4-7.7)	11.3 (10.5-12.1)	10.0 (8.9-11.0)	12.8 (11.6-14.1)	0.59	<0.001	0.75	<0.001
Eczema ever	23.6 (22.6-24.6)	22.1 (21.1-23.2)	22.5 (21.1-24.0)	21.6 (20.1-23.2)	1.09	0.04	1.05	0.42

Abbreviations: CI, confidence interval; OR, odds ratio.

*Unadjusted OR.

whole population. However, aORs of these two factors in rural children with AR failed to reach statistical significance (aOR = 1.03, 95% CI = 0.60–1.76; aOR = 0.83, 95% CI = 0.53–1.32, respectively). The risk factors for physician-diagnosed asthma in the rural area were damp housing, synthetic fiber bedding, use of parasite medication, foam pillow, and carpet flooring, with the highest asthma risk related to the use of foam pillow (aOR = 2.12, 95% CI: 1.14–3.93) and indoor dampness (aOR = 1.58, 95% CI: 1.27–1.98). A total of 398 children kept cows in their farms, but keeping cows in the family was not associated with protection against asthma (aOR = 0.86, 95% CI: 0.60–1.22).

In addition, a propensity score-adjusted analysis was performed to evaluate the factors which may explain the protective effect of agricultural farming on asthma in the rural cohort (Table 4). More than one third (35.5%, 95% CI: 34.7%–36.3%) of children living in the rural area had been exposed to agricultural farming. The initial model evaluated the effect of agricultural farming on asthma, and it has a strong protective effect with an OR of 0.639. With the sequential addition of the environmental factors to the model, the odds ratio gradually increased from 0.639 to 0.997. The increase in the OR was most pronounced after adjustment of poultry exposure (OR rising from 0.780 to 0.997), suggesting that the asthma protection in the farming environment may be largely explained by this factor. Same approach of analysis was used to identify the protective and risk factors for AR (Table S2). The protective effect of agricultural farming on AR was similar to that of asthma, with poultry exposure being an important protective factor against AR in the rural environment (Table 4).

4 | DISCUSSION

This study confirmed that children from rural China had significantly lower prevalence of asthma and related allergies when compared with urban children from Hong Kong. In contrast with the protection of asthma by exposure to livestock in European farms, our study revealed that exposure to predominantly an agricultural farming environment is also protective against the development of asthma. Specifically, poultry exposure was the most important factor associated with asthma protection conferred by living in the rural area. The findings of risk factors such as use of synthetic fiber bedding, use of foam pillows, and carpet flooring replicated the results of our previous study that these factors might explain the higher prevalence of asthma in Hong Kong when compared with children from mainland China.^{15,19}

The current study demonstrates the protective effect of poultry exposure on development of asthma. Farmers in Conghua usually keep a small number of poultry (mainly chicken) for self-consumption rather than for commercial purposes. These free-range chickens live in close proximity with their human host and spend most of the day-time outdoors for foraging, and they may bring a more diversified range of microbes into children's home. During night-time, they are kept in cages inside the house. High loads of bacteria and molds

TABLE 3 Association between demographic and environmental factors and asthma in rural children without and with allergic rhinitis

Factors	All Conghua children (n = 14,118)			Children without AR (n = 12,363)			Children with AR (n = 1202)		
	Prevalence of asthma ever (%)	aOR (95% CI)*	p value*	Prevalence of asthma ever (%)	aOR (95% CI)*	p value*	Prevalence of asthma ever (%)	aOR (95% CI)*	p value*
Age		1.01 (0.92–1.12)	0.76		0.99 (0.88–1.11)	0.80		1.05 (0.87–1.25)	0.63
Gender									
Female	128/6406 (2.0)	1.00	<0.001	93/5878 (1.6)	1.00	0.012	35/424 (8.3)	1.00	0.33
Male	223/7352 (3.0)	1.53 (1.22–1.91)		141/6460 (2.2)	1.40 (1.08–1.83)		80/777 (10.3)	1.24 (0.81–1.91)	
Parental history of asthma									
No	336/13,687 (2.5)	1.00	<0.001	231/12,294 (1.9)	1.00	0.043	103/1174 (8.8)	1.00	<0.001
Yes	16/98 (16.3)	6.77 (3.84–11.92)		4/69 (5.8)	2.90 (1.03–8.17)		12/28 (42.9)	7.86 (3.50–17.65)	
Mother's tertiary education									
Non-tertiary	261/11,870 (2.2)	1.00	<0.001	190/10,807 (1.8)	1.00	0.025	69/871 (7.9)	1.00	0.003
Tertiary	89/1683 (5.3)	2.02 (1.55–2.63)		43/1356 (3.2)	1.50 (1.05–2.13)		46/319 (14.4)	1.96 (1.25–3.06)	
Breastfeeding									
No	57/1674 (3.4)	1.00	0.062	35/1483 (2.4)	1.00	0.25	22/169 (13.0)	1.00	0.23
Yes	290/11,843 (2.4)	0.76 (0.56–1.01)		198/10,711 (1.8)	0.81 (0.56–1.16)		90/1017 (8.8)	0.73 (0.43–1.22)	
Maternal smoking									
None	318/12,652 (3.4)	1.00	<0.001	215/11,429 (1.9)	1.00	0.051	101/1105 (9.1)	1.00	0.049
Yes	13/218 (6.0)	3.00 (1.77–5.10)		8/193 (4.1)	2.07 (1.00–4.28)		5/20 (25.0)	2.96 (1.01–8.70)	
Agricultural farming									
None	259/8862 (2.9)	1.00	0.027	169/7798 (2.2)	1.00	0.059	88/899 (9.8)	1.00	0.92
Yes	93/4923 (1.9)	0.74 (0.56–0.97)		66/4565 (1.4)	0.73 (0.53–1.01)		27/303 (8.9)	1.03 (0.60–1.76)	
Poultry exposure									
None	147/4336 (3.4)	1.00	0.023	92/3709 (2.5)	1.00	0.075	53/493 (10.8)	1.00	0.44
Yes	205/9449 (2.2)	0.75 (0.59–0.96)		143/8654 (1.7)	0.76 (0.56–1.03)		62/709 (8.7)	0.83 (0.53–1.32)	
Damp housing									
None	171/8038 (2.1)	1.00	<0.001	125/7228 (1.7)	1.00	0.037	44/659 (6.7)	1.00	0.001
Yes	181/5747 (3.1)	1.58 (1.27–1.98)		110/5135 (2.1)	1.33 (1.02–1.74)		71/543 (13.1)	2.07 (1.37–3.13)	
Synthetic fiber bedding									
None	237/10,703 (2.2)	1.00	<0.001	158/9645 (1.6)	1.00	<0.001	78/875 (8.9)	1.00	0.50
Yes	115/3082 (3.7)	1.55 (1.23–1.96)		77/2718 (2.8)	1.65 (1.25–2.18)		37/327 (11.3)	1.16 (0.75–1.79)	

(Continues)

TABLE 3 (Continued)

Factors	All Conghua children (n = 14,118)			Children without AR (n = 12,363)			Children with AR (n = 1202)		
	Prevalence of asthma ever (%)	aOR (95% CI)*	p value*	Prevalence of asthma ever (%)	aOR (95% CI)*	p value*	Prevalence of asthma ever (%)	aOR (95% CI)*	p value*
Parasite medication									
No	110/5568 (2.0)	1.00	0.006	83/5128 (1.6)	1.00	0.084	27/406 (6.7)	1.00	0.044
Yes	237/7877 (3.0)	1.38 (1.10–1.74)		152/7032 (2.2)	1.27 (0.97–1.67)		84/775 (10.8)	1.61 (1.01–2.56)	
Foam pillow									
None	340/13,618 (2.5)	1.00	0.017	228/12,221 (1.9)	1.00	0.066	110/1180 (9.3)	1.00	0.18
Yes	12/167 (7.2)	2.12 (1.14–3.93)		7/142 (4.9)	2.09 (0.95–4.60)		5/22 (22.7)	2.10 (0.72–6.15)	
Carpet flooring									
None	328/13,160 (2.5)	1.00	0.050	218/11,801 (1.8)	1.00	0.047	108/1147 (9.4)	1.00	0.71
Yes	24/625 (3.8)	1.55 (1.00–2.39)		17/562 (3.0)	1.68 1.01–2.79		7/55 (12.7)	1.18 (0.49–2.85)	

Abbreviations: AR, allergic rhinitis; CI, confidence interval; aOR, adjusted odds ratio.

*aOR and p values adjusted for age, gender, parental history of asthma, mother's tertiary education, breastfeeding, maternal smoking, agricultural farming, poultry exposure, damp housing, synthetic fiber bedding, parasite medication, foam pillow, and carpet flooring.

have been detected in bedrooms of farm children who had frequent contact with livestock, reflecting the potentially intense microbial exposures of these children.²³ The level of endotoxin, a cell wall component of gram-negative bacteria, has been found to be five times higher in the dust collected from rural households than that of urban families in Guangzhou, southern China,¹² a finding similar to the Amish-Hutterite comparison.⁹ It is noteworthy that most of the current evidence supporting the protective effect of farm living come from Central European studies, where exposure to livestock, especially large farm animals like cows, and consumption of unpasteurized farm milk appear to confer the most potent and consistent protection against asthma and allergies.²⁴ In rural areas of southern China, raising large farm animals are uncommon and rural inhabitants do not consume farm milk. In our Conghua population, only 2.8% (398) of rural families kept cows in their farms whereas 68.1% of the children had contact with poultry. It is conceivable that our study may not have enough power to detect the possible protective effect of exposure to cows in the rural cohort. Furthermore, cows in the rural area in this study are not kept indoor to provide milk. They are used for helping farming activities (e.g., ploughing the field) such that the related microbial exposure for children in rural China may be very different from the exposure to dairy cows in Central Europe.^{5–8}

To further investigate possible mechanisms underlying the asthma-protective effect, we have analyzed blood samples of children from Hong Kong and Conghua and compared with those of rural German children. Our results revealed that rural children, whether from China or Germany, expressed significantly higher mRNA and protein levels of the anti-inflammatory gene TNF- α -induced protein 3 (TNFIP3; A20) and dual-specificity phosphatase-1 (DUSP1), along with lower expression of proinflammatory Toll-like receptor 4 and mitogen-activated protein kinases (MAPKs) than their urban counterparts.^{25,26} Mechanistic studies of cowshed dust collected from Bavarian farms suggested that several bacterial candidates with anti-inflammatory properties in vivo such as the gram-negative bacterium *Acinetobacter lwoffii* F78,^{27,28} gram-positive bacteria *Lactococcus lactis* G121^{27,29} and *Staphylococcus sciuri* W620 might be the important immune drivers.³⁰ These microbial stimuli could induce the immune system towards a Th1 polarization with enhanced immunomodulation, representing a counterbalancing mechanism against the Th2 immunity.³¹ Dust in poultry houses is composed of a complex mixture of dander, chicken feed, litter bedding, and viable and nonviable microorganisms.³² Sequencing analyses of bioaerosols in broiler breeding facilities showed that *Firmicutes* was the predominant phylum of bacteria, characterized by enrichment in *Staphylococcus*, *Salinicoccus*, and *Lactobacillus* at genus level.^{33,34} Fungal communities were of lower concentration in poultry dust and constituted a smaller relative abundance than bacterial phyla.^{33–35} However, these findings were generated from large poultry breeding facilities which could be different from family-run farms with smaller number of free-range chicken as observed in Conghua. It is also possible that some other unmeasured and causal protective factors may be associated with the presence of

TABLE 4 Regression analysis to determine the effect of agricultural farming on asthma and allergic rhinitis

Model	Asthma		Allergic rhinitis	
	Description	Odds ratio	Description	Odds ratio
1	Unadjusted model	0.639	Unadjusted model	0.636
2	Model 1 plus baseline risk factors ^a	0.748	Model 1 plus baseline factors ^b	0.869
3	Model 2 plus age and gender	0.753	Model 2 plus damp housing	0.921
4	Model 3 plus use of parasite medication	0.753	Model 3 plus synthetic fiber bedding	0.921
5	Model 4 plus carpet flooring	0.754	Model 4 plus parasite medication	0.921
6	Model 5 plus foam pillow	0.754	Model 5 plus drinking tap water	0.928
7	Model 6 plus damp housing	0.780	Model 6 plus air conditioning	0.936
8	Model 7 plus synthetic fiber bedding	0.780	Model 7 plus poultry exposure	0.975
9	Model 8 plus poultry exposure	0.997		

^aBaseline risk factors include maternal smoking, mother's tertiary education, breastfeeding, and parental history of atopic diseases (asthma, allergic rhinitis, and eczema).

^bBaseline factors include age, gender, maternal smoking, mother's tertiary education, breastfeeding, and parental history of atopic diseases (asthma, allergic rhinitis, and eczema).

poultry. To further clarify the issue, we are currently collecting environmental samples from this rural community for detailed microbial analyses and to evaluate their biological effects using animal models.

As opposed to the protection associated with exposure to large farm animals in European farms, previous study in rural Beijing also demonstrated that exposure to agricultural farming conferred a similar protection against asthma comparable to that of livestock farming.¹¹ In Central Europe, animal husbandry is a common farming practice, whereas the farming activity in many rural areas in Asia including Conghua is primarily agricultural in nature. Growing fruits and other crops are the predominant farming practice in our study area. Most of these farms in Conghua are relatively small and are operated by individual family. Interestingly, a recent study also demonstrated that only small traditional farms conferred protection against childhood asthma, whereas exposure to large, industrialized farming environment was associated with an increased asthma risk.³⁶

Poultry exposure and agricultural farming were found to be protective environmental factors on asthma irrespective of AR status. Asthma often co-occurs with AR. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) study, about 80% of asthmatic patients have AR, whereas 15%–30% patients with AR have asthma.²² Comorbidity of asthma and AR is associated with increased asthmatic exacerbations and asthma-related hospitalizations, as well as higher annual medical costs.^{37,38} The coexistence of AR with asthma has been found partially due to shared genetic risk variants and causal mechanisms.^{39,40} To determine the potential effect of AR, we further conducted the stratification analysis comparing the relationship between various exposure factors and asthma in rural children without and with AR. The trend of protection conferred by poultry exposure and agricultural farming remained after exclusion of cases with AR, as shown by aORs very similar to those in the whole population. These results suggested that the asthma protection conferred

by poultry exposure and agricultural farming may not be driven by AR in the rural population. However, larger sample size of rural subjects with AR will be needed to confirm this preliminary finding.

Among the risk factors in our rural environment, use of parasite medication was another risk factor for asthma. Helminth infections share many immunological phenomena with allergic disorders, such as a strong Th2 response characterized by high IgE levels and eosinophilia.⁴¹ Different from FcεRI generated in atopic disorders, helminth-elicited IgE is of low affinity, and thus, the cross-reactivity may not lead to mast cell degranulation. Worm parasites need to safeguard their own survival and escape the immune clearance by the host. Immune downregulation associated with helminth infections confers an element of resistance, possibly preventing translation into allergic symptoms.⁴² Hence, it has been postulated that the elimination of worms may remove the helminth-induced immunosuppression and lead to the emergence of symptoms of atopic diseases in individuals who had received anti-parasite medications.

The results of the current study also corroborate with our previous findings of comparative study of children from Hong Kong and cities of mainland China showing that the use of foam pillow and synthetic bedding, as well as damp housing were risk factors associated with asthma.^{15,19} Beddings (pillows, quilts, and mattresses) and carpets are important sources of inhalant allergens, such as house dust mite (HDM). Compared with natural materials such as cotton and feather, synthetic textiles have been shown to contain much higher loads of HDM allergens, thus may induce a higher degree of airway inflammation.^{43–45} Synthetic beddings may also release volatile organic compounds such as isocyanates as well as other fungal and bacterial proinflammatory constituents, which might enhance the allergenic response to HDM.⁴⁶ Further studies are needed to clarify the underlying biological mechanisms of how these factors may affect the immune system and the developing airways in children.

The current study is one of the largest comparative studies investigating the epidemiology of asthma and allergies in urban and

rural children. However, our study has several limitations. Recall bias is always a concern in studies of similar nature as parents of these 5–8-year-old children needed to recall some of the exposure factors early in life. Another limitation of our study was the lack of objective measurements of the recruited subjects. Nevertheless, our survey instruments have been validated in several groups of Chinese children showing consistently high accuracy in predicting asthma-associated bronchial hyperresponsiveness.^{20,21} However, validation studies of the ISAAC questions related to eczema symptoms revealed rather low sensitivity (24%–70%) and positive predictive values (15%–35%) against the gold standard of dermatologist's clinical examination.^{47–49} Other skin conditions such as insect bites or other skin infections might be more common in farm children leading to the results documented in our current study which suggested farm children might have a slightly higher prevalence of eczema when compared with non-farm children. Validation studies of the questions related to AR also revealed similar limitations.^{50,51} We must be cautious in our interpretation of the results related to factors associated with AR in our study (Tables 4 and Table S2).

In conclusion, this large study using validated methodology confirms the markedly lower prevalence of asthma in rural Chinese children when compared with children from Hong Kong. Exposure to poultry and agricultural farming or unmeasured factors related to them may explain the lower prevalence of childhood asthma in children from the rural environment. Our data would complement the findings obtained from different rural populations from around the world. Further mechanistic studies are needed to determine the potential biological mechanisms explaining the protection conferred by poultry exposure. A clear understanding of how various factors in the rural areas protect children from developing asthma will pave the way for the development of primary preventive strategies against a chronic disease affecting millions worldwide.

AUTHOR CONTRIBUTIONS

MR, BS, JL, and GW planned and designed the study, and obtained the funding. YX and MW contributed to the acquisition and analysis of the data. TL, CW, MR, BS, JL, and GW made substantial contributions to the conception and interpretation of the work. YX and MW drafted the initial manuscript, and all authors provided substantial input into the revision and interpretation of the manuscript.

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CONFLICT OF INTEREST

The authors declare to have no conflict of interests directly related to this work. TL reports personal fees from Hong Kong Society for Paediatric Immunology Allergy and Infectious Diseases outside the submitted work. BS reports personal fees from GSK, Novartis, and Sanofi, outside the submitted work. None of the other authors declare any conflicts of interest outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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