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International patterns of the prevalence of pediatric asthma
The ISAAC program

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Just as the occurrence of asthma and allergies can be studied at many different levels including populations, individuals, organs, tissues, or cells, the causes of asthma can be studied at these different levels. All of these approaches are potentially useful, and individual researchers will focus on different levels of analysis depending on their training, areas of interest, and availability of funding [1]. In the past the major contribution of epidemiology to the study of chronic diseases has been on the population level, including analyses of patterns of disease prevalence and incidence across demographic, geographic, and temporal factors ("person, place, and time"). In particular, many of the epidemiologic hypotheses concerning the causes of cancer and chronic diseases such as coronary disease have stemmed, at least in part, from geographic comparisons [2,3].

It could be argued that the striking international differences in cancer incidence might not have become apparent if the cancer incidence analyses had been confined to countries with similar lifestyles, because the differences in cancer incidence (and the lifestyle-related risk factors that cause the incidence patterns) in many instances would not have been sufficiently great. Whole populations or regions of the world may be exposed to risk factors for disease (eg, high levels of cholesterol and low levels of antioxidants in the diet), and the associations of these factors with disease may become apparent only when

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comparisons are made between populations, or between regions of the world, rather than within populations [4,5].

The ISAAC program

The International Study of Asthma and Allergies in Childhood (ISAAC) program arose from the realization that systematic international comparisons of the prevalence of asthma were needed to understand the global epidemiology of asthma better and to provide a framework for etiologic research into the role of different causative and protective factors [6–8]. This unique project has attracted worldwide interest and unprecedented large-scale participation. The program has evolved as a series of phases, each with different methods and objectives.

ISAAC phase one

The aims of phase one were to describe the prevalence and severity of the symptoms of asthma, rhinitis, and eczema in children living in different geographic centers and to make comparisons within and between countries, to obtain baseline measures for assessment of future prevalence trends and to provide a framework for future etiologic research into the causation of these diseases. The emphasis was on simple, validated methods that could be used in a standardized way, at minimal cost, in as wide a range of centers and countries as possible and with high response rates. In particular, it was decided that more sophisticated, invasive, or expensive tests should wait until phase two studies, developed in light of the findings of the phase one surveys.

The study was based on the participation of 3000 children in two age groups. The compulsory age group was 13 to 14 years (self-completion of questionnaires); an optional group of 6- to 7-year-old children (parent/guardian completion of questionnaires) was also studied. In both age groups, simple one-page written core questionnaires were used for assessing symptoms of asthma, rhinitis, and eczema; a video questionnaire [9,10] was also strongly recommended for the 13- to 14-year-olds. The video questionnaire, which involved the audiovisual presentation of clinical asthma, was designed to minimize difficulties associated with the comparison of information among populations with different cultures and languages. The video questionnaire shows rather than describes the signs and symptoms of asthma; for white children, the video questionnaire has been shown to have sensitivity and specificity equivalent to that of written questionnaires concerning bronchial hyperresponsiveness [11].

The older age group was chosen to reflect the period when morbidity from asthma is common and to enable the use of self-completed questionnaires. The younger age group was chosen to allow study of the early childhood years and involved completion of questionnaires by parents or guardians.

The preliminary results from 156 centers in 56 countries and involving more than 750,000 children showed striking international differences in the prevalence of asthma symptoms (Figs. 1,2). The prevalence of self-reported wheezing in the previous 12 months in 13- to 14-year-old children varied from 1.6% to 36.7% in different centers [8,12]. The corresponding prevalence for parent-reported wheezing for the 6- to 7-year-old age group was 0.8% to 32.1%. Although there are limitations in international prevalence comparisons of this kind, a number of observations that can be made from the ISAAC findings have important implications for future asthma research.

Asthma is less prevalent in developing countries

Within certain regions asthma prevalence is generally lower in developing countries than in more affluent countries. For example, in Southeast Asia, the centers with the lowest prevalence of asthma symptoms were in Indonesia and China, and the centers with the highest rates were in Japan, Thailand, and Hong Kong (Table 1). In some instances, the magnitude of the differences were striking: there was a fourfold difference in the prevalence of asthma symptoms in Guangzhou and Hong Kong, areas that are close geographically, have the same predominant ethnic group, but are of contrasting economic wealth and lifestyles. The relationship between asthma prevalence and economic wealth/development

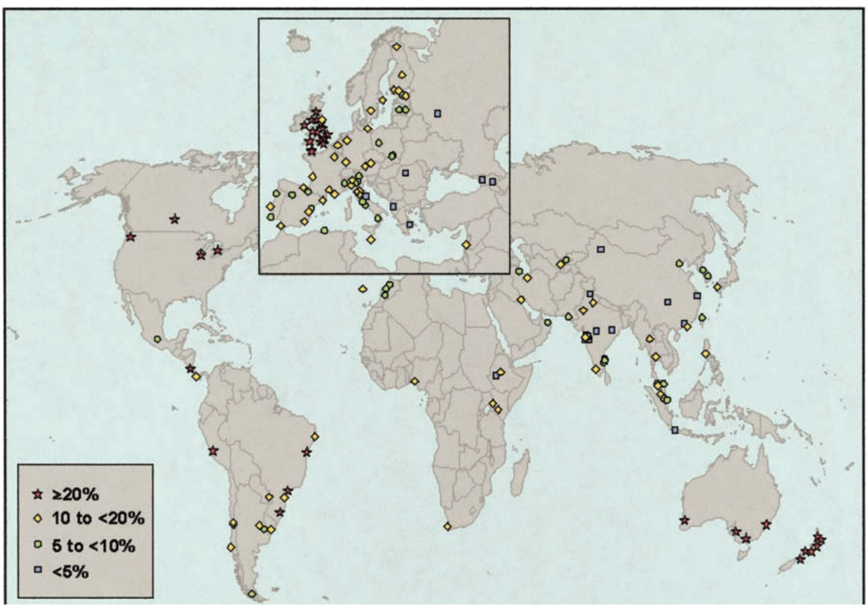

Fig. 1. ISAAC map of asthma symptom prevalence (*From* Asher MI, Anderson HR, Stewart AW, et al. Worldwide variations in the prevalence of asthma symptoms: International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998;12:315–35; with permission.)

Fig. 2. Twelve-month prevalences of self-reported asthma symptoms from written questionnaires (*From* Beasley R, Keil U, von Mutius E, et al, on behalf of the ISAAC Steering Committee. Worldwide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: The International Study of Asthma and Allergies in Childhood (ISAAC). Lancet 1998;351:1225–32; with permission.)

is not as strong as previously suspected, however, and was not apparent in other regions such as Europe and South America.

The highest asthma prevalence rates are in English-speaking countries

Another important pattern is that English-speaking countries have the highest asthma symptom prevalence rates (Figs. 1,2). This overall pattern of international differences between English- and non–English-speaking countries observed with the written questionnaire were maintained with the video questionnaire. This finding suggests that although differences in language or labeling of symptoms such as wheeze may contribute in part to the observed international differences,

Table 1
ISAAC: prevalence of self-reported wheeze in last 12 months in 13- to 14-year-old children from centers in countries in Southeast Asia

	Written questionnaire Wheeze (any) (%)	Video questionnaire Wheeze (at rest) (%)
Indonesia	2.1	1.3
China	3.3–5.1	1.3–3.3
Taiwan	5.2	4.6
Malaysia	6.8–12.3	3.9–6.9
South Korea	7.5–8.3	3.1–5.0
Singapore	9.7	9.9
Philippines	12.3	9.6
Hong Kong	12.4	10.1
Thailand	12.6–13.5	6.0–8.0
Japan	13.4	10.2

Abbreviation: ISAAC, International Study of Asthma and Allergies in Children

they are unlikely to explain the substantial international differences in the prevalence of asthma between English- and non–English-speaking countries seen with both the written and video questionnaires.

A northwest-to-southeast gradient in asthma prevalence exists in Europe

Another striking and unexpected feature was the strong northwest-to-southeast gradient in asthma prevalence that exists in Europe (Fig. 1). This pattern was observed in both age groups and is unexplained by the recognized risk factors for asthma. Together with marked differences in prevalence in other regions of the world, such as Southeast Asia and Latin America, this gradient suggests that the investigation of the causes of asthma can be usefully undertaken on a regional as well as a worldwide basis.

Asthma prevalence patterns are not explained by genetic or ethnic differences

One of the consistent findings of the ISAAC program is that marked differences in asthma prevalence occur in populations with similar genetic or ethnic backgrounds. This difference was particularly evident when considering the findings from similar ethnic groups living within countries such as China (including Hong Kong and Taiwan), India, Italy, and Spain. These findings suggest that whereas genetic predisposition may be important in determining whether asthma develops in an individual, environmental factors in the broadest sense are the major determinants of the prevalence of asthma in a community.

Differences and similarities exist in the international patterns of the prevalence of asthma, allergic rhinoconjunctivitis, and atopic eczema

Comparison of the international prevalence patterns of asthma, allergic rhinoconjunctivitis, and atopic eczema showed marked differences among the different atopic disorders in terms of the centers with the highest prevalence rates, whereas the relative prevalences in the centers with the lowest rates were generally similar [8]. Furthermore, most of the children with symptoms of one disorder did not report symptoms of either of the other two atopic disorders. This finding suggests that there may be important differences in the risk factors or time courses of asthma, allergic rhinoconjunctivitis, and atopic eczema.

The international patterns of asthma prevalence in children are similar to those observed in adults

There was generally good agreement between the international patterns of asthma prevalence found in the European Community Respiratory Health Survey (ECRHS) program [13,14], which was undertaken in 20- to 44-year-old adults and the 13- to 14-year-old children included in the ISAAC program [15]. This observation adds support for the validity of both the ISAAC and the ECRHS findings.

Asthma prevalence patterns are not explained by known risk factors

Encompassing many of these observations, perhaps the most important interpretation of the ISAAC program is that the current recognized risk factors for the development of asthma probably cannot account for the international variations in asthma prevalence that have been observed, or for that matter, the worldwide increases in asthma prevalence. For example, although air pollution is well recognized as an important cause of exacerbations of asthma [16], it could not account for international patterns of asthma prevalence that were observed. Likewise, although sensitization to the house dust mite allergen is an important risk factor for the development of asthma [17], it seems unlikely that exposure to house dust mite explains the international prevalence patterns.

Phase one ecological studies

An extensive series of ecological studies have been undertaken throughout the world where standardized risk factor data have been available to evaluate the strength of associations between the recorded symptom prevalence of childhood asthma and risk factors in different centers. Such ecological analyses need to be interpreted with caution, because a correlation between variables based on group (ecological) characteristics may not necessarily be caused by an association between the variables when based on individual characteristics. Such inappropriate inferences from ecological data are referred to as the ecological fallacy [18]. Ecological analyses are an informative and appropriate method for examining the effect of the social environment and health, if one accepts that environmental factors are major determinants of the international patterns of disease prevalence [19].

To date the ecological analyses based on the ISAAC phase one prevalence data have revealed a number of interesting associations that have implications for the understanding of the causation of asthma and the development of possible intervention strategies.

Diet

The worldwide analysis of food intake and prevalence of asthma symptoms showed a negative association with the consumption of starch, cereals, and vegetables, but not other major food groups [20]. The findings have a number of implications; if they can be generalized, they could provide the basis for public health strategies to reduce the prevalence of asthma in communities by increasing the average daily consumption of these foods. There is a wide range of potential mechanisms that could explain these associations, from the protective effects of antioxidants in vegetables to the effect of diet on bowel microflora. Further research elucidating the relative role of the different mechanisms would contribute to an improved understanding of the causation of asthma.

The relevance of these findings to the developing world is suggested by the recent study from Saudi Arabia in which, after controlling for other determinants, dietary factors were associated with a two- to threefold increase in risk of developing asthma [21]. Of the major food groups, asthmatics consumed less vegetables and milk, fiber, and the antioxidant vitamin E. Similarly, in the first Nutrition and Health Survey in Taiwan, vitamins A and C were negatively associated with asthma, whereas protein-rich and fat-rich foods of animal origin were associated with a higher prevalence of asthma in teenagers [22,23].

It is likely that the changes in diet associated with increasing prosperity and exposure to commercially prepared foods may be responsible in part for the increasing asthma prevalence observed in developing countries. It is likely that a move away from the combination of different nutrients in the balanced diet with which humans have evolved, rather than the exclusion or inclusion of particular nutrients, has been responsible for the observed changes in disease prevalence.

Paracetamol (acetaminophen) use

National paracetamol sales were positively associated with the prevalence of asthma symptoms in children across the centers participating in ISAAC [24]. This finding provides one of the few hypotheses to explain the high prevalence in English-speaking Western countries, which have the highest usage of paracetamol. This finding is consistent with similar ecological analyses from the ECRHS, in which paracetamol sales were positively associated with the prevalence of asthma and bronchial hyperresponsiveness in young adults across centers, with the highest usage in English-speaking countries [24]. It is also consistent with the recent report that frequent (daily or weekly) use of paracetamol is positively associated with asthma including asthma severity [25]. It has been proposed that the frequent use of paracetamol might increase the risk of asthma by depleting levels of reduced glutathione in the airways, thus shifting the oxidant/antioxidant balance in favor of oxidative stress and increasing inflammation.

Tuberculosis rates

The putative role of *Mycobacterium tuberculosis* infection was investigated following the observation that strongly positive tuberculin responses were associated with a significantly lower prevalence of asthma and other atopic disorders in Japanese children [26,27]. When the association between tuberculosis notification rates and asthma prevalence worldwide was investigated, an inverse relationship was observed [28,29]. This finding is consistent with the hypothesis that chronic or severe childhood respiratory infections such as tuberculosis may be protective in reducing the risk of developing asthma and that differences in tuberculous exposure in communities may contribute at least in part to the international patterns of asthma prevalence. This finding is also relevant to the current research efforts to develop a *Mycobacterium*-based vaccine as a preventive strategy for asthma [30,31].

Immunization

It has been proposed that immunization may increase the risk of developing atopic asthma either by a direct effect on the immune system or by a reduction of the burden of infection in early childhood [32]. The ISAAC ecological study of immunization rates and the prevalence of asthma symptoms provided no support for this hypothesis, with the results for diphtheria-pertussis-tetanus (DPT) and measles vaccination supporting a conclusion contrary to that predicted by this theory [33]. This result is reassuring because of the well-recognized importance of mass immunization as a component of the public health prevention of infectious diseases worldwide.

Gross domestic product

The influence of environmental factors related to the wealth of a country have been investigated because of the general observation that the prevalence of asthma seems to be lower in developing countries than in developed countries. This study has been undertaken by determining the relationship between the prevalence of asthma symptoms and standardized markers such as the gross national product per capita of the countries in the ISAAC program. This investigation showed a positive association between higher gross national product and the prevalence of asthma symptoms in the 13- to 14-year-old age group [34], although this association was only of moderate strength, suggesting that environmental factors contributing to the development of asthma are not related only to the wealth of the country (Table 2). The pattern observed suggested that there may be a threshold effect: as the gross national product increases toward a certain level, the changes in society common to most countries result in an increased

Table 2
The median prevalence (with 10th and 90th percentiles) of wheezing during the last 12 months in 13- to 14-year-old children by center grouped into four approximately equally size groups based on the country GNP per capita

	US$100–1140	US$1490–3170	US$3610–17500	US$18060–31490
Number of countries	13	14	14	14
Number of centers	36	30	34	53
Wheeze (%)	5.3 (1.9, 13.0)	11.6 (7.0, 24.2)	11.9 (6.1, 31.4)	14.8 (8.6, 34.1)

Abbreviation: GNP, gross national product
Modified from Stewart AW, Mitchell EA, Pearce N, et al on behalf of the ISAAC Steering Committee. The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Int J Epidemiol 2001;30:173–9.

prevalence of asthma, but this pattern does not occur at higher levels of gross national product.

Tobacco use

Ecological analysis indicated that countries that have high adult male smoking rates have lower rates of asthma prevalence in children [35]. This finding does not involve information on individual exposures and as a result does not contradict the well-established association of active and passive smoking in the development of asthma in the same individuals [36,37]. Rather, this finding indicates that this well-established individual-level association does not account for the international differences in prevalence and that other risk factors for asthma must be responsible for the observed international patterns.

Climate

The association with climate has been examined primarily with data from the 57 centers in 12 countries in Western Europe (Weiland SK, Hüsing A, Strachan DP, et al on behalf of the ISAAC Phase One Study Group. Climate and the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema in children, unpublished data). The rationale for restricting the ecological analysis to this region rather than extending it worldwide is that although the variation in climatic conditions and prevalence of asthma is comparable to the variation worldwide, the differences in living conditions unrelated to climate are much smaller within Western Europe. This analysis showed that the prevalence of asthma symptoms increased with increasing estimated indoor relative humidity. The underlying mechanisms whereby the indoor relative humidity may affect the development of asthma are unclear but may relate to levels of house dust mite and mold exposure. In contrast, mean outdoor temperature and outdoor relative humidity were not associated with the prevalence of asthma symptoms. There was an inverse association between the prevalence of asthma symptoms and altitude [38,39].

ISAAC phase two

Although such ecological analyses are useful for generating rather than proving hypotheses, they do provide the basis for further research. In the ISAAC program, these ecological analyses have led to the second phase in which detailed clinical and environmental data are being obtained in children in 48 centers from 20 countries. Populations that were considered to be potentially informative, such as those with contrasting prevalence of disease or environmental exposures, were chosen for inclusion in phase two [7].

The aims of phase two were to describe the prevalence of objective markers of asthma and allergies in children living in different centers and to make comparisons within and between centers; to assess the relationship between the prevalence of objective markers of asthma and allergies and the prevalence of symptoms of these conditions in children living in different centers; to estimate the extent to which the variation and the prevalence and severity of asthma and allergies in children in different centers can be explained by differences in known or suspected risk factors and to explore new etiologic hypotheses regarding the development of asthma and allergies in children. As with phase one, measurements on representative samples of these populations have been undertaken using standardized instruments.

Although the analyses are ongoing, the initial reports have produced some intriguing findings and have illustrated the considerable potential for this phase of the program. Perhaps the greatest interest at this stage has come from studies that have explored the relationship between allergic sensitization and asthma.

Europe

As part of the second phase of ISAAC, a detailed study was undertaken in communities from two countries at the extremes of the worldwide distribution of asthma prevalence–Albania (low) and the United Kingdom (high) [40]. Phase one studies showed that the prevalence of current asthma symptoms and exercise-induced bronchial responsiveness were six- to tenfold higher in England than in Albania (Table 3). In contrast, the frequency of allergic sensitization was similar in the two countries. These findings indicate that the substantial differences in asthma prevalence across Europe are likely to reflect similar differences in bronchial responsiveness and confirm that they are unlikely to be explained by variations in the occurrence of allergic sensitization. Elucidation of the factors that protect Albanian children (for example) from developing asthma could point to new opportunities for the primary prevention of asthma worldwide.

Table 3
Symptoms, exercise-induced asthma, and atopic sensitization in children from Albania and England

	Albania (%)	England (%)	Odds Ratio
Wheeze in past year:			
0–3 attacks	4.4	9.7	0.4
4–12 attacks	0.3	4.8	0.1
>12 attacks	0.2	1.4	0.1
PEF reduction after exercise:			
≥ 10%	4.3	11.9	0.3
≥ 15%	0.8	5.4	0.1
Skin prick reaction ≥ 3 mm:			
Any allergen	15.0	17.8	0.8

Abbreviation: PEF, peak expiratory flow
Modified from Priftanji A, Strachan D, Burr M, et al. Asthma and allergy in Albania and the UK. Lancet 2001;358:1426–7.

Scandinavia

The relationship between the prevalence of atopy and asthma symptoms differed in a similar study comparing the prevalence of asthma and atopy in children in Estonia and two centers in Sweden [41]. Despite similar rates of current wheezing (8.4% versus 7.9% and 10.2%, respectively) the rates of atopic sensitization were lower in Estonia than in Sweden (14.8% versus 20.1% and 26.8%, respectively). Wheezing children in Sweden had two- to threefold higher rates of positive skin prick tests and bronchial hyperresponsiveness, respectively, than children in Estonia. These findings suggest differential rates of atopic and nonatopic asthma in the different communities and support the concept that wheezing in childhood may represent different asthma phenotypes that differ in relation to atopy [42].

China

The relationship between asthma prevalence and house dust mite exposure, the major indoor allergen to which individuals are exposed, has not been undertaken worldwide because of difficulties associated with the standardization of the measurement of the house dust mite allergen *der* P_1. In a local phase two study, Lai et al [43] reported that levels of house dust mite allergen were similar in houses in Hong Kong and Guangzhou despite the considerable difference in asthma prevalence. This observation is consistent with other studies that have reported that populations exposed to similar house dust mite allergen levels may have markedly different asthma prevalence rates, whereas other populations with markedly different house dust mite allergen levels may have similar rates of asthma prevalence [44].

These findings from different regions of the world, together with other epidemiologic evidence, challenge the commonly held concepts of a strong deterministic association between atopy and asthma [45]. At the individual level it has been calculated that just under one half of asthma cases are attributable to atopy. This finding suggests that the importance of atopy as a cause of asthma may have been overemphasized and is certainly less than that generally considered by clinicians.

Perhaps the key issue that needs to be resolved to understand the international patterns of asthma prevalence, and indeed the major causes of asthma, is not what factors lead to atopic sensitization but rather what factors make an atopic person asthmatic. Resolving this issue requires a better understanding of why only a proportion of atopic individuals develop asthma and which factors determine the organ specificity of the disease state [46].

ISAAC phase three

Divergent international time trends in the prevalence of asthma are of particular interest in exploring the role of different environmental factors. The third phase of the ISAAC program aims to examine time trends in the prevalence of asthma, allergic rhinoconjunctivitis, and atopic eczema in centers and countries that participated in phase one [7]. Phase three also provides the opportunity to describe the prevalence and severity of asthma in centers and countries that are of interest but did not participate in phase one, including a number of isolated, politically unstable, or repressed communities such as Palestine, Tibet, Yugoslavia, Congo, and Cuba. These centers provide both standardized prevalence data and insight into the environmental and lifestyle factors specific to their communities. For example, in the Ramallah District in Palestine, children living in refugee camps had higher asthma prevalence rates than children from neighboring villages or cities [47]. The prevalence of asthma symptoms in Palestine, however, was much lower than that in Israel or in some other countries in the region such as Kuwait and Saudi Arabia.

In China, marked differences have been observed in the prevalence of asthma between rural and urban communities. For example, the prevalence of asthma symptoms in adolescent children from urban Beijing was six- to tenfold greater than that in an outlying rural community [48]. Similar findings have been observed in studies from Africa, in which the rate of exercise-induced asthma may be 50-fold higher in urban communities than in rural communities [49]. This finding suggests that the lifestyle and environmental changes associated with urbanization are crucial factors in determining the prevalence of asthma within communities. It also indicates that, given the widespread process of urbanization within developing countries, the greatest burden in terms of increasing asthma prevalence is likely to occur within these countries, particularly within the densely populated Asian region.

To date 236 centers from 92 countries are undertaking the phase three study, the design of which is similar to the corresponding phase one study. The phase three study also incorporates an additional risk factors questionnaire that obtains environmental information at the individual level. This information should enable the investigation, at an individual level, of hypotheses that have been suggested by the findings of phase one, subsequent ecological analyses, phase two findings, and recent advances in knowledge.

Summary

Like so much research, the findings from the ISAAC program have raised more questions than they have answered. Despite their limitations, the ISAAC findings provide the basis for further studies to investigate factors that potentially contribute to these international patterns and may lead to novel public health and pharmacologic intervention strategies that reduce the prevalence and severity of asthma worldwide.

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