



## Asthma Epidemiology in Chinese: What Have We Learnt So Far?

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Asthma is one of the most common chronic respiratory disorders. With the rapid economic development and industrialisation in many Asian cities, the prevalence of asthma appears to be increasing. In particular, non-standardised questionnaire surveys in Hong Kong and a few cities in Mainland China also suggested that the prevalence of asthma in Chinese might be increasing. Over the past decade, many research studies have supported the "hygiene hypothesis" that infections in early life might prime the immature immune system resulting in protection against subsequent development of atopic diseases. Comparative studies among Chinese children living in different environments have revealed several factors associated with the development of asthma. Longitudinal studies are now needed to confirm the exact role of the identified risk factors for the development of asthma among the Chinese population. Confirmation of the causative role of these factors is crucial for designing primary preventive strategies against the development of asthma in Chinese.

### Introduction

Asthma is one of the most common respiratory disorders in the Western world. Many research studies in different regions of the world have suggested that the prevalence of asthma and related atopic disorders has increased over the past few decades<sup>1</sup>. However, the prevalence of asthma among Chinese was lower when compared with the Caucasians<sup>2</sup>. Studies from Hong Kong also suggested possible increasing prevalence of childhood asthma<sup>3-5</sup>, but the use of different methodologies and lack of precise definitions of asthma cast doubt on the actual trend of asthma prevalence in different regions. Over the past decade, there is increasing use of standardised protocol to study asthma prevalence. The International Study of Asthma and Allergies in Childhood (ISAAC) attempted to study the global variations of asthma and atopic disorders in children by using standardised questionnaire, skin-prick testing and assessment of bronchial hyperresponsiveness<sup>6-8</sup>. Among the Asian countries, prevalence rates of asthma and atopic disorders were found to be higher in more developed places like Japan and Hong Kong. Interestingly, the prevalence of asthma in Hong Kong school children was highest among all the Chinese populations. In our practice, many patients and parents frequently ask whether there are any proven primary preventive measures to reduce the risk of asthma. In this article, we will review the recent research findings of the epidemiology of asthma in Chinese and discuss the possible primary preventive strategies for asthma.

### Asthma epidemiology in Chinese

Although many epidemiological studies of asthma have been performed in Asia including many studies with population of Chinese ethnic background, the lack of standardised methodology made meaningful comparisons between studies extremely difficult. Most studies used simple symptom questionnaires to determine the prevalence of childhood asthma in a particular region. The target age groups were different and many of the questionnaires have not been validated. The patients or their parents' responses are likely to be influenced by their understanding of asthma symptomatology. Some studies used "physician's diagnostic label" as a measure of the prevalence of asthma and a low prevalence of asthma might well be due to under-diagnosis in the community.

To minimise the linguistic problem of the written questionnaire, the International Study of Asthma and Allergies in Childhood (ISAAC) includes a video questionnaire showing children and adolescents with different asthma symptoms in addition to the written questionnaire. After watching a video-tape showing subjects with various asthma symptoms such as wheeze and cough, the subjects were then asked if they have similar symptoms and the frequencies of such symptoms if present. Furthermore, the Phase II protocol of ISAAC also included "objective measurements" such as skin-prick test and bronchial hyperresponsiveness (BHR) testing to supplement the written questionnaire. Several validation studies have been performed in children to assess the accuracy of the ISAAC written and video questionnaires in predicting asthma associated BHR<sup>9,10</sup>. We have performed two studies to assess the ability of the ISAAC written and video questionnaires in estimating BHR in Chinese children<sup>11,12</sup>. The sensitivity and specificity for a positive response to the video questionnaire on the question of wheeze in the past 12 months were 0.56 and 0.86 respectively in predicting BHR. Having a physician diagnostic label of asthma had the highest sensitivity (0.88) and specificity (0.90) in predicting methacholine induced BHR. Therefore, the standardised ISAAC questionnaire appears to be an acceptable tool to assess the prevalence of asthma in Chinese children.

### Prevalence and secular trend of asthma in Chinese

With the use of standardised tools such as the ISAAC questionnaires, the global map of asthma epidemiology is





now available showing marked variations of asthma prevalence in different regions of the world<sup>13</sup>. The more interesting fact is that populations with similar genetic background living in different environments were found to have very different prevalence rates of asthma. Such disparity demonstrated the importance of environmental factors as determinants of asthma. Phase One of the International Study of Asthma and Allergies in childhood was carried out between 1994-1995 and it used standardised questionnaires to assess the prevalence and severity of asthma in schoolchildren of 2 age groups (6-7 and 13-14 years) from many regions of the world<sup>6,13</sup>. As the populations from different countries have markedly different genetic background and they are exposed to different environmental factors, it may be difficult to determine what are the specific factors responsible for the variation in the prevalence of asthma. Comparative studies of Chinese children living in different environments might be more revealing. Chinese children from Hong Kong were found to have the highest prevalence rate of wheeze, which is 2 to 3 folds higher than the rates documented in Mainland China using the same standardised methodology<sup>14</sup>. The 12-month prevalence rates of wheeze in 13-14-yr-old children, 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%. Therefore, environmental factors are likely to be important factors affecting subsequent development of asthma in later life. Furthermore, the prevalence rates of asthma symptoms in the children born in Mainland China and subsequently emigrated to Hong Kong were significantly lower than those children born and raised in Hong Kong<sup>14</sup>. Thus, early environmental and social exposure factors most likely can influence the subsequent development of asthma.

Many recent questionnaire surveys suggest that prevalence of asthma is increasing in many Western countries<sup>15,16</sup>. Increased community awareness of asthma and related atopic disorders are most likely responsible for some of the documented increase. In Hong Kong, there is also evidence suggesting similar increasing trends of asthma prevalence<sup>3-5</sup>. A questionnaire survey of schoolchildren aged 12-18 years performed in 1992 in Hong Kong revealed that the prevalence of asthma and wheeze in the past year were 3.7% and 6.6%<sup>17</sup>. The Phase One ISAAC study was conducted 1995 and the results showed that the prevalence of asthma and wheeze have increased to 11.2% and 12.4% in 13-14 year old children.

We have carried out the phase III ISAAC study in 2002 using the same standardised and validated protocol. When compared with the data obtained in the Phase I study (1995), the prevalence rates of physicians' diagnosis of asthma did not change significantly. They were 11.2% and 10.2%, respectively<sup>18</sup>. However, the control of asthma among the affected children appeared to be better. For those with a diagnostic label of asthma, the prevalence rates of nocturnal wheezing attack in the past year have decreased from 21.2% to 9.5%. Similarly, the prevalence rates of exercise-induced wheezing have decreased from 30.3% to 15.4%. It appears that the prevalence of asthma has not increased over the past 7 years and the control of asthma appeared to have improved. Further analyses of the ISAAC data from the other Asian centres are necessary to find out whether this has been the general trend across different countries in Asia.

## Risk factors for asthma in Chinese children

There have been many studies suggesting a variety of environmental and dietary risk factors are associated with the development of asthma<sup>19-21</sup>. However, one should note that none of these factors have been proven to be causative by prospective studies. Furthermore, no strategies have been proven to prevent the development of asthma in at-risk individuals. It is highly likely that one has to have the underlying genetic predisposition coupled with exposure to important environmental factors at the appropriate time in order to result in the subsequent manifestation of asthma<sup>22</sup>. Furthermore, recent prospective studies revealed that allergen avoidance was not effective as a primary preventive measure for the development of asthma<sup>23,24</sup>.

The prevalence of asthma has been found to be the highest in Hong Kong among the Chinese populations. Usually the same methodology, the prevalence was only one-third of that in Hong Kong in a nearby city of Guangzhou. Given the similar genetic background of the children from Hong Kong and the cities in Mainland China, environmental factors are likely to be important in determining subsequent risk of asthma. We, therefore, used the same Phase II ISAAC protocol to study representative samples of children from three Chinese cities, Hong Kong, Beijing and Guangzhou to determine the possible risk factors that are associated with the development of asthma<sup>25</sup>. More than 10,000 children were recruited from 3 cities for this study. The symptoms of asthma, atopic sensitisation, and early and current environmental exposures were recorded. After adjustment for factors that are known to be associated with asthma such as family history of allergic diseases, educational level of the parents, and sex, six risk factors for the development of asthma were identified. Using gas as cooking fuel, use of foam pillow, and damp housing were strongly associated with asthma and wheeze. Use of cooking quilt, consumption of fruits and raw vegetables were associated with reduced risk of asthma. This study suggests that the six factors or unmeasured factors associated with these may be responsible for the lower prevalence of asthma among children in Mainland China.

In the phase II study of Chinese children, attendance of daycare and the presence of siblings was also found to be associated with reduced risk of asthma symptoms in line with what is suggested by the hygiene hypothesis. The possible biological explanation for the "hygiene hypothesis" is that early childhood infections may up-regulate T-helper (Th) 1 and down-regulate Th 2 immune response<sup>26</sup>. Different immunocompetent cells produce different profiles of cytokine and may either facilitate or suppress IgE production. The major cytokines produced by Th1 cells are interleukin (IL)-2 and interferon gamma (IFN- $\gamma$ ). The important cytokines produced by Th-2 cells are IL-4, IL-5, and IL-13<sup>27</sup>. IL-4 is an important signal to induce switching from the production of IgM to IgE in B cells whereas production of INF- $\gamma$  is induced by viral infections and it inhibits the proliferation of Th-2 cells and the production of IgE. Therefore, frequent early infections may induce Th-1 predominance resulting in relative resistance to the development of atopic disorders.

There have been many recent studies confirming the protective role of farming environment against the





development of asthma and related atopic disease. In a study from Switzerland, schoolchildren raised on a farm had significantly lower rates of seasonal rhinitis symptoms and atopic sensitisation<sup>28</sup>. In a large study with 10,163 German children aged 5-7 years, farmers' children had lower prevalence of hay fever (OR 0.52; 95%CI 0.28-0.99), asthma (0.65, 0.39-1.09), and symptom of wheeze (0.55, 0.36-0.86) than peers not living in an agricultural environment<sup>29</sup>. Furthermore, increasing exposure to livestock was related to a decreasing prevalence of atopic diseases. Another study from Australia revealed that children live on farms devoted to crops were not protected against asthma or atopy<sup>30</sup>. As a whole, these studies suggested that exposure to farm animals is the most important factor associated with protection against the development of asthma or atopy.

There have also been studies investigating the prevalence of asthma and atopic disorders among the populations from both the rural and urban setting. Chan-Yeung et al carried out a questionnaire survey of adults 20-44 years old in rural Beijing. The prevalence of reported asthma attack in the previous 12 months was only 0.67%<sup>31</sup>. Another study of rural and urban Beijing school children using the ISAAC Phase 3 protocol revealed that children from the rural area had significantly lower prevalence of asthma symptoms and atopic sensitisation when compared to children from the urban area<sup>32</sup>. The prevalence of wheeze in the past 12 months in urban Beijing was 5.3% while it was only 1.5% in the rural area. Further studies are needed to determine the exact protective factors against asthma in the rural environment.

### Conclusions

Over the past two decades, there have been many excellent epidemiological studies of asthma performed in many Asian countries. Many of the recent studies in Chinese have used standardised and validated methodology. It is interesting to note the extremely low prevalence of asthma in some regions such as rural China. In Hong Kong, the prevalence of childhood asthma remained at 10% over the past 8 years while the control of asthma appeared to have improved. Over the past decade, many research studies have confirmed the protective role of traditional type of living such as living in a farming environment as suggested by the "hygiene hypothesis". Cross-sectional studies done in Chinese have identified the possible risk factors, which may be important in the development of asthma. It should be emphasised that there is no proven primary preventive strategy for asthma. Well-controlled prospective intervention studies are necessary to test if the identified risk factors have any causative relationship with the development of asthma. Until then, we will be able to advise our patients with evidence-based strategies for primary prevention of asthma.

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