Eur Respir J 2002; 19: 288–293
DOI: 10.1183/09031936.02.002319.02

European Respiratory Journal
ISSN 0903-1936

Individual allergens as risk factors for asthma and bronchial hyperresponsiveness in Chinese children

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ABSTRACT: The role of allergen sensitization in the development of asthma in the Chinese is not clear. This study aims to determine the relationship of sensitization to individual allergens, and the development of asthma and bronchial hyperresponsiveness (BHR) in schoolchildren from three Chinese cities: Hong Kong, Beijing and Guangzhou.

Community-based random samples of 10-yr-old schoolchildren from three Chinese cities were recruited for study using the International Study of Asthma and Allergies in Childhood (ISAAC) Phase II protocol. Subjects were studied by parental questionnaires (n=10,902), skin-prick tests (n=3,479), and methacholine challenge tests (n=608).

The prevalence rates of wheeze in the past 12 months (Hong Kong, 5.8%; Beijing, 3.8%; Guangzhou, 3.4%) and atopy (Hong Kong, 41.2%; Beijing, 23.9%; Guangzhou, 30.8%) were highest in schoolchildren from Hong Kong. Multivariate logistic regression analyses revealed that sensitization to *Dermatophagoides pteronyssinus* (odds ratio (OR)=4.48; 95% confidence interval (CI): 3.02–6.66), cat (2.59; 1.67–4.03), *Dermatophagoides farinae* (2.41; 1.65–3.51) and mixed grass pollen (2.85; 1.24–6.50) were significantly associated with current wheeze. Atopy, defined as having $\geqslant$1 positive skin-prick tests, was not an independent risk factor for current wheeze in children from any of the three cities. Furthermore, atopy (OR=2.53; 95% CI: 1.07–5.97), sensitization to cat (3.01; 1.39–6.52) and *D. farinae* (3.67; 1.93–6.97) were significantly associated with BHR.

The authors confirmed that sensitization to house dust mite and cat was significantly associated with current wheeze and bronchial hyperresponsiveness in Chinese schoolchildren. However, the difference in the prevalence rate of atopic sensitization cannot explain the higher prevalence of childhood asthma in Hong Kong, when compared with those children from Beijing and Guangzhou.

Eur Respir J 2002; 19: 288–293.

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Keywords: Allergen
asthma
atopy
bronchial hyperresponsiveness
children
Chinese

Received: March 27 2001
Accepted after revision September 17 2001

This study was supported by Research Grant Council Earmarked Grant 96/97 No. CUHK 232/96M.

Asthma is one of the most common chronic disorders in childhood. Although there is no gold standard for defining asthma, the diagnosis of asthma in clinical practice is made on the basis of combined information from history, physical examination, and respiratory function tests. Bronchial hyperresponsiveness (BHR) is the best objective marker of asthma and has been considered as one of the criteria for defining asthma epidemiologically [1, 2]. As documented by the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence rates of asthma in schoolchildren vary widely across different regions of the world [3]. Furthermore, many epidemiological studies have consistently documented increasing prevalence of asthma and allergies in different countries [4–8]. The wide variation of asthma prevalence and the recent increasing trend within populations are unlikely to be explained by genetic factors. Environmental factors have been thought to be important in determining disease manifestations. Among the suspected environmental factors associated with asthma, allergen sensitization has been most widely implicated as one of the important risk factors [9].

The prevalence of asthma and allergic diseases in the Chinese population has been reported to be lower than that in the West [3]. Within the Chinese population, the prevalence rate of asthma in schoolchildren was found to be the highest in Hong Kong [3]. The 12-month prevalence rates of wheeze in 13–14-yr-old schoolchildren, as identified by the ISAAC written and video questionnaires, were 12.4% and 10.1%, respectively in Hong Kong while the corresponding figures in mainland China were 4.2% and 2.0%. Allergic sensitization could be one of the factors accounting for such differences between children from Hong Kong and mainland China. Hong Kong is a westernized city with a subtropical climate. Guangzhou is situated approximately 200 km north of Hong Kong and has a similar climate. Beijing, however, is in the temperate zone with relatively low humidity compared to the other two cities. The majority of published studies on the relationship of allergic sensitization and asthma were performed in Caucasians. A small comparative study of three populations of Chinese schoolchildren was conducted previously to assess the relationship of allergic

sensitization and asthma [10]. The findings, however, were not validated with objective measures such as a bronchial challenge test. Only one previous study has utilized bronchial challenge tests in Chinese children, and BHR was shown to be associated with atopy [11]. However, the relative importance of different allergens has not been assessed in the Chinese population.

In this study, the relationship of sensitization to individual allergens and the development of asthmatic symptoms and BHR were evaluated, in schoolchildren from three Chinese cities.

Subjects and methods

The details of subject selection and methods used in this study have been reported elsewhere [12]. In brief, schoolchildren aged 10 yrs from Hong Kong, Beijing and Guangzhou were recruited into the study using primary schools as sampling units. Each subject was given an ISAAC Phase II questionnaire [13] to be completed by the parents or guardians. "Current" symptoms referred to symptoms in the past 12 months. Random subgroups of at least 1,000 children from each city were recruited for skin-prick tests after parental consent was obtained, as described previously [12]. The sensitivity to eight common aeroallergens was assessed: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, *Alternaria tenuis*, mixed tree pollen, mixed grass pollen, cockroach, and mixed moulds. Standardized allergen extracts and control solutions were obtained from ALK (Horsholm, Denmark). Histamine (10 $mg \cdot mL^{-1}$) and diluent were used as positive and negative controls. 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 $\geqslant 3$ mm after subtraction of the negative control was considered positive. Subjects with $\geqslant 1$ positive reactions were considered atopic. To ensure the quality of the skin-prick tests, the procedure was performed by trained technicians and strict adherance to the ISAAC Phase II protocol was observed.

All children with current wheeze identified by the written questionnaire were invited for bronchial challenge test. Equal numbers of control subjects were randomly recruited from all students who reported no symptom of wheeze in the past year. The test was carried out according to the protocol reported by YAN *et al.* [14]. BHR is defined as having a provocation dose of methacholine causing a 20% fall in forced expiratory volume in one second from baseline (PD_{20}) of $\leqslant 7.8$ μmol methacholine. The study protocol was approved by the Ethics Committee of the participating institutions. Informed parental consent was obtained from parents or guardians before the studies were carried out.

All data were entered into a computer twice, by two independent investigators. Data were categorized and analysed statistically [15]. Multivariate logistic regression analysis with adjustment for age and sex was used to test the associations of sensitivity of each allergen, as well as atopy and the dependent variables (current wheeze and BHR). Initially, univariate analyses (*i.e.* analysis performed without adjusting for any of the covariates) were performed. Only allergens found to be statistically significant in the univariate analyses were then tested in a combined analysis to reveal the independent risk factors. The results of the multivariate logistic regression analyses are reported. Results are presented as odds ratios (OR) and 95% confidence interval (CI). A p-value <0.05 was considered to be statistically significant. To compare the effects of atopy and allergen sensitization in the three cities, multivariate logistic regression analyses were performed separately for children from each city. The data of all children were then pooled together in the final analyses with adjustment for the place of residence.

Results

The prevalence rates of asthma symptoms and atopic sensitization in the three study populations, as revealed by the written questionnaires and skin-prick tests are summarized in table 1. Asthma symptoms and atopy were significantly more common in schoolchildren from Hong Kong when compared with those from Beijing and Guangzhou. Similarly, sensitivity to *D. pteronyssinus* and *D. farinae* was significantly more common in Hong Kong than in Beijing or Guangzhou. The prevalence of sensitivity to mixed moulds, however, was highest in Beijing, and it was significantly higher than those in Hong Kong or Guangzhou. A total of 459 subjects reported to have wheeze in the past 12 months. There were 179 from Hong Kong, 159 from Beijing and 121 from Guangzhou. A total of 285 of these subjects (62%) gave consent to undergo the bronchial challenge test. Subjects (n=323) without current wheeze were also recruited from three cities for bronchial challenge test. Therefore, a total of 608 subjects (Hong Kong, 238; Beijing, 193; Guangzhou, 177) underwent bronchial challenge test. Among them, 515 (85%) also gave consent to have skin-prick tests.

Multivariate logistic regression analyses with adjustment for age and sex revealed that sensitivity to *D. pteronyssinus*, *D. farinae*, cat, mixed grass pollen, and mixed moulds were risk factors significantly associated with current wheeze. Table 2 shows the relationship of individual allergens as risk factors for current wheeze in the three cities. Among the allergens tested, sensitivity to *D. pteronyssinus* and *D. farinae* were the most common risk factors associated with current wheeze in the three groups of schoolchildren. Sensitivity to mixed moulds was most common in Beijing (3.2%), and it was found to be a risk factor for current wheeze in schoolchildren from Beijing only. Atopy was not associated with current wheeze in any of the three groups of children.

Table 3 shows the relationship of individual allergens as risk factors for BHR. When subjects from all three cities were analysed as one combined group, atopy, sensitivity to *D. farinae* and cat were found to be risk factors for BHR. Sensitivity to

Table 1. – Prevalence of asthmatic symptoms and atopic sensitization in Chinese schoolchildren by study area

	Hong Kong	Beijing	Guangzhou
Written questionnaire n	3110	4227	3565
Symptoms in last 12 months			
Wheeze	5.8 (5.0–6.7)	3.8 (3.3–4.4)	3.4 (2.8–4.1)
Exercise-induced wheeze	7.7 (6.8–8.6)	4.5 (3.9–5.2)	3.1 (2.5–3.7)
Speech-limiting wheezing	1.8 (1.3–2.3)	0.5 (0.3–0.7)	0.4 (0.3–0.7)
Current asthma	3.3 (2.7–4.1)	2.3 (1.9–2.8)	2.1 (1.7–2.6)
Skin-prick test n	1341	1044	1094
Atopy ($\geqslant$1 positive skin test)	41.2 (38.6–43.8)	23.9 (21.4–26.6)	30.8 (28.1–33.7)
Dermatophagoides pteronyssinus	34.1 (31.5–36.7)	7.5 (5.9–9.3)	20.0 (17.7–22.5)
Dermatophagoides farinae	25.9 (23.6–28.3)	5.7 (4.3–7.2)	17.9 (15.7–20.3)
Cat	3.7 (2.8–4.9)	5.6 (4.3–7.1)	4.3 (3.2–5.7)
Cockroach	11.5 (9.8–13.3)	13.3 (11.3–15.6)	17.3 (15.1–19.7)
Mixed grass pollen	0.7 (0.4–1.4)	1.2 (0.7–2.1)	1.1 (0.6–1.9)
Alternaria tenuis	0.4 (0.1–0.9)	1.5 (0.9–2.5)	0.9 (0.4–1.7)
Mixed moulds	0.4 (0.2–1.0)	3.2 (2.2–4.4)	1.2 (0.6–2.0)
Mixed tree pollen	0.1 (0.0–0.4)	1.0 (0.5–1.8)	0.5 (0.2–1.2)
Subjects n			
Bronchial challenge test	238	193	177
Current wheeze	112	91	82
No current wheeze	126	102	95

Data are presented as n% (95% confidence interval) unless otherwise stated.

D. pteronyssinus was found to be of borderline significance in predicting BHR (p=0.07; OR=2.04; 95% CI: 0.94–4.43). Although sensitivity to *D. farinae* confers the highest risk (OR=3.67) for BHR, the differences between the ORs of this, atopy and cat were not significantly different. For the individual cities, sensitivity to *D. pteronyssinus* and *D. farinae* were the most common factors associated with BHR.

Discussion

Epidemiological studies have documented a progressive increase in the prevalence and morbidity of asthma, which is now one of the most common chronic disorders in childhood. The prevalence rates of asthma and allergic disorders in Asians have been found to be lower when compared with those in the West [16]. This research group has also documented an increasing trend of asthma in schoolchildren from Hong Kong [3]. There is limited data available regarding the role of sensitization to allergens in the development of asthma and bronchial hyperreactivity in Chinese children [11].

The current study is the first to evaluate the relative importance of sensitization to individual allergens for the development of asthma and BHR in Chinese schoolchildren. Using a standardized protocol, the authors confirmed that sensitization to *D. pteronyssinus*, *D. farinae* and cat, were risk factors associated with current wheeze and BHR in Chinese schoolchildren. The authors have validated previously that

Table 2. – Individual allergens as risk factors for current wheeze in Chinese children

Allergen sensitivity	Hong Kong	Beijing	Guangzhou	Total
Atopy	1.54 (0.65–3.62)	0.66 (0.20–2.22)	2.94 (0.92–9.32)	1.29 (0.74–2.24)
Dermatophagoides pteronyssinus	3.03 (1.82–5.06)*	2.28 (0.60–8.66)	11.65 (5.44–24.94)*	4.48 (3.02–6.66)*
Cat	1.46 (0.69–3.08)	2.11 (0.68–6.57)	6.79 (3.06–15.02)*	2.59 (1.67–4.03)*
Dermatophagoides farinae	1.67 (1.02–2.74)*	8.53 (3.74–19.42)*	3.73 (1.87–7.45)*	2.41 (1.65–3.51)*
Mixed grass pollen	5.26 (1.45–19.16)*	0.34 (0.03–3.76)	5.32 (0.87–32.53)	2.85 (1.24–6.50)*
Mixed moulds	0.64 (0.06–7.14)	3.30 (1.10–9.87)*	0.85 (0.21–3.52)	1.30 (0.60–2.80)

Data are represented as odds ratios (95% confidence interval). *: p<0.05.

Table 3. – Individual allergens as risk factors for bronchial hyperresponsiveness in Chinese children

Allergen sensitivity	Hong Kong	Beijing	Guangzhou	Total
Atopy	4.57 (1.90–11.00)*	2.29 (0.35–15.24)	2.20 (0.42–11.45)	2.53 (1.07–5.97)*
Dermatophagoides pteronyssinus	1.19 (0.37–3.88)	13.18 (3.08–56.48)*	4.76 (1.61–14.08)*	2.04 (0.94–4.43)$^{\#}$
Cat	1.64 (0.48–5.60)	6.18 (1.17–32.59)*	3.34 (0.89–15.51)	3.01 (1.39–6.52)*
Dermatophagoides farinae	2.56 (1.12–5.84)*	0.66 (0.05–8.46)	9.52 (3.28–27.66)*	3.67 (1.93–6.97)*

Data are represented as odds ratios (95% confidence interval). *: p<0.05; $^{\#}$: p=0.07.

the Chinese version of the ISAAC written questionnaire was effective in predicting BHR in secondary schoolchildren in Hong Kong [17]. The current study used the same protocol of bronchial challenge test. When all of the subjects recruited for BHR testing from the three cities (n=608) were combined, a positive response to the question on current wheeze had a sensitivity of 0.82 and a specificity of 0.71 for predicting BHR. A potential source of bias in this study was that only 62% of the children with current wheeze gave consent for BHR testing. The impact of such bias, however, is likely to be small because the prevalence of symptoms of eczema and rhinoconjunctivitis, family history of atopy, as well as the frequency of wheezing attacks in the subgroup who underwent BHR testing, were virtually identical to those of the whole group of children with current wheeze (data not shown).

House dust mite exposure and sensitization in early childhood have been found to be associated with subsequent development of asthma in Caucasians [18–20]. Studies of asthmatic children have also revealed an association between asthma symptoms, BHR and atopy [21, 22]. Furthermore, exposure to mite allergen in asthmatic children has been found to be associated with the risk of repeated hospital admissions [23]. VON MUTIUS *et al.* [24] found a higher prevalence of asthma in schoolchildren in West Germany compared with those in East Germany and suggested that the difference in prevalence rates might be explained by sensitization to aeroallergens. There has been only one small comparative study of Chinese children investigating the role of allergen sensitization in the manifestation of asthma [10]. This study recruited Chinese schoolchildren aged 12–18 yrs from Hong Kong, Malaysia and San Bu, China. A subsample underwent skin-prick testing to determine the relationship of allergen sensitization and asthma. Asthma and allergic disorder were 2–6-times higher in schoolchildren from Hong Kong when compared with the other two groups of Chinese children. Within each study population, allergen sensitization was a significant factor associated with asthma. The lack of objective assessment of airway response in this study was a major limitation. Furthermore, the prevalence of atopy in Malaysia was high (64%) and yet the prevalence of asthma was low (1.9%). In addition to allergic sensitization, other factors associated with the "westernized" environment of Hong Kong may also be important for the development of asthma in schoolchildren from Hong Kong [25]. A recent review emphasized that the proportion of cases of childhood asthma attributable to atopy, varied from only 25–63% in cross-sectional studies. Indeed, the present study shows that atopy *per se* is not an independent risk factor for current wheeze. Thus, research efforts should also be directed at other possible aetiological factors for the development of asthma [26].

Cockroach allergy and exposure to high levels of this allergen have also been found to be associated with increased morbidity in asthmatic children in America [27, 28]. However, a recent study of German schoolchildren did not find a relationship between cockroach sensitization and asthma symptoms [29]. The results shown in the present study are in agreement with the German study. Although the prevalence of cockroach sensitization is common in all three cities, such sensitization was neither associated with current wheeze nor BHR, in the subjects studied. Further studies are required to define clearly the role of cockroach allergy in the manifestation of asthma in different populations. In addition, atopy, defined as having $\geqslant 1$ positive skin tests, was associated with current wheeze in the univariate analyses in the subjects studied (data not shown). However, atopy was not independently associated with current wheeze in any of the three groups of children. This finding suggests that asthma symptoms have a strong relationship with sensitization to particular aeroallergens, but not with the nonspecific response of just being atopic alone [26, 30–35]. Furthermore, there are other possible confounders that may influence the results, such as family history of atopy and smoking in the household. When these two factors were included in the statistical model of the analyses, the significant associations remained unchanged (data not shown). However, studies with larger sample sizes are required to clearly define the possible interactions of these factors, upon the associations of allergen sensitization with asthma or BHR.

Finally, it was found that sensitization to house dust mite was significantly more common in schoolchildren from Hong Kong than those from Beijing or Guangzhou. Sensitization to house dust mite was confirmed to be significantly associated with current wheeze and BHR in the studied subjects; therefore, the high prevalence rate of childhood asthma in Hong Kong may be due partly to the high prevalence rate of sensitization to house dust mite. However, the difference in sensitization rate cannot be explained by the difference in allergen exposure because previously the authors have shown that domestic indoor levels of aeroallergens in Hong Kong and Guangzhou were similar [36]. Furthermore, despite a significantly higher rate of sensitization to house dust mite in Guangzhou when compared with that of Beijing, the prevalence of asthma symptoms were similar in Beijing and Guangzhou. Therefore, other factors such as those implicated in the hygiene hypothesis, breast-feeding and dietary factors, most likely also influence the susceptibility in the development of allergen sensitization and asthma.

In conclusion, the authors have evaluated three populations of Chinese schoolchildren using standardized protocol of skin-prick test and bronchial challenge test. This is the first report of the relative importance of sensitization to individual allergens for asthma symptoms and bronchial hyperresponsiveness in Chinese children. The authors have confirmed that sensitization to house dust mite and cat is significantly associated with current wheeze and bronchial hyperresponsiveness in Chinese schoolchildren. However, the difference in the prevalence rates of atopic sensitization among the three cities cannot explain the higher prevalence of childhood asthma in Hong Kong when compared with children from Mainland China. Further studies are necessary to determine the factors which influence the susceptibility in the

development of allergen sensitization in Chinese children.

Acknowledgements. The authors wish to thank M. Tong, A. Chan, C. Chan and K.K.Wong for their technical support, and the children, parents and staff of the schools for their participation in the survey.

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