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The Contribution of ISAAC to the Understanding of Asthma

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The rising trend of asthma prevalence in industrialized countries has become a major public-health issue. However, despite intensive research in past decades, the mechanisms underlying this increase are still largely unclear. One way to investigate the etiology of a disease is through international comparisons of its prevalence. This provides us with the opportunity to evaluate whether our current knowledge of putative risk factors can account for the differences seen among different populations (including different populations with the same ethnic origins) and at different times. Furthermore, this may help identify "new" risk factors that hitherto have not been hypothesized or adequately studied. This approach has been used in the International Study of Asthma and Allergies in Childhood (ISAAC).[1]

WHAT IS ISAAC?

ISAAC is a large-scale, international, epidemiologic study developed in the early 1990s by researchers from New Zealand, Europe, and the United States. Subsequently, this core group included regional representatives from Asia, Africa, the Middle East, and South America. The objectives of ISAAC are threefold: (1) to describe the prevalence and severity of asthma, allergic rhinoconjunctivitis, and atopic eczema in children living in different areas and to make comparisons within and between countries; (2) to obtain baseline measures for assessment of future trends in the prevalence and severity of these diseases; and (3) to provide a framework for further etiologic research into lifestyle, environmental, genetic, and medical care factors affecting these diseases.

Phase I of the study, which aimed to obtain an overview of the global prevalence and severity of asthma, rhinitis, and eczema in children, was carried out in two groups of schoolchildren: 6–7 years and 13–14 years of age. It had a simple and inexpensive design to encourage maximum participation from as many centers as possible around the world. At the same time, the quality of data was ensured by standardization of the investigative tools used and a uniform approach to sampling of subjects. The phase I tools comprised a set of standardized written questionnaires relating to asthma, rhinitis, and eczema for self-completion by the 13- to 14-year-old schoolchildren and for completion by parents/carers of the 6- to 7-year-olds. Standardized methods of translation and back-translation were used to ensure comparability of findings across different populations and language groups. In addition, a video questionnaire showing five scenes of asthma symptoms and signs was used in the 13- to 14-year-old group in an attempt to overcome problems associated with translating the written questionnaire. Indeed, the video questionnaire has been shown to be comparable to the written questionnaire in predicting bronchial hyperresponsiveness to methacholine and is more reproducible.[2,3]

WHAT DO THE PHASE I DATA SHOW?

By the time the main phase I findings were published in 1998,[1] nearly half a million

13- to 14-year-old schoolchildren of diverse ethnic and cultural backgrounds from over 150 centers in more than 50 countries had completed that phase of the study, which focused on the global prevalence and severity of asthma, rhinitis, and eczema. About half of the centers also conducted the survey in the 6- to 7-year-old group. Striking variations in the prevalence of asthma symptoms were observed among different populations, with up to 15-fold differences seen between countries and smaller differences within individual countries. The prevalence of self-reported wheezing in the previous 12 months (current wheeze) ranged from 2.1 to 32.2% in the older age group and from 4.1 to 32.1% in the younger age group.[4] In centers where similar studies had been conducted in the past, evidence showed an increasing trend in asthma prevalence—not only in the developed countries but also in developing countries such as those in the Asia-Pacific region (Table I).[4,5]

Table I

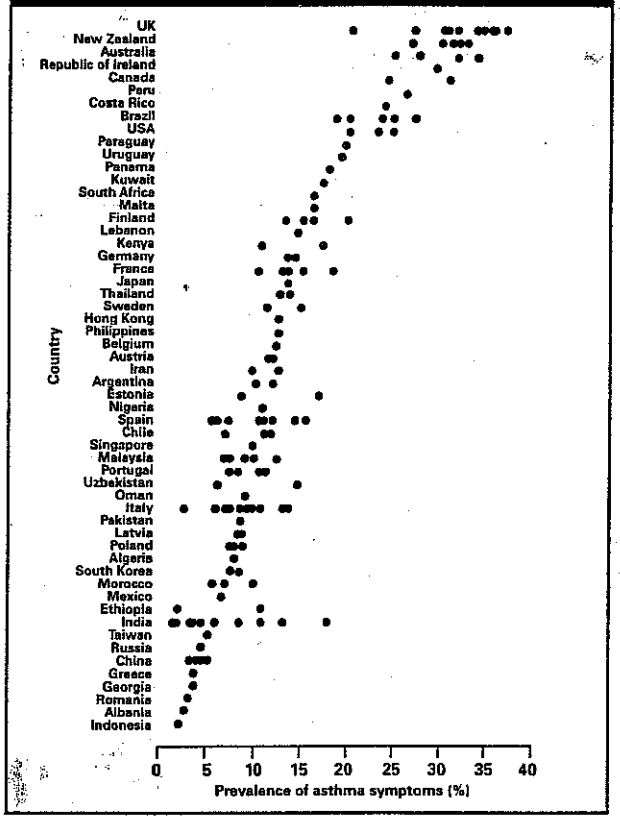
Time Trends in Prevalence of Asthma and Asthma Symptoms in Children of Asia-Pacific Countries

Country/Area	Year	Wheeze (%) Past Year	Wheeze (%) Ever	Ever had Ashtma (%)
China				
Guangzhou	1987			2.4
	1995	3.4	7.8	3.9
Hong Kong	1992	4–7	7–10	7–10
	1995	9.1–12.4	16.4–16.9	7.7–11.2
Indonesia	1981			2.3
	1991			8.2
	1995	2.1–4.1	5.9–6.2	1.6–6.6
Japan				
Western Japan	1982			3.3
	1992		5.2	4.6
	1995	13.4–17.3	26.8–33.7	18.2–18.9
Malaysia				
Kuala Lumpur	1990			13.8
	1995			11.1–13.9
Philippines	1991		20.6	3.9
	1995		20.4–24.1	16.4–17.6
Singapore	1967			3–5.5
	1987			13.7
	1995	9.7–15.7	18.1–25.8	18.5–20.9
Taiwan	1974			1.3
	1985			5.06
	1991			5.8
	1995	5.2–9.6	10.6–16.1	9–12.7
Thailand	1987			4.3
	1995	8.2–13	10.6–16.1	6.7–11.6

Adapted from ISAAC Steering Committee *Eur Respir J* 1998; 12:315-335; Lai CKW et al *Clin Exp Allergy* 1996; 26:5-12.

The highest prevalence of asthma symptoms was seen in English-speaking countries (Fig. 1), i.e., the British Isles, New Zealand, Australia, Canada, and the United States.[6] While differences in language or labeling of symptoms such as wheeze may explain, in part, the international differences, the fact that similar patterns were observed with the video questionnaire suggest that these differences are real. Furthermore, the European Community Respiratory Health Survey (ECRHS) also reported that asthma symptoms were most prevalent in adults of English-speaking countries.[7] It could be hypothesized that these data suggest that genetic influences may be important in the etiology of asthma. However, within English-speaking countries, there is little evidence of ethnic differences in childhood asthma prevalence, indicating that the high prevalence seen is likely to be due to environmental rather than genetic factors.[8]

Figure 1



Wheeze in the previous 12 months for each center, by country, according to mean prevalence for all centers in the country. (Adapted from ISAAC Steering Committee. Worldwide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivits, and atopic eczema: ISAAC. *Lancet* 1998;351:1225-1232.

Even among populations of similar ethnic origins, the prevalence of asthma symptoms varied widely. Thus, children in some Latin American countries (Peru, Costa Rica, and Brazil) had more than twice the 12-month prevalence of wheeze of children in Spain. Chinese schoolchildren in Hong Kong had a fourfold higher prevalence than their counterparts in Guangzhou, a city on mainland China just 150 miles north of Hong Kong that uses the same language and has a similar climate. These findings strongly support an important role for environmental factors in the causation of asthma.

In general, the prevalence of asthma symptoms is higher in more affluent than in developing countries.

Asthma prevalence in western Europe is higher than in less affluent countries in eastern and southern Europe. A similar pattern was seen in Southeast Asia where the most affluent countries (Japan and Hong Kong) have higher prevalence rates of asthma symptoms than the least affluent countries (China and Indonesia). Indeed, ecologic analysis of phase I data revealed a significant positive correlation between the gross national product per capita of 47 countries and the 12-month prevalence of wheeze in their 13- to 14-year-olds.[9] The correlation was not absolute, however, because the highest prevalences were in English-speaking countries, which were mostly in the second gross national product quartile of the countries considered.

WHAT DOES ISAAC TELL US ABOUT THE ETIOLOGY OF ASTHMA?

The ISAAC phase I data provide a useful framework for examining putative risk factors in the development of asthma. Whether any of these factors play an important role can be determined if they can account for the global pattern of asthma prevalence, i.e., the high prevalence in western countries and the association of asthma with affluence.

Air pollution has been considered one of the important causes for the rising prevalence of asthma. Although pollutants such as particulate matter, ozone, sulphur dioxide (SO_2), and nitrogen dioxide can trigger symptoms in asthma sufferers, convincing evidence for their role in the inception of asthma is still lacking. This is further supported by the ISAAC phase I data. Regions such as China and eastern Europe, which have some of the highest levels of particulate matter and SO_2, had a significantly lower prevalence of asthma than the countries of western Europe and North America, Australia, and New Zealand, areas with much better air quality. Ecologic analysis of phase I data in Asian cities also revealed a negative rather than positive correlation between the 12-month prevalence of wheeze and the ambient concentrations of total suspended particles. Similarly, it is unlikely that cigarette consumption can account for the global pattern of asthma prevalence.

While atopy has long been recognized as an important risk factor for asthma, a recent meta-analysis of population surveys suggested that the proportion of asthma cases attributable to atopy is usually less than one-half.[10] The evidence that allergen exposure itself is a primary cause of asthma is relatively weak.[11] Preliminary analysis of the ISAAC phase II data in 10-year-old Chinese schoolchildren showed that atopy may contribute, in part, to the higher prevalence of asthma symptoms in Hong Kong than on mainland China. The prevalence of atopy (defined as at least one positive response to a group of common inhaled allergens) was higher in Hong Kong children (41.2%) than in those from Beijing (23.9%) or Guangzhou (30.8%). The corresponding prevalence rates of 12-month wheeze in the three cities were 5.8%, 3.8%, and 3.4%. Interestingly, despite its higher atopy rate, Hong Kong's levels of indoor allergens—house-dust mite, cat, and cockroach—were similar to those in Guangzhou (Table II). These findings suggest that an increased susceptibility to allergic sensitization may be responsible for the discrepancy in asthma prevalence in different Chinese communities.

Table II

Concentrations of Common Indoor Allergens in Mattresses of Schoolchildren in Hong Kong and Guangzhou*

	Hong Kong	Guangzhou	P
Der p1 (µg/g pf dust)	5.7 (0.1–78)	6.6 (0.1–61.2)	NS
Fel d1 (µg/g of dust)	0.1 (0-3.7)	0.2 (0.02–5.9)	NS
Bla g2 (units/g of dust)	0.1 (0-1.1)	0.1 (0-5.8)	NS

* Values are geometric means (range).

The recognition that a smaller family size is associated with a higher prevalence of atopy and, to a lesser extent, asthma suggests that infection, particularly if it occurs early in life, may have a protective effect on the development of allergic disease. This so-called hygiene hypothesis has gathered momentum in recent years and has been used to explain, at least partly, the higher prevalence of allergy, including asthma, in more affluent societies and the protection afforded by a farming lifestyle.[12] In support of this hypothesis, ecologic analysis of ISAAC phase I data has shown a significant negative correlation between the national tuberculosis notification rates and the lifetime prevalence of wheeze, and between tuberculosis notification rates and the prevalence of 12-month symptoms of allergic rhinoconjunctivitis in 13- to 14-year-old children from 23 countries.[13]

The higher prevalence of asthma and allergy in western countries suggests that a westernized diet may play a role. One of the typical components of the "western" diet is *trans*fatty acids, which are present in dairy products, the fat of ruminant animals, and hydrogenated vegetable fats such as margarine, oils, cakes, chips, and biscuits. One of the possible mechanisms by which *trans*fatty acids may affect the development of allergic inflammation is through their effect on the desaturation and chain elongation of n-6 and n-3 fatty

acids into precursors of lipid mediators such as prostaglandins and leukotrienes. Ecologic analysis of ISAAC data from 10 European countries showed a significant positive correlation between per capita consumption of *trans*fatty acids and the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema.[14] Furthermore, ISAAC data from 53 countries revealed significant negative relationships between the amount of vegetable consumption and the prevalence of symptoms of each of three atopic conditions.[15] Possible mechanisms for this apparent protective effect of fresh vegetables may include their antioxidant activities, influence on intestinal flora, and other unidentified properties.

ARE WE ANY WISER WITH THE ISAAC DATA?

Although the phase I data provide, for the first time, valuable information on the global prevalence of asthma, rhinoconjunctivitis, and atopic eczema, we are still not closer to identifying the causative factors of these diseases. These data are useful, however, in assessing the importance of putative risk factors, including outdoor air pollutants, indoor allergens, infections in early life, and diet. ISAAC data not only call the "established" risk factors into question; they also identify associations that any new theory is required to explain. Recent decades have seen decreasing family size, reduced exposure to infections, and increasing size at birth, as well as increasing use of medical interventions such as immunization and antibiotics. As a result of this "package" of changes in the intrauterine and neonatal environments, we are seeing an increased susceptibility to the development of asthma and/or allergy. Understanding why this increased susceptibility is occurring, and ascertaining which elements of the package of 20th century economic development and lifestyle changes are responsible (or whether the entire package is more than the sum of its parts), represents a significant challenge as well as a major opportunity for asthma epidemiologists in the new millennium. In particular, any factor(s) that can account for the global distribution of asthma will undoubtedly be important in the causation of this common and potentially disabling disease.

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The Role of Leukotrienes in Allergic Rhinitis: Clinical and Experimental Evidence

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INTRODUCTION

Allergic diseases of the nasal airways, lung, and skin have reached epidemic proportions over the past 20 years, with a prevalence of atopy in some developed countries approaching 50%. Allergic rhinitis is characterized by symptoms of sneezing, itching, rhinorrhea, and nasal congestion. These symptoms are the consequences of the local release of mediators from inflammatory cells within the nasal mucosa that stimulate the neural, glandular, and vascular components of the upper airways.

The nasal mucosa is lined by pseudostratified, columnar epithelium, which is composed of ciliated cells, nonciliated goblet cells, and basal cells. Beneath this epithelium is basement membrane,