

Sensitization to inhaled allergens as a risk factor for asthma and allergic diseases in Chinese population

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Background: Allergen sensitization is associated with asthma and allergic disease in children, but such a relationship has not been confirmed in Chinese populations.

Objective: The objective of this study was to evaluate the effects of allergen sensitization and family history of atopy on asthma and allergic disease in Chinese schoolchildren from three southeast Asian populations.

Methods: Written questionnaires on respiratory and allergic symptoms were completed by parents of children of secondary-school age (age range 12 to 18 years) in Hong Kong ($n = 1062$), Kota Kinabalu in eastern Malaysia ($n = 409$), and San Bu in southern China ($n = 737$). A subsample of schoolchildren underwent skin prick testing to common inhalant allergens (Hong Kong 471 children, Kota Kinabalu 321, San Bu 647).

Results: The prevalence of asthma and allergic disease in schoolchildren was highest in Hong Kong, intermediate in Kota Kinabalu, and lowest in San Bu. However, the overall rate of atopic sensitization was similar in the three populations (49% to 63%). House dust mite and cockroach were the two most common allergens causing sensitization and these gave rise to more than 95% of the positive skin test results in all three populations. By regression analysis, mite allergy was associated with rhinitis and asthma in all three populations, and a family history of asthma, rhinitis, or eczema was strongly associated with respective symptoms in the subjects. After adjusting for age, sex, atopic status, and family history of allergic disease, the place of residence remained a significant independent factor for asthma (odds ratio [OR] = 1.0 for Hong Kong, 0.57 for Kota Kinabalu, 0.15 for San Bu, $p < 0.001$), rhinitis (OR = 1.0 for Hong Kong, 0.59 for Kota Kinabalu, 0.15 for San Bu, $p < 0.001$), or eczema (OR = 1.0 for Hong Kong, 0.35 for Kota Kinabalu, 1.01 for San Bu, $p < 0.001$).

Conclusion: Sensitization to indoor allergens was a significant risk factor for asthma and allergic disease, and familial clustering of disease was common in the region. However, the marked difference in disease prevalence in the three southeast Asian populations of Chinese schoolchildren cannot be explained by atopic sensitization and family history alone, and the place of residence was an independent risk factor for asthma and allergies, which suggests an important environ-

mental role in disease pathogenesis. (*J Allergy Clin Immunol* 1997;99:594-9.)

Key words: Asthma, rhinitis, eczema, atopy, allergy, epidemiology, Chinese, skin test, house dust mite, cockroach, indoor allergen

As the evidence for regional variation in the prevalence of asthma and allergic disease mounts,¹⁻⁴ the role of the environment in disease pathogenesis becomes more obvious. Although an increasing number of genetic markers linked to various phenotypic expressions of asthma and atopy have been discovered in recent years,⁵⁻⁷ genetic factors alone cannot explain the marked difference in the prevalence of asthma and respiratory symptoms between German schoolchildren in Munich and Leipzig² and between Chinese schoolchildren in Hong Kong, Kota Kinabalu in Malaysia, and San Bu in South China.³ Rather, the environment in which these children resided was thought to be important in determining disease manifestations.

Among the proposed environmental factors related to asthma pathogenesis, allergen sensitization has been most widely implicated in susceptible persons and was considered the main factor that could explain the difference in the prevalence of asthma and hay fever between schoolchildren from West and East Germany.² Allergic sensitization to house dust mite and cat dander has been associated with the development,^{8,9} exacerbation,¹⁰ and severity of asthma symptoms.¹¹ Sensitization to allergens from indoor rather than outdoor sources also correlates with the degree of bronchial hyperresponsiveness.¹²

Most of the existing data on the relationship of allergen exposure, sensitization, and subsequent risk of asthma and allergic manifestations were derived from white populations, and similar information in Asian populations is lacking. We recently published the results of a study on the prevalence of asthma and allergic disease in Chinese schoolchildren living in three different southeast Asian populations³; in the present paper we evaluate the effects of sensitization to individual common inhaled allergens and family history of atopy as risk factors for the development of asthma and allergy in these three Chinese populations.

METHODS

The details of the subject selection and methods used have been reported elsewhere.³ In brief, children of secondary-school age (age range 12 to 18 years) in Hong Kong, Kota

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Received for publication August 12, 1996; revised Nov. 20, 1996; accepted for publication Nov. 20, 1996.

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0091-6749/97 \$5.00 + 0 1/1/79344

TABLE I. Prevalence of allergic symptoms

Questionnaire response	Hong Kong (n = 1062)	Kota Kinabalu (n = 409)	San Bu (n = 737)
Response rate (%)	89.2	87.6	98.6
Boys	611	134	492
Girls	451	275	245
Prevalence (%) of symptoms (standardized by age and sex)			
Rhinitis ever	29.8 (27.0, 32.6)*	18.3 (14.6, 22.0)*	3.7 (2.3, 5.1)*
Eczema ever	20.1 (17.7, 22.5)*	7.6 (5.0, 10.1)	7.2 (5.4, 9.1)
Wheeze ever	7.8 (6.2, 9.4)	7.7 (5.1, 10.2)	1.9 (0.7, 3.1)*
Wheeze in past 12 mo	3.7 (2.6, 4.8)	4.9 (2.8, 7.0)	1.1 (0.2, 2.0)*
Asthma ever	6.6 (5.1, 8.1)*	3.3 (1.6, 5.0)	1.6 (0.5, 2.7)
Wheeze or asthma ever	11.6 (9.3, 13.9)*	8.2 (5.5, 10.9)*	1.9 (0.7, 3.1)*

Values in parentheses are 95% confidence intervals. Data from Leung and Ho (Thorax 1994;49:1205-10).

*Indicates significant differences from other populations.

Kinabalu in Malaysia, and San Bu in southern China were entered into the study between April and June 1992. They were randomly selected from all grades of schoolchildren attending one of the assigned schools by the local education authorities. Each participant was sent a questionnaire on respiratory and allergic symptoms in Chinese for parental completion. The questionnaire was adapted from standard respiratory questionnaires,^{13,14} and translation into Chinese and back-translation was done to ensure validity of the questions. All participants were ethnic Chinese.

Half of the questionnaire respondents in Hong Kong and all of the respondents in Kota Kinabalu and San Bu were asked to undergo skin prick tests by standard methods. This was done by the same team of investigators from Hong Kong. For skin testing in the three cities a panel of nine common inhaled allergens (Hollister-Stier, Spokane, Wash.) grouped into five allergen groups was used including (1) pollens, comprising a grass mix (Kentucky Blue, Orchard, Redtop, Timothy, Sweet Vernal, Meadow Fescue, Perennial Rye), rye grass (*Lolium Perenne*), and couch grass (*Cynodon Dactylon*); (2) dust mite (*Dermatophagoides pteronyssinus*); (3) mold (mixture of *Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*); (4) cockroach (mixture of American, German, and Oriental spp.); and (5) animal dander, comprising cat, dog, and rat hair. Histamine (10 mg/ml) and normal saline solution were used as positive and negative controls, respectively. The transverse and vertical diameters of the wheal were measured at 15 minutes and mean values recorded as the mean wheal size. Wheals of 3 mm or greater were regarded as positive in the absence of a reaction to normal saline solution and subjects with one or more positive reactions were considered atopic.

A history of wheeze or asthma ever was used in the study as a measure of the "asthma syndrome" that was more accurate than using either asthma alone or wheeze alone. Family history of atopy was defined as one or more of asthma or wheeze ever, rhinitis ever, and eczema ever in at least one parent or sibling. The results of the questionnaire and skin test responses are shown in Tables I and II, respectively. The prevalence of asthma and allergic disease in the subgroup of children who also underwent skin testing was virtually identical to that in the whole group.

The chi-square test was used to assess the association between categorical variables. Logistic regression was done to demonstrate the associations of outcomes of interest (wheeze or asthma ever, rhinitis ever, and eczema) with dependent

variables (age, sex, family history of atopy, and allergic sensitization to the 5 allergen groups). In a separate regression model, the effect of place of residence on outcome measures was assessed with the same dependent variables; in this analysis, a likelihood ratio statistic was obtained to determine differences in odds ratios among the three populations.

RESULTS

Table I shows the distribution of asthma and allergic symptoms in the three study populations. In general, the prevalence of asthma and allergic disease was highest in Hong Kong, intermediate in Kota Kinabalu, and lowest in San Bu. Despite the marked difference in prevalence, the atopy rates were similar across the three study populations and, in particular, there was little difference in the skin test positivity to house dust mite and cockroach, the two most common inhaled allergens causing sensitization in more than 95% of schoolchildren in the region (Table II). The mean wheal sizes in the skin tests positive for *D. pteronyssinus* sensitivity were the largest compared with those of other allergens and followed the same order as the prevalence rates of asthma and allergic disease being largest in Hong Kong, intermediate in Kota Kinabalu, and smallest in San Bu. More than two thirds of the wheals from positive skin test results to *D. pteronyssinus* were ≥ 5 mm in Hong Kong and Kota Kinabalu.

Tables III and IV show the effects of allergen sensitization to inhaled allergens and family history of allergy, respectively, on the prevalence of asthma and allergic disease. The analyses were based on data from the 1439 schoolchildren who completed the questionnaire and who underwent skin testing (Hong Kong 471 children, Kota Kinabalu 321, San Bu 647). Mite allergy was an independent risk factor for asthma and rhinitis in all three study populations with varying effects. In Hong Kong, sensitization to house mold and animal allergens was significantly associated with respiratory allergy whereas pollen sensitivity correlated with eczema only in Kota Kinabalu. In none of the study populations did the presence of specific IgE to cockroach allergens have any

TABLE II. Skin test reactivity by skin wheal size in three study populations

	Reactivity by mean wheal size (%)											
	Hong Kong (n = 471)				Kota Kinabalu (n = 321)				San Bu (n = 647)			
	≥3 mm	3 mm	4 mm	≥5 mm	≥3 mm	3 mm	4 mm	≥5 mm	≥3 mm	3 mm	4 mm	≥5 mm
Pollen												
Grass mix	2.1	1.1	0.6	0.4	2.8	2.8	—	—	3.7	3.4	0.3	—
Rye	2.1	1.3	0.4	0.4	0.3	4.7	0.3	—	4.3	4.1	0.2	—
Couch	4.5	3.0	1.1	0.4	16.2	10.6	3.7	1.9	3.2	2.6	0.6	—
≥1 Of above	6.4				17.2				5.6			
Mite												
<i>D. pteronyssinus</i>	55.4	7.0	4.9	43.5	60.2	8.1	15.0	37.1	42.7	15.1	11.0	16.6
Mold												
Mold mix	23.4	6.8	9.2	7.4	8.2	2.2	3.7	2.3	2.0	1.2	0.5	0.3
Cockroach												
Cockroach mix	25.7	10.4	7.6	7.7	30.5	12.8	12.1	5.6	35.7	15.6	10.4	9.7
Animal												
Cat hair	10.4	5.1	3.4	1.9	3.1	1.2	1.0	0.9	0.3	0.3	—	—
Dog hair	2.3	1.7	0.4	0.2	2.5	1.9	0.3	0.3	0.8	0.6	0.2	—
Rat epithelia	2.8	2.1	0.7	—	3.4	2.5	—	0.9	0.8	0.6	—	0.2
≥1 Of above	12.6				9.1				1.9			
Atopy												
≥1 Positive skin test result	57.7 (53.2, 62.2)				63.9 (58.6, 69.2)				49.0 (45.2, 52.9)			

Values in parentheses are 95% confidence intervals.

TABLE III. Allergen sensitization as risk factor for asthma and allergic disease

	Pollen		Mite		Cockroach		Mold		Animal	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Wheeze or asthma ever										
Hong Kong	1.7	0.7, 4.5	1.9	0.8, 4.7	1.1	0.6, 2.2	3.6*	1.8, 7.2	2.3*	1.2, 4.7
Kota Kinabalu	2.0	0.7, 5.6	5.8*	1.2, 28.8	1.4	0.5, 3.7	0.7	0.2, 3.5	1.7	0.5, 5.6
San Bu	1.2	0.1, 11.7	5.6*	1.0, 30.2	0.6	0.1, 2.7	8.5	0.6, 130.8	9.8	0.6, 162.3
Rhinitis										
Hong Kong	1.2	0.5, 2.9	3.9*	2.1, 7.2	0.9	0.5, 1.6	1.7*	1.0, 2.9	1.8	0.9, 3.4
Kota Kinabalu	1.0	0.5, 2.4	2.8*	1.3, 6.3	0.7	0.3, 1.5	2.4	0.8, 6.8	0.8	0.3, 2.5
San Bu	0.6	0.1, 4.7	2.1	0.7, 6.3	0.9	0.3, 2.9	2.7	0.3, 25.1	2.6	0.3, 24.4
Eczema										
Hong Kong	0.5	0.2, 1.6	1.4	0.7, 2.6	1.1	0.6, 2.0	1.4	0.7, 2.6	1.2	0.6, 2.4
Kota Kinabalu	5.6*	1.8, 17.2	0.6	0.2, 2.1	0.6	0.2, 1.8	2.1	0.5, 9.3	1.5	0.4, 6.3
San Bu	2.7	0.9, 7.4	0.6	0.3, 1.4	1.0	0.4, 2.1	1.7	0.3, 10.0	2.3	0.4, 14.5

Odds ratios (OR) were adjusted for age, sex, family history of atopy, and atopic reaction other than the one of interest. CI, confidence interval.

*Indicates significant associations.

influence on clinical allergic manifestations. In general, family history of a particular allergic disease was associated with the same allergic disease in the children but not with other clinical allergic manifestations (Table IV). An exception was seen in San Bu where a family history of eczema predicted not only eczema in the children but also asthma and rhinitis. Familial clustering of wheeze or asthma ever was particularly strong in San Bu with an odds ratio of 96.7.

The final statistical model assessed the independent effect of place of residence on asthma and allergic disease with adjustment made for age, sex, atopic status, and family history of allergy (Table V). With Hong Kong used as the baseline for comparison, living in San Bu was

associated with a 6 times lower odds of rhinitis and asthma whereas schoolchildren in Kota Kinabalu were 1.8 times less likely to report asthma and rhinitis and 3 times less likely to have eczema.

DISCUSSION

We evaluated the effects of allergen sensitization and family history of atopy on asthma and allergic disease in Chinese schoolchildren living in three southeast Asian cities. The important findings of the study were that (1) marked differences in the prevalence of asthma and allergic disease among the three cities were seen despite similar atopy rates, (2) sensitization to indoor allergens, particularly house dust mite, rather than outdoor aller-

TABLE IV. Family history of allergy as risk factor for asthma and allergic disease

	Family history					
	Wheeze or asthma		Rhinitis		Eczema	
	OR	95% CI	OR	95% CI	OR	95% CI
Wheeze or asthma ever						
Hong Kong	4.2*	2.2, 8.0	1.4	0.8, 2.4	0.7	0.4, 1.2
Kota Kinabalu	5.8*	1.7, 19.5	0.6	0.2, 2.3	1.5	0.4, 5.9
San Bu	96.7*	16.2, 575.8	2.8	0.3, 27.2	5.1*	1.1, 23.8
Rhinitis						
Hong Kong	1.3	0.8, 2.3	4.2*	2.9, 6.0	1.1	0.8, 1.6
Kota Kinabalu	2.3	0.9, 6.1	8.2*	4.0, 17.1	1.5	0.6, 3.9
San Bu	4.0	0.8, 19.5	5.4*	1.3, 22.1	3.6*	1.2, 10.7
Eczema						
Hong Kong	1.7	0.9, 3.1	0.9	0.6, 1.4	8.1*	5.6, 11.7
Kota Kinabalu	2.3	0.6, 8.7	1.9	0.6, 6.1	13.0*	4.2, 40.1
San Bu	1.9	0.4, 9.0	2.2	0.6, 8.9	16.9*	3.2, 34.8

Odds ratios (OR) were adjusted for age, sex, atopic status, and family history of allergic disease other than the one of interest. CI, confidence interval.

*Indicates significant associations.

gens was strongly associated with disease outcomes, (3) familial clustering of asthma and allergic disease was common, and (4) living in Hong Kong conferred a higher risk of asthma and allergy.

Prevalences of asthma and allergic disease vary between genetically distinct populations¹⁵ and genetically similar populations living in different environments.² Studies of migrants showed that the prevalence of asthma and allergies often changed after migration^{16, 17} and the extent of change correlated positively with the duration of exposure to the new living environment.¹⁶ Taken together, these epidemiologic studies emphasize the importance of environmental factors in the pathogenesis of asthma and allergic disease. This concept is further supported by our study, which demonstrated that the place of residence was an independent risk factor for asthma and allergies. One of the environmental factors most implicated in asthma and allergic rhinitis is exposure and subsequent sensitization to indoor allergens including house dust mite, cockroach, and domestic animals. Von Mutius et al.² found a higher prevalence of asthma and hay fever in schoolchildren in West Germany compared with those in East Germany and suggested that the difference in prevalence rates could be explained by sensitization to aeroallergens, particularly mite, cat, and pollen.

There is mounting evidence to indicate lower prevalence rates of asthma and allergic disease in southeast Asian populations compared with those in the West.^{4, 15} We showed that within southeast Asia, disease prevalence also differs markedly among ethnic Chinese populations of similar genetic background. More importantly, the proportion of atopic children was similar among the three populations, which therefore does not allow explanation of the difference in disease pathogenesis, a finding different from the hypothesis of Von Mutius et al.² Nevertheless, within each study popula-

TABLE V. Effect of place of residence on asthma and allergic disease in three Chinese populations

Place of residence	OR (95% CI)
Wheeze or asthma ever	
Hong Kong	1.0
Kota Kinabalu	0.57 (0.27, 1.18)
San Bu	0.16 (0.06, 0.41)
	Likelihood ratio statistic on 2 df = 21.8*
Rhinitis	
Hong Kong	1.0
Kota Kinabalu	0.59 (0.37, 0.94)
San Bu	0.15 (0.08, 0.27)
	Likelihood ratio statistic on 2 df = 51.9*
Eczema	
Hong Kong	1.0
Kota Kinabalu	0.34 (0.18, 0.66)
San Bu	1.01 (0.64, 1.58)
	Likelihood ratio statistic on 2 df = 28.7*

Adjustment was made for age group, sex, atopic status, and family history of allergic disease. Likelihood ratio statistic was obtained to determine significant difference in odds among the three populations. OR, Odds ratio; CI, confidence interval; df, degrees of freedom.

* $p < 0.001$.

tion, aeroallergen sensitization remained an important risk factor for asthma and allergic disease in children.

We found that mite allergy was associated with asthma, wheeze, and rhinitis in all three study populations. Moreover, the size of the wheal on positive skin test findings to house dust mite followed the same order as the prevalence of disease. Positive skin test wheal size has been associated with the occurrence of respiratory symptoms,¹⁸ the severity of bronchial hyperresponsive-

ness,¹⁹ and the severity of asthma morbidity in children.²⁰ The mite allergy rate of 43% to 60% in our study probably reflects heavy infestation of dust mite in south-east Asian coastal regions where the hot and humid climate provides the ideal habitat for dust mite growth. We did not measure dust mite allergens in homes because it was logistically prohibitive to collect and analyze dust samples with identical methods in the three cities at the time of study. Recent data showed that 50% and 69.2% of nonselected homes in Guangzhou and Hong Kong, respectively, contained Der p I levels of ≥ 10 $\mu\text{g/gm}$ of dust in dust samples recovered from mattresses (unpublished data). This suggests that a large number of homes in Hong Kong and Guangzhou are infested with house dust mite and contain mite allergen levels high enough to cause sensitization and asthma symptoms in sensitized subjects.

We found that nearly a quarter of the schoolchildren in Hong Kong were allergic to house mold, and mold sensitization was associated with asthma and rhinitis. Molds are ubiquitously present in homes in Hong Kong because of the warm and humid subtropical climate, and the most prevalent species have been identified as *Cladosporium* sp. (97%), *Penicillium* sp. (37%), and *Aspergillus* sp. (20%).²¹ In a longitudinal study of 981 subjects from infancy to age 4 years, sensitizations to both *Alternaria* and *Cladosporium* were significantly associated with the development of asthma, rhinitis, and eczema.²² In areas where dust mite and cockroach infestations are uncommon, allergy to domestic animals, particularly cat and dog, is a significant risk factor for asthma.²³ Domestic animal allergy can occur in susceptible children irrespective of pet ownership at home.²⁴ In traditional Chinese living in San Bu and Kota Kinabalu, pet keeping is uncommon in comparison with the Westernized city of Hong Kong where animal allergy was significantly associated with asthma. Up to 20% of adults with asthma in Hong Kong were sensitized to cat in a recent survey.²⁵ It is possible that the high prevalence of asthma and allergic disease in Hong Kong could be exacerbated by exposure to mold and animal allergens.

We found that familial clustering of asthma and allergic disease was common and was specific to the disease phenotypes. This could be partly caused by reporting bias by the parents who were more likely to recognize and therefore report symptoms similar to their own in their children. In the rural population of San Bu in southern China, the literacy rate was estimated to be as low as 60% and parents with a low education level might fail to recognize disease manifestations in children other than those manifestations they have themselves, thereby contributing to marked familial clustering of disease. Alternatively, factors common to the family, both genetic and environmental, may be important. A number of chromosome markers that link to asthma and atopy have recently been discovered,⁵⁻⁷ but none has been tested in a Chinese population. Environmental factors common to the family could be responsible for the observed clustering of disease as indicated by the

significant effect of place of residence in our study. A number of epidemiologic studies have suggested an inverse relationship between the occurrence of asthma and allergies and the incidence of respiratory infections^{26,27} and between asthma and atopy and family size.^{27,28} Martinez²⁹ proposed that viral infection, being more common in crowded dwellings, is capable of preferentially directing the maturation of T lymphocytes down a T_{H1} pathway and thereby inhibiting the development of T_{H2} lymphocytes and allergic sensitization, which may ultimately reduce the prevalence rates of asthma and allergic disease in susceptible children. Compared with homes in Western countries, southeast Asian homes tend to be more crowded and contain more family members. We did not assess family size and histories of respiratory infections in our study and the relationships among asthma, family size, and immunization rates in our region warrant further investigation. Crowded home environments would also allow other environmental factors to exert their effects on susceptible subjects, including exposure to air pollutants, tobacco smoke, and certain dietary substances all of which could potentially enhance allergic sensitization and increase asthma and allergic symptoms. Oxides of nitrogen (NO_2) from vehicle emissions and gas-fueled cooking stoves and kerosene space heaters are major components of ambient and indoor air pollutants. Two recent reports showed a synergistic effect between exposure to NO_2 and dust mite extract in causing a bronchoconstrictive response in mite-sensitive persons with asthma.^{30,31} In our study populations, mite allergy is common and many children live in small, crowded apartments with poor ventilation. Although mite allergy is equally prevalent among the three populations, it is plausible that different degrees of exposure to indoor air pollutants such as NO_2 might induce respiratory symptoms in mite-sensitive persons.

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