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ISAAC and risk factors for asthma in the Asia-Pacific

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INTRODUCTION

Asthma is one of the most common chronic disorders in childhood. There is considerable concern over the increase of the prevalence of asthma and related atopic disorders in western countries. Compared to the West, the prevalence of asthma in children from the Asia-Pacific has been reported to be lower.[1] Many epidemiological studies have been performed in the region and the prevalence of asthma appears to be increasing.[2–5] Unfortunately, the lack of standardisation of the study methodology among different studies made comparisons between countries difficult. Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC) developed a simple standardised method for measuring the prevalence of childhood asthma for international comparison.[6] Many countries in the Asia-Pacific have participated in the Phase-One study. These countries include China, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea and Thailand. A total of more than 130,000 children participated in this survey. In this article, we will review the data on asthma prevalence and discuss the possible risk factors associated with asthma in the Asia-Pacific.

ASTHMA PREVALENCE IN THE ASIA-PACIFIC

Before the widespread use of the ISAAC instrument in studying asthma prevalence in the region, there have been many surveys of asthma prevalence in different countries from the Asia-Pacific.[1,7–10] The prevalence, in general, is much lower than those reported in Australia, New Zealand and Western Europe. The reported rates of asthma vary widely from 1.1% to 19.5%.[1] The roles of genetic or environmental factors for the development of asthma and allergic disorders in the Asia-Pacific are largely unknown. A total of 20 centres from 8 countries from this region have participated in the ISAAC Phase One study. The sampling frame was schoolchildren of two age groups (13−14 and 6−7 years old). The total numbers of children studied were 83,826 and 49,476 in the two age groups, respectively. Table 1 summarises the prevalence of asthma symptoms in the 13−14-year-old children as documented by the written and video questionnaires. In general, the highest prevalence rates were found in the more affluent places such as Singapore, Japan and Hong Kong. However, the highest rates of 12-month prevalence of wheeze in 13−14-year-olds from Japan (10.2%) and Hong Kong (10.1%) were still significantly lower than the reported rates from Australia (17.6%) and New Zealand (18.4%) as documented by the video questionnaire.

Table 2 shows the prevalence of asthma symptoms in the 6−7-year-old children. The differences in the prevalence of asthma symptoms among the participating countries are similar to those found in the older age groups. Among the 90 centres from around the world that studied both age groups by the Phase-One protocol, there was a statistically significant correlation ($r = 0.71$, $P < 0.0001$) for the prevalence rates of wheezing in the past 12 months among the two age groups.

Several validation studies have been performed in children to assess the accuracy of the ISAAC written and video questionnaire in predicting asthma-

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Table 1
12-month prevalence of asthma symptoms in 13–14 year old children from the Asia-Pacific

Location	Written questionnaire			Video questionnaire		
	Wheeze	Wheeze disturbs sleep	Severe wheeze limiting speech	Wheeze	Wheeze disturbs sleep	Severe wheeze
China						
Mainland	4.2	0.3	0.7	2.0	0.6	1.2
Hong Kong	12.4	0.5	2.4	10.1	3.8	6.9
Indonesia	2.1	0.8	0.9	1.3	0.6	0.8
Japan	13.4	0.6	2.1	10.2	3.7	5.3
Malaysia	9.6	0.8	1.8	5.9	2.5	3.6
Philippines	12.3	2.0	4.1	9.6	3.9	4.9
Singapore	9.7	1.3	2.4	9.9	3.2	5.0
South Korea	7.7	0.2	2.7	3.7	0.5	1.9
Taiwan	5.2	0.4	0.8	4.6	1.8	2.8
Thailand	13.0	1.1	3.5	6.9	2.1	3.8
Regional	**8.0**	**0.6**	**1.8**	**5.3**	**1.8**	**3.1**

Table 2
Asthma symptoms (Written questionnaire) of 6–7-year-old children in the Asia-Pacific

Location	12-month prevalence				Ever had asthma
	Wheeze	Wheeze disturbs sleep	Exercise wheeze	Nocturnal cough	
Hong Kong	9.1	0.3	6.9	21.7	7.7
Indonesia	4.1	0.7	3.1	9.1	6.6
Japan	17.3	1.2	5.3	9.5	18.2
Malaysia	6.1	0.5	4.3	16.2	10.4
Philippines	11.3	1.4	6.7	30.6	16.4
Singapore	15.7	1.8	8.2	15.0	18.5
South Korea	13.3	0.5	4.4	17.4	8.5
Taiwan	9.6	0.8	6.0	17.0	12.7
Thailand	11.0	0.9	5.1	22.8	9.3
Regional	**9.6**	**0.7**	**5.0**	17.**6**	**10.7**

associated airway hyperresponsiveness.[11,12] We have also performed a comparative study of the ISAAC video questionnaire with the ISAAC written questionnaire for estimating bronchial hyperreactivity (BHR) as demonstrated by methacholine challenge test in Chinese children.[13] A total of 189 secondary school children (aged 12–18 years) were recruited for this study. A positive response to the video questionnaire on the question on wheeze in the past 12 months had sensitivity and specificity of 0.56 and 0.86 in predicting BHR. For the positive response of the same question by the written questionnaire, the sensitivity and specificity were 0.56 and 0.88. It is interesting to note that the question on 'asthma ever' had the highest sensitivity (0.88) and specificity (0.90) in predicting BHR. The ISAAC questionnaire has also been validated to be reliable in predicting airway hyperresponsiveness to hypertonic saline in a population of mixed ethnic background including Asian, European, and African countries.[11] Therefore, it appears that the ISAAC questionnaire is a valid tool for the assessment of asthma prevalence and symptoms in children.

SECULAR TRENDS OF ASTHMA PREVALENCE

There are many studies documenting an increasing prevalence of asthma in western countries.[14–17] Likewise, similar increasing trends were observed in a number of countries in the Asia-Pacific (Table 3).[18–21] A previous survey performed in 1992 in Hong Kong revealed that the prevalence of

Table 3
Secular trend of asthma prevalence in the Asia-Pacific

Location	Year	Age (years)	Asthma ever (%)	Wheeze ever (%)	Reference
Hong Kong	1989	8–10	7.4–7.7	8.3–10.9	1
	1992	12–16	6.6	7.8	7
	1995	13–14	11	20	4
Indonesia	1981	7–15	2.3	–	9
	1998	13–14	1.6	–	6
	1998	6–7	6.6	–	6
Malaysia	1990	7–12	8.7	–	8
	2000	7–12	10.3	12.5	18
Philippines	1991	<15	3.9	–	1
	1998	13–14	17.9	–	6
Singapore	1987	6–19	13.7	–	19
	1996	12–15	20.7	18.6	5
	1996	6–7	18.5	28.6	5
Taiwan	1974	7–15	1.3	–	3
	1985	7–15	5.1	–	3
	1998	13–14	9.0	–	6
Thailand	1987	6–12	4.3	–	20
	1998	6–7	9.5	17.4	21
	1998	13–14	14.2	19.2	21

asthma ever and wheeze in the past year were 6.6% and 3.7% respectively.[7] From the ISAAC Phase-One results from Hong Kong during 1995–1996, the prevalence of asthma ever and wheeze in the past year were 11.2% and 12.4%.[4] Using the same Japanese version of the American Thoracic Society (ATS) children's questionnaire, Nishima demonstrated that asthma prevalence in Japanese children has increased from 3.5% in 1982 to 4.6% in 1992.

Similarly, two surveys using identical methodology performed in Taiwan revealed that the prevalence of childhood asthma has increased from 1.3% in 1974 to 5.07% in 1985.[3] One of the most highly developed countries in the region is Singapore. The prevalence of asthma ever in children has increased from 5.5% in 1967, to 13.7% in 1987, and to 20.7% in 1996.[5] Given the fact that genetic factors are unlikely to be responsible for these increasing trends, it is tempting to speculate that environmental factors are responsible for the increase of asthma in these countries. However, many of these surveys were conducted in the form of written questionnaire only, and increasing awareness of asthma in the community might have been partly responsible for the apparent increase. Therefore, the use of same standardised questionnaire and methodology is important in order to have accurate comparison between countries and assessment of the trends of asthma prevalence. Furthermore, the word "wheeze" used in the written questionnaire may not be easily understood by studied subjects as an equivalent term may not be available in the local languages used in the Asia-Pacific. To overcome this possible methodological problem of translation, the video questionnaire will be a valuable tool to assess the possible increasing trends in the region.

It has been almost 8 years since the ISAAC Phase-One studies were performed in the region. The same countries will participate in the Phase-Three studies using identical methodologies used in the Phase-One study. It is anticipated that the true secular trends, if any, in the prevalence of asthma will be revealed.

ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF ASTHMA

Although genetic factors are important in the manifestation of asthma and allergic disorders, the rapid increase in the prevalence of these disorders is more likely due to changing environmental factors. One of the approaches in assessing the role of environment on asthma is to study the prevalence of asthma in populations of the same ethnic background living in different environments.

Table 4
Prevalence of asthmatic symptoms and atopic sensitization in Chinese schoolchildren from three Chinese cities: ISAAC Phase Two

	Hong Kong		Beijing		Guangzhou	
	%	95% CI	%	95% CI	%	95% CI
Written questionnaire	*N* = 3110		*N* = 4227		*N* = 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
Skin-prick test	*N* = 1341		*N* = 1044		*N* = 1094	
Atopy (⩾1 positive skin test)	41.2	38.6−43.8	23.9	21.4−26.6	30.8	28.1−33.7
D. pteronyssinus	34.1	31.5−36.7	7.5	5.9−9.3	20.0	17.7−22.5
D. farinae	25.9	23.6−28.3	5.7	4.3−7.2	17.9	15.7−20.3
Cockroach	11.5	9.8−13.3	13.3	11.3−15.6	17.3	15.1−19.7

von Mutius et al.[22] found a higher prevalence of asthma and hay fever in schoolchildren in West Germany compared with those in East Germany highlighting the importance of environmental factors on the development of atopic disorders. Leung et al.[7] reported a survey to compare the prevalence of asthma and atopic disorders in Chinese children aged 12−18 years from three Asian cities: Hong Kong, Kota Kinabalu and San Bu. Hong Kong is the most developed and westernised city. San Bu is a small Chinese city located 200 km west of Hong Kong while Kota Kinabalu is a Malaysian city located on the Island of Borneo. Asthma and allergic disorders were 2 to 6 times higher in Hong Kong when compared with the other two groups of children. Within each study population, allergic sensitisation was a significant factor associated with asthma. However, the prevalence of atopy in Kota Kinabalu was high (64%) and yet the prevalence of asthma was low (1.9%). Detailed studies of these populations of Chinese children may prove to be very useful in assessing the possible environmental determinants for asthma.

A large-scale epidemiological study has also been performed in Korea. Kim et al.[23] studied 3219 Korean children aged 7−19 years using a modified ATS respiratory questionnaire, skin-prick test as well as methacholine challenge test. Similar to the Chinese study, the prevalence of atopy was high (35%) but the prevalence of asthma was only 4.6%. These rates of atopy are higher than those found in New Zealand where the asthma prevalence is significantly higher, questioning the role of atopy in the development of asthma especially in the Asia-Pacific.[24]

ISAAC Phase Two has been designed to assess the prevalence of 'objective' markers of asthma and allergic disorders and to investigate the possible environmental determinants of atopic diseases in different population groups.[25] The detailed protocol has been developed for use in 9−11-year-old children, and subjects were studied by parental questionnaires, skin-prick tests, skin examination and bronchial challenge tests. More than 10,000 children from 3 Chinese cities, Hong Kong, Beijing and Guangzhou, were studied using the Phase-Two protocol.[26] Hong Kong is a highly westernised city with subtropical climate. Guangzhou is situated approximately 200 km north of Hong Kong and has a similar climate to Hong Kong while Beijing is in the temperate zone. Prevalence estimates of symptoms and diagnosis of asthma were significantly lower in Beijing and Guangzhou than in Hong Kong (Table 4). In line with the questionnaire results, visible signs of flexural eczema were significantly more prevalent in Hong Kong (3.4%) than in the other two cities (1.1 and 0.8%). Furthermore, atopy and allergic sensitisation to dust mites were significantly more common in children from Hong Kong. Of the subjects recruited in Hong Kong, 440 were born in Mainland China and their median age of migration to Hong Kong was 3.4 years. Being born in Hong Kong was significantly associated with current wheeze (OR 4.07; $P < 0.001$). Table 5 shows the difference in responses to written questionnaire and prevalence allergic sensitisation between children born in Hong Kong and in Mainland China. Being born in Hong Kong remained significantly associated with current wheeze even after adjustment for their atopic status (OR 2.86; $P = 0.04$), indicating factors other than atopy are also important in the development of asthma. Since the prevalence rates of atopic

Table 5
Comparison of children born in Hong Kong and Mainland China: response to ISAAC written questionnaire and prevalence of allergic sensitization within the group of children recruited from Hong Kong

	Hong Kong		Mainland	
	%	95% CI	%	95% CI
Written questionnaire	*N* = 2599		*N* = 440	
Asthma ever	8.6	7.6–9.8	2.1	0.9–3.8
Wheeze in past year	6.5	5.6–7.5	1.4	0.5–2.9
Nocturnal cough in past year	15.0	13.7–16.5	7.1	4.8–9.8
Skin-prick test	*N* = 1232		*N* = 109	
Atopy (⩾1 positive skin test result)	42.9	40.5–45.7	22.0	14.6–31.0
D. pteronyssinus	35.7	33.1–38.4	15.6	9.4–23.8
D. farinae	27.0	24.6–29.6	12.8	7.2–20.6

symptoms and allergic sensitisation in the children born in Mainland China and subsequently emigrated to Hong Kong were comparable to those of children from Beijing or Guangzhou, early-life experience and environmental factors are probably important determinants of subsequent development of asthma and related atopic disorders.

Among the suspected environmental factors associated with asthma, allergic sensitisation has been most widely implicated as one of the most important risk factors in Caucasian children. In particular, house dust mite exposure and sensitisation during early childhood have been found to be associated with subsequent development of asthma in Caucasians.[27,28] In a study of Korean children, the prevalence of asthma was significantly more common among the atopics (6.8%) than the nonatopics (2.7%).[23] Similarly, a study of 3067 schoolchildren aged 11–17 years from Guangzhou showed that bronchial hyperresponsiveness was significantly associated with atopy.[29] These studies, however, did not assess the relative importance of different allergens in the manifestation of asthma in their subjects.

A study of 204 Chinese asthmatic children recruited from a hospital-based specialty clinic revealed that atopy was extremely common among asthmatics (83%). Furthermore, the mean reversibility of FEVI following inhalation of a bronchodilator in atopic and non-atopic patients differed significantly (10.0% vs 4.1%; $P < 0.001$).[30] In the ISAAC Phase-Two study of Chinese children, we confirmed that allergic sensitisation to house dust mite and cat is significantly associated with current wheeze and bronchial hyperresponsiveness in Chinese schoolchildren.[31] However, the difference in sensitisation rate cannot be explained by the difference in allergen exposure as the domestic levels of aero-allergens in Hong Kong and Guangzhou have been found to be similar.[32] In addition, despite a significantly higher rate of atopy and sensitisation to house dust mite in Guangzhou when compared with those of Beijing, the prevalence of asthma symptoms were similar in these two cities. Therefore, other factors such as early viral infections, breast-feeding and dietary factors most likely also play important roles in the development of asthma and allergic sensitisation.

Preliminary analyses from the ISAAC Phase Two data from the three Chinese cities suggested that the use of foam pillow and gas as cooking fuel were also risk factors for asthma symptoms.[33] The use of synthetic-filled pillows and gas as cooking fuel have also been implicated as possible risk factors for asthma in Caucasians.[34,35] Further comparative studies are necessary to clearly define the roles of these factors in the manifestation of asthma in children from the Asia-Pacific.

Outdoor environmental pollution has been thought to be an important factor associated with deterioration of respiratory health. Many cities from the Asia-Pacific region have high levels of outdoor environmental pollutants and yet the prevalence of asthma is relatively low. Although we have demonstrated that increasing levels of outdoor environmental pollutants including nitrogen dioxide and sulphur dioxide were associated with hospital admission rate for childhood asthma in Hong Kong,[36] differences in the levels of outdoor pollutants are unlikely to explain the higher prevalence rate of asthma in Hong Kong when compared with those in Mainland China. The ambient levels of pollutants in Guangzhou are much higher than those in Hong Kong,[37] but the prevalence of asthma in Guangzhou is only about half of that in Hong Kong.

CONCLUSION

With the economic improvement and westernisation of many countries of the Asia-Pacific, we are encountering an increasing prevalence of asthma and related allergic disorders. The exact mechanisms and determinants underlying these increases remain unclear. Although allergen sensitisation in the region has been found to be at least as common as in Caucasians, the current prevalence of asthma is still significantly less in the Asia-Pacific. Epidemiological studies using a standardised protocol, like those of ISAAC, have provided important information for valid comparison of asthma prevalence in the region and around the world. Further comparative and longitudinal studies are necessary to clearly define the possible environmental determinants for the development of asthma and allergic diseases in the Asia-Pacific. Otherwise, it may not be too long before we see the prevalence of asthma in the region catching up with those in Australia and Western Europe.

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